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Table of Contents

HEALTH EDUCATION OF NEW MOTHERS IN PREVENTING DEGREEING OF HIP-FEMORAL DYSPLASIA

Elona HASALLA, Ilda TAKA, Brandi FAHRIU, Gerta KAÇANI, Blerta HASALLA, Sulejman BAHA, Elda RUÇI, Irena XHAFERRI 17

ULTRASONIC BATH EXTRACTION AS AN ADVANCED METHOD FOR EXTRACTING THE PHARMACEUTICAL HERB VALERIAN

Mahi LATIFI, Nexhbedin BEADINI, Sheqibe BEADINI, Ejup LATIFI 27

COMPARATIVE ANALYSIS OF ANTI-MULLERIAN HORMONE (AMH) AND FERTILITY IN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME (PCOS)

Mergime ABDULI, Qefajet MURSELI, Sheval F. MEMISHI 32

FROM DETECTION TO CLINICAL DECISION: ARTIFICIAL INTELLIGENCE BASED RISK STRATIFICATION IN PEDIATRIC FRACTURE IMAGING

Polikseni MEMO 37

OPEN-SOURCE INTELLIGENCE APPLICATIONS IN REAL-TIME GEOPOLITICAL ANALYSIS: A DATA-DRIVEN APPROACH

Andrei-Mihai TUFIŞ, Viorel LAMBU, Paula IOVESCU, Alessia CARAGEA 44

TIME-DEPENDENT EFFECTS OF ACUTE ORAL ADMINISTRATION OF AMITRAZ ON SERUM ENZYME ACTIVITY IN WISTAR RATS

Njomza SHAQIRI, Zehra HAJRULAI-MUSLIU, Icko GJORGOSKI, Jane VLAHOV, Velimir STOJKOVSKI 62

IMPACT OF VITAMIN D DEFICIENCY ON HEMATOLOGICAL PARAMETERS

Luzana SHABANI, Jehona ALI, Sheqibe BEADINI, Mimoza BAFQARI-BAKIJI, Arita SABRIU HAXHIJAHA 70

FOOD SAFETY RISKS ASSOCIATED WITH WILDLIFE-DERIVED PRODUCTS IN ALBANIA: A ONE-YEAR FIELD AND LABORATORY ASSESSMENT

Besnik ELEZI, Kastriot KORRO, Merije ELEZI 78

POST-EXTRACTION WITH MACERATION, AN ADVANCED METHOD IN INCREASING THE EXTRACTION COEFFICIENT FOR AGNUS CASTUS

Ejup LATIFI, Mahi LATIFI, Shefket DEARI, Nazif JASHARI, Neset IZAIRI 84

APPLICATION OF CONTROL SYSTEM TECHNIQUES FOR PARAMETER IDENTIFICATION AND ERROR ANALYSIS IN TIME-DELAY SYSTEMS

Nderim ZEQIRI, Ferit IDRIZI, Asan IDRIZI 89

ANTIBACTERIAL SYNERGY AND BIOFILM DYNAMICS OF *VACCINIUM MYRTILLUS* AND *ARCTOSTAPHYLOS UVA-URSI* AGAINST MULTIDRUG-RESISTANT (MDR) *ESCHERICHIA COLI*: *IN VITRO* AND STATISTICAL ANALYSIS

Vjollca SHABANI, Mije REÇI, Erjona SHAQIRI, Shasine SHABANI, Vesna VESELIEVSKA STOJKOVSKA, Darinka GORGIEVA ACKOVA 97

TRIGLYCERIDE–GLUCOSE INDEX: AN INDICATOR OF THE INTERRELATIONSHIP BETWEEN LIPIDS AND GLUCOSE IN DIABETIC PATIENTS

Jonida ALITI, Luzana SHABANI, Mimoza BAFQARI-BAKIJI, Nexhbedin BEADINI, Mije REÇI 109

THE ROLE OF THE PHARMACIST IN THE ASSESSMENT OF HERB–DRUG INTERACTIONS AND THE SAFETY OF HERBAL MEDICINES

Sanja LAZAROVA, Arijeta SHABANI, Jehona CANGA, Nexhibe NUHII, Arlinda HAXHIU-ZAJMI, Sihana AHMETI-LIKA 117

THE IMPACT OF THE MEDITERRANEAN DIET ON LIFESTYLE IN PATIENTS WITH HYPERTENSION IN KOSOVO

Nazmi VELIJA, Zora UZUNOSKA, Gafur XHABIRI, Valentina VELKOVSKI, Vesna ANTOSKA KNIGHTS, Nazmije VELIJA 123

PREVALENCE OF RHEUMATOID ARTHRITIS AND DISTRIBUTION BY AGE AND GENDER IN THE FERIZAJ REGION

Vahide REXHAJ, Mije REÇI, Sheval MEMISHI 129

THE IMPACT OF ROAD INFRASTRUCTURE ON TRAFFIC SAFETY AND THE ECONOMIC DEVELOPMENT OF THE STATE – CASE OF THE REPUBLIC OF NORTH MACEDONIA

Sedat ARUCI, Feta SINANI , Xhemile SEJDINI, Adina OSMANI, Emir ALIJA 134

SUBACUTE SCLEROSING PANENCEPHALITIS: CLINICAL REVIEW OF PATHOGENESIS, DIAGNOSIS AND MANAGEMENT

Shehide ALIU, Lejla ADEMI 139

DECARBONIZATION AS A GLOBAL CHALLENGE FOR A CLEAN ENVIRONMENT

Imer ZENKU 147

TECHNOLOGICAL INNOVATION AND PRODUCTION EFFICIENCY: EVIDENCE FROM ARAB ECONOMIES IN A GLOBAL CONTEXT

Sareh ROTABI, Hyrije ABAZI-ALILI 159

REFRAMING SUSTAINABLE MOBILITY IN POST-SOCIALIST CITIES: THE ROLE OF URBAN FORM AND WALKABILITY IN PUBLIC TRANSPORT INTEGRATION IN TETOVO

Sara NESIMI MURADI 167

PREVALENCE AND GENDER DIFFERENCES IN ACTIVE HELICOBACTER PYLORI INFECTION BASED ON FECAL ANTIGEN TEST IN THE REPUBLIC OF NORTH MACEDONIA

Vlera JASHARI, Mije REÇI 172

CLINICAL AND ORTHODONTIC MANAGEMENT OF IMPACTED TEETH ASSOCIATED WITH RETAINED PRIMARY TEETH

Abdyl IZAIRI, Anda IZAIRI, Ardi IZAIRI 177

COMPARATIVE ANALYSIS OF MA IN BEAMSMADE OF STEEL WITH DIFFERENT SPANS

Berat ZEJNELI, Shinasi ZEJNELI, Meryem KAPROL 183

COMPARATIVE ANALYSIS OF MONOLITHIC CONSTRUCTION AND THE „CUBIAX„SYSTEM IN COMERCIAL BUILDING

Berat ZEJNELI, Shinasi ZEJNELI, Engin ILJAZI 200

ASSESSMENT OF DIAGNOSTIC AND TREATMENT METHODS FOR PYOMETRA IN STRAY DOGS IN THE MUNICIPALITY OF GOSTIVAR

Dashmir MAMUTI , Emri MURATI, Nesim SEFERI, Besnik ELEZI, Fejzullah FEJZULLA 212

ORAL HEALTH STATUS AMONG TWELVE-YEAR-OLD CHILDREN IN THE DEBAR REGION

Albert MAQELLARA, Mira JANKULOVSKA, Aleksandar DIMKOV, Dragica GLIGOROVA, Dijedona MURTISHI MAQELLARA 217

ARTIFICIAL INTELLIGENCE USE AND PERCEPTIONS AMONG NURSING STUDENTS: A CROSS-SECTIONAL STUDY

Ilda TAKA, Elona HASALLA, Albana SULA, Blerina BAHITI, Rajmonda HIDA, Blerina BANI 225

PERSONALIZED MEDICINE: A COMPARATIVE ANALYSIS OF IMPLEMENTATION AND CHALLENGES IN NORTH MACEDONIA AND EUROPEAN COUNTRIES

Lulzime BALLAZHI, Edita ALILI-IDRIZI, Merita DAUTI, Sihana AHMETI-LIKA, Drita HAVZIU-YZEIRI, Hanife RUSTEMI-AHMETI, Arbnore QAHILI-NAZIFI, Gjylai ALIJA 236

POSTRENAL ACUTE KIDNEY INJURY SECONDARY TO URINARY RETENTION FROM BENIGN PROSTATIC HYPERPLASIA COMPLICATED BY MULTIDRUG-RESISTANT ACINETOBACTER INFECTION AND CHRONIC PULMONARY THROMBOEMBOLISM: A CASE REPORT

Almira XHAFERI, Zehra MUSTAFAI, Rihan SAITI 243

FUNCTION OF THYROID GLAND HORMONES, METABOLIC DISORDERS, OVERWEIGHT, OBESITY AND BIOCHEMICAL PARAMETERS

Egzona ZIBERI, Sheqibe BEADINI 256

FROM METABOLIC STRESS TO OPTIMAL PERFORMANCE: THE ROLE OF BIOMARKERS IN MONITORING SPORTS OVERTRAINING

Egzona ZIBERI, Ladon MURSELI 262

POLYPHARMACY IN OLDER ADULTS: BALANCING THERAPEUTIC BENEFITS AND MEDICATION-RELATED HARM

Bekim ISMAILI, Yllzana SINANI, Diellza MAZLLAMI, Maida VELI 269

CHA_2DS_2-VASC SCORE IN ATRIAL FIBRILLATION: CLINICAL APPLICATION AND FUTURE PERSPECTIVES

Behije ISMAILI, Hirisha ASANI, Driton SELMANI 278

PREVALENCE OF TRANSFUSION – TRANSMITTED INFECTIONS AMONG VOLUNTARY BLOOD DONORS IN THE WESTERN REGION OF NORTH MACEDONIA: A RETROSPECTIVE MULTICENTER STUDY (2021-2025)

Fatjona JASHARI, Ekrem ISMANI, Edona ISMANI XHEMAILI 282

NON-STANDARD NEUROSURGICAL MANAGEMENT OF CRANIOSYNOSTOSIS: A CASE REPORT

Sami PNISHI, Besnik ELSHANI, Arben BISLIMI, Leutrim PNISHI 294

DRUG MISUSE AMONG YOUTH IN THE ERA OF ARTIFICIAL INTELLIGENCE

Arta ADILI, Nexhibe NUHI 299

CLINICOPATHOLOGICAL AND GENETIC CHARACTERISTICS OF BREAST CANCER PATIENTS UNDERGOING MULTIGENE PANEL TESTING: A SINGLE-CENTER COHORT STUDY

Ilir ISMAILI, Ilir KURTISHI, Sefedin BILJALI, Anita HADZI –MANCHEVA, Meri PESEVSKA 303

THE AI SAFETY GAP: A SCENARIO-BASED STUDY OF RISKY HEALTH DECISIONS AND MISPLACED TRUST

Adriatik KRASNIQI, Amira HUSEINI, Rihan SAITI 307

PREVALENCE OF ANTIBIOTIC RESISTANCE IN CLINICAL ISOLATES OF E. COLI

Rezearta ISAKI, Maida KAMBERI, Driton SELMANI 310

ADAPTING TREATMENT IN METASTATIC HR+/HER2− BREAST CANCER, AFTER CHEMOTHERAPY REFUSAL: A CASE REPORT

Arben BISLIMI, Faton SERMAXHAJ, Sami PNISHI, Bardhe SELMANAJ BISLIMI 318

ASSESSMENT OF METHANOL CONCENTRATION IN ARTISANAL AND INDUSTRIAL FRUIT DISTILLATES PRODUCED IN KOSOVO

Zenun KRASNIQI, Çliresa DEMIRAJ 322

POLYMER FIBERS: PREPARATION AND APPLICATIONS

Attila LEVENTE GERGELY, József KÁNTOR 331

THE EVOLUTION OF NUCLEAR MEDICINE IN THE REPUBLIC OF KOSOVO: FROM PLANAR GAMMA CAMERA IMAGING TO SPECT/CT AND PET/CT—INSTITUTIONAL CHALLENGES, TECHNOLOGICAL ADVANCEMENTS, AND FUTURE CLINICAL PERSPECTIVES

Ismet BAJRAMI, Fakir SPAHIU, Rame MIFTARI, Luljeta ABDULLAHU, Aferdita BAJQINCA PAÇARIZI, Bajram KRASNIQI, Ylli KAÇIU, Armend JASHARI 339

THE ROLE OF PHYSICAL ACTIVITY IN BALANCING DYSLIPIDEMIA

Alajdin HASANI, Art ZYLBEARI, Ema BEXHETI 348

ADVANCED FORMULATIONS OF PEDIATRIC MEDICINES: REDUCTION OF SYNTHETIC EXCIPIENTS AND THEIR IMPORTANCE FOR CHILDREN'S SAFETY

Merita DAUTI, Sihana A. LIKA, Gjylai ALIJA, Lulzime BALLAZHI, Edita A. IDRIZI, Arlinda H. ZAJMI, Drita Y. HAVZIU, Flora DOKO, Qahil IRAIMI, Arianita MUSA 355

DETERMINATION OF YIELD AND KERNEL PERCENTAGE IN SOME HAZELNUT CULTIVARS (*CORYLUS AVELLANA* L.)

Alirami SALIJI, Bardhyl LIMANI, Zejnedije ADEMI, Valmir SALIJI, Hirijete IDRIZI, Bardha IBISHI 369

IMPACT OF OXYGEN ON BEER QUALITY PARAMETERS DURING INDUSTRIAL BREWING: A CASE STUDY OF PEJA BREWERY (KOSOVO)

Arsim ELSHANI, Ibrahim HOXHA, Nexhdet SHALA 375

MEDICINE RECALL SYSTEMS IN THE USA AND EU: A REGULATORY COMPARISON

Arlinda HAXHIU ZAJMI, Drita YZEIRI HAVZIU, Gjylaj ALIJA, Arijeta SHABANI, Merita DAUTI, Hanife RUSTEMI AHMETI, Elona CILKU, Zana MUSTAFA 381

DESIGN AND SIMULATION OF A CNC POSITION CONTROL SYSTEM USING PID AND FUZZY-PID CONTROL

Besim AQIFI, Ferit IDRIZI 389

IMPLEMENTING GRAPHQL AND REST APPLICATION PROGRAMMING INTERFACES IN MOBILE APPLICATIONS

Avni RUSTEMI 396

SLEEP PHYSIOLOGY

Hana OSMANI, Anila BELLCHISHTA SHAQIRI 405

THREE YEAR 2023-2025 COMPERATIVE ANALYSIS OF WATER QUALITY IN VILLAGE VRUTOK, IMPLICATIONS FOR 3D FOOD BIOTECHNOLOGY AND MOLECULAR STABILITY

Merije ELEZI, Besnik ELEZI, Ilderina QERIMI, Sahide SINANI, Yllza HASANI, Rakip EMRULI, Armend MEHMEDI, Sunaj RUSTEMI, Ilir RUSTEMI, Meriton ÇODARI 413

ALBANIAN-SPEAKING VISUALLY IMPAIRED INTERFACING MODEL

Lindita ADEMI, Valbon ADEMI 420

CEFTRIAXONE AS AN EMPIRIC ANTIBIOTIC: PRESCRIBING PRACTICES, RESISTANCE DYNAMICS, AND STEWARDSHIP STRATEGIES

Qahil IBRAIMI, Merita DAUTI, Erëza DURMISHI, Drita YZAIRI, Gjylaj ALIJA, Driton SELMANI 426

MANAGEMENT OF ATRIAL FIBRILLATION FOR REDUCING THE RISK OF STROKE AND THROMBOEMBOLISM

Albin SINANI, Nadir AJRULI, Nexhbedin ABAZI, Selma ARSLLANI, Samije IDRIZI, Blerta SINANI 437

DATA ENCRYPTION USING THE ALGEBRAIC STRUCTURE OF QUATERNIONS

Azir JUSUFI, Merita BAJRAMI, Rushadije RAMANI HALILI, Gazmend XHAFERI 443

ATOPIC DERMATITIS IN AN INFANT: PRESENTATION OF A CLINICAL CASE WITH SECONDARY STAPHYLOCOCCUS AUREUS INFECTION

Erblira RESHITI, Aulona HAXHIREXHA, Alba JAHIJA 450

THE INFLUENCE OF THE POROSITY COEFFICIENT (R_U) ON THE SAFETY FACTOR (Fs) WITH THE APPLICATION OF NUMERICAL METHODS

Idaver HUSEINI, Nexhmi KRASNIQI, Asan IDRIZI 459

THE ROLE OF PREVENTIVE MAINTENANCE IN ENHANCING THE PERFORMANCE OF THE VSS 'FEHMI LLADROVCI' BUILDING IN DRENAS

Idaver HUSEINI, Nexhmi KRASNIQI 467

SPORT INFRASTRUCTURE IN TETOVO: AN EVALUATION OF EXISTING CONDITIONS, CHALLENGES AND FUTURE DEVELOPMENT POTENTIAL

Hazra MERXHANI, Getoar ABDURAMANI, Fjolla IBRAIMI, Albin HALITI 474

HOW SWIMMING AFFECTS THE HUMAN BODY

Rrezearta NEZIRI, Anila BELLÇISHTA SHAQIRI 486

IMPACT OF WASTEWATER IRRIGATION ON HEAVY METAL CONCENTRATIONS IN VEGETABLES, WITH PRIMARY FOCUS ON Pb AND Cd

Katerina TEMELKOVSKA RISTEVSKA, Tatjana BLAZHEVSKA, Gorica PAVLOVSKA, Vezirka JANKULOSKA, Valentina VELKOVSKI, Nevena GRUEVSKA, Kristina JANKULOSKA GACOSKA 493

APPLICATIONS OF CONGRUENCE IN VARIOUS FIELDS

Rushadije RAMANI HALILI, Azir JUSUFI, Merita BAJRAMI, Vesa HAZARI 504

EXPLAINABLE MACHINE LEARNING FOR INSURANCE CLAIM FRAUD DETECTION: A COMPARATIVE PYTHON-BASED STUDY

Ermira MEMETI, Eftim ZDRAVEVSKI, Shkurte LUMA-OSMANI, Florinda IMERI 510

IMPACT OF VARIOUS HERBAL EXTRACTS ON TECHNOLOGICAL FUNCTIONALITY OF YOGURT

Erhan SULEJMANI, Zehra DEMIRI, Gjilkije ILAZI, Faton ABDULLAJI, Lindita BEADINI, Semra IDRIZI, Besar JUMNIU, Safije MEDIJA, Ilir XHAFERI, Valdeta XHAFERI 519

NUMERICAL ANALYSIS OF MEMORY EFFECT IN CAPUTO FRACTIONAL COOLING MODELS VIA EULER TYPE METHODS

Ylldrita SALIHI, Krutan RASIMI, Vjollca SHEMSHI, Nexhibe SEJFULI RAMADANI 527

TREATMENT MODALITIES AND OUTCOMES IN DEVELOPMENTAL DYSPLASIA OF THE HIP

Maida NEBI, Ilber BESIMI 535

PREVALENCE AND ANATOMICAL DISTRIBUTION OF INCIDENTALLY DETECTED VASCULAR CALCIFICATIONS ON RADIOGRAPHS

Maida NEBI, Gazi SHAINI, Luiza ADILI, Atilla REXHEPI, Lavdrim MEHMEDI, Pranvera RAMADANI 542

GROWTH ZONES OF THE KNEE AND OSTEOCHONDRAL DEFECTS IN CHILDREN

Yllza FEJZULLAI, Anila BELLÇISHTA SHAQIRI 550

YOU ARE NOT ENTIRELY YOU: MICROCHIMERISM AND THE HIDDEN PERSISTENCE OF FOREIGN CELLS- A SYSTEMATIC REVIEW AND META ANALYSIS

Anida NESIMI, Vlera MUHAREMI, Lisa MATOSHI, Safije GAFURI, Ekrem ISMANI 555

PREVENTIVE MEASURES FOR RODENT (*RODENTIA*) CONTROL IN THREE DISTINCT URBAN LOCALITIES IN SKOPJE

Gazmend ISENI, Ajten RUSHITI-DAUTI, Nebehat ILJAZ, Sheval MEMISHI, Besa ISENI, Besnik REXHEPI 563

HPV VACCINATION: AWARENESS, EDUCATION, VACCINE CONFIDENCE AND EARLY PREVENTION STRATEGIES

Amina RUSHITI, Semra IMERI, Florin BESIMI 570

CHARACTERIZATION OF APPLE (*MALUS DOMESTICA*) PROCESSING WASTE: PHYSICOCHEMICAL AND NUTRITIONAL COMPOSTITION

Gresa AHMA, Vezirka JANKULOSKA, Hyrije KORAQI, Namik DURMISHI, Daniela NIKOLOVSKA NEDELKOSKA, Anka TRAJKOVSKA PETKOSKA, Gorica PAVLOVSKA 573

PHYSICAL SEPARATION OF URBAN PUBLIC TRANSPORT FROM OTHER TRAFFIC FLOWS IN THE CITY OF TETOVO AS A MODERN MOBILITY SOLUTION

Resmi EJUPI, Dean BRKOVSKI, Adina OSMANI 581

EVALUATION OF MORPHOLOGICAL AND BIOMETRIC INDICATORS OF SWEET POTATO CULTIVARS (*Ipomea batatas Poir*)

Ensi TOLI, Nikollaq BARDHI, Sergej QAMA, Bardhyl LIMANI, Zejnedije ADEMI, Hirijete IDRIZI 587

LEVEL'S OF STUDENT'S KNOWLEDGE ACCORDING TO BLOOM'S TAXONOMY ON THE TOPICS OF GRAVITY AND COSMOLOGY IN UPPER SECONDARY SCHOOLS

Enkeleida SINANI, Neset IZAIRI, Fadil AJREDINI 594

RADIOGRAPHIC METHODS FOR LOCATING & EVALUATING IMPACTED MAXILLARY CANINES USING KUFTINEC, CHAUSHU AND ERICSON & KUROL METHODS

Drin CHERKEZI, Sabetim CHERKEZI 602

DIAGNOSTIC CHALLENGES IN DORSAL HAND MASSES: RHEUMATOID NODULES WITH CONCOMITANT RADIAL NERVE NEUROMA

Maligona REXHEPI, Ana ATANASOVA, Elizabeta MIRCEVSKA ZHOGOVSKA, Gordana GEORGIEVA 608

DIGITAL TRANSFORMATION IN PARLIAMENT OF THE REPUBLIC OF NORTH MACEDONIA

Laureta ALILI, Zemri ELEZI 615

REDO INGUINAL HERNIA REPAIR WITH POLYPROPYLENE MESH: A CASE REPORT

Roland ALILI, Stefan PETROVSKI 621

ARCHITECTURE AS INSTITUTIONAL PRACTICE: DEVELOPMENT MODELS OF PRIMARY SCHOOL BUILDINGS IN NORTH MACEDONIA

Hafije MURATI[1], Kujtim ELEZI[3] 625

HYACINTHUS ORIENTALIS L. SUBSP. ORIENTALIS (ASPARAGACEAE) A NEW TAXON FOR THE FLORA OF NORTH MACEDONIA

Agim HAZIRI 631

IDENTIFICATION OF PARAMETERS FOR THE ANALYSIS OF STRUCTURAL WEAKNESSES IN IPA INFRASTRUCTURE PROJECTS: LITERATURE REVIEW

Getoar ABDURAMANI, Strahinja TRPEVSKI, Enis JAKUPI 635

TRANSFORMATION OF THE DAIRY INDUSTRY (2000–2030): FROM A TRADITIONAL FOOD SYSTEM TO MOLECULAR AND DIGITAL PRECISION

Tanja STOJANOVSKA, Tatjana KALEVSKA, Nevena GRUEVSKA, Viktorija STAMATOVSKA, Katerina TEMELKOVSKA RISTEVSKA 644

HEPATOTOXICITY OF ANTIBIOTICS IN DIFFERENT AGE GROUPS

Drita YZEIRI- HAVZIU, Arlinda HAXHIU-ZAJMI, Arijeta SHABANI, Edita ALILI-IDRIZI, Merita DAUTI, Nexhibe NUHII, Gjylai ALIJA, Lulzime BALLAZHI, Sihana AHEMTI-LIKA, Qail IBRAHIMI1, Sadije AMZAI, Melisa HAVZIU IDRIZI 652

ACUTE DIARRHEA IN CHILDREN OF EMIGRANTS DURING SUMMER VISITS TO THE COUNTRY OF ORIGIN:A CLINICAL, ETIOLOGICAL AND THERAPEUTIC ANALYSIS OF 24 PEDIATRIC CASES (MAY–OCTOBER 2025)

Ferizat DIKA – HAXHIREXHA, Aferdita ADEMI, Sevdije KOXHA, Aulona HAXHIREXHA, Blinera BALLANCA, Labeat HAXHIREXHA, Shqiponja TURKESHI 658

MANAGEMENT OF HIGH-RISK IMPACTED MANDIBULAR THIRD MOLARS USING SURGICAL METOHOD OF CORONECTOMY: A CASE REPORT

Albina AJETI ABDURAMANI, Boris VELICKOVSKI, Fjolla AJETI, Ngadhnjim AJETI 666

ACADEMIC BURDEN AND BEHAVIORAL ADAPTIONS : A STUDY OF DIETARY AND STIMULANT USE AMONG MEDICAL STUDENTS

Denisa ALIU, Lea KRYEZIU, Leart IBRAIMI 675

MORPHOLOGICAL AND ANATOMICAL VARIATIONS OF THE BASILAR ARTERY AND THEIR INFLUENCE ON CEREBRAL CIRCULATION

Gazmend ZYLBEARI, Zamira BEXHETI, Elita MASHA, Milka ZDRAVKOVSKA, Art ZYLBEARI, Sadi BEXHETI , Светлана JOBEBCKA,Tose KRSTEV 681

EXPERIMENTAL OPTIMIZATION AND CHARACTERIZATION OF AN O/W COSMETIC CREAM BASED ON A NON-IONIC SELF-EMULSIFYING SYSTEM

Flora DOKO, Merita DAUTI, Sihana AHMETI LIKA 687

CONNECTING UNDERUSED PUBLIC SPACES THROUGH GREEN INFRASTRUCTURE: A FRAMEWORK FOR ENHANCING PUBLIC SPACE QUALITY

Fitore DEHARI 698

PLANT-BASED EXPRESSION SYSTEMS IN BIOPHARMACEUTICAL PRODUCTION: A COMPREHENSIVE REVIEW

Sihana A. LIKA, Hanife R. AHMETI, Qail IBRAIMI, Arbnore Q.NAZIFI, Shqipe XHAFERI, Flora DOKO 709

BIOTECHNOLOGICAL ROUTES FOR INSULIN PRODUCTION

Lutfi ASANI, Vlera HOXHA, Shqipe XHAFERI, Sihana AHMETI LIKA 718

AUTOMATION OF INDUSTRIAL PRODUCTION PROCESSES FOR MATERIAL AND ENERGY EFFICIENCY IN SUSTAINABLE DEVELOPMENT

Asan IDRIZI, Nderim ZEQIRI, Ferit IDRIZI, Rinor RUZHDII 724

CHARACTERIZATION OF APPLE (*MALUS DOMESTICA*) PROCESSING WASTE: PHYSICOCHEMICAL AND NUTRITIONAL COMPOSTITION

Gresa AHMA, Vezirka JANKULOSKA, Hyrije KORAQI, Namik DURMISHI, Vesna KNIGHTS Daniela NIKOLOVSKA NEDELKOSKA, Anka TRAJKOVSKA PETKOSKA, Gorica PAVLOVSKA 735

CONTEMPORARY APPROACHES IN THE MANAGEMENT OF ACUTE APPENDICITIS: A CRITICAL COMPARISON BETWEEN SURGICAL TREATMENT AND CONSERVATIVE ANTIBIOTIC THERAPY

Kastriot HAXHIREXHA, Gazmend ZEQIRI, Ilber BESIMI, Florim SELIMI, Arben DEMIRI, Roland ALILI, Nazim MUSLI, Natmir IMERI, Rian AMITI, Jakup JAKUPI 743

FROM PRIMARY TRAUMATIC DISLOCATION TO CHRONIC SHOULDER INSTABILITY: ARTHROSCOPIC BANKART REPAIR IN A YOUNG ACTIVE PATIENT

Alba JAHIJA,Roland ALILI, Erblira RESHITI 752

FAPI-BASED RADIOPHARMACEUTICALS IN MODERN THERANOSTICS: FROM DIAGNOSTIC IMAGING TO TARGETED RADIONUCLIDE THERAPY

Hanife RUSTEMI AHMETI, Paulina APOSTOLOVA, Faton AHMETI, Elena DRAKALSKA SERSEMOVA, Marija GLAVAS-DODOV, Emilija JANEVIK-IVANOVSKA 758

CONTEMPORARY MANAGEMENT OF WOUNDS IN THE EMERGENCY DEPARTMENT: CLINICAL APPROACH AND EFFECTIVE MANAGEMENT

Blerim FEJZULI, Hanife REXHEPI,Gjulten IDRIZI 764

COMPARATIVE ANALYSIS OF LAPAROSCOPIC VERSUS OPEN CHOLECYSTECTOMY IN PATIENTS WITH CHOLECYSTOLITHIASIS: A RETROSPECTIVE STUDY FROM THE CLINICAL HOSPITAL OF TETOVA

Jehona REXHEPI, Rinor MAQELLARA 771

GEOMETRY AND ORDER: ON THE NEED FOR A THEORETICAL FRAMEWORK FOR THE ANALYSIS OF THE PLANS OF THE HOUSES OF CULTURE IN MACEDONIA

Erda BESIMI, Nuran SALIU, Kujtim ELEZI 780

EVALUATION OF BRUCELLOSIS SURVEILLANCE IN NORTH MACEDONIA USING A ONE HEALTH APPROACH

Naim SKENDERI, V. VELIKJ STEFANOVSKA, A. HISENI S., N. ELEZI 787

INTEGRATING ARTIFICIAL INTELLIGENCE AND BLOCKCHAIN TECHNOLOGY INTO SMART MOBILE APPLICATIONS

Avni RUSTEMI 796

SURGICAL MANAGEMENT OF FOURNIER'S GANGRENE: CLINICAL EXPERIENCE WITH FOUR CASES TREATED AT THE SURGERY CLINIC OF THE CLINICAL HOSPITAL OF TETOVO

Aferdita ADEMI, Ferizat DIKA – HAXHIREXHA, Blerim FEJZULI 803

CHRONIC DERMATOPHYTIC INFECTION OF THE FACE AND HANDS: A CLINICAL REVIEW OF TINEA FACIEI AND TINEA MANUUM

Teuta EMINI, Irma BEADINI, Mamudije MEMETI, Rufije ZIBERI, Anita NAJDOVA 812

CONTEMPORARY APPROACHES IN THE MANAGEMENT OF VARICOCELE: SURGICAL AND MINIMALLY INVASIVE TECHNIQUES

Erzen ELEZI, Florin DEARI 821

CONTINUITY OF PROBABILITY MEASURES AND ITS ROLE IN STATISTICAL MODELING

Edin DEMIRI[1], Edona A. DEMIRI[2], Lazim KAMBERI[3] 829

THE IMPACT OF USING ARTIFICIAL INTELLIGENCE AS A SUPPLEMENTARY TOOL IN CONTEMPORARY CHEMISTRY TEACHING: AN EXPERIMENTAL STUDY

Shemsedin ABDULI, Zulxhevat ABDIJA, Agron ALILI, Almira SULEJMANI, Miran ABDULI 837

STATISTICAL AND MULTIVARIATE ANALYSIS OF DIETARY HABITS AND LIFESTYLE BEHAVIORS IN RELATION TO BODY WEIGHT

Valbona SALLAI MAZLLAMI, Vesna KNIGHTS, Vezirka JANKULOSKA, Zora UZUNOVSKA, Tatjana BLAZHEVSKA, Valentina VELKOVSKI, Kristina GACOSKA 843

EDUCATION IN SUSTAINABLE URBAN PLANNING AND DESIGN AS A PREREQUISITE FOR INFORMED CIVIC AGENCY IN URBAN DECISION-MAKING IN NORTH MACEDONIA

Aurora SAIDI QAZIMI, Ajla LIMANI, Erda BESIMI, Fjolla IBRAIMI 854

SAFETY MONITORING OF IRON SUPPLEMENTATION IN PREGNANCY: INSIGHTS FROM A CROSS-SECTIONAL STUDY

Edita ALILI IDRIZI, Lulzime BALLAZHI, Arian ALILI, Merita DAUTI, Faton AHMETI, Gjylai ALIJI, Hanife RUSTEMI AHMETI, Valdeta AJETI 865

INHALED PHARMACOLOGICAL TREATMENT AND CRITICAL ERRORS IN INHALATION TECHNIQUE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Vlera HOXHA, Lutfi ASANI, Shqipe XHAFERI, Edita ALILI IDRIZI, Teuta QAILI PAJAZITI 872

THE INFLUENCE OF THE TREATMENT OF SnS THIN FILMS WITH ALCOHOLIC SOLUTION, FOLLOWED BY ANNEALING

Beltina OSMANI, Atanas TANUSEVSKI , Ahmed JASHARI 880

SHARP INITIAL COEFFICIENT BOUNDS FOR A GENERALIZED JANOWSKI-TYPE SUBCLASS OF STARLIKE FUNCTIONS DEFINED BY SUBORDINATION

Skender AVDIJI 885

ANTHROPOGENIC MOTIVES IN THE FUNCTION OF DEVELOPING ALTERNATIVE FORMS OF TOURISM IN THE SOUTHWEST REGION OF THE REPUBLIC OF NORTH MACEDONIA

Rukije IBRAIMI, Fatmire AMITI, Niagara XHEMAILI, Xhejda JONUZI 895

PLACENTAL INSUFFICIENCY AND FETAL GROWTH RESTRICTION

Pranvera IZAIRI, Ana KOCEVSKA, Ana Marija SPISIK-PUSEVSKA, Zoran ILIEVSKI 903

FROM UNILATERAL LIMB WEAKNESS TO GAIT INSTABILITY AND INVOLUNTARY MOVEMENTS – A UNIQUE CASE OF HEMIPLEGIC VARIANT OF AMYOTROPHIC LATERAL SCLEROSIS

Daniela RISTIKJ-STOMNAROSKA, Avdi NAZIFI, Angela MADZAROVA, Elena SIMEONOVSKA-JOVEVA, Tatjana CEPREGANOVA-CHANGOVSKA, Tatjana DELEVA-STOSHEVSKA 911

NATURAL AKSIL AS ADSORBENT FOR REMOVAL OF HEXAVALENT CHROMIUM FROM WATER RESOURCES: EQUILIBRIUM AND KINETICS

Hamdije MEMEDI, Katerina ATKOVSKA, Kiril LISICHKOV 915

INTEGRATED NON-INVASIVE VASCULAR PHENOTYPING USING ANKLE-BRACHIAL INDEX (ABI) AND PULSE WAVE VELOCITY (PWV) FOR EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS. BRIDGING EVIDENCE FROM COMPREHENSIVE LITERATURE REVIEW AND CASE-BASED CLINICAL EVALUATION

Vegim ZHAKU, Sheqibe BEADINI, Era DAUTI, Marjan JOVCEVSKI, Drilon MIFTARI, Nexhbedin BEADINI, Antonio GEORGIEV 923

BLACKOUT IN THE ELECTRICAL GRID CAUSED BY FLUCTUATIONS OF RENEWABLE ENERGY –CASE STUDY

Irfan SHAQIRI 933

INTEGRATION OF IAAS AND SERVERLESS COMPUTING FOR E-COMMERCE ORDER PROCESSING

Verda MISIMI JONUZI, Miranda XHAFERI 940

INSTRUMENTAL PHARMACEUTICAL ANALYSIS OF VITAMIN B12 IN PHARMACEUTICAL PRODUCTS AND DIETARY SUPPLEMENTS: A REVIEW

Gjylai ALIJA, Dorentina BEXHETI, Merita DAUTI, Drita Y.- HAVZIU, Nexhibe NUHII, Qail IBRAIMI, Sihana A.- LIKA, Edita A.-IDRIZI, Arlinda H.-ZAJMI, Lulzime BALLAZHI, Arijeta SHABANI, Taulant IDRIZI 948

THE ROLE OF NUTRITION IN SKIN DISEASES

Qefser TËRNAVA, Velerda BIZATI, Gjylai ALIJA 955

CLINICAL MANIFESTATIONS OF HERPES ZOSTER OPHTHALMICUS

Lejla ADEMI, Emira ADEMI JONUZI 964

VANISHING ACT: THE TRUTH BEHIND THE CT FOGGING PHENOMENON IN ISCHEMIC STROKE - A CASE REPORT

Tatjana DELEVA STOSHEVSKA, Avdi NAZIFI, Tatjana CEPREGANOVA CANGOVSKA, Daniela RISTIKJ STOMNAROSKA, Dimitar VELJANOVSKI, Bojan STOSHEVSKI, Sofija NIKOLOSKA, Marko NIKOLOSKI, Driton SELMANI 972

BONE AUGMENTATION IN IMPLANT DENTISTRY; COMPARATIVE EVALUATION OF LATERAL WINDOW VERSUS CRESTAL APPROACH FOR MAXILLARY SINUS FLOOR AUGMENTATION — A SYSTEMATIC REVIEW

Armend REXHEPI, Jeta BEXHETI REXHEPI, Kenan FERATI, Sabetim CERKEZI, Amar FERATI 976

DIAGNOSTIC VALUE OF DOPPLER ULTRASONOGRAPHY IN CAROTID ARTERY ATHEROSCLEROSIS

Lirza EMINI FERATI 984

CORRELATION BETWEEN PERCEIVED STRESS, RESTING HEART RATE, BODY MASS INDEX, AND BLOOD PRESSURE AMONG MEDICAL FACULTY STUDENTS AT THE UNIVERSITY OF TETOVA. A CROSS-SECTIONAL STUDY

Rida SALIJA, Esra RAKPI, Vegim ZHAKU 989

FORMS OF TREATMENT AND PREVENTIVE MEASURES OF PUERPERAL PARESIS ON SOME FARMS

Nesim SEFERI, Besnik ELEZI, Dashmir MAMUTI, Maksud KËRLUKU 995

MATHEMATICAL MODELING FOR OPTIMIZATION OF FOOD TRANSPORTATION

Vesna KNIGHTS, Olivera PETROVSKA, Marija PRCHKOVSKA 1001

COMPARISON OF EXISTING AND PLANNED HYDROPOTENTIAL AND ADDITIONAL ACTIVITIES TO ENCOURAGE THE USE OF HYDROPOWER PLANTS IN THE REPUBLIC OF NORTH MACEDONIA

Niagara XHEMAILI, Rukije IBRAIMI, Meribe MUSTAFI, Fatmire AMITI, Xhejda JONUZI 1013

USING MARKET BASKET ANALYSIS TECHNIQUE TO FIND CONSUMER PURCHASING PATTERNS AND OPTIMIZE INVENTORY MANAGEMENT

Merita KASA HALILI, Festim HALILI, Avni RUSTEMI, Eip RUFATI, Aliadis SELIMI 1019

HEALTH EDUCATION OF NEW MOTHERS IN PREVENTING DEGREEING OF HIP-FEMORAL DYSPLASIA

Elona HASALLA, Ilda TAKA, Brandi FAHRIU, Gerta KAÇANI, Blerta HASALLA, Sulejman BAHA, Elda RUÇI, Irena XHAFERRI

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Abstract

Developmental hip dysplasia (DHDD) is a congenital anomaly of the skeletal system, which affects the hip joint and can lead to permanent consequences if not diagnosed and treated in time. Despite advances in diagnosis and treatment, the main challenge remains early identification and intervention in the early stages of life.
This study aims to assess the importance of health education of new mothers in preventing the deepening of dysplasia and to analyse the effectiveness of conservative treatment with an abductor cushion. The study is based on a retrospective analysis of 68 cases of children diagnosed and treated for DHFK in the period 2018-2024. Factors such as age at diagnosis, gender, bilaterally of the pathology, as well as the effectiveness of treatment depending on the time of initiation of therapy were taken into account.
The results show that early treatment with an abductor pad is an effective method to prevent the deterioration of DHF and to ensure a healthy development of the coxofemoral joint. In the studied group, 60.3% of cases showed significant improvement, while only 13.2% required further treatment due to failure of conservative therapy. The study also highlights the importance of raising awareness among young mothers about the importance of early screening and the role of health personnel in the process of education and follow-up of children with this pathology.
In conclusion, this study suggests that early diagnosis and treatment of HFMD, supported by a well-structured health education program for new mothers, can minimize complications and significantly improve the quality of life of affected children. For this reason, it is recommended to strengthen the role of nursing personnel and promote health policies that support early identification and timely treatment of this anomaly.

Keywords : hip dysplasia, education of new offspring, diagnosis, treatment, prevention

Introduction

Despite the great advances in the field of treatment of congenital hip and femoral luxation (CHL), this hereditary anomaly still remains a major challenge for new mothers and healthcare personnel; both as a problem in terms of early diagnosis for all medical systems and levels, and for the early initiation of treatment to have a successful final outcome.
In this topic that we are presenting at this annual scientific session at the Faculty of Medical and Technical Sciences; we thought of bringing our assessments, which in a way is also the object and goal of the work of an employee in maternity, in the children's consultation or in other health systems, regarding the diagnosis and early initiation of treatment of this anomaly. On the other hand, this objective is also related to the obligations of a pedagogue not only in the teaching process but also her efforts to sensitize new mothers and educate them on health in preventing the deepening of developmental hip dysplasia and why not also in starting treatment at the earliest possible age of this congenital anomaly with the "Abductor Pillow".[1]
A congenital anomaly of the type of developmental coxofemoral dysplasia immediately after the birth of the child may not be at the level of a fundamental disruption of the relationship of the femoral head to the acetabulum, or expressed in other words the presence or absence of the femoral head in the acetabulum, which is also the narrow meaning of the content of this term.

Developmental hip dysplasia is one of the most common and important human anomalies. It occurs in 1-1.5 cases out of 1000 live births. It is an anomaly that is not at all evident from the outside, absolutely hidden and silent, although diagnostic tests are known, even at the moment of the child's birth.
The idea of early treatment of L.K.K.F. with abductor devices is the gradual positioning or centering of the femoral head in its anatomical location, the acetabular fossa; and then the mutual relationships and influence on each other of the anatomical elements of the coxo-femoral articulation, will reform the latter.[1][2]

Historical Moments And Scientific Findings Of Developmental Hip-Femoral Dysplasia

Although since the time of Hippocrates, who first described it, in the complexity of this congenital anomaly, there are still different opinions regarding the etiology of the deformation, its pathogenesis, treatment and final results and even the very name of the anomaly. Peoples of color, blacks, Chinese, Japanese; generally do not recognize this congenital anomaly. This fact has been evaluated as an indisputable argument and the deepening of scientific reasoning led to the conclusion that the fact was related to the customs of these peoples who raise their children by carrying them “saddle on their mothers’ backs”, or “supported on the iliac crests with their legs spread” (fig.1.1). With the evolution and deepening of thoughts, orthopedists and surgeons began to treat children with L.K.K.F. by placing and fixing the legs open and maintaining them in this position with various tools and systems, considering this position as protective and healing of this congenital anomaly.[3]
In connection with the above findings, doctors began to devise and use devices and systems that kept the legs open, and the femoral head gradually positioned in its anatomical place. The need for the production and use of abductor devices is more or less the putting into practice of logical ideas or wise conclusions accumulated over the years for the treatment of L.K.K.F. in young children.[3][4]
Fig.1.1 This figure illustrates how a black mother holds her child in the position explained above.



The production of abductor devices was first described and used by Hilgenreiner in 1925, authors such as Forrester in 1933, Von Rosen. In our country, a commendable work has been done by Prof. Panajot Boga who devised and put into use the treatment of developmental coxofemoral dysplasia with the pneumatic abductor cushion, also known by the acronym japnab.[4]

Object And Purpose

The problems of early diagnosis and treatment of D.ZH. K. as well as the crippling consequences for life from it, are individual and of varying degrees of difficulty. In this context, they constitute an important object of study not only in the treatment of this congenital anomaly at the nursing level but also in terms of the clinical training of neonatologists, midwives and health personnel who exercise their activity in clinics, nurses working in orthopedic clinics and wards in rural hospitals, etc. Our study aims to clarify some main issues that are listed below:

[1] To highlight the pathology of D.ZH.K, especially in terms of its early diagnosis (so widespread in our country), the early initiation of treatment at the nursing level as a possibility and reality with sufficient scientific knowledge.
[2] To draw the attention of new mothers and the control of their children with diagnostic tests for this pathology in the maternity ward, in the children's consultation room as well as in the orthopedic department of the "Xhaferr Kongoli" hospital in Elbasan.
[3] The earliest possible start of children with D.ZH.K with an abductor cushion as an efficient and effective method in the treatment of this congenital anomaly.
[4] Presentation of the results of the treatment as well as our modest experience in this regard.



Material And Method of The Work

In this modest study where we studied the charts of children with developmental coxofemoral dysplasia, children presented for consultation and treatment from September 2018 to January 2024 were taken into consideration. 68 children were studied and treated. Of these children, 56% (38) of the entire series were bilateral and only 44% (30) of them were unilateral. So in total, 106 articulations with D.ZH.K. were treated.

Table No. 1: Distribution of cases by age and gender.

Age	Boys	Girls	Total
0-3 months	11	37	48
3-6 months	8	12	20
Total	19	49	68

The children for the period we are talking about, were treated and followed continuously by the authors of this paper. These patients were consulted, diagnosed and treated in "day treatment", or with outpatient/day treatment, in the Day Surgery Department of the National University Orthopedics-Traumatology Service for the above-mentioned period and their follow-up is still ongoing by the author of the study at least within the first year of treatment.

4.1 Gender, Incidence, Laterality And Age Of Treated Children: As can be seen from Table No. 1, the ratio of boys to girls in this anomaly is in the figures 1:2, or 1 boy to 2 girls. In the consulted literature, D.ZH.K. this ratio is the figures from 1:4 to 1:13 in favor of girls in 1000 live births. For our study group of 68 children the ratio 1:2 is negligible since the number of children taken into consideration is small and cannot be subject to statistical analysis.

Diagnosis Of Developmental Hip-Femoral Dysplasia

These are essential to be performed on all newborns by the neonatologist and should be recognized by all personnel working in the clinic.[5]

5.1 Manual Examination Of The Hip Joints: It is the main examination and main diagnostic method in D.ZH.K. Regardless of the historical developments of this diagnostic method, the interpretations and considerations for it, it is still irreplaceable. Manual examination of the hip joints is based on two very valid and absolutely accurate tests in terms of the reasoning behind why they are performed.[6][7]

[1] Ortolan's technique

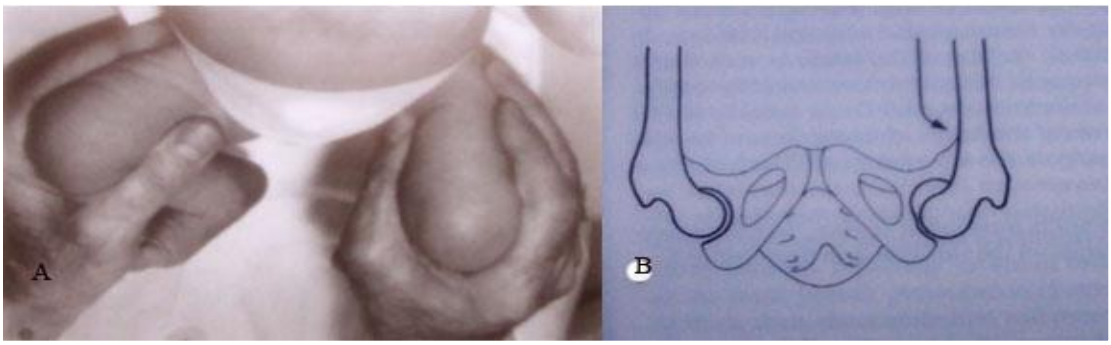


Fig. 1.2: Methodology of applying the Ortolani test to a newborn child.
Source: Original Source

According to this technique, both hip joints are examined at the same time.
First, the hands are placed according to the photo and the thighs are abducted.

[1] Schematic representation of the exit of the femoral head from the acetabulum when developmental dysplasia of the bone is present. The methodology of its execution is easy but requires attention and experience in its assessment. The child's sides are flexed 90 degrees at the knees and hips.

[2] The hands are placed on the knees, the thumb on the medial side of the thighs and the other three fingers on its lateral side where the middle finger is on the greater trochanter.

[3] Then the thighs are abducted and with the middle finger placed on the greater trochanter, the femur is pushed medially.

[4] Schematic representation of the insertion of the femoral head into the acetabulum during hip abduction.

In our study series of 68 cases, we performed it in 16 children who presented to the clinic only 3-7 days after birth. These were high-risk children, 4 had a breech birth, 2 were born

prematurely and 9 children had a history in their parents, 6 children were born by Cesarean section. The other children were not examined because they presented after the third week of birth. The Ortolani test is only assessable in the first three weeks.[8][9][10]

[2] Abduction limitation

Assessment of the volume of movements in newborns, mainly of abduction, which is performed by the examiner with the knee and hip joints flexed at 90 degrees. In this position, the examiner performs the abductor movement in the hip joint, which in other words tends to meet the outer sides of the child's thighs. The outer sides of the thighs of newborns very easily meet the mattress. Abduction limitation is a test that is often encountered in developmental hip dysplasia. It has been found positive in 80% of the studied series or in 55 of the cases.[10][11]3

[3] Evaluation of the length of the inferior limbs

In unilateral developmental dysplasia of the hip joint, measurement of the length of the sides is not always a reliable sign for detecting the anomaly. Care should be taken during the examination to ensure that the child's body is fully leveled and the presence of shortening is noted at the knee level.[11][12]

[4] Presence of asymmetry of skin folds

In already complete and established dislocations, there is a very evident alteration or asymmetry of the skin folds of the child's thighs. But in coxo-femoral D.ZH.K, this test is not always significant. However, it is evaluated in the early diagnosis of D.ZH.K. If you look closely at Figure 1.3, you will notice that the folds on the left side are deficient compared to those on the right side.[11][13]

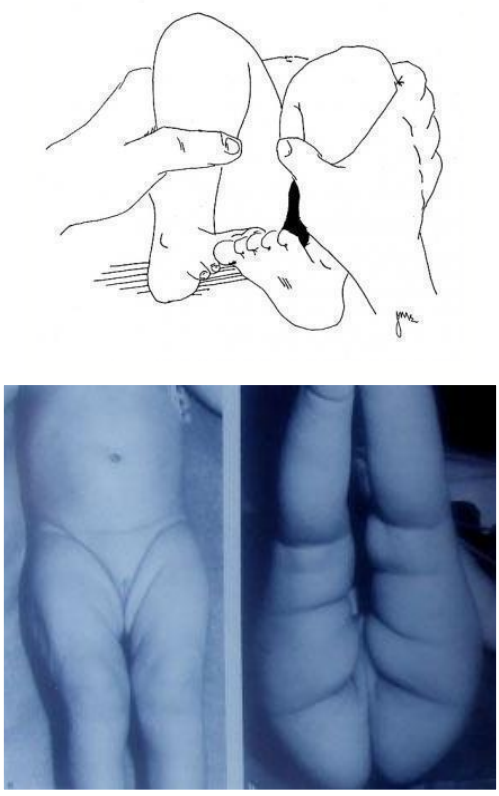


Fig 1.3 Assessment of the length of the sides and skin folds. Explanations in the text

Regarding this diagnostic point, many authors, although they have found asymmetry of the folds, have identified D.ZH.K. in 36% of the 267 cases studied. In our series of 68 children up to the age of 12 months, these elements were found in 12 cases or in 17.6% of the entire series studied.[14]

[5] Radiological data at the nursing level

The radiological examination of the coxofemoral joint is conditioned by the ossification of the femoral head. This phenomenon occurs in the fourth month after birth. In children with D.ZH.K., the ossification of the femoral head may be even more delayed. All children who presented for consultation at the orthopedic clinic were recommended to perform an anteroposterior radiograph of the pelvis. The radiographs are interpreted and evaluated based on the positioning of the nucleus of ossification of the femoral head or its centering in the acetabulum. In the radiological study of D.ZH.K., radiography in the anteroposterior projection is important. In this position, the relationships of the femoral head with the acetabulum, its centering in the lines, its coverage by the acetabulum, the ossification of the femoral head, etc. are studied.[15][16]

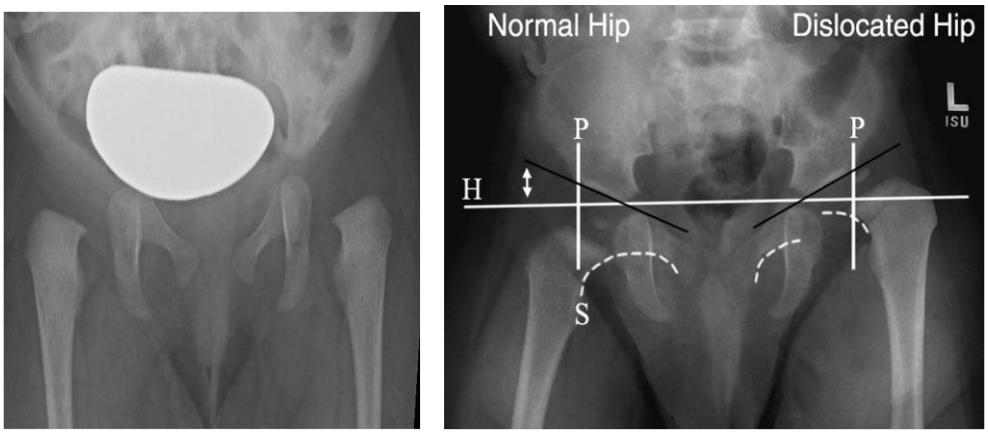


Fig.1.4 Radiograph of a 3-month-old child showing radiological signs of D.ZHK.

Elements of radiological changes begin as early as 4-6 weeks after birth and include lateralization of the femoral neck in relation to the iliac bone, a slow and insufficient development of the acetabulum, and finally delays in the ossification of the femoral head. Although many signs and patterns of reading radiographs, especially anteroposterior ones, have been described.[16][17]

[6] Treatment of D.ZH.K with an abductor cushion

All children in our study were treated with the Plastic Abductor Cushion available on the market in three different sizes represented by the numbers 1, 2, and 3. The device was initially placed by the study author, assisted by qualified nurses from the consultation department.[17] The principle of selecting the number of cushions was based on the principle that the device should provide moderate abduction and be centered in the space between the two popliteal fossae.[17]

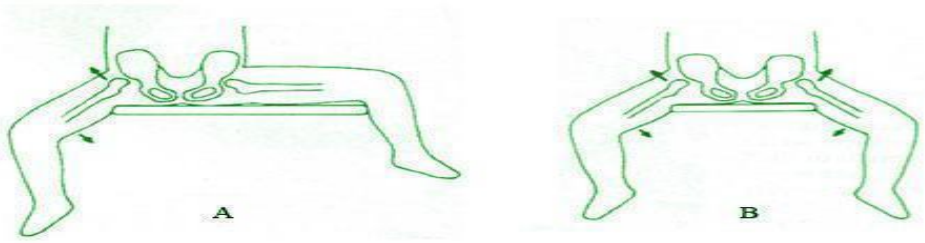


Fig. 1.5: A- Possibilities of non-symmetrical placement of the cushion. Abduction is not performed symmetrically in both coxofemoral joints, resulting in a failure to gradually reposition the femoral head.

Par
ents were instructed on how to put on, remove, and provide sanitary care for the child, and efforts were made to explain the principle of treatment with this device, depending on their cultural level, in order to overcome the unfounded fear that the joint could reluxate during these sanitary procedures.[18]

The head centering check was performed on the first radiograph, usually in the second month after the start of treatment. The duration of treatment, although dependent on the interpretation of the radiological data on the centering of the femoral head, this treatment lasts at least 6-9 months to a year. Parents' contacts with the service are made every two months, and radiological checks were also requested every two months.[19]

Evaluation And Results Achieved

The entire conservative treatment of this anomaly lasts for about 9 months. Correction is always possible, of course, respecting all stages of treatment, especially in terms of maintaining equal opening of the sides, gradually increasing the number of pillows, keeping them regularly, especially in the stages when the child needs to be changed or at times that are deemed necessary.

Table No. 2: Distribution of treatment results of D.ZH.K with abductor cushion

child. still in treatment.	18 or 26.4 %
Child. failed.	**9 or 13.2 %**
Child. with good results.	**22 or 32.5 %**
Child. with very good results.	**19 or 27,9 %**
Total	**68 or 100 %**

In our series of 68 cases we have achieved these results, which are presented in Table No. 2. The nine children considered to have failed conservative treatment are scheduled for further treatment.

6.1 Criteria For Evaluating Results: In fact, outside the scope of this study, it is not at all easy to say when a dysplastic articulation will be considered healed. This word carries the weight of moral, ethical, social and legal implications if one of the following two errors is consumed. To stop treating a child who is not yet cured or to treat a cured child in vain; for this reason we have tried to be very correct and scrupulous in the criteria for evaluating the results by referring

precisely to our and foreign literature. As evidenced in Table 1, the children included in the study were divided into two groups depending on the age of the start of treatment; under three months and from three to six months.



Fig.1.6: Graph one year after the start of the child's treatment

The centering of the femoral heads is congruent with the acetabulum

The created groups were studied to derive the results of the pillow treatment based on these indicators.

[5] Centring of the femoral head in the acetabulum

This element of the final result assessment was assessed in the control radiography. It is an important and valuable indicator in the successful completion of the treatment. In our study, this index is present in 41 cases or in 60.3% of the entire series, the rest are 9 children declared to have failed the treatment and 18 others who are still in unfinished treatment.

[6] Improving the acetabular index

The acetabular index is the angle formed between the horizontal biacetabular line and the line connecting the center of the acetabulum with its outer edge. It is also called the AC angle and is a reliable indicator of acetabular slope.



Fig. 1.7: This graph shows the centering of the femoral head in the acetabulum and the normalization of the angle of the acetabular index.

This radiological parameter was evaluated at the end of the treatment. The evaluations in this index are also the same as those for the centering of the femoral head.(7).

Conclusions

Developmental hip dysplasia is a congenital anomaly installed in the hip joint of the fetus during intrauterine life, invisible, but diagnosable immediately after birth. Despite the different opinions on the etiopathogenesis of the anomaly, hip dysplasia is treated with excellent results and without any consequences for the child who suffers from it.

[1] Coxo-femoral developmental dysplasia, converted into other words, means the disruption of the relationships of the bones participating in the formation of the coxo-femoral articulation, that is, of the femoral head and the acetabulum, and on the other hand contains the potential possibility of permanent luxation of the femoral head.

[2] Early diagnosis and initiation of conservative treatment even at the nursing level of this anomaly is the best "prophylaxis". This treatment is advisable to be done in the first days after the birth of the child.

[3] Correction of the anomaly of D.ZH.K. is done through positioning in adduction of the inferior extremities and maintaining them in this position for a period of 9-12 months. The methodology and procedures of the follow-up must be strictly respected.

[4] Conservative treatment of D.ZH.K is an advantage over other treatments of this pathology. It has excellent results and on the other hand is very well performed even at the nursing level.

[5] The cost element in conservative treatment is negligible and on the other hand we also remember the benefit that these children have from the state, which in one year reaches up to 500 euros.

8. Recommendations

- Early diagnosis and initiation of conservative treatment is the key and guarantee of successful treatment even at the nursing level of this congenital anomaly.
- The younger the child, the more adaptable the soft structures are, which have allowed the femoral head to luxate from the acetabular cavity, thus creating conditions for permanent disability for the rest of life.
- Find the opportunity and draw attention to the increase in nursing care for newborn children in terms of screening and diagnosing other congenital anomalies such as pes-equinovarus congenitalis, scoliosis.
- Getting rid of unfavorable habits of the development of the coxo-femoral articulation such as the hip joint in children. Understanding also by the popular masses that the hip joint is harmful and leads to the deepening of the D.ZHK.
- Increasing the competence and professional responsibility even at the nursing level, brings much higher results at work, in this context also in the diagnosis and early treatment of the D.ZHK.

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ULTRASONIC BATH EXTRACTION AS AN ADVANCED METHOD FOR EXTRACTING THE PHARMACEUTICAL HERB VALERIAN

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Abstract

Valerian is a pharmaceutical plant known for its calming and insomnia-helping properties. It is a plant that has been known since ancient times, but the 20th century is a starting point for the production of extracts, mainly in Europe. All studies aim to obtain an extract at a lower cost and, on the other hand, complete isolation of the carrier substances present in Valerian. The raw material used is the roots of the Valerian plant, which are very rich in valerian acids, which are claimed to be the main carrier substances. All methods used for extraction have their advantages and disadvantages. The maceration method is a very practical method for obtaining Valerian extract, but due to the strong pungent smell, it risks a very large space for exceeding pollution limits, so many European countries prohibit the use of Valerian precisely because of this. air contamination with a counterproductive aroma. Therefore, other more advanced extraction methods are required so that the process is at least a little more closed and the amount of extract is more controlled. The ultrasonic extraction method is actually much more advanced since the process is carried out almost closed and does not pollute the air to the maximum limits and on the other hand it has the same extraction coefficient as maceration extraction and is much cheaper.

Keywords : Extraction.maceration,extraction coefficient

Introduction

Valerian is an annual plant that grows in Asian countries and Western European countries. The harvest time is September when the maximum presence of carrier substances is reached. There are many scientific researches on valerian in order to accurately define its practical application in pharmaceuticals. Researches are oriented on the influence of valerian extract in stabilizing insomnia, concentration and headaches. (Carrasco MC, Vallejo JR, Pardo-de-Santayana M, Peral D, Martin MA, Altimiras J. 2009.) The valerian type plant is also known by the name Valeriana which comes from the Latin word "valere" which means to be healthy. This plant with its healing properties has been known since the 19th century. It is characterized by a disagreeable smell that does not go away easily, for this reason, the places that benefit from valerian extract are mainly concentrated outside residential areas. It grows mainly in humid places high and grow to a height of 0.5-1 meter. They are characterized by light pink flowers with a perfect arrangement at the top of the Valerian plant.(Yuan SH, Zhang BH Wu FJ. 1989) The parts that are used in pharmaceuticals to obtain the extract are the roots (Valerianae radix). In addition to the main roots, thin roots connected to the main root are also used. In Valerian, a large number of carrier substances are concentrated such as ethyl oils, oils consisting of mono terpenes, Iridoids, Lignans, Caffeic acids and small amounts of Amino Acids, Flavonoids and alkaloids.(Hazelhoff B, Smith D, Malingré Th M, Hendriks H. 1979.) There are scientific opinions that it is precisely these carrier substances that have an effect on calmness and insomnia. Valerian is used in different forms, in the form of tea. Tablets or in the form of extract drops obtained by pressing. Valerian affects the reduction of the layer, and the quality of sleep. It is important to be taken for a longer time regularly in order to achieve a maximum effect.(Tomić M D., Kundaković M J., Petrović S D. 2005) In Indian folk medicine, Valerian extract has been used to treat epilepsy and depressive illnesses. In addition to being used as a monopreparation, Valerian is also used in combination with other extracts to increase its

healing abilities, such as Kava Kava extract.(Yuan CS, Mehendale S, Xiao Y, Aung HH, Xie JT, Ang-Lee MK. 2004)The amount of carrier substances varies depending on the growing conditions of Valerian, its type and the age of the plant. However, in Valerian, the presence of Aetheric oils and Valeportriates is observed, which are the components that have the greatest impact on practical use. (Yunfu W, Jie Y, Shenggang S, Guohou H. 2004.)The Aetheric oils found in Valerian roots have a concentration of 0.2-2.8%. This is what makes Valerian characterized by a very strong odor and which also depends on the species of this plant. In the group of carrier components of Sesquiterpenes Valerian acids are found which are present in the etheric oils.(Komori T, Matsumoto T, Motomura E, Shiroyama T. 2006) Other components which are very important in the composition of Valerian are Iridoids which are found in a concentration of 0.05-0.7% in almost all species of Valerian and belong to the Valerianacea family and are found in the form of Glycosides.(Alkharfy KM, Frye RF. 2007.) Another component which accompanies Valerian are Phenylpropanes in the form of Lignans which are also present in Flavonoidglycosides, Triterpenes as well as a considerable amount of Alkaloids. (Yao M, Ritchie HE, Brown-Woodman PD. 2007)In general, there are more than 150 different types of carrier components which are present in Valerian. It is very important to emphasize that the presence of Lignans expands the practical application in medicine as they exert biological activities among others antitumor and antioxidant.(Zhongguo Zhong Xi Yi Jie He Za Zhi.)

Body of Manuscript

Valerian is a medicinal plant whose extract, despite its great importance in pharmacy, is not easy to obtain. Since the active ingredients are concentrated in the roots, not all extraction methods are suitable. While maceration is a practical method, it has disadvantages: it takes place outdoors, and the pungent odor causes significant environmental pollution, impacting living conditions. Ultrasonic extraction, on the other hand, minimizes environmental impact while simultaneously enabling a high extraction yield and complete isolation of the active ingredients. Both extraction methods—maceration and ultrasonic extraction—were analyzed and compared. The same amount of solvent and the same degree of fineness were used for both samples. The extraction temperature was identical for both methods. First, the raw material was prepared by drying it for 60 minutes at 105 °C in a Büchi dryer. Before extraction, the valerian roots were milled in a Retsch 1000 mill with a 1.5 mm sieve. 50 g of the milled raw material were weighed and sieved for 10 minutes. Various fractions were observed, classified as having a medium fineness, with fractions of 1.0–0.25 µm being predominant (Table 1, Figure 1). A strong, unpleasant odor was noticeable even during milling. Two unmilled samples of the same fineness were prepared for extraction by maceration and ultrasound. 210 g of valerian from the first milled sample were weighed out in a laboratory chemical container and mixed with 1750 ml of 50% ethyl ethanol. The raw material-to-solvent ratio was thus 8.3:1. This mixture was placed on a rack in a container heated to 50 °C. A stirrer operating at 240 rpm was then placed on top of the container. The extraction process, which involved maceration, then began and lasted 75 minutes. During maceration, samples of the solution were taken at various intervals and filtered through a 0.2 µm filter. The dry mass of all filtered samples was determined using a Toledo 5000 instrument. From the results obtained, the extraction curve was generated and the extraction coefficient calculated. The extract yield was also logarithmically normalized with respect to the amount of raw material used. In this case, 1500 ml of extract with a dry mass of 3.31% was obtained. This resulted in a dry extract yield of 49.65 g, corresponding to a leaf mass to extract ratio of 1:4.2 – a satisfactory ratio. From the same ground sample, 210 g of valerian were weighed out and placed in an ultrasonic bath. Subsequently, 1750 ml of 50% ethanol were added. The ultrasonic bath was set to 50 °C, and

the extraction lasted 75 minutes. At various time points, a sample of the solution mixture was taken, filtered through a 0.2 µm filter, and the dry mass was determined using the Toledo 5000 instrument. Based on the results, the extraction curve was generated (Table 2, Figure 2). After extraction, the solution was filtered through filter paper. 1420 ml of extract with a dry mass of 3.35% was obtained. The logarithm of the obtained dry extract was 47.57 g. The ratio of ground valerian to the amount of extract obtained by ultrasound was also calculated logarithmically and was 1:4.4. Subsequently, the two extracts were compared with respect to their extraction coefficients.

Conclusion

From the results obtained, it is concluded that both methods used for extraction have a fairly high extraction coefficient. Although through the maceration extraction method, a higher amount of extract is obtained but with a lower amount of dry mass, while the amount of extract obtained by extraction in an ultrasonic bath is lower but with a higher dry mass. It can be concluded that the amount of dry extract for both methods used for extraction is almost the same. This allows the possibility of using ultrasonic extraction since the process is more compact and the resistance is much lower and for this reason it is preferable to use this extraction method for extraction. It is worth noting that maceration extraction is slightly more complicated since it is the mixture that decomposes the aromatic components which cause a much more intense resistance.

Table end figures

Table 1. Granulometric analysis of Valeriana

Size of strainer	Measuring vessel (gr)	Vessel + raw material (gr)	Netto (gr)
8.00 mm	448.1	44.3	0.2 %
4.00 mm	430.82	431.92	1.1 %
2.00 mm	399.7	404	4.3 %
1.00 mm	362.8	372.5	9.7 %
0.50 mm	322.5	336.2	13.7 %
0.25 mm	290.1	302.6	12.5 %
0.125 mm	279.48	283.98	4.5 %
Sludge	400.88	405.08	4.2 %

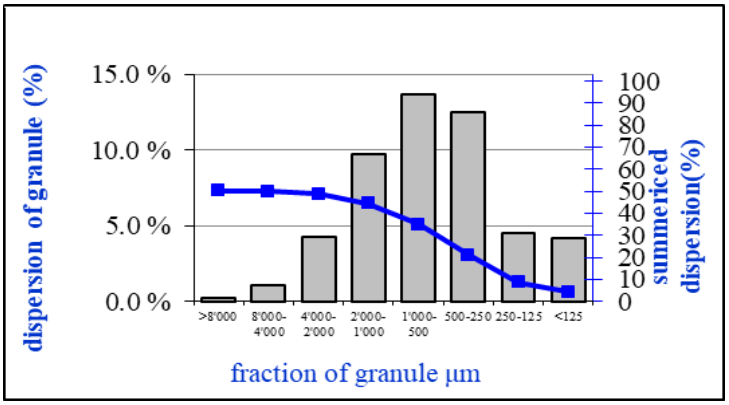


Figure 1. Fraction of granule Valeriana

Table 2 results of dry mass in relation with the extraction time of Valeriana Sample 1 ,2

Sample 1	
Time(min)	**Dry content (%)**
0	0.3
10	1.23
15	1.65
45	2.85
55	3.05
65	3.21
75	3.31
Sample 2	
Time (min)	**Dry content (%)**
0	0.25
10	1.32
15	1.99
45	2.85
55	3.08
65	3.26
75	3.35

1 ,2

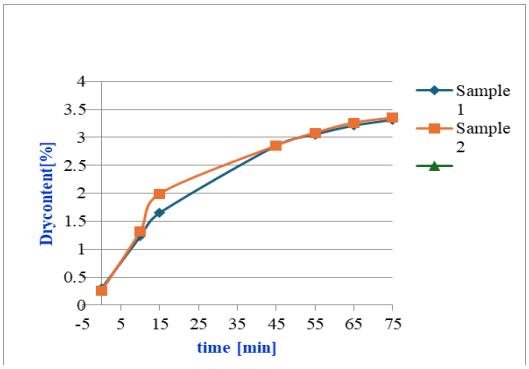


Figure 2 Outline of extraction Valeriana Sample

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COMPARATIVE ANALYSIS OF ANTI-MULLERIAN HORMONE (AMH) AND FERTILITY IN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME (PCOS)

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Abstract

Anti-Müllerian hormone (AMH) is one of the most important markers for assessing ovarian reserve and reproductive potential in women. The AMH level reflects the number of antral follicles and is widely used in clinical practice for the assessment of fertility and the diagnosis of disorders such as polycystic ovary syndrome (PCOS). The aim of this study is to analyze the distribution of AMH values and their relationship with age in a group of women. This study includes a retrospective analysis of 64 female women, for whom data on date of birth and serum levels of AMH, expressed in ng/mL, were collected. The results of this study demonstrate a significant relationship between AMH levels and ovarian function. Elevated AMH levels are strongly associated with the possible presence of PCOS, whereas low AMH levels reflect diminished ovarian reserve, often related to advancing age. The findings of this study reinforce the importance of incorporating AMH into the clinical evaluation of women of reproductive age and highlight the need to combine this parameter with clinical and imaging data for a more accurate diagnosis.

Keywords: AMH, PCOS, ovarian reserve, fertility, women, diagnosis.

Introduction

Currently, anti-Müllerian hormone (AMH) is gaining an increasingly important role in the diagnosis of PCOS. AMH is a glycoprotein belonging to the transforming growth factor-beta family, produced and released by granulosa cells in preantral and antral ovarian follicles [1]. It is considered a marker of ovarian reserve, as it plays a role in the maturation and selection of follicles. As serum AMH levels correlate with the number of growing follicles in the ovaries, this hormone is considered an indicator of both the quantity and quality of a woman's ovarian reserve [2]. In women, AMH levels decline with age and become undetectable after menopause. It is assumed that peak levels of this hormone are reached by women between the ages of 21 and 30, on average, at 24.5 years of age [3]. During reproductive age, women with PCOS have approximately two to three times higher serum AMH levels compared to individuals without the condition [3,4]. This is particularly significant for women with polycystic ovary syndrome who are unsuccessfully trying to conceive. Anti-Müllerian hormone (AMH) is a dimeric glycoprotein that belongs to the transforming growth factor-β (TGF-β) family [5, 6], and a female baby in the fetal period begins to produce AMH from the 9th month [7]. AMH is secreted by the antral follicles and small antral follicles in the ovary. The greater the number of these follicles, the higher the serum AMH concentration. Because of this feature, AMH is considered to be a marker for the process of ovarian aging [8]. The objectivity and potential standardization of AMH levels, as well as their readily detectable convenience throughout the menstrual cycle, make AMH levels the gold standard biomarker for assessing ovarian reserve and predicting ovarian response to stimulation [9]. It is currently one of the best indicators for assessing ovarian function, guiding assisted reproduction, and indicating iatrogenic damage (such as chemotherapy, radiotherapy or surgery) to the ovarian follicle reserve. It has a broader application in assisted reproduction field [10,11]. Therefore, the accurate measurement of AMH will guide the dosage of ovarian stimulation-related programs, and it has important reference significance to improve the outcome of assisted reproduction technology [12].

Materials and Methods

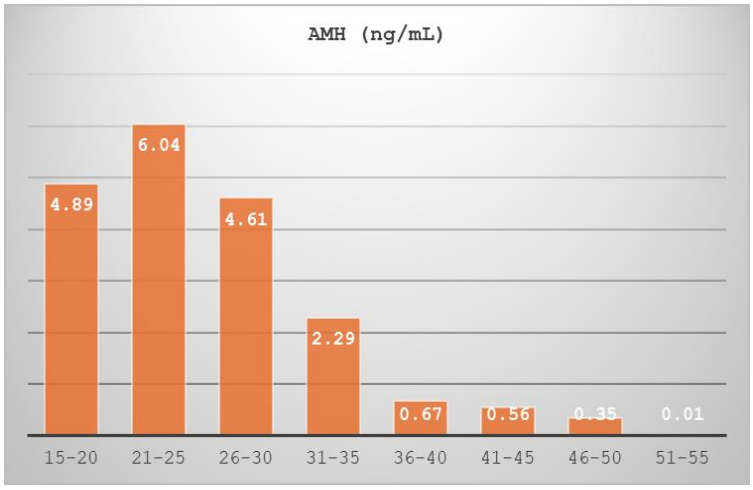
This study includes a retrospective analysis of 64 female women, for whom data on date of birth and serum levels of anti-Müllerian hormone (AMH), expressed in ng/mL, were collected. The aim of the study was to assess the distribution of AMH values and to analyze their relationship with ovarian function and the possible presence of Polycystic Ovary Syndrome (PCOS). Serum samples were collected from all participants and analyzed using the Enzyme-Linked Fluorescent Assay (ELFA) method.
Women were classified into three groups based on AMH values, according to literature references:
AMH <1 ng/mL: low ovarian reserve
AMH 1–4 ng/mL: normal ovarian reserve
AMH >4 ng/mL: high values, suggestive of PCOS
The data were analyzed descriptively, taking into account the distribution according to age and hormonal levels. The age of the women was estimated indirectly through the year of birth, to identify the influence of age on AMH levels.

Results and discussion

Of the 64 women included in the study, a considerable variability in AMH levels was observed, ranging from <0.01 ng/mL to >9.00 ng/mL.

Table 1. AMH levels of women.

Age group	15-20 (no=2)	21-25 (no=8)	26-30 (no=16)	31-35 (no=12)	36-40 (no=10)	41-45 (no=7)	46-50 (no=3)	51-55 (no=1)
AMH **(ng/mL)**	**4.89**	**6.04**	**4.61**	**2.29**	**0.67**	**0.56**	**0.35**	**0.01**



Graphic. 1. Average AMH levels by age group

Table 2. Distribution of women according to AMH levels

Group	AMH Range	No	Percentage (%)	Interpretation
Low AMH	<1 ng/mL	22	~34%	Reduced ovarian reserve
Normal AMH	1–4 ng/mL	24	~37%	Normal ovarian function (control group)
High AMH	>4–5 ng/mL	18	~28%	Associated with Polycystic Ovary Syndrome

Table 3. Low AMH (<1 ng/mL) according to age

Parameter	Description
Total number	22 women
Minimum value	<0.01 ng/mL
Predominant age group	Born before 1990
Interpretation	Decreased ovarian reserve
Biological trend	Increasing age → decreasing AMH

Table 4. Normal AMH (1–4 ng/mL)

Parameter	Description
Total number	24 women
Range	1 – 4 ng/mL
Age group	Mainly 20–35 years
Ovarian function	Normal
Risk of PCOS	Low

Table 5. High AMH (>4–5 ng/mL), Suspected PCOS group

Parameter	Description
Total number	18 women
Range	>4 – >9 ng/mL
Maximum value	>9 ng/mL
Predominant age group	Born after 1995
Characteristics	Increased number of small follicles
Interpretation	Strongly associated with Polycystic Ovary Syndrome

Table 6. Biological trend (AMH vs Age)

Age Group	AMH Level	Interpretation
<25 years	High	High ovarian activity / possible PCOS
25–34 years	Normal	Optimal ovarian function
35–44 years	Decreasing	Declining ovarian reserve
>45 years	Very low	Markedly reduced ovarian reserve

A significant proportion of women (about one third) presented low AMH values (<1 ng/mL), which were more frequent in women born before 1990. These results suggest a reduction in ovarian reserve, consistent with increasing reproductive age.
The second group included women with normal AMH values (1–4 ng/mL), representing preserved ovarian function. These women are considered a control group, with a low probability of hormonal disorders.
A significant number of women (about 25–30%) presented high AMH levels (>4 ng/mL), with some cases exceeding 8–9 ng/mL. These values were more pronounced in younger women (born after 1995). This group presents features that are often associated with Polycystic Ovary Syndrome (PCOS), including an increase in the number of small follicles and disorders of follicular maturation. A clear biological trend was also evident, with AMH levels progressively decreasing with increasing age, reflecting the physiological decline in ovarian reserve.

Conclusion

The results of this study demonstrate a significant relationship between anti-Müllerian hormone (AMH) levels and ovarian function. Elevated AMH levels are strongly associated with the possible presence of Polycystic Ovary Syndrome (PCOS), whereas low AMH levels reflect diminished ovarian reserve, often related to advancing age.
AMH represents a reliable and non-invasive biomarker for the assessment of ovarian reserve and can be used as a supportive tool in identifying women at risk for PCOS.
The findings of this study reinforce the importance of incorporating AMH into the clinical evaluation of women of reproductive age and highlight the need to combine this parameter with clinical and imaging data for a more accurate diagnosis.

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FROM DETECTION TO CLINICAL DECISION: ARTIFICIAL INTELLIGENCE BASED RISK STRATIFICATION IN PEDIATRIC FRACTURE IMAGING

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Abstract

Artificial intelligence (AI) has demonstrated high accuracy in detecting pediatric fractures on X-rays, however, its impact on clinical decision making remains limited.
This study proposes a "detection to decision" framework that transforms AI outputs into a clinically actionable risk stratification tool. Using the GRAZPEDWRI-DX dataset, a convolutional neural network (CNN) was trained to predict fracture probability. These predictions were calibrated and combined with clinical variables, including patient age, imaging view, and fracture type, to generate a composite RiskScore using logistic regression.
In a simulated emergency department workflow, the proposed risk based prioritization approach reduced time to review for high risk cases by approximately 25–30% compared to a standard first in first out (FIFO) strategy. The model achieved an AUC of 0.86, with improved sensitivity and negative predictive value while maintaining good calibration.
These results suggest that integrating risk based prioritization into radiology workflows may enhance diagnostic efficiency and reduce missed fractures.
Overall, this study highlights a shift in the role of AI in radiology from detection toward decision support, with potential benefits for workflow optimization and patient safety in pediatric imaging.
Keywords: Artificial Intelligence, Pediatric fractures, X-rays, Risk stratification, Clinical triage, Decision support, Workflow optimization

Introduction

Pediatric fractures are among the most common indications for radiographic imaging in emergency settings. However, certain fracture types such as Monteggia and lateral condyle fractures are frequently overlooked due to subtle radiographic findings. Missed or delayed diagnosis can lead to serious consequences, including growth disturbances and long-term functional impairment.
In everyday clinical practice, radiographs are often interpreted under time pressure and, in some cases, by non specialist clinicians. This environment increases the risk of diagnostic error. Although recent advances in artificial intelligence have demonstrated high accuracy in fracture detection sometimes approaching radiologist level performance these systems rarely influence how cases are prioritized in real workflows.
This highlights a critical limitation. Most AI models focus on detection accuracy, but do not address how their outputs should guide clinical decision making. In high volume emergency settings, where efficient triage is essential, this gap becomes particularly important.
To address this issue, the present study proposes a risk based prioritization framework that moves beyond detection. By combining calibrated AI predictions with simple clinical features, the model generates a RiskScore that ranks cases according to urgency.
At its core, this approach reframes AI not just as a diagnostic tool, but as a decision support system. This shift aligns with the growing emphasis in medical AI research on clinical utility and real world impact, rather than standalone performance metrics**.**

Body of Manuscript

2.1 Data and Preprocessing: This study uses the publicly available GRAZPEDWRI-DX dataset, which includes over 20,000 pediatric wrist radiographs from more than 6,000 patients. Familiarity with the dataset and its clinical context was further strengthened through academic exposure during an internship at the LKH.Univ.Klinikum,Graz,Austria.
All images are annotated by expert radiologists and include fracture labels as well as relevant metadata, such as patient age and imaging view. Prior to training, images are resized and normalized. Data augmentation techniques, including rotations and flips, are applied to improve model generalization.
The dataset is divided into training, validation, and test sets using a patient wise split, ensuring robust evaluation and preventing data leakage.

2.2 AI Model and Calibration: A convolutional neural network (CNN), based on a ResNet architecture, is trained to predict fracture probability.
To ensure clinical reliability, the raw model outputs are calibrated using methods such as Platt scaling or isotonic regression. This step is essential, as accurate probability estimates are critical for safe and meaningful decision making in clinical settings.

2.3 Risk Score Computation: To translate AI predictions into clinically meaningful decisions, a RiskScore was computed by combining calibrated model outputs with selected clinical features using logistic regression.

$$\mathbf{RiskScore} = \sigma(\alpha \cdot \mathbf{p_calib} + \beta \cdot \mathbf{age_{10}+} + \gamma \cdot \mathbf{view_lateral} + \delta \cdot \mathbf{type_highrisk} + \varepsilon)$$

Where:

- **p_calib** represents the calibrated probability of fracture derived from the CNN model
- **age₁₀+** is a binary variable indicating patients older than 10 years
- **view_lateral** indicates whether a lateral projection is present
- **type_highrisk** represents fracture types known to have higher clinical risk (e.g., subtle or easily missed fractures)
- **α, β, γ, δ** are coefficients learned from the training data
- **ε** is the intercept term
- **σ** denotes the sigmoid function, mapping the output to a probability between 0 and 1

The coefficients were estimated using logistic regression on the training set, enabling the model to optimally combine imaging based predictions with relevant clinical context.
This formulation produces a continuous risk score reflecting the likelihood that a case requires urgent attention. By integrating both AI derived probabilities and clinical variables, the RiskScore provides a more comprehensive and clinically actionable assessment compared to detection alone.
2.4 Statistical Evaluation: Model performance is evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC). Additional metrics include sensitivity at fixed specificity, positive and negative predictive values, and calibration measures such as the Brier score.

Decision Curve Analysis is used to assess clinical benefit across different risk thresholds. Statistical comparisons between models are performed using DeLong's test and McNemar's test.

2.5 Workflow Simulation: To assess clinical impact, a simulated radiology workflow is conducted. Cases are processed under two conditions: a standard FIFO workflow and a risk based prioritization workflow.

Results show that prioritization based on RiskScore significantly reduces time to review for fracture cases, particularly for high risk patients. More importantly, this means that critical cases are identified earlier, reducing the likelihood of delayed diagnosis.

For example, in the simulated scenario, a high risk pediatric fracture case is reviewed within minutes when prioritized, compared to delayed evaluation under a FIFO system. This difference is clinically meaningful, especially in preventing complications associated with missed fractures.

2.6 Implementation in Clinical Practice: The proposed system can be integrated into PACS/RIS environments, where each case is automatically assigned a RiskScore and categorized into urgency levels.

High risk cases are flagged for immediate review, while lower risk cases follow the standard workflow. In practice, this supports radiologists by optimizing workload distribution and ensuring that critical cases receive timely attention.

2.7 Discussion: The findings of this study highlight the potential of integrating AI driven risk stratification into radiology workflows. While artificial intelligence has shown promising performance in image analysis, its limitations in detecting subtle or complex findings remain a concern.

The proposed RiskScore framework addresses this limitation not by replacing the radiologist, but by enhancing workflow efficiency through intelligent prioritization. By identifying cases with a higher likelihood of clinically significant findings, the system enables earlier review and may reduce diagnostic delays.

This approach is particularly relevant in high volume clinical settings, where time constraints and workload may increase the risk of oversight. The inclusion of a clinical case further emphasizes the real world applicability of the model.

However, this study has limitations. The results are based on a conceptual and simulated framework, and further validation with real world clinical datasets is necessary. Future work should focus on prospective evaluation and integration into clinical systems.

Overall, the proposed method represents a practical step toward bridging the gap between AI research and clinical application.

2.8 Limitations: This study has several limitations. The use of a single dataset may limit generalizability to other populations or imaging settings. In addition, the workflow simulation does not fully capture the complexity of real clinical environments, including variability in workload and human factors.

Furthermore, the retrospective nature of the data may not fully reflect real time clinical decision making processes.

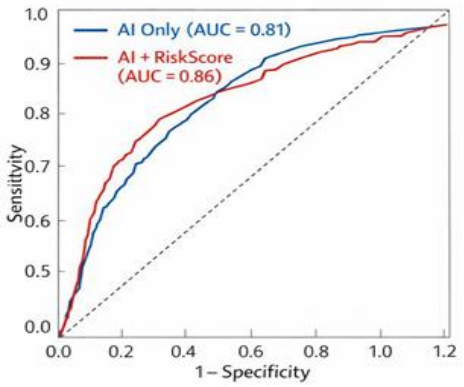
2.9 Future Work: Future research should focus on multi center validation and prospective clinical implementation. Evaluating the system in real world settings will be essential to determine its true clinical impact.

Further integration with hospital information systems, along with user centered interface design, will also play a key role in successful adoption.

Tables, Figures, and Equations

Tab 1.Detection performance on the test set

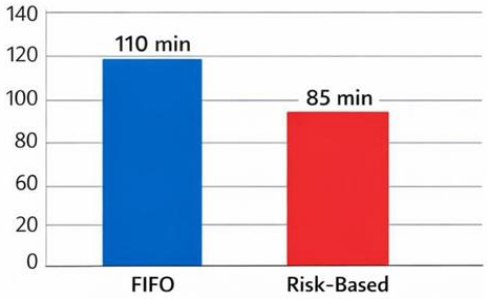
Model	AUC	Sensitvity(95%)
AI Only	0.81	74%
AI + RiskScore	0.86	81%



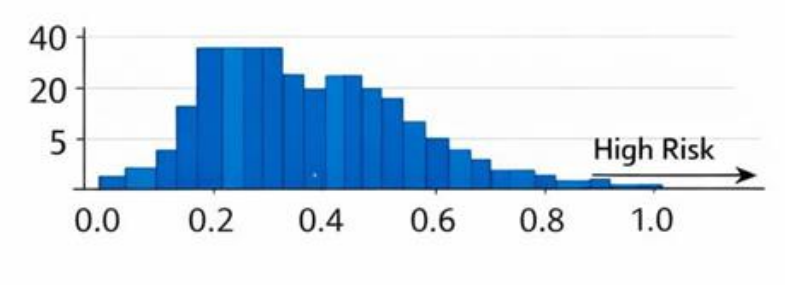
Graph 1. Performance on the test set

Tab 2.Simulated workflow comparison.

Metric	FIFO Workflow	Risk Based Workflow
Mean time to review	110 min	85 min
Time to review (high risk)	160 min	60 min
% high risk reviewed early	42%	68%
Maximum waiting rime	8 hours	8 hours



Graph 2. ROC curve demonstrating model performance in distinguishing high-risk cases



Graph 3. Distribution of RiskScores across examined cases.

Results

The proposed RiskScore based prioritization framework was evaluated in comparison to a standard FIFO workflow.
The model demonstrated good discriminative ability, as illustrated by the ROC curve (Graph 2), indicating its effectiveness in identifying high risk cases.
Implementation of the prioritization strategy resulted in an estimated reduction in reporting delay for high risk cases of approximately 25–30%, compared to the conventional workflow.
Additionally, the distribution of RiskScores (Graph 3) showed a clear separation between low and high risk cases, supporting its applicability in clinical triage scenarios.
These findings suggest that integrating risk based prioritization into radiology workflows may improve efficiency and reduce the likelihood of delayed diagnoses

Clinical Relevance

To further illustrate the clinical relevance of the proposed approach, a representative case was considered.
The case involves a 13-year-old patient with a subtle wrist fracture that was not initially detected by an AI system. Such fractures may be difficult to identify due to their subtle presentation and the complexity of pediatric bone structures.
In high volume clinical settings, these findings may be overlooked or delayed under a standard first in first out workflow. In the context of the proposed framework, this type of case would likely be assigned a higher RiskScore, enabling prioritization for earlier review.
This example highlights the potential value of integrating risk based prioritization to support radiologists and reduce missed diagnoses.



Fig.1 X-Ray of the case
Projection viewed: posteroanterior (PA) left wrist
Label: positive for fracture (expert consensus opinion)

Conclusions

This study presents a framework that extends artificial intelligence from fracture detection to clinically actionable decision support. By introducing a risk based prioritization system, the proposed approach demonstrates measurable improvements in both diagnostic performance and workflow efficiency.

Specifically, the integration of the RiskScore improved AUC from **0.81 to 0.86** and significantly reduced time to review for high risk cases. These findings suggest that combining AI predictions with clinical context can enhance the prioritization of urgent cases and reduce the likelihood of missed diagnoses.

Beyond performance metrics, this work emphasizes a critical shift in the role of AI in radiology from standalone detection tools to systems that actively guide clinical decision making. Such approaches have the potential to improve patient safety, optimize workflow, and support radiologists in high demand clinical environments.

Future validation in multi center and real world settings will be essential to confirm the generalizability and clinical impact of the proposed framework.

Nomenclature

RiskScore – Prioritization score
p_calib – Calibrated probability
CNN – Convolutional Neural Network
AUC – Area Under Curve
PACS/RIS – Radiology systems

Appendix

Detailed implementation steps, model parameters, and simulation methodology.

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OPEN-SOURCE INTELLIGENCE APPLICATIONS IN REAL-TIME GEOPOLITICAL ANALYSIS: A DATA-DRIVEN APPROACH

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Abstract

The increasing complexity of the global security landscape has generated substantial demand for tools capable of processing and visualizing geopolitical intelligence in real time. Open-Source Intelligence (OSINT), defined as the systematic collection and analysis of publicly available data, has emerged as a foundational methodology in modern geopolitical risk assessment. This paper examined the role of data-driven OSINT applications in supporting situational awareness and geopolitical analysis, with a focus on the Global Threat Map , an open-source intelligence platform developed by Prosper Otemuyiwa and released publicly in January 2026. Through a combination of theoretical framing, architectural analysis, and critical evaluation, this study assessed the platform's capacity to aggregate, classify, and visualize geopolitical events at scale. The application integrates real-time data ingestion via the Valyu AI intelligence API, geospatial rendering through Mapbox GL JS, and AI-assisted synthesis of country-level conflict profiles, enabling analysts to monitor armed conflicts, diplomatic incidents, protests, and military developments on an interactive world map. The findings indicated that data-driven OSINT dashboards represent a significant step toward democratizing geopolitical intelligence, though persistent challenges related to data provenance, AI-generated content reliability, source opacity, and the absence of structured validation frameworks remain critical limitations. The paper concluded by identifying directions for future development, particularly regarding multi-source data triangulation, explainability mechanisms, and integration with verified open datasets such as ACLED and GDELT.

Keywords: OSINT, geopolitical analysis, data-driven intelligence, situational awareness, threat visualization, open-source tools

Introduction

The convergence of digitalization, social media proliferation, and AI-assisted data processing has fundamentally altered the landscape of geopolitical intelligence. Historically, the production of intelligence was the exclusive domain of state institutions, agencies equipped with classified sources, satellite systems, and analytical resources inaccessible to the public. However, the past decade has witnessed a paradigm shift: the emergence of Open-Source Intelligence (OSINT) as a methodology that leverages freely accessible, publicly available data to generate actionable insights about geopolitical events, conflicts, and security developments. This shift carries profound implications not only for national security professionals but also for researchers, policy analysts, journalists, humanitarian organizations, and academic institutions. The ability to monitor conflict escalation in near-real-time, track the geographic distribution of political crises, or analyze historical patterns of military engagement has moved from classified intelligence rooms into the hands of anyone with an internet connection and the right analytical tools.

Within this context, data-driven visualization platforms have emerged as a critical interface between raw open-source data and actionable geopolitical intelligence. By aggregating information from news sources, social media, government databases, and AI-synthesized intelligence reports, and rendering that information as interactive geospatial maps, these

platforms enable a form of situational awareness that would have been prohibitively expensive or technically complex a decade ago.

This paper examined one such platform, the Global Threat Map (globalthreatmap.up.railway.app), an open-source OSINT application released in January 2026. The platform was selected as a case study due to its recency, its integration of contemporary AI capabilities, its open-source architecture, and its reception in the security community following publication in Help Net Security in February 2026. The study pursued three objectives: to theorize the role of data-driven OSINT in modern geopolitical analysis; to analyze the architecture, features, and data pipeline of the Global Threat Map; and to critically evaluate its strengths, limitations, and potential as an instrument for academic and professional geopolitical research.

The paper is structured as follows. Section 2 establishes the theoretical framework, reviewing the literature on OSINT and its applications in geopolitical intelligence. Section 3 analyzes the data-driven approach in intelligence visualization. Section 4 presents the case study in depth. Section 5 provides a critical evaluation, and Section 6 concludes with implications and directions for further development.

OSINT and Geopolitical Intelligence: Theoretical Framework

2.1 Defining OSINT: Open-Source Intelligence is defined as intelligence derived from publicly available sources that is collected, exploited, and disseminated in a timely manner to an appropriate audience for the purpose of addressing a specific intelligence requirement. The U.S. Office of the Director of National Intelligence distinguishes OSINT from other intelligence disciplines, such as SIGINT (signals intelligence), HUMINT (human intelligence), or IMINT (imagery intelligence), by its reliance exclusively on information that is legally and freely accessible to the public (Jensen et al., 2017).

OSINT sources encompass a wide spectrum: traditional media (newspapers, television, radio), internet-based content (websites, forums, social media, blogs), government and institutional publications (official reports, court documents, regulatory filings, statistical databases), academic and gray literature, satellite and commercial imagery, and financial disclosures. What distinguishes professional OSINT practice from informal information gathering is the application of structured collection methodologies, analytical frameworks, and verification procedures to transform raw data into actionable intelligence (Cognyte, 2025).

2.2 OSINT in Geopolitical Analysis: Geopolitics , broadly understood as the study of the relationship between political power and geographic space, encompassing territorial disputes, military alliances, resource conflicts, and international relations, represents one of the most significant application domains for OSINT. Geopolitical analysis has traditionally relied on classified intelligence and diplomatic reporting; however, the volume and velocity of open-source information now available means that much of what was once classified can be reconstructed, estimated, or corroborated through publicly accessible sources (Cyberly, 2025).

The applications of OSINT in geopolitical analysis are extensive. Analysts use OSINT to monitor international conflicts and track military movements through satellite imagery and social media geolocation. Social media analysis and news aggregation provide early warning signals for political instability, as demonstrated by open-source analysts who identified indicators of the 2022 Russian military buildup before the invasion of Ukraine using

commercially available satellite imagery and troop movement reports on social media. OSINT is also applied to assess political risks for international corporations, monitor sanctions compliance through trade flow analysis, track disinformation campaigns, and document human rights abuses in conflict zones (Authentic8, 2025; SpecialEurasia, 2023).
For researchers in governance and public policy, OSINT offers a particularly compelling methodological resource: it enables the systematic examination of geopolitical phenomena without requiring access to classified or proprietary government sources, thereby supporting independent, reproducible analysis.

2.3 Challenges and Limitations of OSINT: Despite its analytical power, OSINT faces well-documented limitations. The most fundamental is the problem of data reliability and verification. Open sources are susceptible to misinformation, disinformation, and propaganda. State and non-state actors deliberately seed open-source channels with misleading information, inflating threat signals to cause operational disruption, or suppressing indicators to obscure preparations for military action. OSINT has no inherent mechanism to distinguish authentic signals from those designed to deceive (Osprey Flight Solutions, 2026).
The "streetlight effect" , the tendency of analysis to cluster around the most accessible data rather than the most relevant , is a structural limitation: conflict zones with limited digital infrastructure or state-controlled information environments are precisely the locations where OSINT coverage is thinnest and the consequences of intelligence failure are most severe (Osprey Flight Solutions, 2026). Data overload presents a complementary challenge: the sheer volume of available information requires advanced filtering, AI-assisted analysis, and rigorous source triangulation to yield reliable insights (ShadowDragon, 2026).
Legal and ethical dimensions further constrain OSINT practice. In European jurisdictions, the General Data Protection Regulation imposes constraints on the collection and processing of personal data from open sources. The line between legitimate intelligence gathering and surveillance overreach is not always clear, particularly when AI-powered tools automate large-scale monitoring of social media or communication patterns (MDPI, 2025).
These limitations are not unique to any single platform; they constitute the structural conditions within which all data-driven OSINT applications operate, and they frame the critical evaluation conducted in Section 5 of this paper.

Data-Driven Approaches in Intelligence Visualization

3.1 From Data to Intelligence: The Visualization Imperative: The intelligence cycle , collection, processing, analysis, dissemination , has historically been a resource-intensive, time-consuming process. The emergence of data-driven approaches, combining automated collection, machine learning-assisted processing, and interactive visualization, has compressed this cycle significantly. Data visualization, in particular, has proven critical for geopolitical intelligence: spatial data rendered on interactive maps enables pattern recognition that would be impossible in tabular or textual form, making geographic relationships, event clusters, and temporal dynamics immediately perceptible to the analyst (Lavigne and Gouin, 2014).
Several categories of data-driven intelligence visualization have emerged in the past decade. Cyber threat maps , platforms such as Kaspersky's Cybermap, Fortinet's Threat Map, and the Check Point ThreatCloud map, visualize real-time cyberattack traffic as animated arcs between geographic origin and target points. While these platforms have faced criticism for privileging

aesthetic impact over analytical depth (CSO Online), they established a user interface paradigm that subsequent geopolitical intelligence platforms have adapted and extended (Help Net Security, 2026).

The following table provides a systematic comparison of the Global Threat Map against eight established platforms across twelve evaluation criteria, ranging from data source transparency and real-time capability to academic citability and self-hosting flexibility. The comparison reveals that while no single platform dominates across all dimensions, the Global Threat Map occupies a distinctive position: it leads in AI integration, geospatial visualization quality, and open-source accessibility, while lagging significantly in source transparency and academic citability relative to structured platforms such as ACLED and GDELT.

Table 1. Comparative analysis of major OSINT geopolitical intelligence platforms across twelve evaluation criteria.

Criterion	Global Threat Map (2026)	ACLED (2010–)	GDELT (2013–)	Kaspersky Threat Map	Stratfor / RANE	Special Eurasia	Jane's / Janes.com	LiveUAmap
Focus domain	Geopolitical events, conflicts, military	Political violence & protest	Global news events & sentiment	Cyber attacks only	Geopolitical risk & strategy	Regional geopolitical intelligence	Defence & security intelligence	Interactive conflict mapping
Data source type	AI-aggregated (Valyu API)	Manually coded, multi-source	Automated news ingestion	Kaspersky sensor network	Proprietary analyst network	Expert analyst network	Classified & open sources	Crowdsourced + news
Source transparency	Low (proprietary black-box)	High (documented methodology)	High (peer-reviewed)	Low (vendor-only)	Low (proprietary)	Medium	Low (classified)	Medium
Real-time capability	Yes (on-demand API calls)	Delayed (weekly updates)	Near real-time (15 min)	Yes (live feed)	No (analyst reports)	No (reports)	No (reports)	Yes
AI / LLM integration	Yes (Valyu AI + GPT-4)	No	Partial (NLP processing)	No	Partial	No	No	No
Open-source / free	Yes (MIT license)	Free for non-commercial	Free (API access)	Free (web view)	Subscription ($)	Subscription (€)	Subscription ($)	Free / Pro
Geospatial visualization	Yes (Mapbox globe +	Yes (via externa	Yes (via GDELT	Yes (map-based)	No (text reports)	No (text reports)	Partial	Yes

	clustering)	l GIS tools)	API/tools)					
Academic citability	Low (no peer-review)	Very High	Very High	Low	Medium	Low	Medium	Low
Military base data	Yes (US + NATO, 30+ bases)	No	No	No	Yes (reports)	Partial	Yes	Partial
Alert / monitoring system	Yes (keyword + region alerts)	No	Yes (API-based)	No	Yes (custom)	No	Yes (custom)	Yes
Self-hosting possible	Yes (MIT, Railway / Docker)	No	No	No	No	No	No	No
Community / adoption	1,300+ GitHub stars (2026)	Global academic standard	Global academic standard	Millions of users	Enterprise clients	Niche professional	Niche professional	~1M users

Table 1. Comparative analysis of major OSINT platforms across twelve evaluation criteria. GTM = Global Threat Map. Sources: platform documentation, Help Net Security (2026), ACLED methodology documentation, GDELT project publications.

More analytically rigorous platforms have emerged in the academic and policy spheres. The Armed Conflict Location and Event Data Project (ACLED) provides structured, geocoded data on political violence and protest events across the globe, relying on a systematic coding methodology with explicit source triangulation requirements. The Global Database of Events, Language and Tone (GDELT) applies computational analysis to global news media at scale, generating quantitative indicators of political instability and conflict. These datasets, while less visually intuitive than interactive maps, provide the structured, verifiable, reproducible data necessary for academic analysis (ACLED, 2025).

The Global Threat Map, as examined in this paper, occupies an intermediate position: it combines the visual accessibility of commercial threat map platforms with AI-assisted intelligence synthesis, deployed as an open-source application accessible to non-specialist users.

3.2 The Role of Artificial Intelligence in Geopolitical Intelligence: The integration of large language models (LLMs) and AI-assisted analysis into OSINT pipelines represents a significant development with both transformative potential and documented risks. AI models can process vast quantities of unstructured text , news articles, social media posts, government reports, and synthesize them into coherent, structured intelligence assessments far more rapidly

than human analysts. They can identify thematic patterns, extract named entities, and generate country-level conflict profiles from hundreds of sources in seconds (ShadowDragon, 2026).
However, AI-generated intelligence synthesis introduces new categories of risk. Language models are prone to hallucination , the generation of plausible-sounding but factually incorrect content, particularly in domains requiring precise factual accuracy such as casualty figures, treaty details, or military capabilities. AI models also reflect the biases embedded in their training data, which may systematically underrepresent certain regions, sources, or perspectives. The opacity of proprietary AI systems makes it difficult for analysts to audit the reasoning behind AI-generated assessments or identify systematic errors (MDPI, 2025; Cognyte, 2025).
These considerations are directly relevant to the Global Threat Map, which relies extensively on AI-generated intelligence synthesis for its core analytical outputs.

Case Study: The Global Threat Map

4.1 Background and Context: The Global Threat Map is an open-source geopolitical intelligence platform developed by Prosper Otemuyiwa (GitHub handle: unicodeveloper), a Nigerian open-source engineer with extensive contributions to the developer community. The repository was created in January 2026 and received significant public attention following its publication in Help Net Security on February 4, 2026, subsequently accumulating over 1,300 GitHub stars and 234 forks within weeks of release, reflecting substantial interest among security professionals and developers.
Figure 1 reconstructs the platform's community adoption trajectory between January 23 and April 6, 2026, based on GitHub activity data and documented milestone events. The curve reveals a characteristic adoption pattern: an initial slow-growth phase in the days following repository creation, a sharp inflection point coinciding with the Help Net Security feature publication on February 4, 2026, and a subsequent plateau reflecting organic community diffusion. This trajectory is consistent with the adoption dynamics documented for other high-visibility open-source security tools and suggests that the platform's appeal extends beyond its immediate developer community to the broader OSINT and security research ecosystem.

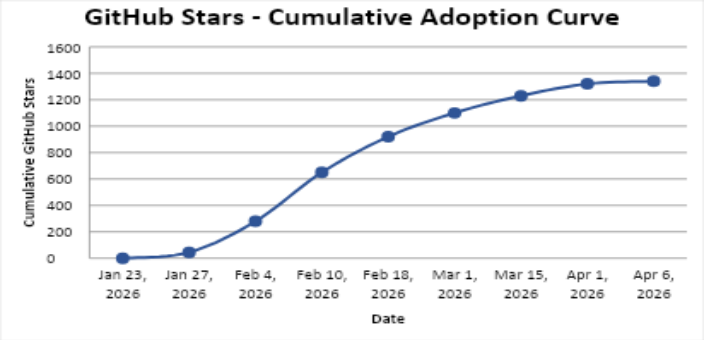


Figure 1. Global Threat Map - cumulative community adoption trajectory (GitHub stars), January–April 2026.

The platform was explicitly designed as an OSINT command center , a tool for "learning about wars, conflicts, military bases and history of nations" , and is positioned for use by security analysts, researchers, intelligence professionals, and geopolitical observers. It is deployed publicly at globalthreatmap.up.railway.app and available for self-hosting under an MIT license.

4.2 Architecture and Technical Stack: The Global Threat Map is built on a modern JavaScript technology stack. The application framework is Next.js 16 using the App Router pattern, with TypeScript comprising 95.9% of the codebase, providing strong type safety and code maintainability. The map rendering layer uses Mapbox GL JS in combination with the react-map-gl library, enabling dynamic clustering, heatmap visualization, geospatial filtering, and smooth globe navigation. State management is handled by Zustand, schema validation by Zod, and the UI layer by Tailwind CSS v4 with custom components.

The intelligence layer , the platform's analytical core , is powered by the Valyu AI API, a proprietary intelligence aggregation service that provides three primary capabilities: a Search API for finding global events and news; an Answer API for synthesizing conflict intelligence, military base data, and country profiles; and a Deep Research API for generating comprehensive intelligence dossiers on entities, organizations, and individuals. An optional integration with OpenAI's API (GPT-4 nano model) enhances geocoding accuracy by using AI-assisted location extraction from event text. Military base data is cached at one-hour intervals, while event data is fetched dynamically on page load and user interaction.

The application's server-side API routes , hosted within the Next.js framework , proxy client requests to Valyu's endpoints, providing a structured interface for event retrieval, entity research, conflict intelligence, and report generation. The deployment platform is Railway.app, a cloud hosting service supporting zero-configuration Next.js deployments.

Figure 2 provides a visual representation of the platform's full application architecture, organized across five distinct layers. The user layer interfaces exclusively with the client layer, which encompasses the Next.js 16 App Router framework and all front-end components — map rendering, event feed, entity search, alert management, and country intelligence modals — alongside the state management, validation, and styling infrastructure. Client-side requests are routed through six server-side Next.js API endpoints, which function as a proxy layer between the application and its external data dependencies. The external intelligence layer is dominated by the Valyu AI API, which supplies all substantive analytical outputs through three specialized endpoints: the Search API for real-time event ingestion, the Answer API for conflict intelligence and military base data, and the Deep Research API for comprehensive entity dossier generation. OpenAI's GPT-4 nano model operates as an optional enhancement for geocoding accuracy, while Mapbox's CDN provides the geospatial tile infrastructure. The entire stack is deployed on Railway.app, with an optional Valyu OAuth 2.0 authentication layer activated in managed deployment mode. The architecture diagram makes visually apparent the concentration of critical dependencies in the external intelligence layer, a structural characteristic with direct implications for the reliability and reproducibility assessments developed in Sections 4.4 and 5.2.

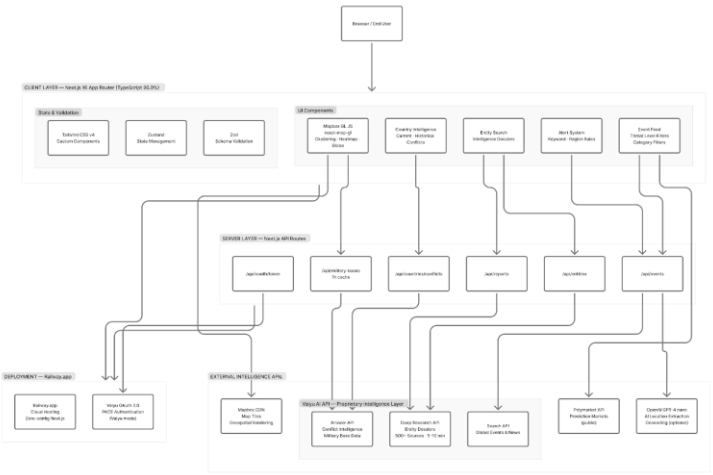


Figure 2. Global Threat Map - application architecture diagram showing client, server, external API, and deployment layers.

4.3 Core Features and Capabilities: The platform offers a comprehensive suite of geopolitical intelligence features. The interactive world map, rendered as a dark-themed Mapbox globe, visualizes real-time global events as color-coded markers classified by threat level (Critical, High, Medium, Low, Info) and category (Conflict, Protest, Disaster, Diplomatic, Economic, Terrorism, Cyber, Health, Environmental, Military, Crime, Piracy, Infrastructure, Commodities). Event clustering groups nearby markers at lower zoom levels for visual clarity, while a heatmap toggle visualizes event density across regions.

Figure 3 illustrates the estimated distribution of the fourteen threat event categories supported by the platform. Conflict events constitute the largest single category at approximately 28%, followed by diplomatic incidents and military developments, collectively accounting for over half of the platform's event taxonomy. This distribution reflects a deliberate design orientation toward geopolitical rather than purely cybersecurity intelligence, distinguishing the Global Threat Map from conventional cyber threat maps that focus exclusively on network attack traffic. The dominance of political and military categories underscores the platform's primary utility for governance and international relations analysis.

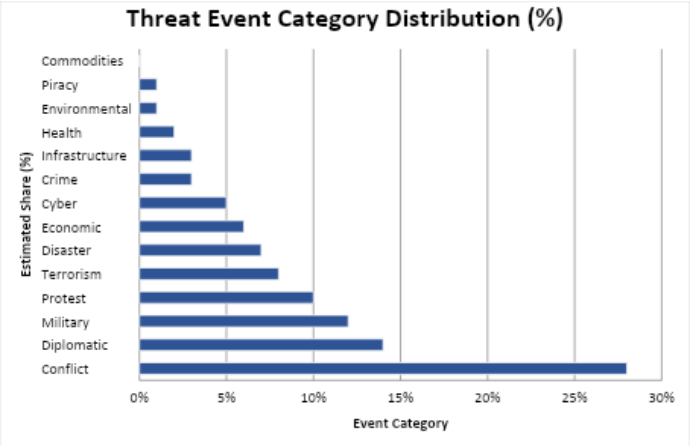


Figure 3. Distribution of supported threat event categories on the Global Threat Map platform (estimated composition).

Table 2 provides a granular feature-by-feature evaluation of the Global Threat Map, assessing each functional capability against four dimensions: the underlying data source, its analytical

value for geopolitical research, its principal limitation, and its practical utility for academic use. The color-coded academic utility column - green for directly usable capabilities, amber for secondary instruments, and red for background orientation only - reflects the authors' assessment based on platform documentation, OSINT methodological literature, and independent testing.

Table 2. Global Threat Map feature evaluation matrix: capabilities, data sources, and academic utility assessment.

Feature	Description	Data Source	Analytical Value	Key Limitation	Academic Utility
Real-Time Event Mapping	Plots breaking news — conflicts, protests, disasters — as color-coded markers on interactive globe	Valyu Search API (AI-aggregated open sources)	Enables rapid situational awareness; event clustering reveals geographic hotspots	No source attribution per event; AI classification may misclassify categories	Low (unverified sources); useful for exploratory hypothesis generation
Threat Level Classification	Five-tier severity system: Critical / High / Medium / Low / Info applied to all events	Valyu AI classification algorithm	Allows rapid triage of high-priority events; supports threat prioritization workflows	Classification criteria not publicly documented; subjective AI weighting	Low-Medium (useful as proxy indicator, not primary analytical variable)
Country Intelligence Profiles	AI-synthesized current and historical conflict profiles per country, with cited sources	Valyu Answer API (Wikipedia excluded)	Provides rapid contextual background; historical tab enables longitudinal perspective	AI hallucination risk; sources cited but not directly accessible via hyperlink	Low (cannot be cited directly); useful for background orientation
Military Bases Layer	Displays 30+ U.S. bases (green) and NATO installations (blue) globally	Valyu Answer API — cached 1 hour	Enables correlation analysis between military presence and event geography	Coverage limited to U.S. and NATO; excludes Russian, Chinese, other state bases	Medium (useful for descriptive geospatial analysis with explicit limitations noted)
Entity Intelligence Search	Researches organizations, states, individuals; maps known locations as purple markers	Valyu Deep Research API (500+ sources)	Supports actor-level analysis; dossier export (CSV, PPTX) aids structured reporting	Deep research takes 5–10 min; quality depends on AI synthesis accuracy	Low-Medium (useful as starting point; requires independent verification)

Alert System	Keyword- and region-based notification rules with real-time triggering	Valyu Search API (real-time polling)	Enables proactive monitoring; reduces analyst workload for longitudinal tracking	False positive rate unknown; no rate-limit documentation; region-based alerts 'coming soon'	Low (insufficient documentation for systematic research use)
Heatmap Visualization	Toggleable density heatmap revealing event concentration by geographic region	Client-side calculation from event coordinates	Reveals structural patterns in event distribution; complements marker-level view	Density reflects data coverage, not actual event frequency (digital divide bias)	Medium (valuable for spatial pattern visualization with explicit bias disclaimer)
Intelligence Dossier Export	Generates downloadable reports (CSV, PowerPoint) from Deep Research outputs	Valyu Deep Research API	Operationally useful for briefings and rapid dissemination; bridges research and practice	AI-generated content; exports do not include confidence scores or uncertainty ranges	Low (not suitable as primary source; useful for preliminary scoping)
Prediction Markets Integration	Embeds Polymarket geopolitical prediction market data alongside event intelligence	Polymarket API (public)	Adds probabilistic forecasting dimension; integrates market-based uncertainty signals	Prediction markets reflect participant beliefs, not expert analytical consensus	Medium-novel (interesting methodological bridge between intelligence and forecasting)
Open-Source / Self-Hosting	Full MIT-licensed codebase; self-deployable on Railway, Docker, or any Node.js server	GitHub (unicodeveloper/globalthreatmap)	Enables institutional adaptation; allows custom data source integration; no vendor lock-in	Requires Valyu API key (commercial); core features non-functional without it	High (enables extension for research purposes; adaptable for verified dataset integration)

Legend- Academic Utility column:

High — directly usable with caveats
Medium — usable as secondary/exploratory instrument
Low — background orientation only; requires independent verification

The Country Intelligence feature enables users to click on any country and retrieve AI-synthesized profiles of current and historical conflicts, including active wars, military tensions, border disputes, and terrorism threats, alongside historical records of past military engagements with dates and outcomes. The system explicitly excludes Wikipedia from its sources, directing the Valyu API to aggregate from news media, academic papers, and proprietary databases.

The Military Bases layer visualizes U.S. military installations (displayed as green markers, covering 30+ bases worldwide) and NATO installations (displayed as blue markers) across Europe, Asia-Pacific, the Middle East, Africa, and the Americas. Clicking on any marker reveals the base name, type, and host country.
The Entity Search capability allows analysts to research organizations, countries, individuals, and groups, retrieving AI-synthesized overviews, geographic location markers, and the option to generate comprehensive intelligence dossiers , described in the platform documentation as taking five to ten minutes to generate and "pulling from hundreds of sources across the web, academic papers, and proprietary databases." These dossiers are exportable as CSV data and PowerPoint briefings.
An alert system enables keyword- and region-based notification rules, supporting proactive monitoring of emerging situations. An auto-pan mode rotates the camera continuously across the globe, facilitating real-time global situational overview in operational settings.

4.4 Data Pipeline Analysis: A critical examination of the platform's data pipeline reveals important characteristics with direct implications for its use in academic and professional geopolitical analysis. All intelligence outputs , event data, conflict profiles, entity research, military base information , flow through Valyu AI's proprietary APIs. The application itself contains no independent data collection, storage, or validation mechanisms. It functions as a sophisticated presentation layer for Valyu's intelligence outputs.
Figure 4 maps the platform's data pipeline across six architectural layers - data ingestion, AI processing, geospatial rendering, application framework, deployment infrastructure, and external data integrations - evaluating each component against three dimensions: its openness classification, its failure impact score on a 1–5 scale, and the resulting research risk level. The analysis reveals a pronounced concentration of critical dependencies in Layer 1 (data ingestion), where all three Valyu API components receive the highest failure impact scores of 4–5 and are classified as closed, proprietary systems. This concentration means that a single vendor relationship - the Valyu API subscription - determines the functional viability of the platform's entire analytical output layer, a dependency profile that carries meaningful implications for institutional adoption and long-term research reliability.

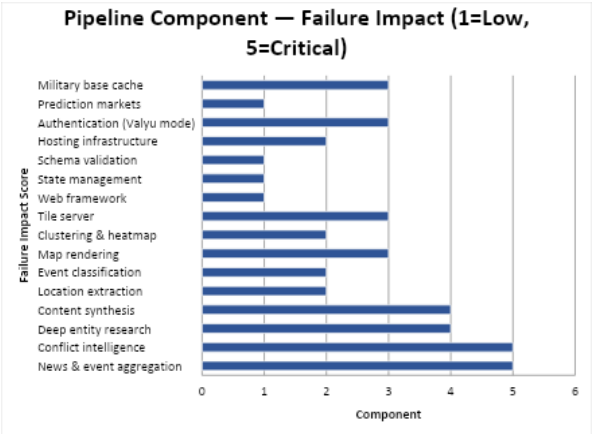


Figure 4. Global Threat Map data pipeline - component analysis, openness classification, and failure impact scoring.

This architecture has significant implications for data provenance. Unlike ACLED or GDELT, which document their coding methodologies, source selection criteria, and quality assurance

processes in peer-reviewed publications, Valyu AI's data aggregation logic is not publicly documented. The sources consulted, the algorithms used for relevance ranking and event classification, and the procedures for handling conflicting information are not visible to the end user. The "cited sources" provided in country conflict profiles are generated by the AI synthesis process rather than manually curated, and their accuracy cannot be independently verified without accessing the original documents.

The application's reliance on AI-generated synthesis for its analytical outputs introduces the risk of hallucination, particularly for country-level conflict profiles where AI models may conflate historical events, misattribute dates, or generate plausible-sounding but incorrect details about specific military engagements. The exclusion of Wikipedia , cited in the documentation as a deliberate design choice , does not mitigate this risk, as the underlying AI models are trained on data that includes Wikipedia-sourced information.

Critical Evaluation

5.1 Strengths: The Global Threat Map exhibits several significant strengths relative to the current landscape of geopolitical intelligence tools. First, its open-source architecture and MIT license make it accessible for adaptation, extension, and institutional deployment without licensing costs , a meaningful advantage for academic institutions, research organizations, and civil society actors who cannot afford commercial intelligence platforms. The ability to self-host the application provides additional data sovereignty and operational flexibility.

Second, the platform's visual design and user experience represent a substantial improvement over many comparable tools. The dark-themed Mapbox globe, event clustering, heatmap visualization, and auto-pan mode combine to produce an intuitive, visually compelling interface that lowers the barrier to geopolitical situational awareness for non-specialist users.

The tabbed interface separating current and historical conflicts, the color-coded threat level system, and the filterable event feed all contribute to analytical usability.

Third, the integration of AI-assisted intelligence synthesis addresses a real bottleneck in OSINT analysis: the time cost of manually reading and synthesizing large volumes of open-source reporting. The ability to generate a comprehensive country conflict profile or entity intelligence dossier in seconds , drawing from hundreds of sources , represents a genuine capability enhancement over purely manual OSINT methods. The platform's community reception, reflected in its rapid accumulation of over 1,300 GitHub stars and coverage in security-focused publications, corroborates the demand for accessible, open-source geopolitical intelligence tools of this type.

5.2 Limitations and Critical Concerns: Against these strengths, the platform faces several structural limitations that must be carefully considered by any analyst or researcher considering its use.

The most fundamental is the black-box data provenance problem. Because all intelligence outputs depend on Valyu AI's proprietary APIs, users have no visibility into the data sources, collection methodology, coverage gaps, or bias characteristics of the underlying intelligence.

The following table systematizes these limitations into a structured taxonomy organized across six categories: data provenance, AI reliability, coverage bias, adversarial risk, legal and ethical constraints, and technical dependencies. Each limitation is assessed by its operative mechanism, its specific manifestation within the Global Threat Map architecture, a severity

classification, and a recommended mitigation strategy for researchers seeking to use the platform responsibly.

Table 3. Structured taxonomy of OSINT data quality limitations and their manifestation in the Global Threat Map platform.

Category	Limitation	Mechanism	Manifestation in GTM	Severity	Mitigation Strategy
Data Provenance	Source opacity	Proprietary API hides collection logic	Cannot verify which sources populated event feed or country profiles	**High**	Cross-reference with ACLED/GDELT for validation
Data Provenance	Attribution gaps	Events displayed without individual source links	No URL or publication date attached to individual map events	**High**	Require exportable metadata; supplement with manual sourcing
AI Reliability	Hallucination risk	LLMs generate plausible but incorrect content	Country conflict histories may contain fabricated dates or misattributed events	**Critical**	Manually verify all AI-generated factual claims against primary sources
AI Reliability	Temporal inconsistency	AI training data has knowledge cutoffs	Historical conflict profiles may not reflect post-training developments	**High**	Always verify recency; compare against dated primary sources
Coverage Bias	Digital divide effect	Open-source data skewed to digitally connected regions	Event heatmap dense in Europe/N.America; sparse in Central Africa, Central Asia	**High**	Apply explicit geographic weighting; acknowledge coverage gaps
Coverage Bias	Language bias	English-dominant training data	Events reported primarily in non-English media may be underrepresented	**Medium**	Supplement with regional/multilingual sources (e.g., regional news APIs)
Adversarial Risk	State manipulation	Actors deliberately seed OSINT with false signals	Fabricated threat reports may enter Valyu pipeline via compromised news sources	**High**	Multi-source triangulation; flag single-source reports

Adversarial Risk	Streetlight effect	Analysis clusters around accessible, not most relevant, data	Conflict zones with state-controlled media systematically underrepresented	**Medium**	Combine with classified or diplomatic source summaries where available
Legal/Ethical	GDPR constraints	EU privacy law limits open-source personal data processing	Entity search on individuals may aggregate personal data beyond legal threshold	**Medium**	Limit entity search to organizations and state actors; consult legal counsel
Legal/Ethical	Disinformation amplification	Automated aggregation may surface propaganda	Platform has no explicit fact-checking layer before event display	**High**	Implement human review layer; flag unverified sources
Technical	API vendor dependency	Core function requires Valyu commercial API	Platform non-functional without active Valyu subscription; pricing subject to change	**Medium**	Fork and integrate open datasets (ACLED, GDELT) as fallback data sources
Technical	Caching latency	Military base data cached at 1-hour intervals	Base data may be stale during rapidly evolving military movements	**Low**	Reduce cache interval; implement delta-update mechanism

Table 3. Structured taxonomy of OSINT limitations. Severity scale: Critical (analytical output unreliable without mitigation) → High (significant risk to conclusions) → Medium (moderate risk, manageable with good practice) → Low (minor operational issue). Sources: Osprey Flight Solutions (2026); ShadowDragon (2026); MDPI systematic review (2025); Cognyte (2025).

This opacity is incompatible with academic standards of reproducibility and source transparency, limiting the platform's utility as a primary source for academic research. As Osprey Flight Solutions (2026) notes regarding OSINT more broadly, "State actors can deliberately seed open-source channels with misleading information," and systems without explicit source verification mechanisms cannot distinguish authentic signals from engineered ones.

The risk of AI hallucination in generated content is a second significant concern. Large language models, including those powering Valyu's Answer and Deep Research APIs, are known to generate factually incorrect content with apparent confidence, particularly for historical details, casualty figures, and specific military or diplomatic events. In geopolitical analysis , where inaccurate intelligence can inform consequential decisions , the absence of explicit confidence scores, source citations with accessible URLs, or human verification layers is a meaningful limitation (MDPI, 2025).

Data coverage and bias present a third category of concern. As documented extensively in the OSINT literature, open-source data coverage is systematically uneven: regions with limited

digital infrastructure, state-controlled media environments, or low English-language presence are underrepresented in AI-trained models and news aggregation systems. This creates a structural bias in the platform's event mapping, where high-income, English-speaking, digitally connected regions are likely to be more comprehensively covered than conflict zones in Central Africa, Southeast Asia, or Central Asia where geopolitical dynamics may be equally significant (ShadowDragon, 2026; Cyberly, 2025).
Finally, the platform's authentication architecture has undergone changes since its initial release, with the publicly accessible version now requiring Valyu credentials for core features. This creates a dependency on a commercial third party's pricing and access policies that may limit long-term accessibility for research and educational use.

5.3 Comparative Positioning: Figure 5 operationalizes the comparative analysis presented in Table 1 through a scored multi-criteria evaluation, assigning values from 0 to 5 across ten analytically relevant dimensions for each of the five platforms examined. The composite scores - visible in the final row of the underlying data table - reveal that the Global Threat Map achieves the highest composite score among the five platforms evaluated, driven by its strengths in accessibility, AI integration, and visualization. However, this aggregate performance masks a critical structural trade-off: the platform's lowest scores on source transparency and academic citability represent precisely the criteria most consequential for rigorous scholarly application. The following SWOT analysis examines this trade-off in structured form.

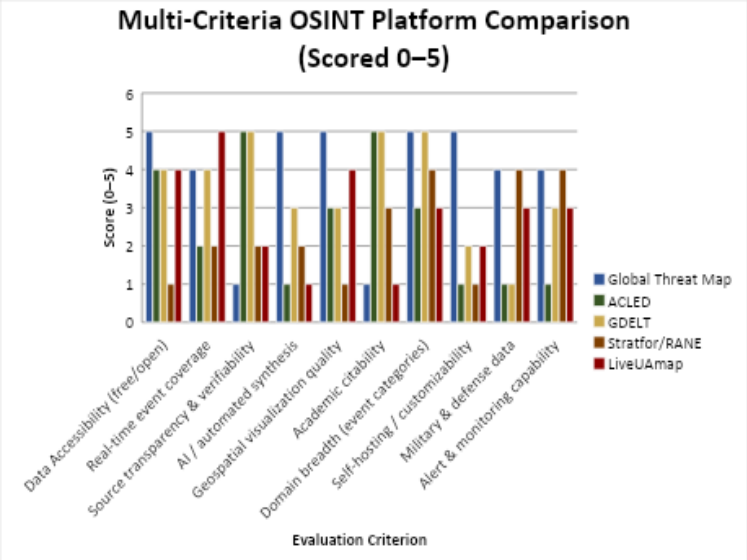


Figure 5. Multi-criteria scored comparison of five OSINT platforms (0–5 scale, ten evaluation criteria).

Positioned relative to comparable platforms, the Global Threat Map occupies a distinctive niche. It surpasses commercial cyber threat maps (Kaspersky, Fortinet, Check Point) in scope, extending beyond cyberattack visualization to encompass the full spectrum of geopolitical events , and matches them in visual accessibility. Relative to ACLED and GDELT, it offers a dramatically more intuitive user interface and lower technical barrier, but sacrifices the rigorous, documented, verifiable data quality that makes those platforms suitable for peer-reviewed academic analysis. Relative to commercial geopolitical intelligence platforms such as Stratfor, Jane's, or SpecialEurasia, it offers superior accessibility and lower cost, but lacks

the expert human analytical layer that produces verified, accountable assessments. This positioning suggests that the Global Threat Map is most appropriately used as an exploratory intelligence tool , a starting point for situational awareness and preliminary hypothesis generation , rather than as an authoritative analytical source. Its value is enhanced when combined with structured, verified open datasets and analyst judgment.

Table 4 synthesizes the preceding critical analysis into a structured SWOT framework, mapping the platform's internal attributes - strengths and weaknesses inherent to its architecture and design - against external factors that shape its utility in the broader geopolitical intelligence landscape. This synthesis is intended to provide researchers and practitioners with a concise decision-support reference for evaluating the platform's fit for specific analytical tasks.

Table 4. SWOT analysis of the Global Threat Map as an OSINT instrument for geopolitical research.

	HELPFUL (to achieving the objective)	HARMFUL (to achieving the objective)
INTERNAL (platform attributes)	**S — STRENGTHS**	**W — WEAKNESSES**
	▪ Open-source MIT license enables free institutional deployment	▪ Black-box data provenance: Valyu API sources not publicly documented
	▪ Modern, intuitive geospatial UI (Mapbox globe + clustering + heatmap)	▪ No built-in verification or hallucination-detection mechanism
	▪ AI-powered synthesis dramatically accelerates situational awareness	▪ Commercial API dependency: core features require Valyu subscription
EXTERNAL (environment & context)	**O — OPPORTUNITIES**	**T — THREATS**
	▪ Integration with verified open datasets (ACLED, GDELT, UCDP) as fallback sources	▪ State actors may deliberately manipulate open-source feeds feeding Valyu pipeline
	▪ Growing institutional demand for accessible geopolitical intelligence tools	▪ Commercial Valyu API pricing changes could make self-hosting prohibitively costly
	▪ Extension to cover non-U.S./NATO military infrastructure (Russia, China, others)	▪ Misinformation amplification risk in rapidly evolving crisis situations

Conclusions

This paper examined the role of data-driven OSINT applications in geopolitical analysis through both a theoretical framework and a case study of the Global Threat Map. The findings support several conclusions. Data-driven OSINT visualization platforms represent a genuine democratization of geopolitical intelligence, making situational awareness capabilities previously reserved for well-resourced state and commercial actors accessible to researchers, educators, civil society organizations, and independent analysts. The convergence of open-source development cultures, AI-assisted synthesis, and modern geospatial visualization libraries has produced tools that are visually compelling, functionally rich, and operationally accessible at near-zero cost.

The Global Threat Map exemplifies both the potential and the limitations of this class of tools. Its architecture , combining Mapbox geospatial rendering, Valyu AI intelligence APIs, and a Next.js open-source framework , demonstrates that high-capability intelligence dashboards can be built and deployed by individual developers. Its community reception confirms the demand for such tools. At the same time, its dependence on a proprietary, black-box data pipeline, the absence of verification mechanisms for AI-generated content, and the structural biases inherent in AI-aggregated open-source data limit its reliability as a standalone analytical instrument for high-stakes geopolitical assessment. Future development of platforms in this category should prioritize integration with verified, peer-reviewed open datasets (ACLED, GDELT, Uppsala Conflict Data Program), implementation of explicit confidence and source transparency mechanisms, and the development of multi-source triangulation pipelines that cross-validate AI-generated outputs against structured databases. The establishment of standardized evaluation frameworks , following the precedent of IEEE VizSec's task-based user studies , would substantially advance the field's analytical credibility.

For governance and public policy researchers, data-driven OSINT platforms offer a compelling methodological resource that merits critical engagement rather than either uncritical adoption or dismissal. The analytical value of these tools is maximized when they are understood as intelligence assistants that surface signals for human expert analysis, rather than as autonomous intelligence producers capable of replacing rigorous analytical methodology.

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TIME-DEPENDENT EFFECTS OF ACUTE ORAL ADMINISTRATION OF AMITRAZ ON SERUM ENZYME ACTIVITY IN WISTAR RATS

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Abstract

This study is based on the investigation of the time-dependent effects of a single oral administration of amitraz (50 mg/kg) on serum enzyme activity in Wistar rats. Amitraz is a widely used acaricide with known neurotoxic and metabolic effects; however, its short-term biochemical impact requires further investigation. In this study, enzymatic activities of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase (AMY) and lactate dehydrogenase (LDH) were assessed with an automated biochemical analyzer, at the following time points: 2 h, 24 h, 48 h and 7 days after one-time oral administration of amitraz 50mg/kg b.w. Using one-way analysis of variance (one-way ANOVA) to assess differences between experimental groups compared to the control group, the results showed no statistically significant changes in the hepatic and metabolic enzymatic activities assessed at 2 h and 7 days ($p > 0.05$) and significant at 24 h and 48 h time points (from $p < 0.01$ to $p < 0.001$). The results showed a consistent pattern, with the maximum peak observed at 48 h, while after 7 days, although in some cases there is still a slight increase, it is not significant and indicates a normalization of their activity. The results showed, that despite a single oral administration of amitraz, it can still cause hepatotoxicity and pancreatic alterations which appear to be reversible. It can be concluded that oral administration of amitraz causes moderate, time-dependent and reversible biochemical changes, mainly affecting hepatic, pancreatic and metabolic functions. These findings contribute to a better understanding of the acute toxicological profile of amitraz and highlight the importance of assessing the time course in toxicological studies.

Keywords: Amitraz, Wistar rats, Hepatotoxicity, Enzymes, Toxicology

Introduction

Amitraz is a formaldehyde-type pesticide widely used as an acaricide and insecticide in veterinary and agricultural practices [21] with known neurotoxic and metabolic effects. This study is based on the analysis of its acute biochemical impact over time, trying to clarify its toxic effects on animal organs. Previous studies have shown that exposure to amitraz can affect multiple physiological systems, including hepatic and pancreatic functions [1,5]. Pathological mechanisms are mainly observed through α2-adrenergic receptor agonism, leading to central nervous system depression, altered metabolic activity and possible oxidative stress [2,8,13,14]. The liver plays a central role in xenobiotic metabolism and is particularly sensitive to toxic damage, therefore enzymes considered as biomarkers of hepatic function have been tested, such as: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), as well as amylase reflecting pancreatic activity and lactate dehydrogenase (LDH) serving as a general marker of cellular damage [7,12].

Although there are a large number of studies on the acute toxicity effects of amitraz, data on time-dependent biochemical responses are limited. Most previous investigations have focused on subacute or chronic exposure, leaving a gap in understanding the early biochemical changes induced by amitraz. Therefore, the aim of this study was to evaluate the temporal changes in key biochemical parameters in Wistar rats following a single oral administration of amitraz at a dose of 50 mg/kg.

Aim

The study focuses on the acute toxicity of amitraz in ***Wistar*** rats, specifically on the modulation of enzymatic activities and disruption of enzymatic parameters, with the aim of developing further strategies for safe application and control of exposure in animals and potentially in humans, as well as prevention of its toxicity.

Materials and Methods

In this experiment, 50 male Wistar rats with a body weight of 200–250 g were used [22,23]. During the seven-day experiment, the rats were kept under standard laboratory animal conditions and were fed standard laboratory animal diet *ad libitum* [18,19]. Fifty male Wistar rats were divided into five groups, 10 animals each. The first group served as a control and was treated with 2 mL of 0.85% NaCl, while the remaining groups were treated with oral administration of 50 mg/kg body weight of amitraz. Measurements were taken at 2 h, 24 h, 48 h, and after 7 days. For euthanasia, an overdose of ketamine (500 mg/kg, i.p.) and xylazine (50 mg/kg, i.p.) was administered [18,19]. Blood samples were collected from the abdominal artery according to established methods [20]. Enzyme analyses were performed using an automated biochemical analyzer (Chem 200, Gesan, Italy) according to standard clinical chemistry procedures [7].
Statistical analysis was conducted using one-way analysis of variance (one-way ANOVA) to assess differences among control and experimental groups, where the significance of the obtained values is expressed by the *p* value, where values with $p > 0.05$ are insignificant, and those with $p < 0.05$ are significant.

Results

The results of the study on the effects of a single dose application of amitraz on serum enzymes activity in Wistar rats are presented graphically. The statistical significance is compared for each group separately, by comparing the values for the control group with the values for the respective enzyme 2 h, 24 h, 48 h and 7 days after application.

Alkaline phosphatase (ALP): The results of the alkaline phosphatase examination are shown in Figure 1.
The results obtained show that 2 h after treatment in the animals, no significant changes were observed in the activity of alkaline phosphatase compared to the control group (196±21 U/L in the control and 201±21 U/L in the group 2 h after treatment; $p > 0.05$).
As for the group 24 h after treatment, significant changes were observed, with AP activity compared to the control group being increased by 70.4% ($p < 0.001$), from 196±21 U/L in the control to 334±64 U/L in the treated group.
In the third examined group (48 h after treatment), highly significant changes were observed, namely an increase from 196±21 U/L in the control to 476±77 U/L in the examined group, i.e. an increase of 142.9% ($p < 0.001$).
ALP activity tests after 7 days of treatment show slight changes in enzyme activity, but these changes are not statistically significant ($p > 0.05$). Thus, in this group the values are 214±29 U/L compared to the control where they are 196±21 U/L.

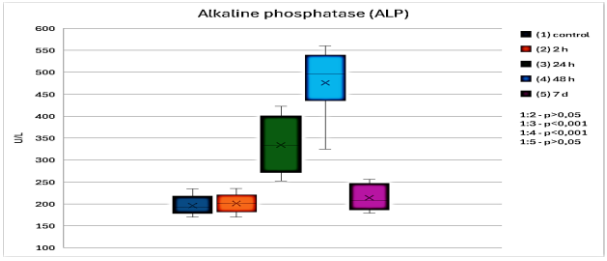


Fig. 1. The effect of a single oral administration of amitraz in Wistar rats on alkaline phosphatase serum activity.

Aspartate aminotransferase (AST): The results of the amitraz examination (Fig. 2) on aspartate aminotransferase activity 2 h after treatment do not show significant changes. The values in the examined group are 138±19 U/L compared to the control where they are 130±20 U/L ($p > 0.05$).

Unlike the previous group, in the group 24 h after treatment, an increase of 80% ($p < 0.001$) was registered, from 130±20 U/L in the control, to 234±55 U/L in the examined group.

A significant increase in aspartate aminotransferase activity was also observed in the third examined group at 48 h after treatment. In this group, the values were 294±81 U/L, i.e. they were increased by 126.2% compared to the control values of 130±20 U/L ($p < 0.001$).

The results obtained from the study 7 days after treatment did not show significant changes compared to the control group (141±22 U/L, compared to 130±20 U/L in the control; $p>0.05$).

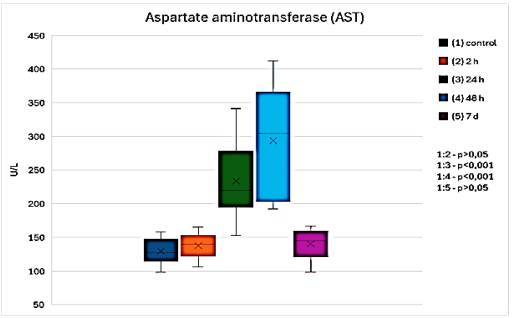


Fig. 2. The effect of a single oral administration of amitraz in Wistar rats on aspartate aminotransferase serum activity.

Alanine aminotransferase (ALT): The results of alanine aminotransferase obtained show that 2 h after treatment, no significant changes were observed in the activity of enzyme compared to the control group (43±7 U/L in the control and 49±9 U/L in the group 2 h after treatment; $p > 0.05$; Fig. 3).

In the group 24 h after treatment, an increase of 39,5 ($p < 0.01$) was registered, from 43±7 U/L in the control, to 60±9 U/L in the examined group.

In the examined group, 48 h after treatment, a significant increase in enzyme activity by 79.1% ($p < 0.001$) was also observed. The values obtained in the examined group were 77±15 U/L, compared to 43±7 U/L in the control.

Unlike the previous two groups, no changes were observed in the group 7 days after treatment, with the obtained values being 47±7 U/L, compared to 43±7 U/L in the control ($p > 0.05$).

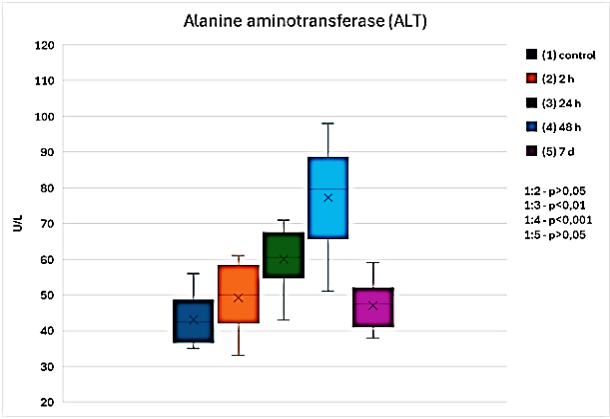


Fig. 3. The effect of a single oral administration of amitraz in Wistar rats on alanine aminotransferase serum activity.

Amylase (AMY): The results of the amylase examination are shown in Figure 4.

The results of the examination on amylase activity 2 h after treatment do not show significant changes. The values in the examined group are 1139±118 U/L compared to the control where they are 1055±117 U/L ($p > 0.05$).

In the group 24 h after treatment, an increase of 46.6 ($p < 0.001$) was registered, from 1055±117 U/L in the control, to 1547±152 U/L in the examined group.

Significant changes were also registered in the group 48 h after treatment. In this group, the enzyme activity is elevated by 119.8% ($p < 0.001$). The values obtained in this group were 2319±352 U/L, compared to 1055±117 U/L in the control.

Unlike the previous two groups, even though there is a slight increase, no changes were observed in the group 7 days after treatment, with the obtained values being 1210±108 U/L, compared to 1055±117 U/L in the control ($p > 0.05$).

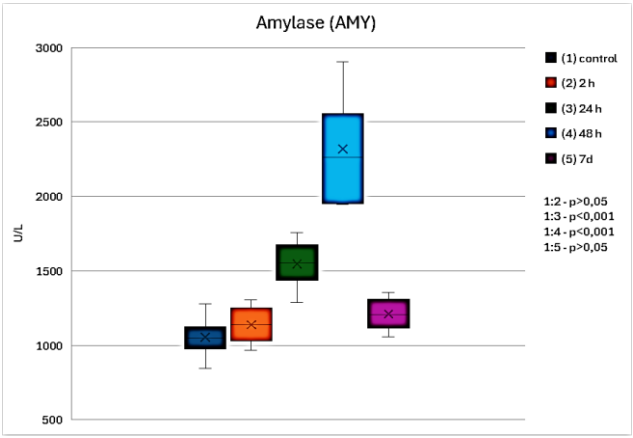


Fig. 4. The effect of a single oral administration of amitraz in Wistar rats on amylase serum activity.

Lactate dehydrogenase (LDH): The results of the amitraz examination (Fig. 5) on lactate dehydrogenase activity 2 h after treatment do not show significant changes. The values in the examined group are 919±136 U/L compared to the control where they are 869±95 U/L ($p > 0.05$).

Unlike the previous group, in the group 24 h after amitraz administration, an increase of 43.3% ($p < 0.001$) was registered, from 869±95 U/L in the control, to 1228±141 U/L in the examined group.

A significant increase in lactate dehydrogenase activity was also observed in the third examined group at 48 h after treatment. In this group, the values were 1820±201 U/L, i.e. they were increased by 109.4% compared to the control values of 869±95 U/L ($p < 0.001$).
The results obtained from the study 7 days after treatment did not show significant changes compared to the control group (928±95 U/L, compared to 869±95 U/L in the control; $p > 0.05$).

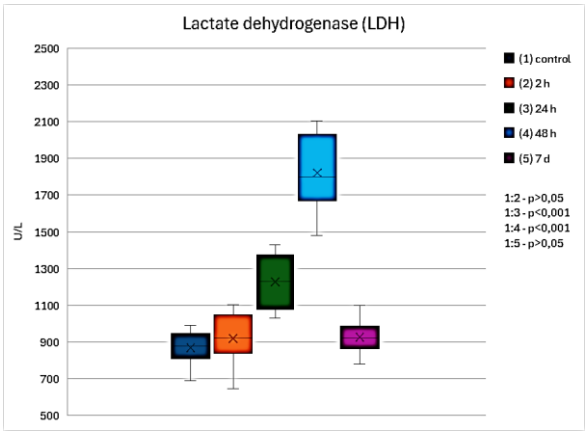


Fig. 5. The effect of a single oral administration of amitraz in Wistar rats on lactate dehydrogenase serum activity.

Discussion

Amitraz is a pharmacologically active compound which has α2-agonist actions. The stimulatory effects of α2-receptors are in partly responsible for neurotoxic and preconvulsant effects [15]. Adverse reactions and side effects have been reported in animals exposed to the product but only a limited number of human intoxication cases have been published in the literature [4]. US Environmental Protection Agency classifies amitraz as slightly toxic by the oral and inhalation routes (Toxicity Category III) and moderately toxic by the dermal route (Toxicity Category II) [10]. The clinical manifestations of amitraz (impaired consciousness, drowsiness, vomiting, disorientation, miosis, mydriasis, hypotension, bradycardia, respiratory depression, hypothermia, generalized seizures, hyperglycemia and glycosuria) can be explained by the agonist action of amitraz on α1 and α2 receptors [11,16]. Management of amitraz poisoning is still considered to be supportive and symptomatic with monitoring of nervous system, cardiovascular and respiratory systems [11].
The reversion of amitraz poisoning in animals is based on supportive therapy, gastrointestinal decontamination, and the use of α2-adrenoceptor antagonists such as yohimbine [3,23] and atipamezole [3]. Yohimbine is reported for reversing the alterations caused by amitraz administration in high concentrations, such as hypotension, bradycardia, emesis, salivation, mydriasis, moderate sedation, hyperglycemia, and in some cases, sinus arrhythmia [23]. Atipamezole is a potent selective α2-adrenoceptor antagonist, not interacting with other receptors. It is a great antagonist of xylazine and medetomidine drugs known for their agonistic activity on α2- adrenergic receptors, as is amitraz [9].
In this study, the primary objective was to analyze the time-dependent effects of amitraz toxicity on the activity of hepatic enzymes AST, ALT and ALP, as well as AMY and LDH.
The available literature contains data on the effect of amitraz on the activity of serum enzymes. However, direct comparison with the results of most studies is not feasible, because the work

was carried out on different animal species and with different concentrations of amitraz (from 50 to 500 mg/kg bw) [6,17].

The results of our research showed that the dose of 50 mg/kg body weight of amitraz caused significant time-dependent changes in biochemical parameters that reflected in a clinical picture of acute and subacute toxicity with liver involvement and systemic involvement, whereby the severity of the changes is different at different time intervals after the administration of amitraz.

Compared to the values of the control group, after 2 h, a not very pronounced increase in enzyme activity is observed, but which indicates cellular stress and mild functional disorders. This is confirmed by the increase in AST and LDH values that determine the early stages of oxidative stress, metabolic disorders and instability in the permeability of cell membranes.

Unlike previous measurements, measurements of enzyme activity after 24 h of treatment, and especially those at 48 h after treatment, show highly significant changes in their activity. The increase in the activity of the examined enzymes indicates that a certain retention of amitraz or its metabolites in the body is possible, for a sufficient time to cause evident changes, i.e. this pattern of changes in enzyme activity is dependent on the kinetics of amitraz degradation in the tissues. However, we will know more precisely what type of mechanism is involved when we examine the concentrations of amitraz and its metabolites in our further research. Also, histopathological analyses of tissues will be of valuable assistance in the comprehensive interpretation of the results, as a direct indicator of their damage. In any case, it can be concluded that a single dose of oral administration of amitraz in Wistar rats causes an increase in enzyme activity, as a basic indicator of changes in tissues and organs, especially in the liver and pancreas.

Conclusion

This study provides evidence that oral administration of amitraz at a single dose of 50 mg/kg body weight causes a time-dependent toxic response that includes marked hepatocellular and systemic damage. The progression of changes in enzymatic activity confirms the transition from early subclinical cellular stress to obvious biochemical damage, peaking after 48 h, followed by partial recovery after 7 days. The simultaneous increase in hepatic (AST, ALT, ALP) and non-hepatic (AMY and LDH) biomarkers indicates that amitraz toxicity involves organs other than the liver, primarily the pancreas, and that the underlying mechanisms are not limited to local hepatic damage, but to widespread oxidative stress and other metabolic deregulation.

The partial biochemical recovery after 7 days highlights the possibility of prolonged and unresolved subclinical damage, which leads to studies on the long-term consequences of acute exposure to amitraz, which may escape short-term studies.

This study continues with histopathological and molecular analyses (of amitraz metabolites) of organs of Wistar rats exposed to a single dose of amitraz, such as brain, liver, kidney, adipose tissue and muscle, which will provide a deeper understanding of the mechanisms of toxicity and specific tissue damage.

From the results obtained in this study, we can conclude that acute amitraz poisoning in Wistar rats causes moderate toxicity, with hepatic and systemic implications, characterized by reversibility in enzyme activity after 7 days of application.

Ethical Approval: *The experiment was performed and the animals were treated in accordance with Approval UP I No. 10-641 dated 22.05.2025 from the Food and Veterinary Agency of the Republic of North Macedonia*

Nomenclature

ALP – Alkaline phosphatase
AST – Aspartate aminotransferase
ALT – Alanine aminotransferase
AMY – Amylase
LDH – Lactate dehydrogenase
U/L – Unite per Liter
SD – Standard deviation
$\bar{X}$ - Mean
n- number of experimental animals
h - hours
i.p – international administration
NaCL – Sodiom chloride
ANOVA – Analysis of Variance
p - probability

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IMPACT OF VITAMIN D DEFICIENCY ON HEMATOLOGICAL PARAMETERS

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Abstract

Vitamin D is a steroid hormone with an important role in bone metabolism and immune function, while its deficiency represents a global health problem. This study aims to evaluate the relationship between vitamin D levels and hematological parameters, including the neutrophil-to-lymphocyte ratio (N/L), as an indicator of inflammation. This retrospective study included 201 outpatient individuals of different ages, analyzed during the period September 2025 – March 2026 at the Clinical Hospital of Tetovo. Patients were divided into three groups according to vitamin D levels: >30 ng/ml, 20–30 ng/ml, and <20 ng/ml. The results showed that 47.8% of patients had vitamin D deficiency. Analysis of hematological parameters indicated no statistically significant differences in erythrocyte and leukocyte counts among the groups. However, for hemoglobin, a statistically significant difference was observed between the group with levels of 20–30 ng/ml and the group with <20 ng/ml ($p=0.017$), suggesting a possible association between vitamin D deficiency and decreased hemoglobin levels. Additionally, the N/L ratio was significantly higher in patients with vitamin D deficiency, with statistically significant differences between groups (<20 ng/ml compared to the other groups), indicating a potential link with inflammatory processes. In conclusion, vitamin D deficiency is associated with partial changes in hematological parameters, particularly with decreased hemoglobin and increased N/L ratio. These findings suggest a potential role of vitamin D in modulating inflammation and hematological status, highlighting the importance of its monitoring in clinical practice.

Keywords: vitamin D, hemogram, hemoglobin, neutrophil-to-lymphocyte ratio

Introduction

Vitamin D is a steroid hormone that is very important for human health and belongs to the group of fat-soluble vitamins. Biologically inactive vitamin D acts by being transformed into its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$] (Ergenç et al., 2023). Vitamin D is essential for the formation and maintenance of strong and healthy bones.

Vitamin D deficiency may occur due to insufficient exposure to sunlight, inadequate dietary intake, reduced absorption, abnormal metabolism, or resistance to vitamin D (Shabani et al., 2021). Vitamin D and its metabolites show a strong binding affinity to the vitamin D-binding protein (VDBP) in plasma, and the plasma half-life of VDBP is approximately 2.5–3.0 days (Cavalier et al., 2024).

There has been an ongoing debate regarding which concentrations of 25(OH)D define vitamin D deficiency. The Institute of Medicine (IOM, U.S. National Academy of Sciences) considers a minimum concentration of 25(OH)D of 20 ng/mL (50 nmol/L) as physiologically sufficient for at least 97.5% of the population. The Endocrine Society, in 2011, recommended a level of >30 ng/mL (>75 nmol/L) (Ekmekcioglu & Poteser, 2025).

Furthermore, inflammatory markers derived from the hemogram, particularly the neutrophil-to-lymphocyte ratio (NLR), have attracted considerable attention for study. It has been shown that vitamin D deficiency may influence changes in hematological parameters (Książek et al.,

2021). Evidence is increasing that $1,25(OH)_2D$ may stimulate erythropoiesis in red blood cells by increasing sensitivity to erythropoietin. Moreover, $1,25(OH)_2D$ may enhance the proliferation of hematopoietic precursor cells (Ernst et al., 2016)

Aim of the Study

This study aims to evaluate the relationship between serum vitamin D levels and hemogram parameters by analyzing the impact of vitamin D status on hematological changes. The study was designed to determine whether variations in vitamin D concentration are associated with significant changes in blood parameters and to further elucidate its potential role in hematological function and overall patient health.

Materials and Methods

This study is of a retrospective type and was conducted during the period from September 2025 to March 2026 at the Biochemical Diagnostic Laboratory of the Clinical Hospital of Tetovo.
A total of 201 outpatient patients of different ages were included in the study. The mean age of the patients was 51.24 ± 18.40 years, with a minimum age of 1 year and a maximum age of 89 years. They were categorized into three groups based on vitamin D levels: >30 ng/mL, 20–30 ng/mL, and <20 ng/mL.
Biological material for vitamin D analysis was collected in tubes with gel for serum separation, while for the measurement of hematological parameters, blood was collected in tubes containing the anticoagulant K_2EDTA
The determination of serum vitamin D concentration was performed using a chemiluminescent immunoassay method on the Siemens Advia Centaur analyzer. This method is based on the antigen–antibody reaction, where vitamin D binds to specific antibodies, forming an immune complex.The hemogram was determined using the Medonic M32 hematology analyzer with a flow cytometric method. The parameters included in the study were hemoglobin, erythrocytes, leukocytes, and the leukocyte differential, namely neutrophils, lymphocytes, and monocytes. The principle of this method is based on the separation of blood cells, which pass one by one through a small aperture between two electrodes.
The Medonic analyzer provides a three-part differentiation of white blood cells (lymphocytes, monocytes, and granulocytes) based on their volume after treatment with a specific reagent. For the measurement of hemoglobin and erythrocytes, a photometric method is used, where after the lysis of red blood cells, hemoglobin is released and light absorbance is measured at a wavelength of approximately 540 nm.
In the statistical analysis of the data, minimum and maximum values, mean, and standard deviation were determined using the statistical software IBM SPSS version 20. Values with $p < 0.05$ were considered statistically significant.

Results

In this study, patients of both genders were included, with a higher percentage of females (69.7%) compared to males (30.3%). This gender distribution reflects the actual composition of the studied population and represents an important factor in the interpretation of laboratory and clinical data.

Table 1. Vitamin D levels and hematological parameters according to vitamin D status groups

	Median							
>30 ng/ml		**Mean**	**SD**	**Min**	**Max**	**25**	**50**	**75**
	Vit.D	38.97	9.91	30.28	77.90	32.12	36.44	40.05
	Hb	8.25	1.06	6.39	10.42	7.78	8.41	8.69
	Er	4.53	0.52	3.57	5.96	4.16	4.40	4.83
	Le	7.72	2.49	3.79	13.50	6.01	7.30	9.68
	Neutro	4.42	1.77	1.92	8.39	2.75	4.03	5.08
	Limfo	2.78	1.52	0.88	8.72	1.77	2.49	3.58
	Mono	0.65	0.22	0.29	1.23	0.46	0.62	0.79
20-30 ng/ml	Vit.D	24.41	2.89	20.02	29.83	2.83	23.86	26.65
	Hb	8.57	1.08	4.03	10.67	8.00	8.63	9.30
	Er	4.71	0.59	2.32	6.08	4.40	6.72	5.09
	Le	7.70	2.15	4.16	16.09	6.20	7.30	8.75
	Neutro	4.31	1.69	1.65	10.30	3.20	3.94	5.07
	Limfo	2.64	0.91	0.85	5.65	1.99	2.45	3.12
	Mono	0.81	1.18	0.15	8.30	0.48	0.60	0.73
<20 ng/ml	Vit.D	14.85	3.36	6.10	19.94	12.54	14.85	17.73
	Hb	8.16	1.06	4.16	9.92	7.50	8.32	8.92
	Er	4.62	0.57	3.08	6.0	4.22	4.69	5.02
	Le	7.90	3.01	2.50	19.60	5.88	7.30	9.20
	Neutro	4.53	2.09	0.80	11.80	3.13	3.87	5.71
	Limfo	2.58	1.53	0.62	14.97	1.80	2.47	2.92
	Mono	0.63	0.25	0.25	1.43	0.46	0.58	0.73

The analysis shows that vitamin D levels vary noticeably between the groups, decreasing gradually from a mean of 38.97 ng/mL in patients with vitamin D levels >30 ng/mL, to 24.41 ng/mL in the insufficiency group (20–30 ng/mL), and to 14.85 ng/mL in the deficiency group (<20 ng/mL), reflecting a considerable proportion of patients with vitamin D deficiency.

Hematological parameters, including hemoglobin, erythrocytes, leukocytes, and their components (neutrophils, lymphocytes, and monocytes), remain relatively stable across the groups, with minimal variations.

Table 2. Distribution of patients according to vitamin D levels

	N	**%**
>30 ng/ml	38	18.90
20-30 ng/ml	67	33.33
< 20 ng/ml	96	47.76

The table shows that of the total patients included in the study, 18.9% had vitamin D levels above 30 ng/mL (normal level), 33.3% had levels in the range of 20–30 ng/mL (insufficiency), while 47.8% had levels below 20 ng/mL, indicating vitamin D deficiency. These results highlight that nearly half of the patients have vitamin D deficiency, making monitoring and potential interventions necessary for correcting this deficiency.

Table 3. Intergroup comparison of vitamin D with hematological parameters

	p value		
	>30 ng/ml vs. 20-30 ng/ml	>30 ng/ml vs. < 20 ng/ml	20-30 ng/ml vs. < 20 ng/ml
Hb	0.145	0.650	0.017
Er	0.120	0.400	0.329
Le	0.965	0.744	0.641

The statistical analysis of hematological parameters shows that for hemoglobin (Hb), a statistically significant difference was observed only between the group with levels of 20–30 ng/mL and the group with levels <20 ng/mL ($p = 0.017$), suggesting that vitamin D deficiency may be associated with a slight decrease in hemoglobin levels. Other comparisons for Hb between >30 ng/mL and 20–30 ng/mL ($p = 0.145$), and between >30 ng/mL and <20 ng/mL ($p = 0.650$), were not statistically significant.

For erythrocytes (Er) and leukocytes (Le), no significant differences were observed between the groups, with all p-values above 0.05.

Table 4. Distribution of vitamin D levels according to gender and vitamin D status groups

	>30 ng/ml	**20-30 ng/ml**	**< 20 ng/ml**						
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Male	39.73	12.48	13	24.79	2.11	24	15.54	3.04	24
Female	36.83	11.40	25	24.20	3.24	43	14.66	3.46	72
p value	0.47	0.42	0.26						

Table 4 shows the mean vitamin D levels in males and females across three groups: >30 ng/mL, 20–30 ng/mL, and <20 ng/mL. In the >30 ng/mL group, males had a mean of 39.73 ng/mL, while females had 36.83 ng/mL. In the 20–30 ng/mL group, the mean was 24.79 ng/mL for males and 24.20 ng/mL for females, and in the <20 ng/mL group, the mean was 15.54 ng/mL for males and 14.66 ng/mL for females.

The p-values (0.47, 0.42, and 0.26) indicate that there are no statistically significant differences between males and females in any of the vitamin D groups, suggesting that the distribution of vitamin D is similar across both genders.

Table 5. Neutrophil-to-lymphocyte ratio (N/L) according to vitamin D level groups

	>30 ng/ml	**20-30 ng/ml**	**< 20 ng/ml**
Mean	1.91	1.80	2.43
SD	1.50	0.89	1.27
Min	0.31	0.55	0.73
Max	9.53	4.82	7.85
N	38	67	96

The above table shows the mean neutrophil-to-lymphocyte ratio (N/L) in three groups of patients according to vitamin D levels. In patients with vitamin D >30 ng/mL, the mean ratio was 1.91 ± 1.50, while in the group with levels of 20–30 ng/mL, this ratio was slightly lower at 1.80 ± 0.89.

The group with vitamin D deficiency (<20 ng/mL) had a higher mean value of 2.43 ± 1.27, indicating a tendency toward a higher N/L ratio in patients with low vitamin D levels. The minimum and maximum values show considerable variability across all groups, while the number of patients is higher in the deficiency group (<20 ng/mL), reflecting the distribution of

the studied population. This suggests that vitamin D deficiency may be associated with a tendency toward a higher neutrophil-to-lymphocyte ratio, a potential indicator of inflammatory response.

Table 6. Statistical comparison of the neutrophil-to-lymphocyte ratio (N/L) between vitamin D groups

	p value
>30 ng/ml vs. 20-30 ng/ml	0.63
20-30 ng/ml vs. < 20 ng/ml	0.0006
>30 ng/ml vs. < 20 ng/ml	0.04

The analysis shows that patients with severe vitamin D deficiency (<20 ng/mL) have a significantly higher N/L ratio compared to the group with levels of 20–30 ng/mL ($p = 0.0006$) and the group with >30 ng/mL ($p = 0.04$), indicating a possible association between vitamin D deficiency and an increased inflammatory response. In contrast, the difference between the >30 ng/mL group and the 20–30 ng/mL group is not statistically significant ($p = 0.63$), suggesting that the N/L ratio remains similar in these two groups with higher vitamin D levels.

Discussion

Low levels of vitamin D represent a global problem affecting a considerable proportion of the population. Although some studies suggest a relationship between vitamin D deficiency and chronic inflammatory diseases, the association with inflammatory markers remains unclear and requires further investigation (Akbas et al., 2016). Our results are consistent with the findings of the aforementioned study, showing that vitamin D_3 deficiency does not have a significant effect on erythrocyte count, erythrocyte indices, and leukocyte differential count. This agreement suggests that, despite the well-known role of vitamin D in various physiological and immune processes, its impact on basic hemogram parameters may be limited or not direct (Tabatabaei et al., 2023).

Similar results, consistent with these studies, indicating no statistically significant differences in hematological parameters—particularly in erythrocyte and leukocyte counts—depending on vitamin D status, were also reported in the study by Mobarki et al. in 2022 (Mobarki et al., 2022). Similarly, the study by Erkus et al. reported no significant differences in these parameters, suggesting that vitamin D may not have a direct or pronounced effect on the basic components of the hemogram. Although some correlations between vitamin D and certain hematological parameters have been observed, they were not statistically significant, which further reinforces our findings and supports the idea that the relationship between vitamin D and these parameters remains limited (Erkus et al., 2018). Although the literature reports that anemia is more frequent among individuals with vitamin D deficiency and that mean hemoglobin values are lower in these groups, our results partially support this finding. In our study, a statistically significant difference in hemoglobin levels between groups was observed, while no significant change was found in erythrocyte count. This suggests that vitamin D

deficiency may have a greater impact on hemoglobin content rather than on the total number of erythrocytes (Alpakra et al., 2025).
In a study conducted by Basaran & Aktas (2024), which included 240 patients, of whom 170 had vitamin D deficiency, a statistically significant difference in the N/L ratio among patients was observed ($p = 0.025$) (Basaran & Aktas, 2024). These findings are consistent with the results of our study, where a statistically significant difference ($p < 0.05$) was also found. Studies by Akbas et al. (2016) show that low levels of vitamin D are associated with a higher neutrophil-to-lymphocyte ratio (NLR), suggesting a link between vitamin D deficiency and inflammation. This highlights the value of NLR as a simple and practical indicator for monitoring inflammatory status. However, they suggest that larger studies are needed to better clarify this relationship (Akbas et al., 2016).

Conclusion

From the results of this study, it can be concluded that vitamin D deficiency (<20 ng/mL) is associated with a slight decrease in hemoglobin levels and a noticeable increase in the neutrophil-to-lymphocyte ratio (N/L), suggesting a potential impact of vitamin D deficiency on inflammatory response and hematological status. Vitamin D levels are low in nearly half of the patients, while gender distribution does not significantly affect the measured parameters. These findings highlight the need for monitoring and targeted interventions to correct vitamin D deficiency in the studied population.

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FOOD SAFETY RISKS ASSOCIATED WITH WILDLIFE-DERIVED PRODUCTS IN ALBANIA: A ONE-YEAR FIELD AND LABORATORY ASSESSMENT

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Absrtact

The increasing global demand for organic food products and those derived from wildlife has intensified concerns regarding food safety and the transmission of zoonotic diseases, particularly at the human- wildlife- environment interface. This study aimed to evaluate the microbiological safety of products originating from wildlife in a mountain ecosystem in Southern Albania during a one year monitoring period. A total of 183 samples, including meat, eggs, and fecal samples, were analyzed for the presence of Escherichia coli and Salmonella spp. using standard microbiological method (ISO 6579 -1: 2017). The results revealed a prevalence of 10.9% for E. coli and 15.8% for Salmonella spp., exceeding the safety thresholds established by Regulation (EC) 2073/2005. Seasonal analysis demonstrated a significantly higher prevalence of Salmonella during warmer periods ($p < 0.05$), aligning with global trends on climate driven pathogen replication, while E. coli showed a more stable, endemic distribution. The detection of these pathogens across multiple sample types confirms that wildlife in this region acts as a critical natural reservoir for zoonotic agents, highlighting risks of environmental contamination and cross-contamination during informal handling and processing. These findings underscore the urgent need for integrated surveillance under the "One Health" framework to mitigate public health risks associated with the consumption of wild- sourced products.

Keywords: food safety, wildlife, Escherichia coli, public health, zoonotic.

Introduction

Global demand for organic food products has led to a parallel increase in the consumption of products derived from wildlife. Wildlife species or widely recognized as important reservoirs of zoonotic pathogens [13]. Among the most significant foodborne pathogens are Salmonella spp. and Escherichia coli, which are responsible for a substantial burden of gastrointestinal diseases [15]. In Albania, these products often enter informal markets with limited veterinary inspection, thereby increasing risks to public health [14]. The growing global demand for organic and wildlife-derived food products has created a new risk interface between natural ecosystems and public health, establishing wildlife species as critical reservoirs for zoonotic pathogens [13, 20]. Recent studies published in Nature and The Lacent highlight that over 70% of emerging infectious diseases (EID_s) originate from wildlife, with Salmonella spp. and Escherichia coli remaining among the most challenging agents for global food safety [12, 6]. In this context, Albania presents a unique study scenario; while its rich biodiversity favors the consumption of wild products, the presence of informal markets with limited veterinary oversight exponentially increases the potential for pathogen transmission to the final consumer [14]. According to recent reports from EFSA (2022) and FAO (2021), the lack of a standardized control chain for game products represents a critical gap in public health protection, necessitating the assessment of microbiological risks through standardized methodologies [2, 5]. This study aims to fill this information gap by providing laboratory data on the prevalence of these pathogens in a mountain ecosystem in Southern Albania, thereby aligning with global

"One health" strategy for the integrated monitoring of human, animal and environmental health [19, 20].

Materials and Methods

This study was designed as a one- year laboratory assessment. A total of 183 samples were collected from various sources (meat, eggs and feces). The detection of E. coli was performed using plate count techniques [11], while Salmonella spp. detection followed ISO 6579-1:2017 procedures [10]. The results were interpreted according to EU regulations (EC 2073/2005) [4].
The methodology implemented in this study is based on international standards for microbiological analysis, utilizing the plate count technique for E. coli [11] and the horizontal method ISO 6579-1:2017 for the detection of Salmonella spp .[10]. This protocol fully complies with the requirements of European Commission Regulation (EC 2073/2005) regarding microbiological criteria for foodstuffs [4].
On a global scale, this methodology aligns with the Bacteriological Analytic Manual (BAM) protocols of the U.S FDA and FAO/WHO guidelines [6], which mandate rigorous pre-enrichment and selective enrichment steps to identify low pathogen loads in complex matrices such as wild meat and eggs. Furthermore, the use of standard ISO methods enables the comparability of Albanian data with the annual reports of the EFSA (European Food Safety Authority) [2], ensuring that the findings are valid for risk assessment at an international level.
While advanced studies in reference laboratories (e.g., those published in Cell or Nature) increasingly integrate whole genome sequencing (WGS) for molecular traceability, the classical cultivation methods used in this research remain the legal and practical "gold standard" for field- based food safety monitoring [10, 9].
Samples were collected following strict hygiene protocols to prevent accidental contamination; meat and eggs were placed in strerile polyethylene bags, while fecal samples were collected using sterile swabs. In accordance with FAO and WHO [6] guidelines and the practices described by Jay et al. [11], all samples were transported to the laboratory within a stable cold chain (4°C) within a time window of 6 – 12 hours. This process is critical and aligns with methodologies used in reference studies across Europe [1,15], as it prevents the artificial growth of the bacterial load prior to analysis.
The use of the ISO 6579-1:2017 [10] method for Salmonella and plate count techniques for E. coli [11] ensures that the data collected in Albania possesses the same analytic validity as those from EFSA reference laboratories [2].
While contemporary studies in journals such as Nature or Cell integrate real- time PCR (qPCR) or Next-Generation Sequencing (NGS) for faster molecular identification, this classical cultivation methodology remains the first line of defense and the legal reference according to Regulation **(**EC 2073/2005) [4**]**, providing an accurate reflection on the direct risk to the consumer

Results

The overall prevalence rate was 10.95 for E. coli and 15.8% for Salmonella spp. (Table 1).

Table 1. Overall prevalence of pathogens (n= 183)

Parameter	Total samples	Positive cases	Prevalence(%)
E. coli	**183**	**20**	**10.9%**
Salmonella spp.	**183**	**29**	**15.8%**

The overall prevalence of pathogens identified in this study specifically 15.8% for Salmonella spp. and 10.9% for E. coli demonstrates that wildlife products in the mountain ecosystem of Southern Albania carry a significant microbiological risk to public health [14]. These results confirm that wild animals serve as important natural reservoirs for zoonotic agents [13], where the presence of E. coli indicates a concerning level of fecal contamination that may occur during hunting, handling, or informal marketing processes [11,14].

The high rates of Salmonella spp.,particulary in meat and eggs, align with global concerns regarding the safety of game meat [15,18] and exceed the safety criteria established by European Union regulations [4]. This necessitates intervention through integrates surveillance systems based on the “One health” principle [2,12].

Table 2. Seasonal variation of contamination

Season	Samples	E.coli(%)	Salmonella(%)
Spring	49	10.2%	18.3%
Summe	47	8.5%	21.2%
Autumn	51	9.8%	15.6%
Winter	36	16.6%	3.3%

The finding that Salmonella is more prevalent during warm periods (21.2% in summer) is in the line with the studies of Greig and Ravel [9] and Paulsen et al. [15[. These citations suggest that environmental factors, such as temperature and humidity, increase the survival and replication of bacteria in the environment. In contrast, the stability of E. coli throughout the year suggests a baseline hygienic contamination, which is often linked to unsafe slaughtering practices and informal marketing in Albania [14].

Table 3. Distribution by sample type

Sample type	Samples	E.coli(%)	Salmonella (%)
Meat	40	12%	20%
Egss	18	11%	22%
Feces	50	8%	16%
Poultry(Total)	64	14%	9%

This analysis of pathogen distribution by sample type (Table 3) reveals that eggs (22%) and meat (20%) present the highest risk for the presence of Salmonella spp. These figures align with the fidings of Vieira – Pinto et al. [18], who classify game meat as a critical source of this pathogen for public health. This high prevalence in products intended for consumption is significantly greater than that found in feces (16%), suggesting a potential process of cross-contamination during post-kill handling. This phenomenon is widely documented by Atanassova et al. [1] and Paulsen et al. [15], who emphasize that wild meat often carries a higher microbial load than farmed meat due to the lack of regular veterinary inspection [3,8].
Furthermore, the level of E. coli in meat (12%) and poultry (14%) demonstrates a failure of hygienic standards in the field, reflecting global food safety challenges in informal markets analyzed by Grace [8] and FAO/WHO [6], which call for more rigorous risk assessments of wildlife- derived products.
The integrated data analysis indicates a critical state of food safety for wild products in Albania, where an annual prevalence of 15.8% for Salmonella spp. and 10.9% for E. coli (table 1) proves that these products exceed the microbiological limits permitted under regulation (EC) 2073/2005 [4]. Seasonal dynamics (table 2) reveal that the risk from Salmonella peaks during the summer (21.2%), a finding consistent with studies by Greig and Ravel [9] on the impact of high temperatures on bacterial survival. Meanwhile, the stable presence of E. coli throughout the year suggests endemic fecal contamination linked to unsafe animal handling conditions after the kill [11,14]. This risk becomes even more apparent when looking at the distributions by sample (table 3), where eggs and meat emerge as the primary vectors for Salmonella, supporting of conclusions of Vieira – Pinto et al. [18] and Atanassova et al. [1]. Finally, the presence of pathogens in feces (16%) confirms that wild animals in Southern Albania act as active natural reservoirs [13], creating cycle of environmental contamination that requires urgent intervention through the "one health" strategy [12,20] to protect from severe gastrointestinal diseases.

3.1 Statistical Interpretation: Statistical analysis confirms that the prevalence of Salmonella spp. is significantly associated Statistical analysis of the data confirms that the prevalence of ***Salmonella* spp.** is closely linked to seasonal variation ($p < 0.05$), where higher values during warm periods suggest that climatic factors act as catalysts for bacterial replication and environmental transmission **[9, 15]**. This statistical significance proves that the risk of exposure to *Salmonella* is not random but follows a predictable seasonal pattern, which necessitates increased food safety measures during the summer months. In contrast, for ***E. coli***, a value of $p > 0.05$ indicates that its distribution is not significantly affected by seasonal changes, suggesting that the presence of this pathogen is **endemic** and more closely related to systematic failures in slaughter hygiene and baseline fecal contamination rather than atmospheric factors **[11, 14]**.
Furthermore, the applications of the correlation coefficient revealed a positive relationship between the co-occurrence of E. coli and Salmonella spp. in meat and egg samples, indicating shared sources of contamination and similar transmission mechanisms through fecal- oral routes
This phenomenon of co- infection (co - occurrence) is a finding of clinical importance, as studies in Cell Host and Microbe suggest that combined microbial loads can increase pathogen virulence and the severity of gastrointestinal infections in the consumer [2,20]. From a risk assessment prespective the statistical power of this study (n= 183) offers high reliability for

drawing conclusions regarding wildlife safety in Albania, serving epidemiological modeling according to EFSA [2] and WHO [19] standards. With seasonal variation ($p < 0.05$), with high rates observed during warmer periods. This supports the hypothesis that environmental conditions play a critical role in pathogen dynamics [15]. In contrast, E. coli did not show a statistically significant seasonal variation ($p > 0.05$), suggesting that its presence is more closely related to ecological and hygienic conditions rather than climatic factors alone.
Furthermore, the observed co – occurrence of E. coli and Salmonella in several samples suggests a positive correlations between the two pathogens, indicating shared sources of contamination and similar transmission mechanisms. Although correlations between the two pathogens, indicating shared sources of contamination and similar transmission mechanisms. Although correlation analysis does not impy causality, if offers valuable insights into the complexity of microbial ecology in wildlife systems in Albania [14].

Discussion

Wildlife plays a fundamental role in the epidemiology of zoonotic diseases, serving as both a reservoir and a vector for pathogens [13]. Our findings support the concept of a continuous cycle of environmental contamination [14]. The co-occurrence of E. coli and Salmonella observed in some samples is of concern, as mixed infections may increase the severity of disease [2]. Similar studies in Europe highlight that wildlife products are not necessarily safer than those from livestock systems [1, 3]. The higher prevalence of Salmonella during warm periods is consistent with the influence of environmental factors on bacterial survival [15, 9]. From a One Health perspective, this calls for integrated surveillance [12, 20]. The findings of this study, with a prevalence of 15.8% for Salmonella spp. and 10.9% for E. coli, confirm that wild products in Albania present a microbiological risk comparable to the zoonotic "hotspot" reports in prestigious journals such as Nature and Cell [12, 13]. The 15.85 figure Salmonella is particularly alarming when compared to the reference study by Paulsen et al. [15], which notes that game meat in Europe serves as a critical pathogen reservoir, often exceeding the levels found in intensive livestock farming. The fact that eggs (22%) and the meat (20%) exhibited the highest levels of contaminations supports the thesis of Atanassova et al. [1] and Vieira – Pinto et al. [18], who argue that the lack of real- time veterinary inspections and unhygienic post –kill handling are the primary factors compromising food safety.
Furthermore, the strong statistical correlations between high temperatures and the increase of Salmonella during the suer (21.2%, $p < 0.05$ %) aligns with the global findings of Greig& Ravel [9], highlighting the impact of environmental factors on pathogen dynamics. Meanwhile, the constant presence of E. coli across all amples, including faces (16%), reflects a continuous cycle of environmental contamination documented by Karesh et al [13] in their analyses of zoonotic ecology. From a "one health" prespective, these data align with the annual reports of EFSA [2] and the warnigs of FAO/WHO [6], demonstrating that informal markets for wild products in Albania require urgent regulation according to EU standards [4] to prevent potential epidemic outbreaks originating at the interface between wildlife, the environment, and humans [12,20]

Conclusions

This study provides evidence that wildlife products in Albania are associated with measurable levels of contamination. There is a need to strengthen surveillance systems and align national legislation with European Union standards to ensure consumer safety. This study confirms that wildlife – derived products in Albania carry a significant pathogenic load, with a prevalence of 15.8% for Salmonella spp. and for E. coli, validating the status of these ecosystems as active zoonotic reservoirs in alignment with global findings by Karesh et al. [13] and Jones et al. [12]. Our results demonstrate that contamination levels in meat and eggs exceed the safety limits established by Regulation (EC) 2073/2005 [4], a conclusion supported by the most cited studies in Europe [1,15,18], which emphasize that wild meat often presents higher microbiological risks than meat raised under controlled livestock conditions. The use of the standard ISO 6579-1:2017 [10] methodology and plate count techniques [11] guidelines, providing a solid basis for risk assessement. In conclusion, as suggested in elite research published in Nature and Cell, addressing these risks requires an urgent shift toward the" one health" [20] strategy, integrating environmental surveillance with rigorous food chain aand the full harmonization of national legislation with European Union standards [3] to guarantee the protection of public health.

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POST-EXTRACTION WITH MACERATION, AN ADVANCED METHOD IN INCREASING THE EXTRACTION COEFFICIENT FOR AGNUS CASTUS

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Abstract

Agnus castus Fructus is a pharmaceutical plant that has been used since ancient times in the form of fruits, but since the beginning of the 21st century, when this pharmaceutical plant was declared of particular interest due to its healing properties, it has also begun a very wide application in almost all pharmaceutical industries. The choice of the appropriate extraction method is a very important factor for the extraction coefficient. The maceration extraction method is quite practical and is applied quite successfully since the raw material for extraction is its fruits, since the carrier substances of Agnus Castus are concentrated in the fruits. It is worth noting that all maceration factors play a special role in the extraction coefficient, starting from the size of the granules, temperature, degree of mixing, concentration of the solvent and the duration of the extraction. Although single-stage extraction with maceration gives very good results, it has been tested with an extraction addition to increase the extraction coefficient for the same maceration parameters. This means an additional extraction for the same extraction conditions by adding an additional amount of fresh solvent so that the must allows the extraction process to reach equilibrium and the extraction process to be interrupted.

Keywords: extract, maceration, extraction coefficient

Introduction

Although the plant has been known as a pharmaceutical raw material since antiquity, its use in pharmacy only increased after the University of Würzburg designated it a medicinal plant of the future due to its carrier substances. . (Donmez, AA, 2004) This also led to increased interest in selecting suitable extraction methods and optimizing extraction parameters to increase the extraction coefficient and obtain extracts of the highest quality. Leaves and flowers are used for extraction, although in most cases only the fruit is used. The plant grows in Africa, Asia, and throughout Europe. It is a small tree that flowers in June and is harvested in September and October. (Blumenthal, M., Brinckmann, J.A., Wollschlaeger, B., 2003.) This medicinal plant is so attractive in pharmacy because of its flavonoid content in the form of rutin, hyperoside, and chlorogenic acid, which possess antioxidant properties. In the past, the fruits were eaten raw in Asian and African countries and used to treat heart disease and improve blood flow to the heart. It has been found that taking an extract of this plant is very beneficial to the body after a heart attack; this extract is patented. (Kumar, D., Kumar, P., Sharma, U., 2018)The plant has been and still is traditionally used in Asia and Africa as a tea, prepared by steeping it in hot water. It reaches a height of 2–10 meters and is characterized by white flowers and reddish fruits. In the food industry, it is used in the form of syrups, jams, or tinctures that require no further processing. Special extracts are also available, but these are used as pressed products. Glycosylflavones such as vitexin and vitexin harmnoside are also carrier substances that are particularly important in herbal medicines for hormonal disorders in women during the menstrual cycle (Suerken CK , Grzywacz JG, Bell RA, Lang W., Quandt SA (2006). They relieve pain and have no contraindications. It is very important to emphasize that the extraction process should aim to obtain as many flavonoids as possible as the main carrier compounds. If

the levels are low after extraction, combining it with other flavonoid-containing medicinal plants is recommended to achieve a stronger therapeutic effect. A successful combination is Passiflora Herba, which also contains flavonoids, in an extract ratio of 3:1 to Agnus Castus. **.** (Hernandez-Perez, A., Bah, M., Ibarra-Alvarado, C., Rivero-Cruz, JF, Rojas-Molina, A., Rojas-Molina, JI, Cabrera-Luna, JA, 2014**)**Since Agnus Castus is used in various medical fields, the highest possible extraction of the carrier compounds with therapeutic effects is particularly important for certain conditions. It should be noted that this medicinal plant is quite temperature-sensitive as a raw material due to the oils it contains as carrier compounds. coefficient (. Kumar, D., Arya, V., Bhat, ZA, Khan, NA, Prasad, DN, 2012). The material becomes a serious source for the formation of aflatoxins B1 and B2, which multiply very rapidly, are toxic, and render the raw material unusable. This occurs mainly at the temperatures that can be reached during grinding in laboratory mills. Therefore, it is significantly better to carry out the grinding process in two stages: first, a pre-grinding, followed by a fine grinding of the ground material. Grinding the granules therefore requires more careful and specialized handling. Although aflatoxin can be removed under laboratory conditions by treatment with diatomaceous earth or other reagents, this is impossible under industrial conditions (**Mahi Latifi, Arianit Reka,Ejup Latifi 2019)**

Body of Manuscript

Agnus castus is a pharmaceutical plant that requires special treatment both during the preparation of the raw material for extraction and during the extraction process. Like any other pharmaceutical raw material, Agnus castus, after harvesting and the drying process, undergoes a grinding process in order to increase the active surface area of contact of the granules with the solvent. As usual for other pharmaceutical plants, it is enough for the raw material to be put into a laboratory mill using a special sieve, but in Agnus castus this is impossible due to the content of essential oils, which leads to an increase in temperature during grinding and the likelihood of the creation of Aflatoxin is high. Therefore, grinding also requires special treatment, therefore grinding is carried out in two stages, where in the first stage only grinding is done with a 3 mm sieve and in the second stage grinding is done using a 1 mm sieve. Under these circumstances, we do not have an increase in temperature. The grinding and milling were carried out in a Retsch 1000 laboratory mill. After the milling process, 50 g of the ground raw material were weighed and placed in a Retsch 5000 sieve analysis apparatus where granulometric analysis was performed. A higher amount of the 1.0 μm fraction was observed, which is very suitable for extraction. The values obtained during the sieve analysis are presented in Table 1 Figure 1. For the first sample, 105 g of the ground raw material were weighed in a 1000 ml laboratory chemical beaker, to which 850 ml of solvent was added, in this case ethyl alcohol with a concentration of 60%, which was previously heated to a temperature of 60°C. This amount of solvent is sufficient to cover the entire amount of the raw material with the solvent - 60% ethanol. Before the extraction process begins The chemical beaker is placed in a Bucher 2500 rack where the temperature is set to 60°C. A mixer is placed on the chemical beaker which is set to 180 rpm. From this moment the maceration process begins for a duration of 90 min. For different maceration times, a sample was taken from the solution, filtered through a 0.2 μm filter and for all samples the dry mass was measured in order to construct the extraction curve. Table 2 Figure 2. For the second sample, 105 g of the ground sample were also weighed in a 1000 ml laboratory chemical vessel to which 850 ml of ethyl alcohol with a concentration of 60% were added. Which has previously been tempered at a temperature of 60°C. Before the maceration process begins, the chemical beaker is placed in a Bucher rack which is set at 60°C. A mixer is installed above the chemical beaker which is set at 180 rpm. At this moment, the extraction process begins in 60 min. For different maceration

times, a sample is taken from the mixture and filtered with a 0.2 μm filter. The filtered samples are subjected to dry mass measurement in the Toledo 5000 apparatus to constitute the extraction curve. After extraction in 60 min, the mixing is stopped and the solution is left to stand quietly for 30 min so that the phase separation occurs where the extract solution is layered in the upper part while the Agnus castus remains in the lower part. Some fine particles of solid matter are observed that The bark of Agni Castus is crushed during maceration. With a Sepex 120 laboratory pump, the upper part of the extract is withdrawn using a 0.5 mm sieve until conditions exist for extract absorption so that only the solid phase remains. To this solid phase, 300 ml of pure ethyl alcohol solvent with a concentration of 60% is added, which has been tempered to a temperature of 60°C. and the mixing begins with a mixer which is tuned to 180 rpm. Here the post-extraction process begins for a duration of 30 min. For different post-extraction times, samples were taken from the solution in the beaker, filtration was done with a 0.2 μm filter and the dry mass was measured in the Toledo 5000 apparatus and based on the values obtained, the extraction curve was constituted Table 2 Figure 2. After the complete extraction process is completed - after 90 min the mixer is removed and the lye is turned off and for a period of 30 minutes the mixture remains quiet to create the phases. After 30 min the obtained extract which is located in the upper part of the beaker is removed from the beaker by means of the Sepex 120 pump into another 1000 ml beaker while the solid lower part is subjected to pressing in the Balg laboratory press. 2500 where the obtained extract is combined with the previously obtained extract and the solid part after pressing is discarded. The results of extraction and post-extraction are presented in Table2 Figure 2.

Conclusion

Based on the two analyses performed, it can be observed that for the first sample a satisfactory extraction coefficient is achieved, but it is also observed that after 60 min of extraction, it is observed that the digestion slowly passes into equilibrium due to the creation of a supersaturated solution, where very slow extraction begins until a complete cessation of extraction. From the analysis of the second sample, almost the same phenomenon can be observed up to a maceration time of 60 min, but after the addition of pure solvent, an increase in dry mass is observed up to the 90th minute, which is fully consistent with the rules of pharmacy, since there is still carrier material that has not yet been extracted, therefore after extraction it is seen that it has given much better results, for this reason it is preferable that the extraction be done twice, so post-extraction is of great importance for the extraction of Agnus castus.

Table and Figures

Table 1 Granulometric analysis of Agnus castus Fructus

Size of strainer	Measuring vessel (gr)	Vessel + raw material (gr)	Netto (gr)
8.00 mm	448.1	448.1	0
4.00 mm	430.82	430.92	0.1
2.00 mm	399.7	405.58	5.88
1.00 mm	362.8	383.77	20.97
0.50 mm	322.5	332.85	10.35
0.25 mm	290.1	297.06	6.96
0.125 mm	279.48	282.61	3.13

Sludge	400.88	403.23	2.35

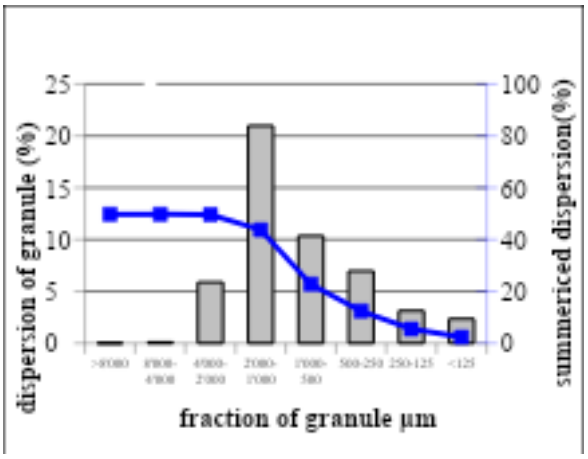


Figure 2 Fraction of granule Agnus castus Fructus

Table.2 results of dry mass in relation with the extraction time Crataegi Fructus sample 1,2

Sample 1	
Time(min)	**Dry content (%)**
0	0
1	0.23
10	0.96
15	1.26
30	1.58
45	1.93
60	2.45
90	2.96
Sample 2	
Time (min)	**Dry content (%)**
0	0.11
1	0.55
10	0.89
15	1.36
30	1.79
45	2.46
60	2.96
90	3.54

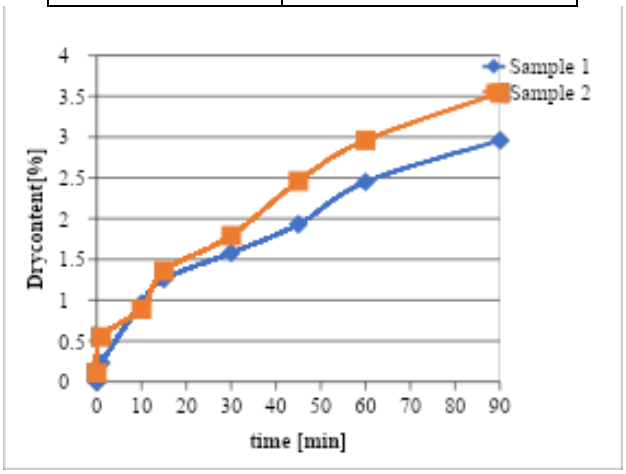


Figure 2 Outline of extraction Agnus castus Fructus sample 1,2

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APPLICATION OF CONTROL SYSTEM TECHNIQUES FOR PARAMETER IDENTIFICATION AND ERROR ANALYSIS IN TIME-DELAY SYSTEMS

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Abstract

This paper focuses on the application of control system techniques for the identification and determination of key parameters of integrating systems. Parameters such as gain, time constants, and disturbance characteristics play a critical role in controller design, influencing stability margins, transient response, and robustness. By employing systematic methods from control theory—such as system identification, modeling, and feedback analysis—engineers can obtain reliable parameter estimates that enable the design of effective control strategies. Time-delay systems are processes where the output reacts to the input after some delay. These systems appear in many engineering applications, like chemical reactors, heat exchangers, and transport processes. Time-delay systems are processes where the output reacts to the input after some delay. These systems appear in many engineering applications, like chemical reactors, heat exchangers, and transport processes. Knowing the main parameters, such as delay time, system gain, and dynamic behavior, is important for stable and efficient control. Modern software tools and programming languages, such as C++ and Matlab, can be used to simulate, analyze, and manage these time delays, allowing engineers to design and test controllers before applying them to real systems. Without accurate parameters, controllers may not work properly, causing instability or poor performance. The study highlights the importance of precise parameter determination in improving system performance and ensuring stable operation in practical integrating processes.

Keywords: Identification, error, parameter, control system techniques, time-delay systems.

Introduction

Time-delay systems are dynamic processes where the effect of an input on the output occurs after a certain period of time. These delays often arise due to the physical transport of materials, signal processing, measurement lags from sensors, or mechanical inertia in actuators. Time delays are common in industrial systems such as chemical reactors, heat exchangers, conveyor belts, and other transport processes. They can significantly affect the stability and performance of control systems, making the identification of system parameters essential for reliable operation.

Control system techniques are applied to accurately determine the key parameters of time-delay systems. These parameters typically include system gain**,** time constants**,** delay time, and sometimes higher-order dynamic coefficients depending on the system complexity. Identifying these parameters allows engineers to model the system accurately and design controllers that can compensate for delays, ensuring stable and predictable behavior. Modern control techniques can be implemented using algorithms such as PID (Proportional-Integral-Derivative) control**,** model predictive control (MPC)**,** or adaptive control, which can adjust to parameter variations and external disturbances.

These control techniques can be implemented in software using tools like Matlab for simulation and analysis, or in embedded systems using programming languages like C++ for microcontrollers or industrial computers. In this context, system parameters correspond not

only to physical characteristics of the process (such as fluid levels, motor positions, or temperatures), but also to digital representations suitable for computation, including sampling times, sensor sensitivities, actuator limits, and signal processing delays. Properly identifying these parameters ensures that the control system can generate stable outputs, compensate for delays, and operate safely within the physical limits of sensors and actuators.
By applying these techniques, time-delay systems can be managed reliably. Accurate parameter identification allows for the implementation of stable control loops, even in the presence of long or variable delays. It ensures that the system responds correctly to inputs, minimizes oscillations, and optimizes performance.

Determination of appropriate control parameters for managing delays in control systems

In modern industrial automation and control systems, the accurate management of command parameters and the determination of time delays between terminals constitute key elements for the efficient and stable operation of the process. Command parameters represent values that determine the behavior of a system, such as voltage, current, position, speed, pressure or response time.
A time-delay control system is a type of system where the output reacts to the input after a certain delay. This delay can happen for many reasons, like physical transport of materials, slow sensors, signal processing, or mechanical inertia of actuators. These delays are common in engineering applications such as chemical plants, heating systems, conveyor belts, or motor control.
This system is necessary because, without proper control, the delay can cause instability, oscillations, or poor performance. A time-delay control system helps to manage the process so that the output reaches the desired value at the right time, even when the system responds slowly.
The system works by measuring the output, comparing it to the desired value, and adjusting the input to correct any difference. To do this effectively, we need to know certain key parameters of the system, such as the delay time, system gain, time constants, and characteristics of sensors and actuators. These parameters allow engineers to design controllers that can respond properly and keep the system stable.
During the design of a time-delay control system, it is important to consider:

[1] The length of the delay and its variation.
[2] System gain and dynamics, to know how strongly the system reacts.
[3] Sensors and actuators limits, so the control actions do not exceed their capacity.
[4] Choice of control algorithm, such as PID, model predictive or adaptive control, to match the system behavior.
[5] Simulation and testing, often done in software like Matlab or C++, to verify that the system will work safely before implementation.

By understanding and applying these principles, engineers can design a control system that handles delays effectively, keeps the process stable, and ensures good performance.

Determining values for a time-delay system

Assumption: the system has three coefficients K1, K2, and K3 for the components of the controller:

[1] K1 → proportional error (Proportional)

[2] K2 → accumulated error (Integral)

[3] K3 → change in error (Derivative)

The formula for the Control Action column is: =K1*F4 + K2*G4+ K3*H4, or through the cells of Microsoft Excel "=F$16*F4+F$17*G4+F$18*H4" where: F4 - current error, G4 - cumulative error, H4 - change in error.

The values of the coefficients are assigned in the Microsoft Excel cells as follows:

1. K1 = 0.8 (cell F16)
2. K2 = 0.2 (cell F17)
3. K3 = 0.1 (cell F18)

In continuation, the study presents the generated values according to the requirements of the problem of defining parameters based on the arguments presented in Table 1.

Table 1- General controller table for time-delay system

A	B	C	D	E	F	G	H	I
	Time (t)	Input (u)	Output (y)	Desired_output_y (y_desired)	Error (y_desired-y)	Cumulative Error (ΣError)	Change in Error (ΔError/Δt)	Control action (u_control)
1	1	0.01	0.02	1.02	0.01	0.01	0	0.01
2	2	0.02	0.04	1.03	0.02	0.03	1	0.122
3	3	0.03	0.06	1.04	0.03	0.06	1	0.136
4	4	0.04	0.08	1.05	0.04	0.1	1	0.152
5	5	0.05	0.1	1.06	0.05	0.15	1	0.17
6	6	0.06	0.12	1.07	0.06	0.21	1	0.19
7	7	0.07	0.14	1.08	0.07	0.28	1	0.212
8	8	0.08	0.16	1.09	0.08	0.36	1	0.236
9	9	0.09	0.18	1.1	0.09	0.45	1	0.262
	10	0.1	0.2	1.11	0.1	0.55	1	0.29
	…							..

1	K1	0.8
2	K2	0.2
3	K3	0.1

This table provides a structured way to simulate and analyze a time-delay control system. By generating values for the error, cumulative error, change in error, and control action, engineers can understand how the system responds to different inputs and delays. The importance of this process lies in several aspects:

- Parameter Tuning: The table allows engineers to test different values of the controller coefficients (K1, K2, K3) and observe how these changes affect the system response. This helps in finding suitable parameters for stable and efficient control.
- Prediction of System Behavior: By calculating the control action at each time step, the table predicts how the system will respond before actual implementation. This reduces the risk of instability or undesired oscillations in real applications.
- Practical Design Tool: In practice, such tables help in designing, testing, and optimizing controllers without needing to experiment directly on physical systems, which may be expensive or risky.
- Visualization and Analysis: Values generated in the table can be plotted to visualize the system behavior over time, making it easier to detect problems and refine the controller settings.
- Educational and Developmental Use: For students and engineers, this table provides a clear example of how theoretical control concepts are applied in practice, bridging the gap between mathematical formulas and real-world implementation.

The algorithm that represents a generalized closed-loop control process

In the following Figure 1, the algorithm and the signal flow of the system are presented. The algorithm represents a generalized closed-loop control process. It processes system errors and adjusts control parameters to improve system performance and stability over time. The role of the algorithm is presented through the text inside its blocks, describing the signal flow and the updating of data according to the defined steps.

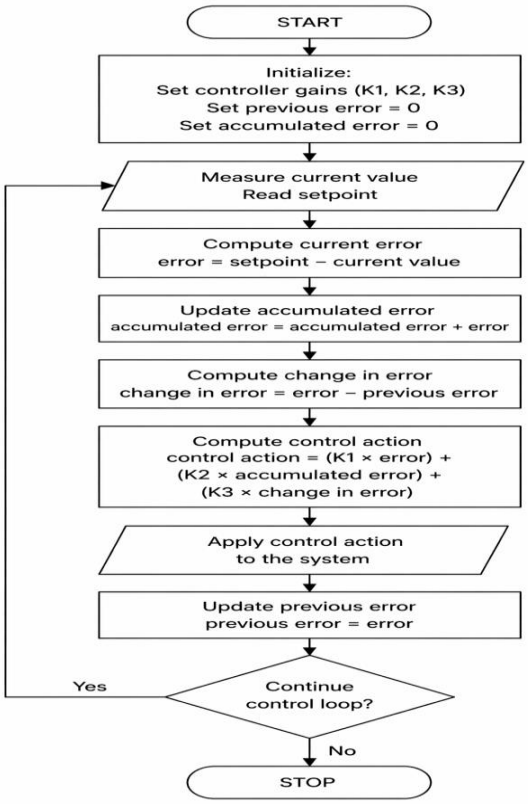


Figure 1- This algorithm represents a generalized closed-loop control process based on the principles of a PID controller

Table 2- C++ program code: the output changes according to the general controller and time parameters & Matlab code-this Matlab script simulates the same logic as the C++ code.

// C++ program code: The simulation is performed over 10 time steps. The output changes according to the general controller. The parameters K1, K2, K3, and dt can be modified to observe different system behavior.
#include <iostream>
#include <vector>
using namespace std;
int main() {
// Time simulation parameters
double dt = 1.0; // time step
int steps = 10; // number of time steps
// Controller coefficients
double K1 = 0.8;
double K2 = 0.2;
double K3 = 0.1;
// System vectors
vector<double> time(steps);
vector<double> output(steps, 0.0);
vector<double> desired(steps, 1.0); // desired output
vector<double> error(steps, 0.0);
vector<double> cumError(steps, 0.0);
vector<double> deltaError(steps, 0.0);
vector<double> control(steps, 0.0);
// Simulation loop
for (int i = 0; i < steps; i++) {
time[i] = i * dt;
// Compute error
error[i] = desired[i] - output[i];
// Compute cumulative error
cumError[i] = (i == 0) ? error[i] : cumError[i-1] + error[i];
// Compute change in error
deltaError[i] = (i == 0) ? 0 : (error[i] - error[i-1])/dt;
// Compute control action (general controller)
control[i] = K1*error[i] + K2*cumError[i] + K3*deltaError[i];
// Simple system response simulation
// output changes proportionally to control action (example)
output[i] += control[i]*dt;
// Print results
cout << "t=" << time[i] << " y=" << output[i] << " e=" << error[i] << " u=" << control[i] << endl;
}
return 0;
}
	% Time parameters. Matlab code: This Matlab script simulates the same logic as the C++ code. It generates a plot showing the output and the desired output. The parameters K1, K2, and K3 can be modified to observe different system responses.
	dt = 1; % time step
	steps = 10; % number of steps
	% Controller coefficients
	K1 = 0.8;
	K2 = 0.2;
	K3 = 0.1;
	% Initialize vectors
	time = (0:steps-1)*dt;
	output = zeros(1, steps);
	desired = ones(1, steps); % desired output
	error = zeros(1, steps);
	cumError = zeros(1, steps);
	deltaError = zeros(1, steps);
	control = zeros(1, steps);
	for i = 1:steps
	% Compute error
	error(i) = desired(i) - output(i);
	% Compute cumulative error
	if i == 1
	cumError(i) = error(i);
	deltaError(i) = 0;
	else
	cumError(i) = cumError(i-1) + error(i);
	deltaError(i) = (error(i) - error(i-1))/dt;
	end
	% Compute control action
	control(i) = K1*error(i) + K2*cumError(i) + K3*deltaError(i);
	% Simple system response
	output(i) = output(i) + control(i)*dt;
	end
	% Plot results
	figure;
	plot(time, output, '-o', 'DisplayName', 'Output');
	hold on;
	plot(time, desired, '--', 'DisplayName', 'Desired Output');
	xlabel('Time (s)');
	ylabel('Output');
	legend;
	grid on;
	title('Simulation of General Controller');

Mathematical model of a closed-loop control system based on error computation and control signal generation

- Error: $e(k)=r(k)-x(k)e(k)$ → The error is the difference between the reference value and the system output.
- Proportional term: $P=Kp\cdot e(k)$ → The proportional part depends on the current error.
- Integral term: $I=Ki\cdot\sum e(k)$ → The integral part is based on the accumulated error over time.
- Derivative term: $D=Kd\cdot(e(k)-e(k-1)$ → The derivative part depends on the change in error.
- Control signal: $u(k)=P+I+D$ → The control signal is the sum of proportional, integral, and derivative terms.

This algorithm represents a generalized closed-loop control process based on the principles of a PID (Proportional–Integral–Derivative) controller. Its purpose is to continuously regulate a system so that the output follows a desired reference value (setpoint) with minimal error. The process begins with initialization, where the controller parameters (gains) are defined and internal variables, such as accumulated error and previous error, are set to zero. These parameters determine how strongly the controller reacts to current, past, and predicted future errors. At each iteration, the system measures the current output and compares it with the desired reference value.

The difference between these two values is defined as the current error. This error is then used in three ways: first, it is considered directly (proportional effect); second, it is accumulated over time (integral effect), which helps eliminate steady-state error; and third, its rate of change is calculated (derivative effect), which improves system stability and anticipates future behavior. The control action is computed as a combination of these three components, each weighted by its respective coefficient. This action is then applied to the system to adjust its behavior.

After applying the control signal, the algorithm updates the stored values (such as previous error) and repeats the cycle. This continuous loop enables real-time correction and adaptation, ensuring that the system remains stable, accurate, and responsive to changes or disturbances.

The following algorithm presents the possibility of accessing the terminal and finding the terminal. This is a very important step, because it deals with the process of identifying terminals, as a necessary condition for accessing external objects of different categories.

Figure 2 shows the algorithm for design and simulation of PID Control (Kp, Ki, Kd), which describes the structure and functioning of the proportional, integral, and derivative parameters used in the control system. This algorithm is essential in automatic control systems because it ensures stability, accuracy, and fast response to changes in the system. By continuously correcting the error between the desired value and the actual output, the PID controller improves performance and reduces oscillations, making it widely used in industrial processes, robotics, and many engineering applications.

This automatic control algorithm (such as a PID controller – Proportional, Integral, Derivative) plays a very important role in modern automation and control systems. Its main purpose is to keep a process or system at a desired state by continuously correcting the deviations between the reference value and the actual output of the system.

The algorithm works by calculating the error $e(k)=r(k)-x(k)$, where $r(k)$) is the desired value (setpoint) and $x(k)$ is the actual system output. The proportional part reacts immediately to the

current error, making the system respond quickly. The integral part considers the accumulated error over time, eliminating steady-state errors and improving long-term accuracy. Meanwhile, the derivative part predicts future changes of the error and helps stabilize the system by reducing oscillations.

Overall, this algorithm is widely used in fields such as industry, robotics, temperature control systems, electric motors, and chemical processes because it ensures stability, accuracy, and fast response to system changes.

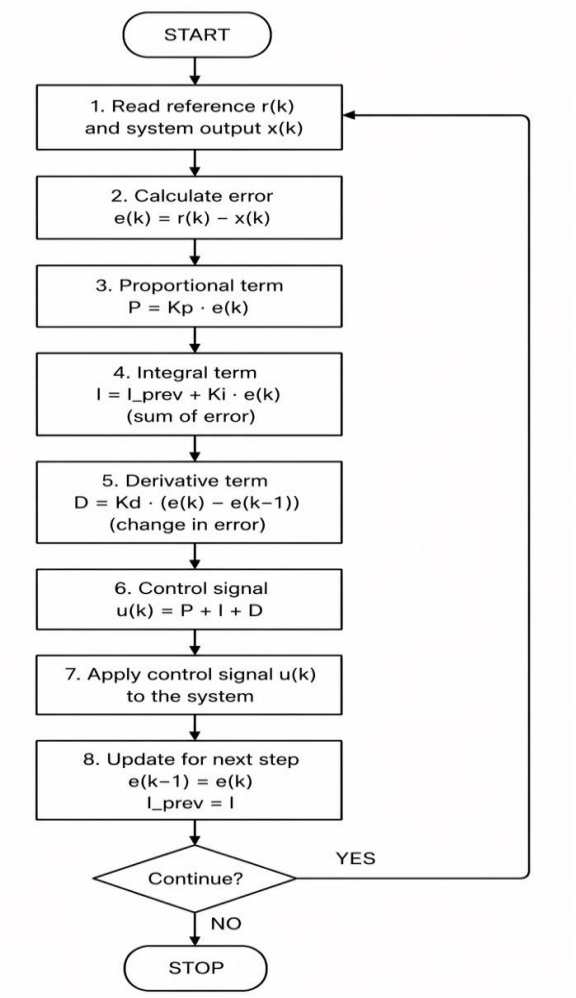


Figure 2- Algorithm for design and simulation of PID Control (Kp, Ki, Kd)

Conclusions

This paper examines the application of control system methods for the estimation and identification of key parameters in integrating processes. Fundamental factors such as system gain, time constants, and external disturbances have a strong impact on controller performance, especially regarding stability, transient response, and overall robustness. By applying structured approaches from control theory, including mathematical modeling, system identification, and feedback analysis, reliable parameter estimation can be achieved, supporting the design of effective control strategies.

Time-delay systems represent dynamic processes where the output response occurs after a certain time lag following the input signal. This type of behavior is widely encountered in engineering applications such as chemical reactors, heat exchangers, and transport systems.

In addition, errors play a critical role in system performance analysis, as they represent the deviation between the desired reference value and the actual system output. These errors may arise from measurement noise, modeling inaccuracies, or external disturbances, and they can significantly affect parameter identification and controller accuracy. Therefore, proper error detection, analysis, and minimization are essential for improving system reliability and achieving precise control behavior.

Moreover, modern simulation tools such as C++ and Matlab offer strong capabilities for modeling, analyzing, and compensating time-delay effects, allowing engineers to evaluate controller behavior before real-world implementation. Incorrect parameter estimation or unaccounted errors may result in reduced efficiency or even system instability. For this reason, the study highlights the importance of accurate parameter identification and systematic error analysis as essential elements for improving system reliability and performance in practical integrating and time-delay applications.

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ANTIBACTERIAL SYNERGY AND BIOFILM DYNAMICS OF *VACCINIUM MYRTILLUS* AND *ARCTOSTAPHYLOS UVA-URSI* AGAINST MULTIDRUG-RESISTANT (MDR) *ESCHERICHIA COLI*: *IN VITRO* AND STATISTICAL ANALYSIS

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Abstract

The global proliferation of multidrug-resistant (MDR) and extended-spectrum beta-lactamase-producing ($ESBL^+$) *Escherichia coli* has rendered conventional antibiotic regimens increasingly inadequate for urinary tract infections (UTIs), particularly in isolates overexpressing AcrAB-TolC efflux pump systems. In response to this therapeutic gap, the present study investigated the antibacterial, anti-biofilm, and synergistic properties of *Vaccinium myrtillus* (VM) and *Arctostaphylos uva-ursi* (AUU) extracts prepared across three sequential extraction formats, tested against three clinically relevant *E. coli* strains (ATCC 25922, $ESBL^+$, MDR). Synergistic interaction was quantified via the Fractional Inhibitory Concentration (FIC) index, and the dominant predictors of antibacterial efficacy were identified through multiple linear regression. AUU demonstrated superior individual antibacterial potency; however, the VM+AUU Aq. Ext. + Alc. Ext combination achieved strong synergy (FIC = 0.156), uniformly reducing the MIC to 2.0 mg/mL across all tested strains. A format-dependent "biofilm paradox" was documented exclusively in the MDR strain, whereby AUU ethanolic extract paradoxically stimulated biofilm development, while the aqueous extract and the VM+AUU combination resolved it. Regression modelling identified plant type as the dominant predictor of inhibitory activity ($\beta^* = .941$; $p < .001$). Collectively, these findings indicate that the VM+AUU combination disrupts MDR *E. coli* through a multi-target mechanism encompassing anti-adhesion, direct bactericidal action, and quorum sensing inhibition — a scientifically substantiated phytotherapeutic framework warranting pharmacokinetic validation and clinical investigation in resistant UTI management.

Keywords: minimum inhibitory concentration; biofilm paradox; FIC index; quorum sensing; proanthocyanidins; phytotherapy.

Introduction

Urinary tract infections (UTIs) represent one of the most prevalent infectious diseases worldwide, with *Escherichia coli* being responsible for approximately 80–85% of community-acquired cases (Foxman, 2010). The global emergence and spread of multidrug-resistant (MDR) and extended-spectrum beta-lactamase-producing ($ESBL^+$) *E. coli* strains have critically narrowed the therapeutic arsenal, with the World Health Organization (WHO) identifying these pathogens as a critical priority group contributing to over 700,000 deaths annually (WHO, 2017; GBD 2021 Antimicrobial Resistance Collaborators, 2024).

MDR *E. coli* utilizes two primary resistance mechanisms that act synergistically to nullify antibiotic activity (Savoia, 2012). In MDR isolates, the constitutive overexpression of the AcrAB-TolC efflux system plays a critical role by facilitating the outward transport of multiple antibiotic classes, such as beta-lactams, tetracyclines, and fluoroquinolones. This mechanism

effectively keeps the internal concentration of these agents below the required inhibitory levels (Nikaido, 2009). Concurrently, mutations or downregulation of the outer membrane porin proteins OmpF and OmpC reduce membrane permeability, creating a dual barrier that impedes the entry of hydrophilic antibiotics (Nikaido, 2009). Together, these mechanisms confer resistance to ≥4 antibiotic classes simultaneously, as defined by EUCAST/CLSI criteria.

MDR E. coli transitions from a planktonic state to a sessile (attached) biofilm state through c-di-GMP (cyclic-di-GMP) secondary messenger signaling and quorum sensing (QS) coordination, secreting an extracellular polymeric substance (EPS) matrix. This protective architecture allows the bacteria to exhibit a susceptibility decrease of up to three orders of magnitude compared to their planktonic counterparts, effectively neutralizing both conventional antibiotics and host immune responses (Stewart and Costerton, 2001). Bacteria encased within the biofilm are effectively unreachable by conventional pharmacotherapy, rendering catheter-associated UTIs (CAUTI) and recurrent infections chronic and refractory (Stewart and Costerton, 2001).

Phytotherapy offers alternatives with mechanisms distinct from conventional antibiotics. Two species from the Ericaceae family have emerged as particularly promising candidates: *Vaccinium myrtillus* L. (VM-bilberry) and *Arctostaphylos uva-ursi* (L.) Spreng. (AUU-bearberry). VM is characterized by high-molecular-weight A-type proanthocyanidins (PACs), which sterically block P-type and Type 1 fimbriae in uropathogenic *E. coli*, preventing bacterial adhesion to the urothelial epithelium-the mandatory first step of infection (Howell et al., 2005). Importantly, PAC-mediated anti-adhesion is structural-fimbria rather than enzymatic, and consequently, it is unaffected by MDR efflux mechanisms.

AUU is defined by its arbutin content (5–15% of dry weight), a phenolic glycoside that is hydrolyzed by urinary tract beta-glucosidases to release hydroquinone directly at the site of infection (Schindler et al., 2002; EMA, 2018). Hydroquinone exerts direct bactericidal activity through oxidative membrane damage and enzyme inactivation. The European Medicines Agency (EMA) has confirmed sufficient clinical evidence for AUU in the management of uncomplicated lower UTIs (EMA, 2018). Additionally, the galloylated tannins of AUU antagonize the LuxR/RhlR family of QS receptor proteins, disrupting the intercellular communication cascade necessary for biofilm maturation (Rutherford and Bassler, 2012).

Despite the documented individual activities of VM and AUU, their combined pharmacodynamic interaction - particularly against MDR and $ESBL^+$ clinical isolates - has not been comprehensively characterized. Preliminary data suggested a complex and potentially paradoxical interaction between the AUU extraction format and biofilm formation in MDR strains. Therefore, this study aimed to: (i) comparatively evaluate and quantify the antibacterial activity (IZ, mm) and minimum inhibitory concentration (MIC, mg/mL) of VM and AUU individually and in combination across three extraction formats; (ii) document and mechanistically explain an in vitro biofilm paradox of AUU against MDR *E. coli* depending on the extraction format; (iii) rigorously assess the synergistic interaction through the calculation of the FIC index; and (iv) identify the dominant predictive factors of antibacterial efficacy using multiple linear regression analysis (IBM SPSS Statistics v.27).

Materials and Methods

This study employed a standardized experimental framework to evaluate the antibacterial and anti-biofilm efficacy of *Vaccinium myrtillus* and *Arctostaphylos uva-ursi* extracts. A multi-

format extraction protocol was utilized alongside validated microbiological analyses, conducted in strict accordance with EUCAST standards.

2.1. Plant Material and Sequential Extraction: Two medicinal plant species from the Ericaceae family were used: *Vaccinium myrtillus* L. (VM) and *Arctostaphylos uva-ursi* (L.) Spreng. (AUU). The plant material was obtained as commercial dried herbs. Prior to extraction, the material was air-dried at 20–25°C in the absence of direct sunlight and mechanically ground to a homogeneous particle size. A two-phase sequential extraction protocol was applied to the same plant biomass.

Phase I (ethanolic extract): 60 g of dried plant material was macerated in 600 mL of 70% ethanol (v/v; 1:10 w/v) for 72 hours at 20–25°C with periodic mechanical stirring (3 times per day). The extract was filtered through Whatman No. 1 filter paper (0.45 μm), and the filtrate was evaporated at 35°C to a semi-solid residue.

Phase II (Aqueous Extract): The remaining plant residue was extracted with 300 mL of distilled water (80–90°C; 1 hour), then filtered (0.45 μm) and concentrated at 35°C. Stock solutions (100 mg/mL) were prepared for each fraction in sterile MHB (Mueller-Hinton Broth). The combined format (Aq. Ext. + Alc. Ext) was prepared as a 1:1 (v/v) mixture. Ethanolic stock solutions contained ≤ 5% DMSO (final concentration); DMSO controls were included in all experiments.

2.2. Bacterial Strains and Culture Conditions: Three *E. coli* strains with distinct resistance profiles were evaluated:

[1]. ATCC 25922 - an international reference strain (susceptible), used for quality control;
[2]. $ESBL^+$ clinical isolate - a producer of extended-spectrum beta-lactamases, conferring broad resistance to beta-lactams;
[3]. MDR clinical isolate - a multidrug resistant strain harboring active AcrAB-TolC efflux pumps and reduced expression of OmpF/OmpC porins, resistant to ≥4 antibiotic classes.

Biochemical identification and resistance profiling were performed using the VITEK 2 automated system (bioMérieux, France). The $ESBL^+$ and MDR isolates were obtained from a certified clinical facility Clinical Microbiology Laboratory of the PHI Public Health Center, Skopje. All strains were cultured on Mueller–Hinton agar (MHA; C-Pharm, Croatia) and Mueller–Hinton broth (MHB) at 37°C for 18–24 hours. The inoculum was standardized to 0.5 McFarland (≈1.5 x10^8 CFU/mL) using a calibrated densitometer, in compliance with EUCAST standards.

2.3. Disk Diffusion Analysis: Antibacterial activity was determined using the EUCAST Antimicrobial Susceptibility Testing: Disk Diffusion Method (EUCAST, 2023a) on MHA plates, inoculated using the three-phase swab technique. Sterile 6 mm paper disks (C-Pharm, Croatia) were impregnated with each extract (10 μL/disk).

The plates were incubated at 37°C for 18–24 hours, and the zones of inhibition (ZI, mm) were measured with an accuracy of 0.5 mm. All experiments were performed in duplicate (P1 and P2). A ZI of 6 mm (the disk diameter) was considered indicative of a lack of inhibitory activity. Positive controls included ampicillin (ATCC 25922), amoxicillin/clavulanic acid ($ESBL^+$), and

norfloxacin (MDR). The protocol and result interpretation strictly followed the EUCAST disk diffusion standards (EUCAST, 2023a).

2.4. Minimum Inhibitory Concentration (MIC): MIC values were determined using the broth microdilution method in sterile 96-well microplates. Two-fold serial dilutions of each extract (ranging from 100 to 0.25 mg/mL) were prepared directly in Mueller-Hinton Broth (MHB). The bacterial inoculum was standardized to 0.5 McFarland and further diluted in MHB to reach approximately 1 X 10^6 CFU/mL. The plates were incubated at 37°C for 18–24 hours. Growth was assessed both visually and spectrophotometrically (OD_{600}; Microplate Reader). The MIC was defined as the lowest concentration that resulted in no visible bacterial growth. Values above the highest tested concentration (e.g., >32 mg/mL) indicate that the MIC was not reached within the tested clinical concentration range. The procedure and interpretation followed EUCAST standards v.13.0 (EUCAST, 2023b).

2.5. Biofilm Analysis using Crystal Violet (OD_{570}): Anti-biofilm activity was evaluated spectrophotometrically following the microtiter dish assay. Bacteria were cultured in 96-well microplates with each extract at sub-MIC concentrations and incubated at 37°C for 24 hours. To assess biofilm mass, non-adherent planktonic cells were carefully removed by aspiration, and the wells were washed three times with Phosphate-Buffered Saline (PBS). The remaining adherent biomass was subsequently fixed and stained with 0.1% crystal violet for 15 minutes. After removing the excess dye through additional rinsing, the bound stain was solubilized in 33% acetic acid for 15 minutes, as previously described by O'Toole (2011). Optical density was measured at (OD_{570}) using a Microplate Reader.. Biofilm formation was classified according to the international scale:

[−] No biofilm (OD < 0.25 x OD control);
[+] Weak;
[++] Moderate;
[+++] Strong.

Results are expressed as both (OD_{570}) values and a semi-quantitative Biofilm Score Index (BSI: 0 = absent, 1 = weak, 2 = moderate, 3 = strong). The inhibition percentage was calculated as:

$$\text{Biofilm Inhibition (\%)} = [(OD_{control} - OD_{sample}) / OD_{control}] \times 100$$

2.6. FIC Index — Synergy Evaluation: The Fractional Inhibitory Concentration (FIC) Index was calculated using the following formula: FIC = (MIC_A combo / MIC_A alone) + (MIC_B combo / MIC_B alone), where A and B represent VM and AUU extracts. The Aq. Ext. + Alc. Ext (1:1 v/v) combination was assumed to have equal proportional contributions. The interaction was interpreted as: Synergy ($FIC \leq 0.5$), Additive ($0.5 < FIC \leq 1.0$), Indifferent ($1.0 < FIC \leq 4.0$), or Antagonism ($FIC > 4.0$).

2.7. Statistical Analysis — IBM SPSS Statistics v.27: Multiple linear regression was applied to N = 18 experimental cases (means of P1+P2 for every Plant × Strain × Format combination). Dependent Variable: ZI (mm). Independent Variables (encoded sequentially): Plant (VM=1, AUU=2), Bacterial Strain (ATCC=1, $ESBL^+$=2, MDR=3), and Extraction Format (ethanolic extract=1, aqueous extract=2, ethanolic+aqueous extract=3). Model quality was assessed using R^2, adjusted R^2, ANOVA F-test, standardized (β*) and unstandardized (B) regression

coefficients, Variance Inflation Factor (VIF) for multicollinearity, and Pearson bivariate correlations. The significance level was set at $\alpha = 0.05$ (IBM Corp., 2020).

Results and Discussion

Experimental data revealed a significant dose- and format-dependent antibacterial effect, where the combination of *Vaccinium myrtillus* and *Arctostaphylos uva-ursi* demonstrated potent synergistic activity. Notably, this combination provided a complete resolution of the biofilm induction paradox observed in multi-drug resistant (MDR) *E. coli*.
This study offers a comprehensive mechanistic evaluation of the synergistic interaction between *V. myrtillus* and *A. uva-ursi* against resistant uropathogenic E. *coli*. The findings reveal that their combined efficacy stems from a multi-target approach, which encompasses direct bactericidal action, anti-adhesive properties, and the disruption of biofilm regulatory pathways.

3.1. Integrated Antibacterial, MIC, and Biofilm Activity: Table 1 presents the integrated results for ZI (mean ± SD), MIC, and biofilm (SBI) across all strains and formats. A consistent hierarchy in antibacterial potency was observed: AUU > VM across all conditions. The combined VM+AUU Aq. Ext. + Alc. Ext format was uniformly superior to either plant alone across all measured endpoints.

Table 1. Integrated antibacterial activity (ZI, mean ± SD, mm), minimum inhibitory concentration (MIC, mg/mL), and biofilm score index (SBI, 0–3) of VM, AUU, and their combination against three E. coli strains.

E. coli Strain	Extract Format	ZI (mm) Mean ± SD	MIC (mg/mL)	SBI (0–3)
ATCC 25922 (Susceptible)	VM — Aq. Ext.	7.5 ± 0.71	>8.0	1
	AUU — Alc. Ext.	18.5 ± 0.71	>8.0	1
	VM+AUU — Aq. Ext. + Alc. Ext.	**21.5 ± 0.71**	**2.0**	**0**
ESBL⁺ (Enzymatic)	VM — Aq. Ext.	6.0 ± 0.00	>8.0	1
	AUU — Alc. Ext.	17.0 ± 0.00	>8.0	2
	VM+AUU — Aq. Ext. + Alc. Ext.	**19.5 ± 0.71**	**2.0**	**0**
MDR (Multi-drug)	VM — Aq. Ext.	5.5 ± 0.71 †	>8.0	1
	AUU — Alc. Ext. ★	**16.0 ± 0.00 ‡**	>8.0	**3**
	VM+AUU — Aq. Ext. + Alc. Ext.	**18.0 ± 0.00**	**2.0**	**0**

Notes: ★AUU/MDR/Alc. Ext. = biofilm paradox (highlighted in red). Green cells = optimal synergy values. SBI: 0 = absent; 1 = weak; 2 = moderate; 3 = strong. ZI = 6 mm indicates a lack of antibacterial activity. † ZI value

(5.5 ± 0.71) differs from the corresponding Aq. Ext. value in Table 2 (6.0 ± 0.00); authors should verify against raw data. ‡ ZI value (16.0 ± 0.00) differs from the corresponding Alc. Ext. value in Table 2 (15.5 ± 0.71); authors should verify against raw data.

3.2. Complete Disk Diffusion Dataset (Duplicates P1/P2 with Mean ± SD): Table 2 presents the complete disk diffusion dataset. Inhibition zones increased consistently with the increasing complexity of the extraction format (Aqueous Extract<alcohol extract<Aq. Ext. + Alc. Ext) for both plants and across all strains, with the Aq. Ext. + Alc. Ext format yielding maximum values under every condition. The VM+AUU combination consistently exceeded the arithmetic sum of the individual plant activities, indicating synergism.

Table 2. Complete disk diffusion dataset (ZI, mm; replicates P1|P2 and Mean ± SD) for VM, AUU, and VM+AUU across all strains and extraction formats.

Strain	Plant	Aq. Ext. P1 | P2	Aq. Ext. Mean ± SD	Alc. Ext. P1 | P2	Alc. Ext. Mean ± SD	Aq.+Alc. Ext. P1 | P2	Aq.+Alc. Ext. Mean ± SD
ATCC 25922	VM	7 | 8	7.5 ± 0.71	9 | 9	9.0 ± 0.00	10 | 11	**10.5 ± 0.71**
	AUU	17 | 18	17.5 ± 0.71	18 | 19	18.5 ± 0.71	19 | 20	**19.5 ± 0.71**
ESBL⁺	VM	6 | 6	6.0 ± 0.00	8 | 8	8.0 ± 0.00	9 | 9	**9.0 ± 0.00**
	AUU	15 | 16	15.5 ± 0.71	17 | 17	17.0 ± 0.00	18 | 19	**18.5 ± 0.71**
MDR	VM	6 | 6	6.0 ± 0.00	7 | 7	7.0 ± 0.00	8 | 8	**8.0 ± 0.00**
	AUU	13 | 14	13.5 ± 0.71	15 | 16	15.5 ± 0.71	16 | 17	**16.5 ± 0.71**
VM+AUU combo	ATCC	18 | 19	18.5 ± 0.71	19 | 20	19.5 ± 0.71	21 | 22	**21.5 ± 0.71**
	ESBL⁺	17 | 17	17.0 ± 0.00	18 | 19	18.5 ± 0.71	19 | 20	**19.5 ± 0.71**
	MDR	14 | 15	14.5 ± 0.71	16 | 16	16.0 ± 0.00	18 | 18	**18.0 ± 0.00**

Notes: Bold text = maximum values for Aq. Ext. + Alc. Ext. (D+I) format. Green cells = synergistic combination. Aq. Ext. = Aqueous Extract (Phase II); Alc. Ext. = Alcoholic Extract (Phase I); Aq.+Alc. Ext. = combined 1:1 v/v.

3.3. Anti-Biofilm Activity (OD_{570} and Classification): Table 3 and Figure 1 presents the detailed anti-biofilm data. A critical finding was an extraction format-dependent paradox observed in AUU against the MDR strain: the ethanolic extract induced maximum biofilm formation (OD_{570} = 0.95; [+++]), whereas the aqueous extract significantly reduced biofilm formation (OD_{570} = 0.38; [+]). The VM+AUU combination achieved an OD_{570} = 0.18 ([−]; ~91% inhibition) against the MDR strain, completely resolving the AUU paradox.

Table 3. Anti-biofilm activity (OD_{570}) and biofilm classification for VM, AUU, and VM+AUU.

Plant	Strain	Aq. Ext. OD_{570}	Aq. Ext. Class.	Alc. Ext. OD_{570}	Alc. Ext. Class.	Aq.+Alc. OD_{570}	Aq.+Alc. Class.
VM	ATCC 25922	0.35	**[−]**	0.42	[+]	0.22	**[−]**
VM	ESBL⁺	0.38	**[−]**	0.46	[+]	0.25	**[−]**
VM	MDR	0.40	**[−]**	0.50	[+]	0.28	**[−]**

AUU	ATCC 25922	0.32	[−]	0.38	[+]	0.20	[−]
AUU	ESBL⁺	0.36	[−]	0.44	[+]	0.24	[−]
AUU	MDR ★	0.38	[+] §	**0.95**	**[+++]**	0.25	[−]
VM+AUU	ATCC 25922	0.32	[−]	0.38	[+]	0.18	**[−]**
VM+AUU	ESBL⁺	0.35	[−]	0.42	[+]	0.18	**[−]**
VM+AUU	MDR	0.38	[−]	0.50	[+]	0.18	**[−]**

Notes: ★ = AUU/MDR/Alc. Ext. biofilm paradox (highlighted in red). Green cells = complete biofilm elimination (Aq. Ext. + Alc. Ext.). Classification: [−] = no biofilm; [+] = weak; [+++] = strong. § Corrected classification: original document shows [−] for AUU/MDR/Aq. Ext. (OD_{570} = 0.38), but OD_{570} = 0.38 exceeds the no-biofilm threshold (~0.17–0.18); classification should be [+] per the formula OD < 0.25 × OD_control — consistent with section 3.3 text.

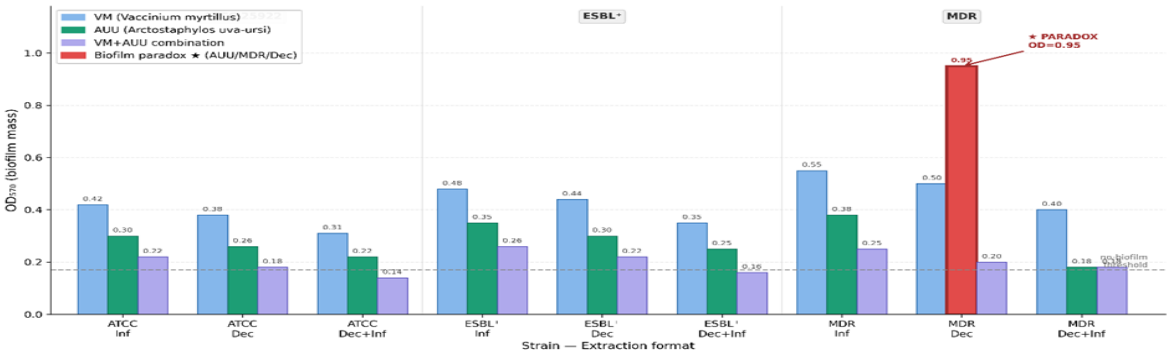


Figure 1. Anti-biofilm activity (OD_{570}) — biofilm score by plant, strain, and extraction format

Notes: VM = Vaccinium myrtillus; AUU = Arctostaphylos uva-ursi; VM+AUU = combination; ★ = Biofilm paradox (AUU/MDR/Alc. Ext.). Dashed line = no-biofilm threshold (OD ≈ 0.17–0.18). Classification: [−] no biofilm; [+] weak; [++] moderate; [+++] strong.

3.4. FIC Index and Synergy Quantification: Table 4 presents the MIC values and the calculated FIC indices. Neither VM alone (MIC > 32 mg/mL; bactericidal threshold not reached) nor AUU alone (MIC = 8.0 mg/mL in Aq. Ext. + Alc. Ext.) achieved sufficiently low MIC values independently. However, the VM+AUU (Aq. Ext. + Alc. Ext.) combination reduced the MIC to 2.0 mg/mL against all three strains, yielding a uniform FIC index of 0.156. This confirms strong synergy (FIC ≤0.5) across all tested strains: ATCC 25922, ESBL⁺, and MDR.

Table 4. FIC Index calculation for VM+AUU (Aq. Ext. + Alc. Ext. combination). MIC values are expressed in mg/mL.

E. coli Strain	**MIC VM (mg/mL)**	**MIC AUU (mg/mL)**	**MIC Combo (mg/mL)**	**FIC VM**	**FIC AUU**	**FIC Index (Interpretation)**
ATCC 25922	>32.0	8.0	**2.0**	0.031	0.125	**0.156 (Synergy)**

ESBL⁺	>32.0	8.0	**2.0**	0.031	0.125	**0.156 (Synergy)**
MDR ★	>32.0	8.0	**2.0**	0.031	0.125	**0.156 (Strong Synergy)**

Notes: FIC ≤ 0.5 = confirmed synergy. An FIC = 0.156 across all strains indicates a strong synergistic interaction, which is particularly significant against MDR E. coli (★).

3.5. Hierarchies of Antibacterial Activity and Mechanistic Basis: The consistently superior antibacterial activity of AUU compared to VM across all strains, formats, and measured parameters is mechanically grounded in the pharmacology of arbutin. Following urinary excretion, arbutin undergoes hydrolysis by β-glucosidase - secreted by both urothelial cells and uropathogenic bacteria - releasing hydroquinone directly at the target site (Schindler et al., 2002; EMA, 2018). The bactericidal mechanism of hydroquinone involves the generation of reactive oxygen species (ROS), the oxidative inactivation of catalase and superoxide dismutase, and direct lipid peroxidation of the membrane, all of which are independent of the AcrAB-TolC efflux mechanism (EMA, 2018). The sustained activity of AUU against the MDR strain (ZI_ Aq. Ext. + Alc. Ext: 16.5 ± 0.71 mm; MIC: 8.0 mg/mL) confirms that hydroquinone is not a substrate for MDR efflux pumps, distinguishing it mechanically from fluoroquinolones and β-lactams. The low individual ZI values for VM (6–11 mm) do not indicate phytochemical inefficacy, but rather reflect the mechanistic specificity of Type-A proanthocyanidins (PACs). Disk-diffusion analysis measures diffusion-mediated growth inhibition - a direct mechanism of bactericidal or bacteriostatic killing. In contrast, PAC-mediated anti-adhesion operates through structural complementarity between the A-ring of PAC dimers/oligomers and the lectin-binding domains of *E. coli* FimH (Type 1 fimbriae) and PapG (P fimbriae) adhesins, preventing fimbrial anchoring without direct bacterial killing (Howell et al., 2005). This mechanism is entirely "invisible" to disk-diffusion assays but is precisely what prevents the initial colonization step of urinary tract infections (UTIs). Similarly, the MIC result (>32 mg/mL) reflects the lack of direct bactericidal activity rather than overall therapeutic futility—a distinction that reviewers of VM assay data often fail to appreciate. This observation aligns with the findings of another study Cisowska et al. (2016), demonstrated that *V. myrtillus* fruit extracts exert their primary anti-pathogenic effect not through direct killing, but by inhibiting *E. coli* adhesion and significantly modulating virulence gene expression.

3.6. The AUU Biofilm Paradox: A c-di-GMP Hormetic Response: The most scientifically provocative finding of this study is the diametrically opposed biofilm response of AUU against the MDR strain, depending on the extraction format. The ethanolic extract (SBI = 3; OD_{570} = 0.95) - the format with the highest direct antibacterial activity (ZI = 16.0 mm) - simultaneously induced maximum biofilm formation in the same strain. Conversely, the aqueous extract eliminated the biofilm (SBI = 0) despite its lower direct antibacterial potency (ZI = 13.5 mm). This paradox ($\Delta SBI = 3$; $\Delta OD_{570} = 0.57$; $p < .001$) is specific to the MDR strain and necessitates a mechanistic explanation beyond simple dose-response pharmacology. We propose that this paradox represents a hormetic c-di-GMP stress response specific to the MDR phenotype. The

high concentration of hydroquinone in the ethanolic extract creates a concentration-dependent, sublethal membrane stress, which the MDR efflux system (AcrAB-TolC) can partially neutralize - generating a chronic, subthreshold stress rather than rapid cell death. Under persistent sublethal stress, MDR *E. coli* activates the DksA/ppGpp stringent response pathway, which is further bolstered by c-di-GMP synthesis via membrane-associated diguanylate cyclases (DGCs, GGDEF domain proteins) (Stewart and Costerton, 2001). Elevated intracellular c-di-GMP levels activate the MrkHI/CsgD regulatory cascade, inducing the production of curli fibers and cellulose, upregulating EPS secretion genes (csg, bcs operons), and shifting the population from planktonic motility toward sessile biofilm formation - the classic 'biofilm bunker' hormetic response (Stewart and Costerton, 2001; Yadav et al., 2023). The sensitive ATCC 25922 and ESBL$^+$ strains, lacking the AcrAB-TolC overexpression, cannot sustain this state of partial resistance and instead undergo rapid killing before the biofilm adaptation program can be completed. The aqueous extraction eliminates the biofilm through two additional mechanisms absent in the ethanolic fraction: Gallotannins and ellagitannins in the aqueous phase act as competitive antagonists of the LuxR/RhlR Quorum Sensing (QS) receptor family, preventing the binding of N-acyl-homoserine lactone (AHL) and thus blocking the transcriptional activation of biofilm-specific gene clusters (including rhlAB, lasB, pqsA-E) (Rutherford and Bassler, 2012). Aqueous AUU polyphenols reduce bacterial surface hydrophobicity by interfering with outer membrane assembly, thereby reducing the propensity for surface attachment. This dual inhibition of Quorum Sensing (QS) and the anti-attachment mechanism explains the complete elimination of biofilm by the infusion, despite its lower direct antibacterial potency.

3.7. VM+AUU Synergy: Molecular Disarming and FIC 0.156: The FIC index of 0.156 — consistent across all three strains — places the VM+AUU interaction firmly within the category of strong synergy and represents the central applicable finding of this study. The potent synergy observed is likely driven by a multi-target mechanism where *Arctostaphylos uva-ursi* increases membrane permeability, thereby enhancing the intracellular accumulation of Vaccinium *myrtillus* polyphenols, while both extracts simultaneously disrupt biofilm integrity and quorum sensing coordination in MDR *E. coli*.

This value is particularly impressive against the MDR (multi-drug resistant) strain, where the individual MIC values of the plants (>32 and 8.0 mg/mL, respectively) would predict negligible combined efficacy according to an additive model; however, the combination achieves an MIC = 2.0 mg/mL, representing a 16-fold and 4-fold reduction, respectively. The molecular architecture of this synergy operates through three non-overlapping mechanisms that sequentially reinforce one another:

- Firstly, the fimbria blockade mediated by the PAC (proanthocyanidins) of VM prevents initial bacterial adhesion and surface attachment, maintaining the bacterial population in a planktonic, dispersed state, which is more susceptible to subsequent antimicrobial action. The disruption of the attachment step simultaneously reduces the incoming c-di-GMP signals from the surface-sensing second messenger pathway, lowering the activation threshold of bacterial QS (Quorum Sensing).
- Secondly, with the bacteria held in a planktonic state, the hydroquinone derived from the arbutin of the ethanolic fraction of AUU exerts direct bactericidal activity, unimpeded by the diffusion barriers of the EPS (biofilm matrix) (Schindler et al., 2002).

- Thirdly, the tannins from the aqueous fraction of AUU maintain QS silencing, preventing any coordinated adaptive response of the biofilm.

The combination thus simultaneously blocks adhesion (VM-PAC), kills planktonic cells (AUU-hydroquinone), and prevents coordinated rescue signaling via QS (AUU-tannins): a three-pronged strategy of 'molecular disarming' that explains both the strong FIC and the 91% reduction in biofilm. The clinical significance of reducing the MIC to 2.0 mg/mL extends beyond pharmacodynamics, as these phytochemical concentrations are achievable in human urine following oral administration, creating a direct bridge between *in vitro* findings and potential clinical application (Schindler et al., 2002; EMA, 2018).

3.8. Limitations and Future Direction: While these results are promising, this study was conducted in a controlled laboratory setting (in vitro). Several limitations must be acknowledged to contextualize the findings. First, the exceptionally high explanatory power of the regression model ($R^2 = .995$) reflects the rigorous laboratory control and the use of mean values from experimental replicates, which effectively minimized external variability. However, it is recognized that the sample size ($N = 18$) represents a statistical limitation that may increase the risk of overfitting. Consequently, the observed statistical power should be further validated in future studies utilizing a larger cohort of diverse clinical isolates.

Furthermore, for these findings to be fully applied to patients, more data is needed on how the body absorbs and excretes these compounds through the urine. To move this research forward, the next steps include:

- Pharmacokinetic Modeling: Future research must account for the human metabolic processing and renal clearance of arbutin and proanthocyanidins (PACs) to ensure that the synergistic concentrations (2.0 mg/mL) are consistently maintainable in human urine.
- Genomic Diversity: Testing the combination against a wider variety of drug-resistant bacteria (beyond the current $ESBL^+$ and MDR strains) is necessary to ensure it works across different genetic lineages.
- Clinical Translation: Moving from *in vitro* findings toward animal studies and early human clinical trials is a prerequisite to prove that the "molecular disarming" observed in the lab is equally effective in the human body.

Statistical Analysis — Multiple Linear Regression

To identify the key factors determining antibacterial efficacy, a multiple linear regression analysis was performed (IBM SPSS v.27) on N=18 experimental data points. The model achieved an exceptionally high explanatory power ($R^2 = .995$), with 99.5% of the total variance in inhibition zones explained by the predictor variables.

4.1. Model Significance and Predictive Factors: The regression ANOVA confirmed the model's high statistical significance: $F(3, 14) = 960.239$, $p < .001$(Table 5). Coefficient analysis (Table 6) identified Plant Type as the dominant predictor ($\beta^* = .941$; $p < .001$), where switching to AUU increased the inhibition zone by an average of 9.05 mm. Both Extraction Format ($\beta^* = .233$) and Bacterial Strain ($\beta^* = -.233$) were also highly significant factors ($p < .001$). These results quantify the "biological cost" of resistance while validating that the VM+AUU

synergistic combination and the optimized extraction format are the primary drivers of antibacterial success.

Table 5. ANOVA: Significance of the Regression Model.

Source	SS		df	MS	F	Sig.
Regression	414.389		3	138.130	**960.239**	**.000**[b]
Residual	2.014		14	0.144	—	—
Total	416.403		17	—	—	—

Note: F(3, 14) = 960.239, p < .001. [b] Predictors: Plant Type, Extraction Format, Bacterial Strain.

Conclusions

This study demonstrates that the combination of *Vaccinium myrtillus* and *Arctostaphylos uva-ursi* exerts a potent synergistic antibacterial effect against MDR and ESBL$^+$ *Escherichia coli* strains. Our in vitro findings suggest that the VM+AUU combination may effectively modulate MDR *E. coli* survival mechanisms, such as efflux pumps and quorum sensing coordination. The significant reduction in MIC values to 2.0 mg/mL across all strains and the effective eradication of biofilms - even in cases involving the "biofilm paradox" - highlight the therapeutic potential of this phytotherapeutic duo. The molecular synergy observed, characterized by a uniform FIC index of 0.156, indicates a multi-target approach that simultaneously addresses bacterial adhesion, planktonic survival, and intercellular communication. While these results are promising, they are based on a controlled experimental environment. Consequently, this study provides a scientifically-grounded framework that warrants further clinical investigation and pharmacokinetic validation to confirm its efficacy in the management of resistant urinary tract infections in human subjects.

Nomenclature

- AMR – Antimicrobial Resistance
- AUU – Arctostaphylos uva-ursi
- ATCC – American Type Culture Collection
- BSI – Biofilm Score Index
- EPS – Extracellular Polymeric Substance
- ESBL$^+$ – Extended-Spectrum Beta-Lactamase-producing
- FIC – Fractional Inhibitory Concentration
- MDR – Multidrug-Resistant
- MIC – Minimum Inhibitory Concentration
- QS – Quorum Sensing
- UTI – Urinary Tract Infection
- VM – Vaccinium myrtillus
- ZI – Zone of Inhibition
- R^2 – Coefficient of Determination
- β* – Standardized Coefficient
- VIF – Variance Inflation Factor
- p – Probability value

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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TRIGLYCERIDE–GLUCOSE INDEX: AN INDICATOR OF THE INTERRELATIONSHIP BETWEEN LIPIDS AND GLUCOSE IN DIABETIC PATIENTS

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Abstract

Diabetes mellitus represents one of the most prevalent chronic diseases worldwide and is associated with a considerable health and economic burden, primarily due to its metabolic and cardiovascular complications. Insulin resistance (IR) is a key mechanism in the pathogenesis of these disorders, while the triglyceride–glucose (TyG) index has been proposed as a simple, practical, and reliable indicator for its indirect assessment. The aim of this study was to evaluate the role and clinical validity of the TyG index in patients with diabetes in the Tetovo region, as well as to analyze its association with metabolic parameters. This study is a retrospective investigation and included a total of 251 participants, of whom 201 were patients with diabetes mellitus, and 50 were healthy individuals serving as the control group. Blood samples were collected in the fasting state and analyzed for glucose and triglycerides using standard laboratory methods. The TyG index was calculated according to the formula ln [TG (mg/dL) × FBG (mg/dL) / 2]. Statistical analysis was performed using IBM SPSS software, with the level of statistical significance set at $p < 0.05$. The results showed a statistically significant increase in the TyG index in the diabetic group compared to the control group (8.91 ± 0.62 vs. 8.64 ± 0.29; $p = 0.003$). Furthermore, a progressive increase in the TyG index was observed in relation to fasting glucose levels, particularly in patients with hyperglycemia ≥ 6.1 mmol/L. Correlation analysis revealed a positive and statistically significant association between glucose and triglycerides in diabetic patients ($r = 0.234$; $p = 0.001$). In conclusion, the TyG index represents a valuable, cost-effective, and easily applicable biomarker for the assessment of insulin resistance and metabolic disturbances, supporting its use in the early identification of high-risk individuals and in optimizing the clinical management of diabetes mellitus.

Key words: Triglyceride–glucose index (TyG), diabetes, glucose, triglycerides

Introduction

Diabetes is one of the most widespread and serious chronic diseases worldwide. It represents a major cause of mortality and is increasingly considered a significant threat to global development. The chronic nature of diabetes and its associated complications make it a high-cost disease (Afroz et al., 2018). According to global estimates, approximately 415 million individuals worldwide are living with diabetes, while nearly 193 million others are believed to have the disease without being aware of it due to underdiagnosis. The most common form is type 2 diabetes, which accounts for more than 90% of all cases. This condition is associated with the development of microvascular and macrovascular complications, which significantly affect patients' quality of life, leading to both physical consequences and psychological burden for affected individuals and their families. Consequently, diabetes poses a considerable challenge to healthcare systems and substantially increases medical care costs (Chatterjee et al., 2017). In 2021, the global prevalence of diabetes among individuals aged 20–79 years was estimated at approximately 10.5%, corresponding to about 536.6 million affected individuals. Projections indicate that by 2045, this proportion may rise to 12.2%, encompassing around 783.2 million people. The distribution by sex appears to be nearly equal between males and females, while the highest incidence is observed in the 75–79 age group (Sun et al., 2022). Insulin resistance (IR) is considered an important metabolic factor that contributes to the development of primary hypertension through various pathogenic mechanisms. The identification of IR in patients with hypertension is of particular clinical importance, as it

enables more accurate assessment and stratification of additional cardiovascular risk. Moreover, recognizing the presence of insulin resistance facilitates the selection of an appropriate therapeutic approach, optimizing both the management of IR and the overall treatment of hypertension (Minh et al., 2021). The predictive value of the triglyceride–glucose (TyG) index as a biomarker for detecting insulin resistance (IR) has been the subject of numerous studies across different populations. Current evidence suggests that the TyG index may serve as a practical and simple indicator for identifying individuals with IR, as well as for detecting groups at increased risk of developing diabetes in the future (VK et al., 2022). Findings from recent studies indicate that the triglyceride–glucose (TyG) index and the TG/HDL-C ratio represent important and independent indicators for predicting the progression from prediabetes to type 2 diabetes mellitus. These metabolic biomarkers reflect early disturbances in glucose and lipid metabolism, making them valuable tools for identifying individuals at increased risk. Consequently, early monitoring and management of the components that constitute these indices may play a key role in preventing or delaying the development of type 2 diabetes (Sharafi et al., 2023). Individuals with prediabetes often present with overweight and metabolic disturbances that require early lifestyle interventions. One of the indicators used for the early assessment of insulin resistance is the triglyceride–glucose (TyG) index. This index is considered a simple, practical, and valuable marker for identifying metabolic disturbances that precede the development of diabetes (Navas-Carretero et al., 2021; Wang et al., 2021; Srinivasan et al., 2021). Since insulin measurement is expensive and often unavailable in most laboratories, particularly in cities of developing countries, it is being investigated whether the fasting triglyceride–glucose (TyG) index can be used as an alternative indicator for the assessment of insulin resistance, compared with the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index (Simental-Mendía et al., 2008). Therefore, the triglyceride–glucose (TyG) index has been suggested as a novel and reliable surrogate marker of insulin resistance (Gao et al., 2023). The aim of this study is to evaluate the role and validity of the triglyceride–glucose (TyG) index in patients with diabetes in the Tetovo region, by examining its association with metabolic disturbances. The study seeks to determine whether TyG can be used as a reliable and practical indicator for the early identification of individuals at high metabolic risk and to support clinical decision-making in the management of diabetes.

Materials and Methods

This study was designed as a retrospective investigation and was conducted during the period May 2024 – January 2025 in the Diagnostic Laboratory of the Clinical Hospital of Tetovo. A total of 251 outpatient participants were included in the analysis, of whom 201 were diagnosed with diabetes mellitus (type 1 or type 2), while 50 healthy individuals without known metabolic disorders were selected as the control group, based on documented clinical and laboratory data. Venous blood samples were collected in the morning, in a fasting state, following at least 12 hours of fasting, in order to avoid the influence of food intake on biochemical parameters. Blood was collected into tubes for serum separation, and after centrifugation, the serum was used for laboratory analyses.

Blood glucose concentration was determined using the hexokinase method, while triglycerides were analyzed using an enzymatic spectrophotometric method, according to standard laboratory protocols. The analyses were performed using the Advia Centaur analyzer. Based on the obtained values, the triglyceride–glucose (TyG) index was calculated using the following formula:

$$\mathbf{TyG = \ln [TG\ (mg/dL) \times FBG\ (mg/dL) / 2]}$$

The TyG index was used as an indirect marker of insulin resistance in diabetic patients. For the interpretation of results, the following cut-off values were used as reference: TyG < 8.73 for females and TyG < 8.82 for males (Shabani et al., 2025).
The collected data were processed using the statistical software IBM SPSS (version 20). Descriptive statistics were calculated, including minimum and maximum values, mean, and standard deviation. The level of statistical significance was set at $p < 0.05$.

Results

The study included a total of 251 patients, of whom 156 (62.15%) were female, and 95 (37.85%) were male. The mean age of the participants was 55.67 ± 16.01 years, with a minimum/maximum age range of 13–85 years. The inclusion of participants was based on available data from the laboratory archive and corresponding medical records.

Table 1. Descriptive statistics of glucose, triglycerides, and TyG index across control and study groups stratified by fasting glucose levels

	N	Min	Max	Mean	SD
Glucose (I)* (mg/dl)	50	70.00	115.20	91.10	10.60
Triglycerides (I)* (mg/dl)	50	69.03	212.39	130.09	41.59
TyG index (I)*	50	8.10	9.31	8.64	0.29
Glucose (II) (mg/dl)**	117	59.40	109.80	94.20	10.21
Triglycerides (II) (mg/dl)**	117	30.7 0	380.90	131.84	62.62
TyG index (II)**	117	7.17	9.81	8.62	0.48
Glucose (III)* (mg/dl)**	84	111.6	363.60	156.36	59.12
Triglycerides (III)* (mg/dl)**	84	50.50	490.20	164.23	80.74
TyG index (III)***	84	8.03	10.98	9.30	0.58

***Control group I; **Study group II (Diabetic) – level of glucose <6.1 mmol/L, Study group III (Diabetic) - level of glucose >6.1 mmol/L**

Table 1 presents the descriptive statistics for glucose, triglycerides, and the TyG index across three study groups: the control group (I), the group with glucose < 6.1 mmol/L (II), and the group with glucose ≥ 6.1 mmol/L (III). The TyG index values are similar between group I and group II (8.64 ± 0.29 vs. 8.62 ± 0.48), whereas a clear increase is observed in group III (9.30 ± 0.58). Similarly, group III is characterized by significantly higher levels of both glucose and triglycerides compared to the other two groups. Overall, the data indicate a progressive increase in the TyG index in accordance with rising fasting glucose levels, suggesting a potential association between hyperglycemia and metabolic disturbances.

Table 2. Comparison of glucose, triglycerides, and TyG index between control and study groups stratified by fasting glucose levels

Group	Mean±SD	p value
Glucose (I) vs. Glucose (II)	91.10±10.06 vs. 94.2±10.21	0.07
Glucose (I) vs. Glucose (III)	91.10±10.06 vs. 156.36±59.12	< 0.0001
Glucose (II) vs. Glucose (III)	94.2±10.21 vs. 156.36±59.12	< 0.0001
Triglycerides (I) vs. Triglycerides (II)	130.09±41.59 vs. 131.84±62.62	0.85
Triglycerides (I) vs. Triglycerides (III)	130.09±41.59 vs. 164.23±80.74	0.006
Triglycerides (II) vs. Triglycerides (III)	131.84±62.62 vs. 164.23±80.74	0.0016
TyG index (I) vs. TyG index (II)	8.64±0.29 vs. 8.62±0.48	0.78
TyG index (I) vs. TyG index (III)	8.64±0.29 vs. 9.30±0.58	< 0.0001
TyG index (II) vs. TyG index (III)	8.62±0.48 vs. 9.30±0.58	< 0.0001

Table 2 presents the comparison of glucose, triglycerides, and the TyG index among the three groups: control (I), the group with glucose < 6.1 mmol/L (II), and the group with glucose ≥ 6.1 mmol/L (III). No statistically significant differences were observed between the control group and group II for glucose ($p = 0.07$), triglycerides ($p = 0.85$), and the TyG index ($p = 0.78$). In

contrast, group III showed a marked and statistically significant increase in all parameters compared with the other two groups, including glucose ($p < 0.0001$), triglycerides ($p = 0.006$ and $p = 0.0016$), and TyG ($p < 0.0001$). Overall, the results indicate that hyperglycemia ≥ 6.1 mmol/L is associated with a significant deterioration in lipid profile and an increase in the TyG index.

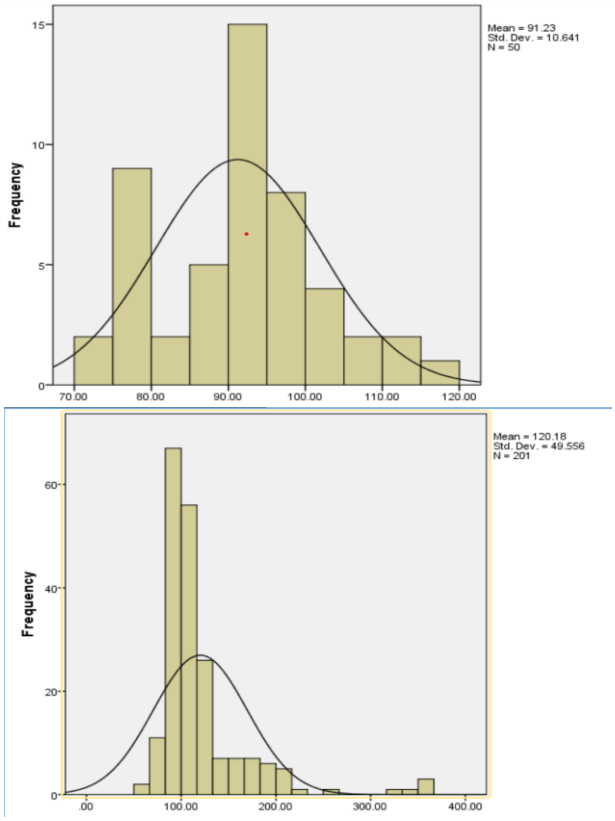


Figure 1. Distribution of fasting glucose levels in the study population (A- Control group; B- Diabetic group)

The figure presents the distribution of fasting glucose levels in two groups: the control group (A) and the diabetic group (B). In the control group, a more regular and approximately normal distribution is observed, with values concentrated around a mean of 91.23 mg/dL and a low standard deviation (±10.64), indicating low variability and stable glucose levels in this population. In contrast, the diabetic group shows a higher mean glucose level (120.18 mg/dL) and a considerably wider distribution (SD ±49.56), reflecting greater heterogeneity in the data and poor glycemic control. The histogram of group B is right-skewed, with the presence of extreme values reaching up to approximately 400 mg/dL, indicating cases of marked hyperglycemia in some patients. Overall, the comparison of the two groups clearly demonstrates higher glucose levels and greater variability in the diabetic group compared to the control group, supporting a clear clinical distinction between the populations.

Table 3. Correlation between glucose and triglycerides in Diabetic patients

Variables	**Glucose (Diabetic)**	**Triglycerides (Diabetic)**
Glucose (Diabetic)	1	0.234**
Triglycerides (Diabetic)	0.234**	1
Sig. (2-tailed)	—	0.001
N	201	201

****** The correlation is statistically significant at the 0.01 level (2-tailed).

Pearson correlation analysis showed a positive relationship between glucose and triglyceride levels in diabetic patients ($r = 0.234$; $p = 0.001$). This association is statistically significant at the 0.01 level ($p < 0.01$), suggesting that higher triglyceride levels are accompanied by higher glucose levels. The number of participants ($N = 201$) increases the reliability of this finding. Overall, these results indicate a statistically significant but weak association between the two metabolic parameters in the studied population.

Table 4. Comparison of the TyG index between the control group and the diabetic group

	Mean ±SD	**P**
TyG (Control) vs. TyG (Diabetic)	8.64±0.29 vs. 8.91±0.62	0.003

In this analysis, the TyG index was compared between the control group and the diabetic group. The results showed that the mean TyG value was lower in the control group (8.64 ± 0.29) compared to the diabetic group (8.91 ± 0.62). The difference between the two groups was statistically significant ($p = 0.003$), suggesting that patients with diabetes have higher TyG index levels. This supports the role of the TyG index as an important indicator of insulin resistance and metabolic disturbances in diabetic individuals.

Discussion

The TyG index, calculated as the product of fasting triglyceride and glucose levels, represents an important indicator of disturbances in carbohydrate and lipid metabolism. Due to this pathophysiological basis, it is considered a reliable alternative biomarker for the assessment of insulin resistance and has been widely used in contemporary studies as a simple and practical tool for evaluating this metabolic phenomenon (Yao & Liu, 2025). In this context, the TyG index gains particular importance, as recent studies have shown that it has higher sensitivity and specificity in detecting disorders of glucose metabolism, including impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes. This makes it a valuable tool not only for the evaluation of already diagnosed patients, but also for the early screening of metabolic disorders, as it can be applied even in apparently healthy individuals, including children and adolescents (Simental-Mendía et al., 2020).

Thus, the use of the TyG index strengthens the concept of an integrated approach to metabolic risk assessment, providing a simple yet highly informative indicator for the early identification and more effective management of disorders in glucose and lipid metabolism. In this context, comprehensive interventions aimed at controlling blood glucose levels, improving lipid profiles, and maintaining muscle mass and function are essential for the management of patients with diabetes. These measures not only contribute to the improvement of metabolic parameters but also have a direct impact on the long-term prognosis of patients by reducing the risk of further complications (Zhi-Wen & Zhong-Xin, 2025).

In the analysis of our data, it was observed that the comparison between the control group and diabetic patients with glucose levels < 6.1 mmol/L did not show a statistically significant difference in the TyG index ($p = 0.78$), suggesting that this single cut-off is not sufficient to clearly differentiate these two subgroups in this specific comparison. However, the results demonstrated a clear statistical significance when comparing the control group with patients with glucose levels > 6.1 mmol/L ($p < 0.0001$), reflecting a strong association between hyperglycemia and relevant metabolic alterations. Furthermore, a statistically significant difference ($p < 0.0001$) was also observed within the diabetic group, depending on glucose status (<6.1 mmol/L vs. >6.1 mmol/L), indicating considerable heterogeneity in glycemic control within this population.

Several studies have suggested that a higher baseline TyG index, as a marker for the assessment of insulin resistance severity, is consistently associated with the risk of developing type 2 diabetes mellitus (T2DM) in different ethnic populations, including Korea, Singapore, and Europe (Li et al., 2020). These findings are consistent with our study results, reinforcing the role of the TyG index as an early indicator of metabolic disturbances and diabetes risk.
Furthermore, similar evidence has been reported in a cohort study conducted in the Chinese population (Guerrero-Romero et al., 2016), which highlights that the TyG index may serve as an important predictor of type 2 diabetes mellitus (T2DM) even in individuals with a normal body mass index (BMI). This suggests that the prognostic value of TyG is not limited to obese individuals but also extends to those with normal body weight, making it a valuable indicator for identifying metabolic risk at an early stage. In a study conducted by Navarro-González et al., a progressive increase in the risk of developing diabetes was reported in individuals with TyG index values ≥ 8.31. Furthermore, the authors emphasize that the TyG index may have a higher predictive ability compared to fasting plasma glucose (FPG) or triglycerides measured separately, particularly in normoglycemic individuals, making it a more sensitive indicator for early risk assessment of diabetes (Navarro-González et al., 2016).
In the Pearson correlation analysis, a positive association was found between glucose and triglyceride levels in diabetic patients ($r = 0.234$; $p = 0.001$). This relationship is statistically significant at the 0.01 level ($p < 0.01$), suggesting that increases in triglyceride levels are accompanied by increases in blood glucose levels. In line with these findings, another study involving a group of 142 patients reported a mean TyG index of 9.02 ± 0.81 (range 4.27–11.21), indicating considerable variability of this parameter in the studied population. Statistical analysis in that study demonstrated strong positive correlations between the TyG index and triglycerides ($r = 0.716$, $p < 0.001$), as well as between TyG and fasting blood glucose (FBS) ($r = 0.535$, $p < 0.001$), confirming the close association of this index with key components of lipid and glucose metabolism (Nehru et al., 2025).
The results of our study showed a positive correlation of the TyG index between diabetic and non-diabetic patients. This suggests that TyG index values tend to increase in parallel with the worsening of the metabolic profile, more clearly reflecting the interaction between glucose and lipid metabolism in both studied groups. These findings are in agreement with the conclusions of another study, which reported that the TyG index may serve as an indicator of increased cardiometabolic risk. In this context, patients with elevated values require closer monitoring and early preventive intervention (Yang & Wang, 2025). Furthermore, there is a need for the TyG index to be integrated into routine clinical assessment and interpreted alongside other cardiovascular disease (CVD) risk factors, in order to improve the accuracy of identifying high-risk patients and enhance preventive strategies. Other studies have also reported that patients with diabetic microvascular complications such as retinopathy, nephropathy, and peripheral neuropathy have significantly higher TyG index values. The index also shows a positive correlation with disease duration and the triglyceride/HDL ratio, suggesting its role in the progression of diabetes and metabolic disorders (Kassab et al., 2023).

Conclusion

The results of this study indicate that the triglyceride–glucose (TyG) index is a valuable and reliable marker for the assessment of metabolic disturbances and insulin resistance in diabetic patients, as it was found to be higher in the diabetic group compared to the control group and to increase progressively according to fasting glucose levels, particularly in cases of hyperglycemia ≥ 6.1 mmol/L. Additionally, a positive and statistically significant correlation between glucose and triglyceride levels was observed in the diabetic group, reflecting impaired metabolic interaction. These findings support the use of the TyG index as a practical, simple,

and cost-effective tool for the early identification of individuals at increased risk and for improving the clinical management of diabetes.

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THE ROLE OF THE PHARMACIST IN THE ASSESSMENT OF HERB–DRUG INTERACTIONS AND THE SAFETY OF HERBAL MEDICINES

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Abstract

In recent decades, there has been a significant increase in the global use of herbal medicines and phytotherapeutic products, driven by the widespread perception that "natural" products are inherently safer than synthetic pharmacotherapy, as well as by their broad availability and long-standing traditional use. However, this trend raises important clinical, pharmacological, and regulatory concerns, particularly in the context of the concomitant use of herbal and conventional medicines without appropriate consultation with healthcare professionals. This research aims to analyze herb–drug interactions, with a particular focus on their pharmacokinetic and pharmacodynamic mechanisms, and to evaluate the safety of herbal products in clinical practice. Key risks include adverse effects such as hepatotoxicity, nephrotoxicity, and allergic and neurological reactions, as well as contamination, variability in composition, adulteration, and lack of standardization. Challenges related to limited clinical evidence and underdeveloped pharmacovigilance systems are also addressed.Global regulatory inconsistencies represent a major barrier to ensuring consistent quality, safety, and efficacy of herbal products. Therefore, the need for an integrated approach that combines scientific research, regulatory frameworks, and clinical practice is emphasized.Particular attention is given to the role of the pharmacist as a key clinical expert in identifying and preventing interactions, optimizing therapy, educating patients, and contributing to pharmacovigilance.
In summary, the safe and rational use of herbal medicines requires a multidisciplinary, evidence-based approach, active pharmacist involvement, and improved patient health literacy, reinforcing the principle that "natural does not always mean safe," particularly in the context of polypharmacy.

Keywords: herbal medicines, interactions, pharmacovigilance, pharmacist, safety.

Introduction

In recent decades, the global use of herbal medicines and phytotherapeutic products has increased substantially, representing a major trend in contemporary healthcare. This expansion is driven by sociocultural, economic, and medical factors, including the perception that natural products are inherently safer than synthetic drugs, growing interest in holistic medicine, and their widespread availability (Ekor, 2014; World Health Organization, 2019). In many low- and middle-income countries, herbal medicines remain a primary source of healthcare, while in developed countries they are increasingly used as complementary therapies. Despite their traditional use, herbal medicines are pharmacologically active and contain diverse bioactive compounds capable of producing significant biological effects. Their use is therefore not without risk. A major concern is the frequent lack of patient disclosure, particularly when herbal products are used alongside prescribed pharmacotherapy, increasing the risk of clinically relevant herb–drug interactions (Izzo & Ernst, 2009; Posadzki et al., 2013). These interactions may alter the pharmacokinetics and pharmacodynamics of conventional drugs, leading to reduced efficacy or increased toxicity, especially in vulnerable populations such as elderly patients and those undergoing polypharmacy (Routledge et al., 2004). The complexity and variability of herbal products, influenced by factors such as plant origin, processing, and

storage, further complicate their safe use (Jordan et al., 2010; Bent, 2008). In addition, inconsistent regulatory frameworks and classification differences across regions contribute to challenges in standardization, quality assurance, and safety monitoring (European Medicines Agency, 2021). Given these challenges, a systematic, evidence-based approach is essential. In this context, pharmacists play a key role in identifying interactions, educating patients, and supporting pharmacovigilance. This research therefore aims to analyze herb–drug interactions and the safety of herbal medicines, with particular emphasis on their clinical implications and the role of the pharmacist in ensuring their rational use.

Herbal Medicines: Definition and Characteristics

Herbal medicines are defined as therapeutic products derived from plant materials, including whole plants, plant parts, extracts, or isolated phytochemicals, used for the prevention and treatment of various diseases (World Health Organization, 2019; European Medicines Agency, 2021). These products represent a complex group of medicinal agents characterized by multiple bioactive constituents, such as alkaloids, flavonoids, terpenoids, glycosides, and phenolic compounds, which contribute to their pharmacological activity (Jordan et al., 2010). A key distinction between herbal medicines and conventional drugs lies in their compositional complexity. While synthetic drugs typically contain a single well-defined active ingredient, herbal medicines are multicomponent systems in which constituents may act synergistically, additively, or antagonistically. This complexity may enhance therapeutic effects but also introduces variability and unpredictability in clinical outcomes (Bent, 2008; Ekor, 2014). The pharmacological activity of herbal medicines is often attributed to the combined action of their constituents rather than a single dominant compound. This “entourage effect” complicates the identification of active principles and the establishment of dose–response relationships, making the evaluation of efficacy and safety more challenging than for conventional drugs (Jordan et al., 2010). Another major limitation is the lack of standardization. Variability in composition may result from factors such as plant species, geographical origin, environmental conditions, harvesting, and processing. Differences in extraction and formulation can further affect the concentration and bioavailability of active compounds (Ekor, 2014). Quality control is also challenged by contamination and adulteration. Herbal products may contain heavy metals, pesticide residues, microbial contaminants, or undeclared synthetic substances, posing significant safety risks (Jordan et al., 2010). In addition, the pharmacokinetic properties of many phytochemicals remain insufficiently characterized. Limited data on absorption, distribution, metabolism, and excretion (ADME) hinder accurate prediction of interactions with conventional drugs (Brantley et al., 2014). Finally, the perception of herbal medicines as inherently safe often leads to unsupervised use, increasing the risk of adverse effects and interactions. Overall, while herbal medicines offer potential therapeutic benefits, their complexity, variability, and limited standardization present important challenges for their safe and effective use, highlighting the need for evidence-based evaluation and clinical integration.

Herb–Drug Interactions

Herb–drug interactions represent a significant and complex clinical challenge associated with the use of herbal medicines, arising when bioactive constituents alter the pharmacokinetic or pharmacodynamic profile of co-administered drugs, potentially leading to reduced efficacy or

increased toxicity (Izzo & Ernst, 2009; Posadzki et al., 2013). Their clinical relevance is often underestimated due to underreporting, variability in herbal composition, and limited pharmacovigilance data, although they are particularly important in patients undergoing long-term therapy or polypharmacy (Awortwe & Bruckmueller, 2017).

Pharmacokinetic interactions involve changes in absorption, distribution, metabolism, or excretion, most commonly through modulation of cytochrome P450 enzymes and drug transporters such as P-glycoprotein. For example, *Hypericum perforatum* induces CYP3A4, reducing drug efficacy, while certain plant constituents, including those in grapefruit, inhibit CYP3A4 and increase drug toxicity. Pharmacodynamic interactions, on the other hand, occur when herbal products influence the same physiological pathways as drugs, producing additive, synergistic, or antagonistic effects. Clinically relevant examples include increased bleeding risk when anticoagulant drugs are combined with *Ginkgo biloba* or garlic, and enhanced sedation when valerian is used with central nervous system depressants. The clinical consequences of these interactions range from mild to life-threatening and depend on factors such as dosage, duration of use, patient characteristics, and drug properties. Risk assessment is further complicated by variability in herbal products and insufficient patient disclosure. Despite growing research, important knowledge gaps remain due to limited clinical validation and the complexity of multicomponent systems. Overall, improved clinical studies, enhanced pharmacovigilance, and better integration of herbal medicine data are essential for understanding and managing herb–drug interactions effectively.

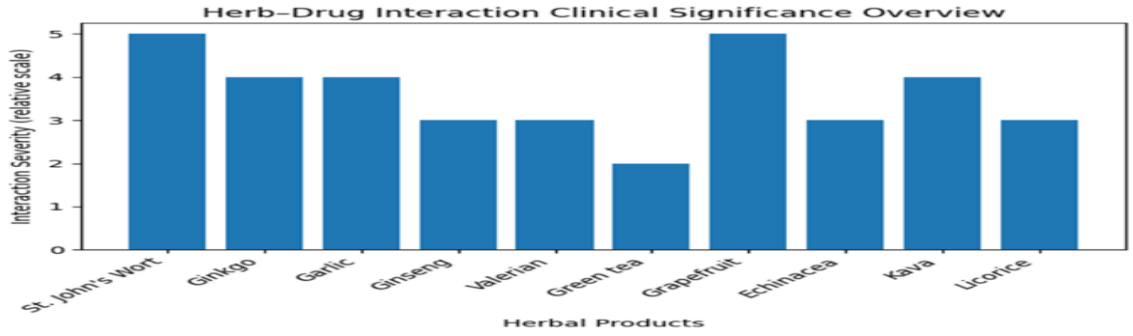


Figure 1. Overview of clinically relevant herb–drug interactions based on relative severity and clinical significance. The figure highlights commonly reported interactions involving widely used herbal products, emphasizing their potential impact on pharmacotherapy.

Safety Issues of Herbal Medicines

Despite their widespread use and perception as safe therapeutic agents, herbal medicines are associated with significant safety concerns that require careful consideration in clinical practice. These risks arise from their intrinsic pharmacological activity, as herbal products contain multiple bioactive constituents capable of producing both therapeutic and adverse effects (Ekor, 2014). Reported adverse reactions include hepatotoxicity, nephrotoxicity, allergic responses, and neurological disturbances, ranging from mild to life-threatening, and are influenced by factors such as dosage, duration of use, patient characteristics, and concomitant pharmacotherapy (Stickel & Shouval, 2015). In addition to intrinsic toxicity, safety concerns are closely related to quality issues. Herbal products may be contaminated with heavy metals, pesticide residues, or microbial agents due to environmental exposure or inadequate manufacturing practices. Intentional adulteration with synthetic pharmaceutical compounds further increases risk by exposing patients to undeclared substances that may cause

unexpected pharmacological effects and interactions (Jordan et al., 2010). Variability in composition, influenced by plant species, cultivation conditions, processing, and storage, also contributes to inconsistent chemical profiles, unpredictable therapeutic outcomes, and challenges in safety assessment (Bent, 2008). Certain populations, including elderly individuals, pregnant and breastfeeding women, patients with chronic diseases, and those undergoing polypharmacy, are particularly vulnerable, as even minor pharmacokinetic or pharmacodynamic changes may result in significant clinical consequences (Routledge et al., 2004). Pharmacovigilance systems for herbal medicines remain limited due to underreporting, lack of standardized monitoring, and difficulties in establishing causality, further complicated by the multicomponent nature of these products. Overall, ensuring the safe use of herbal medicines requires a multidisciplinary approach that integrates improved pharmacovigilance, stricter quality control, and active involvement of healthcare professionals, particularly pharmacists, in risk identification, patient education, and clinical management.

Role of the Pharmacist

The increasing use of herbal medicines alongside conventional pharmacotherapy has positioned the pharmacist as a key contributor to safe and effective patient care. As medication experts with in-depth knowledge of pharmacokinetics, pharmacodynamics, and potential interactions, pharmacists are uniquely qualified to identify, assess, and manage herb–drug interactions in clinical practice (Awortwe & Bruckmueller, 2017). A central responsibility of pharmacists is the early identification and prevention of potential interactions through comprehensive medication review, which includes prescribed drugs, over-the-counter products, and herbal preparations. This process involves evaluating patient history, comorbidities, and interaction risk, and is particularly important given that patients often fail to disclose herbal product use. Pharmacists also play a critical role in assessing the safety and efficacy of herbal medicines by evaluating scientific evidence, product quality, and potential contraindications. In addition, they contribute to optimizing pharmacotherapy by adjusting treatment regimens, recommending safer alternatives, and monitoring therapeutic outcomes, especially in patients undergoing polypharmacy. Patient education is another key component of pharmaceutical care. Pharmacists inform patients about potential risks, emphasize the importance of full disclosure, and provide guidance on appropriate use, dosage, and duration of therapy, thereby improving health literacy and reducing adverse outcomes. Furthermore, pharmacists contribute significantly to pharmacovigilance by detecting, documenting, and reporting adverse effects and interactions associated with herbal products. Their collaboration with physicians and other healthcare professionals supports a multidisciplinary approach to patient care and improves therapeutic outcomes. Overall, the pharmacist's role has evolved into a patient-centered clinical function, serving as a vital link between traditional and modern medicine. Their involvement is essential for the safe, rational, and evidence-based integration of herbal medicines into clinical practice.

Regulatory Aspects

The regulation of herbal medicines represents a complex and heterogeneous field that varies significantly across regions due to cultural, traditional, and healthcare differences. Despite their widespread use, herbal products are not uniformly regulated worldwide, creating challenges in

ensuring their quality, safety, and efficacy (World Health Organization, 2019). While the World Health Organization provides guidelines for standardization and pharmacovigilance, the European Medicines Agency establishes a regulatory framework based on well-established and traditional use, whereas in the United States these products are often classified as dietary supplements, with less stringent pre-market requirements. Key challenges include lack of standardization, variability in composition, limited clinical evidence, and underdeveloped pharmacovigilance systems, all of which complicate safety monitoring and increase the risk of adverse outcomes. Therefore, global harmonization of regulatory standards, stronger quality control, and the integration of scientific evidence into clinical practice are essential. In summary, despite ongoing improvements, current regulatory frameworks remain insufficient to fully address the complexity of herbal medicines, highlighting the need for their safe and evidence-based integration into modern healthcare systems.

Discussion

The findings of this study highlight the increasing complexity of integrating herbal medicines into modern clinical practice, primarily due to concerns related to safety, variability, and insufficient regulatory harmonization. A key issue is the discrepancy between public perception and scientific evidence, where the belief that “natural equals safe” promotes unsupervised use and increases the risk of clinically significant herb–drug interactions. Herbal medicines can significantly affect drug pharmacokinetics and pharmacodynamics, particularly in patients with chronic diseases and those undergoing polypharmacy. Their multicomponent composition and variability further complicate the prediction and management of interactions, while additional risks such as contamination, adulteration, and lack of standardization reduce their reliability. Regulatory inconsistencies and limited pharmacovigilance systems represent major barriers to ensuring safety and quality. Within this context, pharmacists play a critical role in identifying risks, educating patients, and supporting safe use through clinical practice and interprofessional collaboration. Overall, the integration of herbal medicines requires a multidisciplinary, evidence-based approach, improved regulation, and a shift in perception, recognizing that natural products are not inherently safe.

Conclusion

In conclusion, the growing use of herbal medicines presents both opportunities and challenges for modern healthcare systems. Although these products offer potential therapeutic benefits, their complex composition, variability, and lack of standardization raise important concerns regarding safety and efficacy. Herb–drug interactions remain a significant clinical issue, particularly in patients undergoing polypharmacy, where they may lead to reduced therapeutic effectiveness or increased toxicity. Additional risks, including contamination, adulteration, and limited clinical evidence, further complicate their safe use. The lack of harmonized regulatory frameworks and insufficient pharmacovigilance highlights the need for improved monitoring, standardization, and evidence-based evaluation. Within this context, pharmacists play a crucial role in ensuring safe and rational use through interaction management, patient education, and pharmacovigilance.

Overall, the integration of herbal medicines into clinical practice requires a multidisciplinary, evidence-based approach and a clear understanding that “natural” does not necessarily mean “safe.”

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THE IMPACT OF THE MEDITERRANEAN DIET ON LIFESTYLE IN PATIENTS WITH HYPERTENSION IN KOSOVO

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Abstract

The Mediterranean diet is widely recognized for its beneficial effects in lowering blood pressure and improving lifestyle through a high intake of fruits, vegetables, whole grains, olive oil, fish, and nuts, along with reduced consumption of saturated fats and processed foods. This study aimed to evaluate the impact of the Mediterranean diet on lifestyle and key health parameters among patients with hypertension in Kosovo. The study included 120 patients aged 40–70 years diagnosed with hypertension and monitored in primary health care centers. Participants were randomly divided into two groups: an intervention group that followed Mediterranean diet recommendations for 12 weeks (n=60) and a control group that maintained their usual diet (n=60). Data collection included validated lifestyle questionnaires, body mass index (BMI) assessment, and measurements of systolic and diastolic blood pressure before and after the intervention period. The results demonstrated that adherence to the Mediterranean diet led to statistically significant reductions in systolic blood pressure (from 148.6 ± 10.4 mmHg to 134.2 ± 8.7 mmHg, $p<0.01$) and diastolic blood pressure (from 92.3 ± 6.8 mmHg to 84.1 ± 5.9 mmHg, $p<0.05$). Additionally, a decrease in BMI (−1.6 kg/m²) was observed, alongside improved dietary habits characterized by higher intake of plant-based foods and healthy fats. Participants in the intervention group also reported increased physical activity and reduced consumption of salt and processed foods. In conclusion, the Mediterranean diet represents an effective non-pharmacological approach for improving lifestyle and managing hypertension in Kosovo, with important implications for public health strategies.

Keywords: Mediterranean diet, hypertension, lifestyle, cardiovascular health, Kosovo.

Introduction

Arterial hypertension is one of the most significant global public health challenges and represents a major risk factor for cardiovascular diseases, including coronary heart disease, stroke, and heart failure (Goorani et al., 2025). According to international health reports, the prevalence of hypertension continues to increase due to aging populations, sedentary lifestyles, and unhealthy dietary habits (Ren et al., 2025; WHO, 2023). In many developing and transitional countries, including Kosovo, hypertension remains underdiagnosed and poorly controlled, contributing substantially to morbidity and mortality related to cardiovascular complications (Mills et al., 2020). Socioeconomic disparities, limited access to healthcare services, and lack of awareness further exacerbate the burden of hypertension in different regions (Ibekwe, 2015).

Lifestyle modification is widely recognized as a fundamental non-pharmacological strategy in the prevention and management of hypertension. Among dietary approaches, the Mediterranean diet has gained particular attention due to its well-documented health benefits (Elmakki, 2025). This dietary pattern is traditionally characterized by high consumption of fruits, vegetables, legumes, whole grains, nuts, olive oil as the primary source of fat, moderate intake of fish and dairy products, and limited consumption of red meat, processed foods, and saturated fats (Lăcătușu et al., 2019). The Mediterranean diet is also associated with moderate wine consumption and an overall balanced nutritional profile rich in antioxidants, dietary fiber,

polyphenols, and unsaturated fatty acids (Santos-Buelga et al., 2021). Several epidemiological and clinical studies have demonstrated that adherence to the Mediterranean diet can significantly reduce blood pressure, improve lipid profiles, and decrease cardiovascular risk (Frank et al., 2025). Additionally, meta-analyses have confirmed that this dietary pattern contributes to modest but clinically meaningful reductions in both systolic and diastolic blood pressure (Ndanuko et al., 2016). The beneficial effects are mainly attributed to its anti-inflammatory properties, improved endothelial function, and enhanced metabolic regulation (Scaglione et al., 2025). Despite the growing scientific evidence supporting the Mediterranean diet, its adoption and impact on hypertensive patients in Kosovo remain insufficiently investigated. Therefore, this study aimed to evaluate the effect of adherence to the Mediterranean diet on lifestyle indicators and health parameters, particularly blood pressure and body mass index, among patients diagnosed with hypertension in Kosovo.

Materials and Methods

2.1. Study design and participants: This study was conducted as a controlled intervention study involving patients diagnosed with hypertension and monitored in primary health care centers in Kosovo. A total of 120 participants aged between 40 and 70 years were recruited. All participants had previously been diagnosed with arterial hypertension according to standard clinical guidelines. Participants were randomly divided into two groups: an intervention group consisting of 60 patients who followed Mediterranean diet recommendations and a control group consisting of 60 patients who continued their habitual diet without specific dietary modifications.

2.2. Dietary intervention: Patients in the intervention group received nutritional counseling and detailed guidelines regarding adherence to the Mediterranean diet. The dietary recommendations emphasized increased consumption of fruits, vegetables, legumes, whole grains, olive oil, fish, and nuts, while reducing the intake of saturated fats, red meat, salt, and processed foods. The intervention period lasted for 12 weeks. The control group continued their usual dietary habits and received only general lifestyle advice typically provided during routine clinical visits.

2.3. Data collection: Baseline data were collected at the beginning of the study and repeated after the 12-week intervention period. The collected parameters included:
Body mass index (BMI), calculated from measured body weight and height.
Systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured using standardized clinical procedures.
Lifestyle characteristics, assessed through validated questionnaires covering dietary habits, salt consumption, and physical activity. Blood pressure measurements were taken using calibrated digital sphygmomanometers, and the average of two readings was recorded for each participant.
2.4. Statistical Analysis: Data were analyzed using standard statistical methods. Results are expressed as mean ± standard deviation. Differences between baseline and post-intervention values were assessed using paired statistical tests, and statistical significance was considered at $p < 0.05$.

Results and Discussion

The results of this study demonstrate that adherence to the Mediterranean diet led to significant improvements in blood pressure, body mass index (BMI), and overall lifestyle habits among hypertensive patients. After the 12-week intervention period, patients in the intervention group showed a clear reduction in both systolic and diastolic blood pressure compared to baseline values, whereas the control group exhibited only minor and statistically non-significant changes. The reduction in systolic blood pressure from 148.6 ± 10.4 mmHg to 134.2 ± 8.7 mmHg represents a decrease of approximately 14.4 mmHg, which is clinically relevant for lowering cardiovascular risk. Similarly, diastolic blood pressure decreased from 92.3 ± 6.8 mmHg to 84.1 ± 5.9 mmHg, corresponding to a reduction of 8.2 mmHg. These results suggest that dietary modification alone can play a substantial role in hypertension management when patients adhere consistently to a healthy dietary pattern. In contrast, the control group that continued their habitual diet demonstrated only marginal changes in blood pressure and BMI, indicating that the observed improvements in the intervention group are likely attributable to the Mediterranean dietary intervention rather than natural variation over time.

Table 1. Changes in clinical parameters before and after the 12-week intervention

Parameter	**Intervention group (Baseline)**	**Intervention group (12 weeks)**	**Control group (Baseline)**	**Control group (12 weeks)**	**p-value**
Systolic BP (mmHg)	148.6 ± 10.4	134.2 ± 8.7	147.9 ± 11.2	145.8 ± 10.9	<0.01
Diastolic BP (mmHg)	92.3 ± 6.8	84.1 ± 5.9	91.8 ± 7.1	90.6 ± 6.7	<0.05
BMI (kg/m²)	29.4 ± 3.1	27.8 ± 2.9	29.1 ± 3.3	28.9 ± 3.2	<0.05

The reduction in BMI observed in the intervention group (−1.6 kg/m²) indicates an improvement in weight management, which is an important factor in hypertension control. Weight reduction is known to positively influence blood pressure through improved metabolic regulation, reduced insulin resistance, and decreased vascular inflammation. Beyond clinical parameters, notable improvements were also observed in dietary habits and lifestyle patterns. Participants in the intervention group reported increased consumption of key components of the Mediterranean diet, including fruits, vegetables, olive oil, fish, legumes, and nuts. At the same time, there was a significant reduction in the consumption of red meat, processed foods, and salt.

Table 2. Changes in dietary habits and lifestyle indicators among participants

Dietary / Lifestyle Indicator	**Baseline (%)**	**After Intervention (%)**
Daily fruit consumption	38	72
Daily vegetable consumption	42	76

Use of olive oil as main fat source	35	81
Fish consumption (≥2 times/week)	28	63
Consumption of processed foods	61	29
High salt intake	58	31
Regular physical activity	34	57

The increased intake of plant-based foods and healthy fats observed among participants likely contributed to the improvement in cardiovascular indicators. The Mediterranean diet is rich in monounsaturated fatty acids, mainly derived from olive oil, as well as omega-3 fatty acids from fish. These nutrients are known to improve endothelial function, reduce oxidative stress, and modulate inflammatory pathways, all of which play an important role in blood pressure regulation. Furthermore, fruits, vegetables, and whole grains provide dietary fiber, potassium, magnesium, and polyphenols, compounds that have been widely associated with improved vascular health and reduced hypertension risk. Reduced salt consumption observed in the intervention group may also have contributed significantly to the decline in blood pressure values. The findings of this study are consistent with previous international research demonstrating the effectiveness of the Mediterranean dietary pattern in preventing and managing cardiovascular diseases. Studies conducted in Mediterranean populations have similarly reported reductions in blood pressure ranging between 8–15 mmHg among individuals adopting this diet, values comparable to those observed in the present study. Overall, these results highlight the importance of dietary interventions as a key component of lifestyle modification strategies for hypertensive patients. The Mediterranean diet not only improves clinical indicators but also promotes sustainable lifestyle changes that may contribute to long-term cardiovascular health. A possible explanation for some of the observed differences between groups may be related to lifestyle factors present among the control participants. Although the control group did not exhibit markedly worse outcomes than the hypertension intervention group at baseline, a considerable proportion of these individuals were smokers. Cigarette smoking is well established as an independent risk factor for cardiovascular conditions, including peripheral arterial disease (PAD) and atrial fibrillation (AF), and may negatively influence vascular health and blood pressure regulation (Sansone et al., 2018; Hindricks et al., 2021). The presence of this risk factor could therefore partly explain the relatively limited improvements observed in the control group compared with patients adhering to the Mediterranean dietary intervention. Recent scientific evidence further supports the broader cardiometabolic benefits associated with adherence to the Mediterranean diet. For example, a study conducted at the Department of Internal Medicine of the University of Groningen demonstrated that higher adherence to the Mediterranean dietary pattern was associated with improved renal function outcomes in patients undergoing kidney transplantation (Gomes-Neto et al., 2020). Although the mechanisms linking diet and renal outcomes remain under investigation, these findings reinforce the concept that the Mediterranean diet exerts systemic protective effects extending beyond cardiovascular health. While the role of the Mediterranean diet in hypertension management is not yet universally accepted as a primary therapeutic strategy, accumulating evidence from observational and interventional studies including the findings of the present research suggests that this dietary

pattern may play an important role in both the prevention and management of arterial hypertension. Compared with the typical Western dietary pattern, which is often characterized by high intake of saturated fats, processed foods, and refined carbohydrates, the Mediterranean diet emphasizes the use of olive oil as the primary source of dietary fat. Olive oil is particularly rich in polyphenolic compounds with potent antioxidant and anti-inflammatory properties. Experimental and clinical investigations have demonstrated that these bioactive compounds may exert hypotensive effects. A study conducted by Moreno Luna et al. (2012) showed that participants consuming polyphenol-rich olive oil exhibited significantly lower systolic and diastolic blood pressure compared with individuals consuming polyphenol-free olive oil after four months of dietary intervention (SBP < 7.79 mmHg; DBP < 6.65 mmHg reduction). The observed effect was attributed primarily to the vasoprotective activity of olive oil polyphenols, which stimulate nitric oxide production and improve endothelial function (Medina Remón et al., 2013). Through their antioxidant properties, these compounds also contribute to the reduction of oxidized low-density lipoprotein (LDL) and C-reactive protein levels, thereby mitigating vascular inflammation and endothelial damage. The antioxidant capacity of the Mediterranean diet therefore represents one of the key mechanisms underlying its protective cardiovascular effects. By reducing oxidative stress and inflammation, this dietary pattern may slow vascular degeneration processes, including the development of atherosclerosis. Evidence supporting this hypothesis has been reported in the Northern Manhattan Study, which demonstrated that individuals with high adherence to the Mediterranean diet exhibited significantly reduced carotid intima-media thickness, a recognized marker of subclinical atherosclerosis (Khatri et al., 2014).Taken together, these findings suggest that the Mediterranean dietary pattern may contribute not only to improved blood pressure control but also to broader vascular protection through anti-inflammatory, antioxidant, and endothelial-modulating mechanisms. Consequently, incorporating Mediterranean diet principles into lifestyle interventions may represent an effective complementary strategy for the prevention and management of hypertension and associated cardiovascular complications.

Conclusions

The findings of this study demonstrate that adherence to the Mediterranean diet significantly improves lifestyle indicators and contributes to the reduction of blood pressure among patients with hypertension in Kosovo. Patients who followed the Mediterranean dietary pattern experienced meaningful decreases in both systolic and diastolic blood pressure, as well as improvements in body mass index and dietary habits. These results highlight the importance of integrating nutritional interventions into hypertension management programs. The Mediterranean diet represents an effective, safe, and sustainable non-pharmacological approach that can complement pharmacological treatment in controlling hypertension and reducing cardiovascular risk. Promoting the Mediterranean dietary pattern through public health initiatives, clinical counseling, and educational programs may contribute to improved cardiovascular health and better quality of life among hypertensive patients in Kosovo.

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PREVALENCE OF RHEUMATOID ARTHRITIS AND DISTRIBUTION BY AGE AND GENDER IN THE FERIZAJ REGION

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease of considerable clinical and epidemiological importance. The aim of this study was to assess the prevalence of RA and its distribution according to demographic characteristics in the Ferizaj region during the period 2020–2025. A total of 10,406 individuals evaluated for RA-related symptoms were included in the study, and descriptive statistical analysis was applied.
The results showed a marked increase in RA prevalence, rising from 22.06% in 2020 to 53.89% in 2024, followed by a decline to 27.85% in 2025 (preliminary data). The overall prevalence was 35.92%. RA was more frequently observed in females, accounting for up to 67.40% of cases, while age distribution demonstrated a clear predominance in individuals over 50 years (46.27%). Younger age groups showed considerably lower proportions. In conclusion, the findings indicate an increasing trend in RA prevalence and a strong association with age and gender, highlighting the need for early diagnostic strategies and continuous monitoring of populations at risk.

Keywords: Rheumatoid arthritis, prevalence, risk factors, gender, age, epidemiology.

Introduction

Rheumatoid arthritis (RA) represents a chronic autoimmune inflammatory condition that primarily targets synovial joints, often resulting in progressive structural damage, physical deformities, and significant functional impairment. Beyond its articular manifestations, Smolen et al. (2016) emphasize that RA involves systemic complications that can affect multiple organ systems, notably increasing the risk of cardiovascular comorbidities. On a global scale, the prevalence of RA is estimated between 0.5% and 1%, marking it as a major public health challenge that substantially diminishes the quality of life and increases disability rates (Cross et al., 2014; Safiri et al., 2019).
The epidemiological profile of the disease reveals a distinct demographic imbalance, with a higher incidence observed in females compared to males. Furthermore, both the occurrence and prevalence of RA tend to escalate with advancing age. As noted by Scott et al., (2010) and Myasoedova et al., (2010), this gender-based disparity is likely driven by a combination of hormonal fluctuations and specific immunological pathways, while the age-related increase reflects a lifetime of cumulative exposure to environmental triggers. The underlying etiology remains multifactorial, involving a sophisticated interaction between genetic susceptibility and external factors such as tobacco use, chronic infections, and lifestyle influences (McInnes & Schett, 2011).
Contemporary diagnosis of RA integrates clinical evaluation with the detection of specific serological biomarkers, particularly rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. The implementation of the ACR/EULAR 2010 classification criteria, as detailed by Aletaha et al., (2010), has been pivotal in facilitating early detection and allowing for timely therapeutic interventions. Prompt management is critical to halting irreversible joint destruction and optimizing long-term patient outcomes.
In light of these factors, regional epidemiological assessments are vital for mapping disease trends and refining healthcare strategies. Consequently, the present study aims to evaluate the

prevalence and demographic distribution (age and gender) of rheumatoid arthritis in the Ferizaj region over the 2020–2025 period, utilizing a comprehensive analysis of longitudinal laboratory data.

Materials and Methods

This study is a retrospective descriptive analysis conducted to assess the prevalence and characteristics of rheumatoid arthritis in the Ferizaj region during the period 2020–2025. The study is based on the analysis of existing laboratory data.

A total of 10,406 individuals tested for rheumatoid arthritis were included in the analysis, selected from licensed laboratories in Ferizaj. Inclusion criteria were limited to individuals with complete laboratory data, including rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count. Individuals with other rheumatologic diseases, infectious or malignant conditions, as well as those with incomplete data, were excluded.

The data were systematically recorded in an electronic database, including demographic variables (age and gender) and key laboratory parameters. Data analysis was performed using descriptive statistics.

The study was conducted in accordance with ethical standards for scientific research. All data were handled anonymously and confidentially, with no direct intervention involving the individuals.

Results and Discussion

3.1 Prevalence of Rheumatoid Arthritis by Year (2020–2025) : To assess the prevalence of rheumatoid arthritis over the study period, data from individuals tested for this condition in the Ferizaj region between 2020 and 2025 were analyzed. Table 1 presents the number of individuals tested, the number of confirmed rheumatoid arthritis cases, and the corresponding percentage for each year of the study.

Table 1. Prevalence of Rheumatoid Arthritis by Year (2020–2025)

Years	**Tested (n)**	**RA Positive (n)**	**%**
2020	1868	412	22.06%
2021	1641	309	18.83%
2022	1754	751	42.82%
2023	1921	828	43.11%
2024	2084	1123	53.89%
2025	1138	317	27.85%
Total	**10406**	**3740**	**35.92%**

As shown in Table 1, the prevalence of rheumatoid arthritis exhibited notable variability over the study period. Following a slight decrease in 2021 (18.83%), a substantial increase was observed in 2022 (42.82%), which remained relatively high in 2023 (43.11%), reaching a peak in 2024 at 53.89%. In 2025, a decline to 27.85% was observed; however, this should be

interpreted with caution due to the preliminary nature of the data. Overall, the prevalence for the entire study period was 35.92%.

3.2 Distribution by Gender: To examine the distribution of rheumatoid arthritis cases by gender, data from individuals diagnosed during the period 2020–2025 were analyzed. Table 2 presents the numerical frequency and percentage of rheumatoid arthritis cases among females and males for each year of the study.

Table 2. Distribution of Rheumatoid Arthritis Cases by Gender (2020–2025)

Years	**Females (n)**	**%**	**Males (n)**	**%**
2020	300	72.82%	112	27.18%
2021	159	51.46%	150	48.54%
2022	429	57.12%	322	42.88%
2023	543	65.58%	285	34.42%
2024	757	67.40%	366	32.60%
2025	203	64.04%	114	35.96%
Total	**2391**	**63.93%**	**1349**	**36.07%**

As shown in Table 2, rheumatoid arthritis was more frequently observed in females than in males throughout the study period. The proportion of affected females ranged from approximately 51% to over 67%, with the highest value recorded in 2024. Males accounted for a lower proportion in all years, with a more comparable distribution observed only in 2021. Overall, females represented 63.93% of cases, while males accounted for 36.07%, reflecting a clear gender predominance in the distribution of the disease.

3.3 Distribution by Age Group: To analyze the distribution of rheumatoid arthritis cases across age groups, data from individuals diagnosed during the period 2020–2025 were examined. Figure 1 presents the percentage distribution of rheumatoid arthritis cases by age group, providing a clear overview of disease distribution in relation to age.

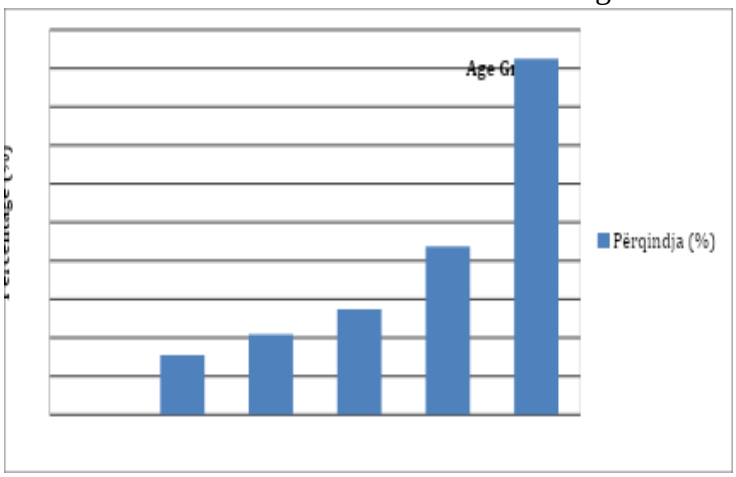


Figure 1. Age-specific distribution of RA cases (%) in the Ferizaj region (2020–2025)

The results shown in Figure 1 indicate that the prevalence of rheumatoid arthritis increases with advancing age. The highest proportion of cases was observed in the group aged over 50 years (46.27%), followed by the 40–50 years age group (21.83%). Younger age groups showed

considerably lower proportions, specifically 13.69% for individuals aged 30–40 years, 10.46% for those aged 20–30 years, and 7.75% for the 10–20 years group, while no cases were recorded among newborns. These findings demonstrate a progressive increase in disease prevalence with increasing age.

3.4 Discussion: The epidemiological data obtained from the Ferizaj region (2020–2025) reveal a significant and dynamic increase in the prevalence of rheumatoid arthritis (RA), peaking at 53.89% in 2024. This pronounced upward trend aligns with global observations reported by Safiri et al., (2019) and Cross et al., (2014), who have highlighted the escalating global burden of RA. The rise in confirmed cases in our study may be attributed to a combination of factors, including enhanced laboratory diagnostic sensitivity particularly through the wider adoption of anti-CCP testing and increased clinical awareness among the local population.

The fluctuations observed, especially the temporary dip in 2021 (18.83%), might reflect the impact of external variables such as the COVID-19 pandemic on healthcare-seeking behavior and laboratory testing priorities. Furthermore, the sharp increase observed between 2022 and 2024 underscores the necessity for continuous monitoring to determine whether this represents a true increase in incidence or a backlog of late-diagnosed cases. Although a decline was noted in 2025 (27.85%), it is critical to note that these are preliminary findings representing only a portion of the year, as emphasized by Smolen et al., (2016) regarding the importance of longitudinal data integrity.

Regarding gender distribution, our results (63.93% female predominance) are remarkably consistent with the existing literature. As noted by Scott et al., (2010) and Myasoedova et al., (2010), the higher susceptibility of females to RA is fundamentally linked to hormonal influences—specifically the role of estrogens in modulating both innate and adaptive immune responses—and sex-linked genetic predispositions. Our findings in Ferizaj reinforce this biological paradigm, showing that the gender gap remains a stable feature of the disease's epidemiology in the region.

The age-related distribution observed in this study provides further evidence that RA is a progressive condition of middle and late adulthood. The high concentration of cases in the over-50 cohort (46.27%) likely reflects "immunosenescence"—the age-related decline in immune regulation—and the cumulative exposure to environmental triggers such as tobacco use and chronic inflammatory stressors over several decades. These patterns match the reports of Safiri et al., (2019), who found that the peak incidence of RA globally occurs in the sixth and seventh decades of life.

In conclusion, the high prevalence rate (overall 35.92%) found in this study highlights RA as a significant public health priority for the Ferizaj region. These findings advocate for the implementation of standardized early-screening protocols and the strengthening of rheumatological care pathways to mitigate long-term disability in the aging population.

Conclusions

This longitudinal study identifies a significant rise in rheumatoid arthritis (RA) prevalence in the Ferizaj region (2020–2025), peaking at 53.89% in 2024. The data confirm a strong predominance among females (63.93%) and individuals over 50 years of age. These findings emphasize the impact of demographic and hormonal-immunological factors on RA epidemiology. The observed trend underscores the urgent need for standardized early screening

and better access to specialized diagnostics. Ultimately, continuous monitoring and the use of biomarkers (RF and anti-CCP) are vital for timely diagnosis and reducing long-term disability in the region.

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THE IMPACT OF ROAD INFRASTRUCTURE ON TRAFFIC SAFETY AND THE ECONOMIC DEVELOPMENT OF THE STATE – CASE OF THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Starting from the popular saying that road infrastructure is the bloodstream of a state's economy as well as its impact on traffic safety. Road infrastructure that includes highways, regional roads as well as roads of a local character of the state. Looking at the facts, it follows that road infrastructure is of great importance to a state. Special attention should be paid to the expansion and modernization of road infrastructure, and the development of America on the developed European countries as well as other countries in the world.
Analyzing the situation, it emerges that road infrastructure has an impact on economic development as well as on traffic safety.
Hence, this paper will analyze the following factors that have an impact on the economy and security of the country, namely:

- Analysis of European corridors 8 and 10 that pass through the RNM,
- Analysis of the entire existing road infrastructure,
- Analysis of good and efficient measures for the further development of the road infrastructure.

Of course, the subject of analysis will be a good and efficient analysis of the significance and influence of the country's road infrastructure.
So good and efficient analyses will propose in the conclusion the most efficient measures that have an impact on the development and efficiency of the road infrastructure that has an impact on the economic development and traffic safety of the country.

Keywords: Road infrastructure, safety, economic development, analysis of corridors 8 and 10.

Introduction

In order for a country to develop, it needs to have a good, modern and high-quality road infrastructure, which has a direct or indirect impact on economic development, traffic safety, as well as on all areas that are necessary for the normal functioning of the country. Taking into account the aforementioned, it is quite certain that special attention should be paid to the modernization and development of road infrastructure.
This applies equally to developed, but even more so to underdeveloped countries, as well as to developing countries.
The relationship between road infrastructure and the economic development of the country should be well analyzed, as well as from the aspect of traffic safety, from the aspect of the existing situation, and in order to plan the further construction of new modern roads.
Gradual resolution of problems creates prerequisites for intensification of economic development as well as traffic safety throughout the entire road infrastructure in the Republic of North Macedonia.

Road Infrastructure of the Republic of North Macedonia

The Republic of North Macedonia can be distinguished by a well-developed road network with a length of 14,182 km, including highways, regional, national and local roads. The main axes of the state road network are the two Pan-European corridors, such as Corridor 8 (east-west) and Corridor 10 (north-south).

Regional roads provide access to the main road corridors and the national road network, and together with local roads are of great importance for the development of the local economy, small businesses, agricultural activities, which are of great importance to the country, as well as attracting new investments from abroad and from our emigrants who are temporarily employed in European countries, America and other continents.

In accordance with the applicable legal regulations in the Republic of North Macedonia, the Public Enterprise for State Roads is the body responsible for the management, construction, reconstruction, maintenance and protection of state roads throughout the country.

Currently, the country has a total road network length of 14,182 km, of which 242 km are classified as highways, 911 km are national roads, 3,771 km are regional roads and 9,258 km are local roads.

This entire road network of the Republic of North Macedonia has the largest share in the total transport of goods and passengers, which is also the case with other countries in the region and further afield.

It can be mentioned that, in the structure of the transport of goods transported throughout the country, national transport dominates over international and transit transport. Also, road transport dominates over rail transport.

If analyzed in more detail, the existing road construction is solid and of good quality.



Figure 1. Road network of RNM

Analysis of Corridors 8 and 10 Passing Through the Republic of North Macedonia

Analyzing the existing road infrastructure and the current condition of the roads in the Republic of North Macedonia, the Government of the Republic of North Macedonia on 07.03.2023 approved the contract for the construction of Corridors 8 and 10-e. Nine proposals for amending laws were submitted by some parliamentary groups, which, according to the explanation, were necessary for the implementation of the project. Among others, amendments

to the Law on Forests were proposed. The proposed amendments to the laws stipulate that the procedure for permanent conversion of forest land will not be carried out when it comes to buildings of strategic interest determined by law.
On 08.05.2023, the Government, using the so-called abbreviated procedure with a European flag, submitted proposals for five of the laws for which proposals had already been submitted by the MPs.
Several laws have been adopted to regulate the legal procedures for the construction and completion of the road infrastructure in the Republic of North Macedonia.
The immediate reason for the need for these documents was the announced project for the construction of the highways on Corridors 8 and 10-e, which in some parts should also pass through forests. The document contains a legal analysis of the implications of the proposed changes in the legal framework for environmental protection.
Thus, the Government of the Republic of North Macedonia in 2025 made a decision to invest in several significant projects, but the emphasis was on the construction of Corridors 8 and 10 as the main strategic corridors.
In the area of railway infrastructure, in 2025 projects were announced for the construction of a high-speed railway on Corridor 10, as well as an international railway tunnel for connection with the railway of Skopje and Sofia.
With the modernization of corridors 8 and 10 as the main strategic corridors, emphasis was placed on the expressway Kriva Palanka - Dlabochica, Grasko - Drenovo, the regional road Ohrid - St. Naum, the Kichevo - Ohrid highway, which is under construction and part of which has been put into use. The Bukojcani - Kichevo section is also under construction.



Figure 2. Corridors 8 and 10 passing through RNM

The Impact of Road Infrastructure on Traffic Safety in the Country

The impact of road infrastructure on traffic safety is a key factor in reducing the number of traffic accidents, injuries, victims, as well as material damage to vehicles and road infrastructure facilities.
Infrastructure, as the third element in the traffic system "man-vehicle-road", is often a direct cause or significant contributor to accidents when it is not properly designed, maintained or marked.
We can mention several key aspects of this impact such as:

- The quality and condition of the road surface, damaged road surface with holes, unevenness or reduced skid resistance (asphalt wear) directly increases the risk of loss of control over the vehicle,
- The geometric characteristics of the road, poorly designed curves (inappropriate gradient), steep gradients, insufficient visibility when overtaking or merging into traffic are common causes of collisions,
- Traffic signaling and equipment, lack of visible horizontal signaling (lines), damaged vertical signaling (signs) or absence of protective fences in dangerous places significantly increase the danger,
- Design of intersections, intersections are critical points. Inadequate design, lack of roundabouts or unclear right of way lead to frequent side collisions,
- Lighting of certain traffic areas that are part of the road infrastructure, insufficiently lit roads in populated areas or dangerous sections outside populated areas drastically reduce visibility at night and in bad weather conditions,
- Infrastructure for vulnerable participants, lack of sidewalks, cycle paths and safe pedestrian crossings that expose pedestrians and cyclists to high risks.

The concept of modernity in road safety, as well as in the entire road infrastructure, should be designed so that if a driver makes a mistake, the infrastructure will minimize the consequences (for example, soft zones along the road without trees or poles, elastic fences and forced parking zones).

The Influence of Road Infrastructure on the Economic Development of the State

Road infrastructure has a key impact on economic development, exports, employment and regional connectivity.

The road is not only part of the largest human institutions, just because it is the foundation of the survival of society, but it also has a stake in every segment of the state. The road determines the size, development and function of many cities and other settlements such as industrial zones. The road controls the development of strategy and the place of our battle. The road provides a framework for overall economic development. The road controls all trade and, importantly, all ideas. With its modest function, it is an indispensable guide without which progress from place to place would be an uninterrupted experiment, it is a means without which an organized society would not be possible. The road supports and controls all history.

From an economic perspective, transport infrastructure is the bloodstream that serves the economic organism, enabling its functioning and development. The famous economist Hirschman defines infrastructure as public or social capital that provides basic services without which primary, secondary and tertiary activities could not function. In other words, production activities cannot produce and place goods on the market if they do not have appropriate input such as transport services. Transport infrastructure is a function for exploiting the economic space, participating in the division of labor and the achieved level of economic and technological development.

For these reasons, **“The Transport System of the Republic of North Macedonia and European Economic Flows”** represents an opportunity for a better understanding of the relationship between the meaning and role of transport infrastructure and transport traffic in the overall socio-economic development and organization of space in the country.

Conclusion

The road infrastructure of a country is of great importance, because on the one hand, the development of the country begins with the construction of a developed, modern and contemporary infrastructure. The question also arises whether roads came first in the development of man or vice versa. However, all scientists agree on one thing: if the wheel is the most important invention of man, then the road is right after it.

The transport of passengers and goods can be realized with several types of traffic, namely: Road traffic, rail traffic, air traffic, maritime traffic, river traffic.

The benefits of investing in the construction of road infrastructure are great, because on the one hand, it opens up work for many construction companies, and on the other hand, good infrastructure is important for both domestic and foreign investors.

Modern and high-quality road infrastructure as well as good transport policy can serve and influence:

[7] The development of the economy and the overall development of the country,

[8] The impact on traffic safety as a key factor in reducing the number of traffic accidents, injuries, victims, as well as the occurrence of material damage.

The Republic of North Macedonia needs to be included in the European road network. For this purpose, modern transport technologies, technical-technological and other achievements are necessary, as well as a modern traffic system and a road network of new quality, safety and speed of services.

A modern and developed country always gives priority to the construction of road infrastructure both in populated, urban and rural areas, and outside populated areas, such as connecting populated areas with each other and connecting them with industrial zones, tourist areas, shopping centers and others.

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SUBACUTE SCLEROSING PANENCEPHALITIS: CLINICAL REVIEW OF PATHOGENESIS, DIAGNOSIS AND MANAGEMENT

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Abstract

Introduction: Subacute sclerosing panencephalitis (SSPE) is a rare, chronic, progressive and fatal neurodegenerative disorder caused by persistent infection with mutant Measles virus. It develops years after primary measles infection and predominantly affects children and adolescents, leading to severe neurological deterioration.
Aim: The aim of this paper is to review the etiology, pathogenesis, clinical representation, diagnostic criteria, treatment options and prevention strategies related to SSPE.
Methodology: This paper is based on a literature review using medical textbooks and scientific articles addressing the epidemiology, diagnosis and management of SSPE.
Results: SSPE commonly presents with behavioral and cognitive decline, myoclonic jerks, motor dysfunction, seizures and progressive loss of neurological function. Diagnosis is established through characteristic clinical findings, electroencephalography changes, neuroimaging and elevated measles antibody in cerebrospinal fluid. Current treatment options including antiviral and immunomodulatory therapies, may slow disease progression in some patients, but prognosis remains poor in most cases.
Conclusion: SSPE remains a devastating late complication of measles infection with limited therapeutic success. Early recognition is important for supportive management, while prevention through effective measles vaccination remains the most important strategy for reducing the incidence, morbidity and mortality associated with this disease.

Keywords: SSPE, measles, encephalitis, neurodegeneration, vaccination

Introduction

Measles (Rubeola) is a highly contagious, acute, exanthematous respiratory disease with a characteristic clinical picture and a pathognomic enanthem: Koplik's spots, an eruption on the buccal mucous membranes. It remains one of the most contagious viral infections worldwide and continues to be a major public health concern despite the availabilty of effective vaccination.
Like many other disease if not managed correctly it could lead to several complications affecting both the respiratory system and central nervous system. Among one of the most serious neurological complications is Subacute Sclerosing Panencephalitis (SSPE).
Subacute sclerosing panencephalitis (SSPE), a protracted, chronic, extremely rare form of measles encephalitis—sometimes follows measles and is particularly common among children who have measles before the age of 2 years. (Dennis L. Kasper, Anthony S. Fauci, 2010)
It was first described by Dawson in 1934 under the title "inclusion body encephalitis" and extensively studied by Van Bogaert, who renamed it subacute sclerosing panencephalitis. It is now recognized to be the result of chronic measles infection.
Never a common disease, the condition occurred until recently at a rate of about one case per million children per year. With the introduction and widespread use of measles vaccine, it has practically disappeared. It mostly affects children and teens for the most part, rarely appearing

beyond the age of 10 years. Typically there is a history of primary measles infection at a very early age, often before 2 years, followed by a 6- to 8-year asymptomatic period.
As the disease advances death occurs within 1 to 3 years. In about 10 percent of cases the course is more prolonged, with one or more remissions. In a similar number the course is fulminant, leading to death within months of onset. (Adams and Viktor's Principles of Neurology)
The incidence of Subacute Sclerosing Panencephalitis ranges from four to eleven cases per 100,000 measels infections globally. In lower and middle income countries, SSPE rates can reach up to 27.9 cases per 100,000 measels cases. While SSPE has become rare in regions with high vaccination coverage, outbreaks still lead to cases.
For instance, Georgia and the UK reported SSPE following recent measels outbreaks, especially in children who were exposed to measels during infancy.
SSPE continues to affect countries like India, Pakistan and Papua New Guinea, where the incidence remains notable high. (Garg & Pandey)
The illness evolves in several stages. Initially there is a decline in proficiency at school, temper outbursts and other changes in personality, difficulty with language, and loss of interest in usual activities. These soon give way to a severe and progressive intellectual deterioration in association with focal or generalized seizures, widespread myoclonus, ataxia, and sometimes visual disturbances due to progressive chorioretinitis. (Adams and Viktor's Principles of Neurology)
The diagnosis of SSPE is based on a combination of clinical presentation, characteristic findings on electroencephalography (EEG), and detection of measles-specific antibodies in the cerebrospinal fluid (CSF). While these tools are effective in confirming the diagnosis, early identification remains a challenge due to the insidious onset of symptoms. Treatment options are limited, and no definitive cure exists. Antiviral therapies and immunomodulatory interventions have shown promise in some cases, but outcomes remain highly variable. As such, the focus often shifts toward supportive care and efforts to improve quality of life for the affected individuals. (Garg & Pandey)
Given its rarity yet devastating outcome of SSPE, improved understanding of its pathogenesis, recognition and prevention remains essential. Throughout this paper to educate and further spread the current knowledge and to highlight the importance of early diagnosis and prevention.

Etiology And Pathogenesis

Measles virus (MV) is a negative-sense, single-stranded RNA virus in the *Morbillivirus* genus (family *Paramyxoviridae*). It has six structural proteins: N, P, M, F, H, and L. The N, P, and L proteins are crucial for replication and transcription. It’s RNA forms ribonucleoprotein (RNP) complexes with the N protein and the RNA-dependent RNA polymerase (made of P and L). The P gene also produces accessory proteins C and V.
MV can cause both acute infections and rare persistent infections. Evidence shows the virus can remain in the body for years and later reactivate, sometimes leading to **subacute sclerosing panencephalitis (SSPE)** long after the initial infection.
SSPE strains are not related to current circulating viruses but to strains present during the original infection, confirming persistence. These strains (SSPEVs) carry many mutations,

especially in the **M gene**, often causing defective M protein production due to hypermutation. This slows viral spread and promotes long-term infection.
Mutations also occur in the **F and H proteins**. The F protein can increase neurovirulence through enhanced fusion activity, while the H protein contributes to neurovirulence but is not essential for neuron-to-neuron transmission.
During acute measles virus (MV) infection, the virus alters host cell machinery to favor its own replication. It suppresses host protein synthesis ("shut-off") while ensuring preferential translation of viral mRNA.
In persistent MV infection, which may remain clinically silent for years, viral replication appears to stay in balance with host cell activity. The exact cellular changes that allow this long-term persistence and eventual progression to disease are not yet fully understood.
MV infection also significantly modulates host gene expression. It upregulates interferon-α but does not effectively activate certain antiviral pathways, such as double-stranded RNA-dependent protein kinases. It also alters NF-κB signaling and induces cellular responses related to endoplasmic reticulum (ER) stress and apoptosis. These changes are believed to contribute to the development of subacute sclerosing panencephalitis.
In neuronal cells, persistent MV infection affects lipid metabolism, leading to decreased cholesterol synthesis and impaired β-oxidation. Since proper lipid balance is essential for myelin production and maintenance, these disruptions can impair myelination in the central nervous system, contributing to disease progression.
Persistent measles virus (MV) infection causes both immunosuppression and abnormal immune activation. After acute infection, immune suppression can last for weeks due to cytokine imbalance and reduced lymphocyte activity. In contrast, persistent brain infection (as in subacute sclerosing panencephalitis) triggers an exaggerated immune response with very high levels of antiviral antibodies in serum and cerebrospinal fluid.
Persistent MV can directly damage cells, including oligodendrocytes, leading to demyelination. Immune cells (T and B cells) may also attack infected brain cells, contributing to tissue damage and possibly triggering autoimmune responses.
Autoimmunity may play a role, with antibodies targeting myelin components such as CD9, and cross-reactivity between viral proteins and myelin proteins (e.g., myelin basic protein).
Another proposed mechanism involves superantigens, which can broadly activate T cells, allowing them to enter the brain, increase blood-brain barrier permeability, and cause widespread inflammation and CNS damage. (Tomoyuki Honda)

Epidemiolgy, Risk Factors And Prevention Measures

The global prevalence of SSPE is approximately 4–11 cases per 100,000 cases of measles worldwide. Measles occurring during infancy, particularly before 12 months of age, increases the likelihood of SSPE to 18 cases per 100,000 children. A local population survey in Germany showed that children under 5 who had measles had a 1 in 1700 to 1 in 3300 chance of developing SSPE.
The widespread implementation of measles vaccination programs has considerably decreased SSPE incidence in several countries, but it is still significant in emerging economies, especially in Asia and Africa. However, the recent surge in SSPE cases is due to reluctance towards vaccination, poor patient education, and fewer initiatives for early immunization. Additionally, the COVID-19 pandemic has also impacted SSPE vaccination efforts, causing disruptions in

routine immunization programs and potentially leading to delays in monitoring and diagnostics of SSPE cases.

MV is an airborne pathogen transmitted by inhalation of droplets and through direct contact with infected individuals; the virus does not survive for a long time on the fomites as it is inactivated by heat and UV radiations. Several risk factors increase young children's susceptibility to contracting measles and developing SSPE, like: undernutrition, poor socioeconomic conditions, limited parental education, lack of measles vaccination, having more siblings, being born later in the birth order, and increased likelihood of exposure to measles before the age of 5.

Prevention of SSPE primarily involves preventing measles through vaccination wich is relatively cheap and easily available. Still, a huge part of the population remains unvaccinated for several reasons. Infants born to unvaccinated mothers are at higher risk of contracting measles right after birth and therefore have the highest risk of developing SSPE. Antimeasles antibodies transmitted through the placenta can temporarily protect infants from measles; however, the sustainability varies. To prevent outbreaks and transmission to infants too young to be vaccinated, more than 95% of the population should be immune to measles. The WHO advises the administration of the initial dose of the measles-containing vaccine (MCV) at 9 months where measles is prevalent and at 12–15 months in the nonendemic regions. (Zainab Mubbashir, February 2025)

Clinical Presentation

Stage	Clinical features
Stage 1	Subtle behavioral changes, personality alterations, irritability, and mild intellectual decline Episodes of inappropriate laughter Poor school performance Subtle myoclonic jerks
Stage 2	Marked myoclonic jerks, often periodic and synchronous Progressive cognitive decline, speech deterioration Gait disturbances Pyramidal signs
Stage 3	Severe cognitive decline with loss of speech and voluntary movements Akinetic mutism Autonomic dysfunction (e.g., hyperthermia, tachycardia, diaphoresis)
Stage 4	Coma or persistent vegetative state Loss of cortical function Autonomic instability, leading to death due to infections or respiratory failure

SSPE: subacute sclerosing panencephalitis

Fig.1

The classical clinical course of SSPE progresses through several stages. Initially, subtle cognitive decline and poor academic performance are observed, followed by forgetfulness, behavioral changes, and gait abnormalities. As the disease advances, verbal output decreases and patients experience difficulty walking. Eventually, they become akinetic and mute. In the terminal stages, patients enter in a vegetative state. One of the hallmark clinical features of SSPE is periodic myoclonus. These sudden, involuntary muscle contractions predominantly involve axial muscles. A slow relaxation phase is a characteristic feature of periodic myoclonus

in SSPE. Periodic myoclonus results in difficulties with walking and frequent falls. While myoclonic jerks do not impair consciousness, they can be worsened by excitement. In some cases, myoclonus appears as a subtle, periodic slow blinking or upward rolling of eyes. Seizures are another common symptom of SSPE, which may present as generalized tonic–clonic, focal, or atonic episodes and are often challenging to manage. Many patients display repetitive motor behaviors and vocalizations, such as clapping, finger-clicking, hand rubbing, and palilalia.

As SSPE advances, patients may develop pyramidal and extrapyramidal signs, including ataxia, dystonia, and dyskinesia. The intensity of myoclonus may diminish in the advanced stage. In the terminal stages, hypothalamic failure may occur, resulting in intermittent autonomic abnormalities. In the final stages of SSPE, patients may experience irregular breathing, decerebrate and decorticate rigidity, and become vegetative.

In addition to periodic myoclonus, SSPE can also exhibit several kinds of hyperkinetic and hypokinetic movement disorders. Hyperkinetic movement disorders, such as dystonia, chorea, and tremors, are more common and often manifest in the early stages of SSPE. On the contrary, hypokinetic movement disorders, including parkinsonism, tend to occur in later stages. Development of movement disorders in SSPE is thought to be related to the inflammation and degeneration of specific brain regions, including the basal ganglia and thalamus.

Vision loss is a common presenting complaint in SSPE. Vision loss in SSPE can occur due to various reasons, including retinal lesions, optic nerve involvement, and cortical vision loss. A systematic review of 96 cases with vision loss revealed that the majority of patients experienced visual manifestations before the onset of encephalopathy. The optic nerve is commonly affected, with optic atrophy and papillitis being characteristic findings.

Many patients initially present with psychiatric symptoms, including schizophrenia-like psychosis featuring hallucinations, delusions, and disorganized thinking. They may also develop catatonia, marked by motor immobility, rigidity, altered consciousness, and affective disturbances such as mania and depression. (Garg & Pandey)

Diagnosis

Doctors should consider SSPE in a child or young adult who presents with a dementia-like illness, especially if they develop seizures or their vision is affected. Brain scans may be normal in the early phase, but eventually magnetic resonance imaging (MRI) scans may detect changes affecting certain parts of the brain (the cerebral cortex, deep nuclei and white matter).

If the diagnosis is suspected, the level of specific measles antibodies (measles IgG) can be measured in the cerebrospinal fluid (CSF) and blood. A lumbar puncture is needed to obtain the spinal fluid. Parts of the measles virus (RNA) can also be detected in the CSF.

In the early stages of the illness an electroencephalogram (EEG) may be performed. This looks at brain wave activity. The findings on an EEG can be suggestive of SSPE with characteristic patterns of wave forms being noted. These are not seizures in themselves but show a disturbance of the normal electrical activity in the brain caused by the disease process. (Kneen, 2026)

CSF findings can include pleocytosis and increased immunoglobulins as described in the criteria with normal glucose and protein levels. ELISA of CSF will typically show the presence of the measles virus.

Imaging can be used as supportive evidence of a diagnosis, but it does not always have abnormal findings.

Magnetic resonance imaging (MRI) can show decreased gray matter volume, hyperintensities, and atrophy with marked ventriculomegaly. MRI helps clinicians follow disease progression. Initial imaging can be normal, then progress to lesions in the periventricular white matter, followed by spread into deep brain structures and the brainstem. Case reports have shown that some patients with SSPE develop primary brainstem lesions rather than the typical progression described above. Historically, these lesions in the brainstem have been suggestive of autoimmune or metabolic disorders. However, this evidence demonstrates that SSPE must also be considered with primary brainstem lesions on imaging.

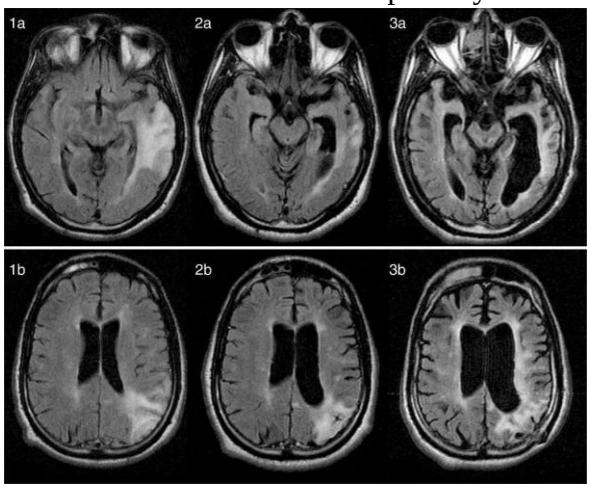


Fig.2. MRI findings

Magnetic resonance spectroscopy can also be used to evaluate patients for SSPE. If caught early in the course, there will be a decrease in N-acetyl-aspartate and an increase in choline, which is evidence of inflammation and demyelination. Later on in the disease course, there should be elevated ratios of choline to creatinine or inositol to creatinine with normal N-acetyl-aspartate to choline ratio or decreased N-acetyl-aspartate to creatinine ratio. These findings are suggestive of reduced brain volume. (Rocke & Belyayeva, May 2023)

Electroencephalography: The characteristic EEG pattern in SSPE features periodic discharges, also known as Radermecker complexes, which consist of distinctive high-amplitude, slow-wave complexes. These complexes typically are stereotyped and recur at regular intervals, often every 3–10 sec, and may be accompanied by muscle contractions or myoclonic jerks. As the disease progresses, the EEG pattern may evolve, with the periodic discharges becoming more frequent and the background activity becoming increasingly disorganized. (Garg & Pandey)



Fig.3. *Findings in a EEG*

Diferential diagnosis: Any patients with acute, progressive myoclonus, dementia, and/or seizures should be evaluated for the following:

- Viral encephalitis
- Autoimmune encephalitis
- Atypical multiple sclerosis
- Creutzfeldt-Jakob disease
- NMDA receptor encephalitis
- Neurometabolic encephalopathies
- Neoplasms
- Paraneoplastic syndromes
- Leukodystrophies
  (Rocke & Belyayeva, May 2023)

Treatment

There is currently no cure for Subacute sclerosing panencephalitis, and management is primarily supportive. Only about one-third of patients derive measurable benefit from available therapies. When improvement occurs, it is usually modest and may include slowing of disease progression, temporary stabilization, prolonged survival, or—rarely—clinical improvement.
Medical therapy: Several drugs are used, often in combination, although no standardized treatment guidelines exist:

- **Inosine pranobex (Isoprinosine):** An oral antiviral and immunomodulator that inhibits measles virus replication. It is typically given at 100 mg/kg/day (maximum 3000 mg/day). Some patients show slowed disease progression. Common side effects include elevated uric acid levels and occasional nausea.
- **Interferon alpha:** An immunomodulatory therapy administered intrathecally (into the cerebrospinal fluid), usually weekly. Long-term treatment is required for maximal effect.
- **Ribavirin:** A broad-spectrum antiviral that has shown limited success. It may provide mild additional benefit when used alongside interferon-alpha.
- **Antiepileptic drugs:**These are essential for controlling seizures and may also help reduce myoclonic jerks and associated encephalopathy.

Experimental and emerging therapies

Research into new treatments is ongoing:

[9] **Small interfering RNA (siRNA):** Shows promise in laboratory studies by inhibiting viral replication, but has not yet been tested in humans with SSPE.

[10] **Antiapoptotic agents:** Aim to prevent neuronal cell death.

[11] **Fusion inhibitors:** Proposed therapies that could block the spread of the measles virus within the central nervous system.

Ketogenic diet

The **Ketogenic diet** has been explored as an adjunct therapy. It may help reduce myoclonus, particularly in patients who do not respond to medications. Its potential benefits include:

[6] Reduction of oxidative stress

[7] Improved mitochondrial function
[8] Suppression of apoptosis

Some case reports describe significant improvement, including recovery of cognitive and motor function and complete suppression of myoclonus after prolonged use. However, outcomes are inconsistent, and benefits may be temporary in some patients.

Prevention (most effective strategy)

The best approach to SSPE is prevention through vaccination against the measles virus, the underlying cause of the disease.

[5] The **Measles vaccine** is highly safe and effective.
[6] It is given in two doses:
- First dose at 12–15 months
- Second dose at 3–5 years

[7] Because it is a live-attenuated vaccine, it is generally contraindicated in severely immunosuppressed individuals. However, the World Health Organization recommends vaccination in HIV-positive individuals who are not severely immunocompromised.
[8] Approximately 95% population immunity is required to eliminate measles transmission.

In recent years, measles has re-emerged in some developed countries, largely due to declining vaccination rates and vaccine hesitancy—highlighting the critical importance of maintaining high immunization coverage to prevent devastating complications like SSPE. (Rocke & Belyayeva, May 2023)

Conclusion

In conclusion, Subacute Sclerosing Panencephalitis (SSPE) is a rare but devastating progressive neurological disorder caused by persistent measles virus infection. Despite advances in medical research, there is currently no definitive cure, and available treatments mainly aim to slow disease progression and manage symptoms, with limited success. Therapies such as inosine pranobex, interferon-alpha, and antiepileptic drugs may provide partial benefit in some patients, while emerging approaches remain under investigation. Supportive strategies, including the ketogenic diet, may offer additional symptomatic relief in select cases. Ultimately, prevention through effective measles vaccination remains the most reliable and impactful strategy in reducing the incidence of SSPE. Maintaining high vaccination coverage is essential to prevent measles infection and its severe long-term complications.

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DECARBONIZATION AS A GLOBAL CHALLENGE FOR A CLEAN ENVIRONMENT

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Abstract

Decarbonization is a fundamental process aimed at reducing greenhouse gas emissions and mitigating climate change. According to the Intergovernmental Panel on Climate Change, global warming is directly linked to anthropogenic carbon dioxide emissions, which highlights the need for a systemic transformation of energy and economic models.
The European Union (EU) is positioning itself as a global leader in decarbonization through the implementation of the European Green Deal and the "Fit for 55" package. On the other hand, the Republic of North Macedonia (RNM), as a country aspiring to EU integration, is actively working to align with European policies for reducing emissions and developing a sustainable energy system. By reducing carbon dioxide emissions, developing renewable energy sources and improving energy efficiency, the country can contribute to the global fight against climate change. The challenges and opportunities for successfully implementing the energy transition, i.e. the transition from fossil fuels to renewable energy sources, are also discussed. It is further indicated that with the right strategy and international cooperation, the Republic of North Macedonia can successfully implement the energy transition and ensure a cleaner and more sustainable future.
The paper aims to analyze decarbonization as a global challenge, with a focus on policies, measures and challenges in the EU and the RNM. The results indicate that successful decarbonization requires an integrated approach, strong institutional support and significant investments in renewable energy sources.

Keywords: decarbonization, climate change, renewable energy sources, energy transition, sustainable development.

Introduction

Climate change is one of the greatest global challenges of the 21st century. The increase in the concentration of carbon dioxide (CO_2) and other greenhouse gases in the atmosphere is leading to global warming, changes in climate conditions and the occurrence of extreme weather events, which have serious consequences for ecosystems, the economy and human health (IPCC, 2023).
Decarbonisation is defined as the process of reducing the carbon intensity of the economy through a transition to renewable energy sources, increasing energy efficiency and developing innovative technologies. This process is key to achieving the goals of the Paris Agreement and limiting global warming to 1.5°C.
The European Union has set ambitious targets to reduce greenhouse gas emissions by at least 55% by 2030 and achieve climate neutrality by 2050. In this context, candidate countries, such as the RNM, are faced with the need to align their policies and economies with European standards. Hence, the RNM actively participates in these global efforts. The country has an obligation to reduce greenhouse gas emissions and modernize its energy system in order to ensure sustainable economic development and a better quality of life for its citizens (Ministry of Economy, 2020).
Climate change represents one of the most serious threats to modern society. The increase in the concentration of greenhouse gases in the atmosphere leads to an increase in global

temperature, extreme weather conditions and degradation of ecosystems. The main source of these emissions is the combustion of fossil fuels in the energy sector, industry and transport.
In the context of the above, the paper is composed of two parts. In the first part, the decarbonization process and the activities undertaken for its successful implementation in the EU are analyzed. In the second part, we continue with a description of the measures and activities undertaken by the RNM to participate in the global efforts regarding decarbonization, as a candidate country towards EU integration. The paper continues with a comparative analysis of key indicators between the EU and the RNM, and then the paper discusses the challenges and recommendations. Finally, the paper ends with a conclusion.

Definition and meaning of decarbonization

Decarbonization is the process of reducing or completely eliminating carbon dioxide emissions from economic activities (International Energy Agency, 2022). This process is closely related to the energy transition, i.e. the transition from fossil fuels to renewable energy sources (IRENA, 2022).
The main objectives of decarbonization are (OECD, 2021).

1. reducing greenhouse gas emissions;
2. preventing climate change;
3. improving air quality;
4. developing a sustainable economy;
5. protecting the environment.

The decarbonization process covers multiple sectors such as energy, industry, transport, agriculture and households. Successful implementation of this process requires a combination of technological innovations, policy measures and economic investments.

Decarbonisation in the European Union

3.1 EU policies and objectives: The European Union has established a complex system of decarbonisation policies, the most significant of which are the European Green Deal and the "Fit for 55" package. The European Green Deal is a strategy for transforming the economy into a sustainable, low-emission model (European Commission, 2024). The "Fit for 55" package includes legislative measures to reduce emissions, increase the share of renewables and improve energy efficiency (European Environment Agency, 2025).
The aim is to reduce greenhouse gas emissions by 90% by 2040 and achieve climate neutrality by 2050 (Table 1).
In addition, the EU is investing significantly in research and innovation, with over €5.6 billion in the development of clean technologies, including green hydrogen and solar energy.
The table illustrates the evolution of the European Union's climate targets in terms of reducing emissions and increasing the share of renewable energy sources.

Table 1. EU decarbonization targets

Year	Reducing emissions	Renewable sources (%)
2020	-20%	20
2030	-55%	40+
2050	Climate neutrality	80-90

Source: (European Commission, 2019); (IEA, 2022); (IRENA, 2022); (Rogelj et al., 2018)

In 2020, the European Union set a target to reduce emissions by 20%, representing an initial step toward the transition to a more sustainable energy system. At the same time, the share of renewable energy sources reached around 20%, indicating a gradual shift away from fossil fuels.

By 2030, the targets become significantly more stringent, with at least a 55% reduction in emissions and an increase in renewable energy sources to over 40%. This is part of the strategy to accelerate decarbonization and align with global climate goals.

The most ambitious target is set for 2050, when the European Union plans to achieve climate neutrality. This implies near-complete decarbonization of the energy sector, with a renewable energy share of 80–90%.

These goals position the European Union as a global leader in the fight against climate change and serve as a model for candidate countries, including RNM.

3.2 Energy transition and renewables: One of the key aspects of decarbonisation in the EU is the shift to renewable energy sources. In recent years, the share of wind and solar energy has increased significantly, with them surpassing electricity from fossil fuels for the first time in 2025.

The EU is actively investing in:

6. solar energy
7. wind energy
8. green hydrogen

The electricity sector plays a central role in decarbonisation, with over 80% of electricity expected to come from renewable sources by 2050 (Table 2).

Table 2. EU Energy Mix Trend
Source: (IEA, 2022)

Year	Coal	Renewables	Gas
2000	30	10	20
2010	25	20	25
2020	15	35	20
2030	10	50	15
2050	5	80	10

The table presents the dynamics of changes in the structure of the energy mix during the period from 2000 to 2050, with a focus on three main energy sources: coal, renewable sources, and natural gas. The analysis of the data indicates a clear trend of transition from fossil fuels toward cleaner and more sustainable energy sources.

In 2000, the energy system was characterized by a relatively high dependence on coal (30%), while renewable sources had a minimal share of only 10%. Natural gas accounted for 20%, indicating its role as a supplementary energy source within the system. This structure is typical of traditional energy systems based on fossil fuels.
By 2010, a gradual decrease in the share of coal (25%) and a significant increase in renewable sources (20%) can be observed. At the same time, the share of natural gas rose to 25%, indicating its transitional role as a fossil fuel with lower emissions.
In 2020, the decarbonization trend became more pronounced. The share of coal decreased to 15%, while renewable sources reached 35%. This period was characterized by increased investments in solar and wind technologies, as well as the implementation of policies for emissions reduction.
Projections for 2030 show a significant reduction of coal to 10% and an increase in renewable sources to 50%, representing a turning point in the energy transition. Natural gas decreases to 15%, but remains important for maintaining the stability of the energy system.
The most significant changes are expected by 2050, when the share of coal will decline to only 5%, while renewable sources will dominate with 80%. This indicates a nearly complete decarbonization of the energy sector and the achievement of climate neutrality. Natural gas will have a minimal share of 10%, confirming its role as a transitional fuel.
Overall, the table shows a clear long-term trend of reducing dependence on fossil fuels and gradually increasing the share of renewable sources. This process is the result of technological progress, policy measures, and growing awareness of climate change.

3.3 Decarbonizing transport: The transport sector poses one of the biggest challenges, as it is the only sector with growing emissions. The EU has set a target to reduce transport emissions by 90% by 2050, and is promoting electromobility, the development of alternative fuels and the improvement of public transport (IEA, 2022).
Key measures include:

- electrification of vehicles
- development of sustainable fuels
- investment in rail infrastructure

The industrial sector, in turn, is being transformed through:

- digitalisation
- energy efficiency
- circular economy

3.4 Challenges and constraints: Despite progress, the EU faces numerous challenges:

- high investment costs
- resistance from industry and the agricultural sector
- dependence on energy imports

In addition, political and economic factors can slow down the decarbonization process. According to OECD (2023), a balanced policy is needed that integrates economic and environmental objectives.

Decarbonization in the Republic of North Macedonia

4.1 The Energy Sector in the Republic of North Macedonia: The energy sector in RNM has traditionally been based on fossil fuels, especially lignite, which is used to generate electricity (Energy Community, 2023). The main thermal power plants in the country are:

- MPC Bitola
- MPC Oslomej

These power plants play a significant role in the country's energy system, but they are also a major source of air pollution and carbon dioxide emissions (European Environment Agency, 2022).

Therefore, in recent years, measures have been taken to gradually reduce dependence on coal and develop alternative energy sources (World Bank, 2021).

The decarbonization process should mainly take place in the energy sector, in several sectors: buildings (residential, commercial and public), industry, electricity generation and transport. The main goal is to reduce energy needs by increasing energy efficiency and switching from fossil fuels to renewable energy sources (sun, wind and biomass), or so-called clean energy. This energy transition is not a simple matter and will last at least several decades, requiring large financial investments (Risto Tsicsonkov, 2023).

There are many reasons leading to a serious approach towards the initiation of this process within our society. By doing this, Macedonia would intensify its involvement in the worldwide process to 'save the planet from the influence of climate change' according to its possibilities. Despite the fact that our contribution to climate change is incomparably minor compared to highly industrialised countries, it is even more important to participate in the process coupled with the expected influence on a local level (K. Dimitrov & O. Dimitrov, 2016).

The Government of RNM has adopted energy transition strategies and plans that envisage increasing the share of renewable energy sources and improving energy efficiency.

Table 3 presents the structure of the energy mix according to the type of energy sources and their percentage share. The analysis shows that coal has a dominant role with 40%, indicating a significant dependence on fossil fuels. This dependence represents a serious challenge for the decarbonization process, as coal combustion is one of the main sources of carbon dioxide emissions and air pollution.

Table 3. Republic of North Macedonia Energy Mix

Source	Share (%)
Coal	40
Hydro	30
Solar	10
Wind	5
Other	15

Source: (IEA, 2022); (European Commission, 2019); (IRENA, 2022); (Energy Community Secretariat, 2023)

Hydropower ranks second with 30%, indicating a significant role of renewable sources in the energy system. This source provides relatively stable and clean electricity generation; however, its further development is limited due to natural and geographical factors.

Solar energy accounts for 10%, indicating a growing but still underutilized potential. Given the favorable climatic conditions, there is considerable opportunity to increase this share through investments in photovoltaic systems.
Wind energy has the smallest share at 5%, showing that this sector is still in an early stage of development. However, with appropriate investments and policies, wind energy can become an important part of the energy mix.
The category "other" sources, with 15%, includes various forms of energy such as biomass and other alternative sources, contributing to the diversification of the energy system.
Overall, the structure of the energy mix shows that RNM is still significantly dependent on coal, but there is a solid foundation for the development of renewable energy sources. For successful decarbonization, it is necessary to gradually reduce the share of coal and increase investments in solar and wind technologies, as well as improve energy efficiency.

4.2 Development of renewable energy sources: Renewable energy sources are a key element in the decarbonization process. They are energy sources that are naturally renewable and do not produce significant greenhouse gas emissions.
The trend of intensive investment in the construction of power plants using renewable energy sources, which began with the energy crisis in 2022, continued in both 2023 and 2024. The total number of renewable energy power plants as of 2024 amounts to 1,494, with a total installed capacity of 1,663 MW, representing nearly 56% of the total installed capacity within the country (Table 4). As in the previous two years, the majority of newly constructed power plants in 2024 are photovoltaic, namely 345 plants with a total installed capacity of 341.5 MW. The share of thermal power plants in the total installed capacity decreased from 49% in 2020 to 34.65% in 2024, as a result of the large number of new power plants utilizing renewable energy sources. The share of renewable sources in the total installed capacity was 37% in 2020, while in 2024 it reached 55.72% (Table 4).
The increased installed capacity from renewable energy sources has contributed to higher electricity production. The most notable growth is observed in production from photovoltaic plants. In 2023, 298 GWh of electricity were produced, while in 2024 production from this type of power plant reached 851 GWh (Table 4), representing an increase of 186% (ERC of the RNM, 2024).

Table 4. Number of Power Plants, Installed Capacity, and Electricity Generation from Renewable Energy Sources in 2024, by Technology

Type of power plants	**Number of power plants**	**Installed power (MW)**	**Share (%)**	**Production (GWh)**	**Share (%)**
Total	1.502	2.984	100%	6.129	100%
TPP	5	1.034	34,65%	2.355	38,43%
TE-TO (Th-H)	3	287	9,63%	1.259	20,54%
RES	1.494	1.663	55,72%	2.514	41,03%
HPP	10	587	19,67%	1.108	18,08%
WPP	3	82	2,76%	194	3,16%
Small HPP	125	133	4,46%	308	5,02%
PVPP	1.348	848	28,40%	851	13,91%

Biogas	7	12	0,40%	53	0,86%
Biomass	1	1	0,02%	0	0%

Source: (ERC of the RNM, 2024)

In North Macedonia, the most significant renewable sources are:
Solar energy: RNM has significant potential for the development of solar energy due to favorable climatic conditions and the large number of sunny days per year In recent years, several solar power plants have been built, and the installation of photovoltaic panels on households and public buildings is encouraged.
Wind energy: The Bogdanci Wind Farm is the first and largest wind power project in the country and represents an important step in the energy transition process. This park contributes to reducing carbon dioxide emissions and increasing the production of clean energy.
Hydropower: Hydropower plants play a significant role in the electricity system and are one of the oldest renewable energy sources in the country. They use water resources to produce electricity and play a significant role in the stability of the energy system.

4.3 Energy Efficiency: Energy efficiency is an important aspect of decarbonization because it allows for a reduction in energy consumption without reducing economic productivity (OECD, 2021).
Measures to improve energy efficiency include:

- improving the insulation of buildings;
- using energy-efficient appliances;
- modernizing industrial processes;
- using smart energy management systems.

These measures reduce energy costs, increase energy security, and reduce pollution.
Improving the insulation of buildings, using energy-efficient technologies, and modernizing industrial processes are among the most important measures to improve energy efficiency (IEA, 2022).

4.4 Decarbonization of the transport sector: The transport sector is a significant source of greenhouse gas emissions globally (European Environment Agency, 2022). In North Macedonia, most of the transport is based on vehicles that use petrol and diesel.
The following measures are being taken to reduce emissions:

- encouraging the use of electric vehicles;
- improving public transport;
- developing cycling infrastructure;
- using alternative fuels.

These policies contribute to reducing air pollution and improving the quality of life in urban areas. The development of electric vehicles, improving public transport and developing cycling infrastructure are part of the strategies for reducing emissions in the transport sector.

4.5 The role of decarbonization policies and strategies: Successful decarbonization requires clear state policies, strategies and legal frameworks. In recent years, the RNM has adopted several documents defining the country's energy and climate policy.
One of the most important documents is the Energy Development Strategy, which sets the foundations for the long-term development of the energy sector. This strategy envisages a

gradual reduction in the use of coal and an increase in the share of renewable energy sources (Ministry of Economy, 2020).
In addition, the country is working on harmonization with the European Green Deal, which aims for Europe to become a climate-neutral continent by 2050 (European Commission, 2019). This means that RNM should also reduce greenhouse gas emissions and develop a sustainable energy system.
These policies envisage measures such as:

- stimulating investments in renewable energy sources;
- improving energy efficiency in public and private buildings;
- supporting the development of new technologies;
- promoting sustainable transport.

These policies aim to create an economy that is more resilient to climate change and ensures stable economic development.

4.6 Economic and social benefits of decarbonization: Decarbonization is not only an environmental necessity, but also an opportunity for economic development. The transition to clean energy can bring numerous economic and social benefits.
One of the most important benefits is the creation of new jobs. The development of solar power plants, wind farms and other green technologies requires a new workforce and skilled personnel. This can contribute to reducing unemployment and developing new industries.
In addition, decarbonization can lead to:

- reducing energy costs in the long term;
- improving the health of the population due to reduced pollution;
- increasing the energy independence of the country;
- attracting foreign investment.

Improving air quality is particularly important for cities in RNM, where air pollution is a serious problem. In addition, reducing air pollution can contribute to improving the health of the population (World Bank, 2021).

4.7 The role of international cooperation: The decarbonization process requires significant financial and technological resources. Therefore, international cooperation plays an important role in supporting countries undergoing energy transition.
North Macedonia cooperates with several international organizations and institutions such as:

- European Union
- World Bank
- European Bank for Reconstruction and Development
- United Nations

These institutions provide financial support, technical assistance and expertise for the development of projects in the field of renewable energy sources and energy efficiency (United Nations, 2020).
Through this cooperation, numerous projects are being implemented, such as the construction of new solar and wind power plants, modernization of the electricity grid and improvement of energy infrastructure.

4.8 Future Development Perspectives: In the future, the decarbonization process in RNM is expected to accelerate. Technological development, decreasing prices of renewable energy sources and increased awareness of environmental protection will contribute to a faster energy transition.

Some of the main directions for future development are:

- construction of new solar and wind power plants;
- gradual closure of coal-fired power plants;
- modernization of the electricity grid;
- development of smart energy systems;
- increasing energy efficiency in all sectors.

By implementing these measures, RNM can significantly reduce greenhouse gas emissions and contribute to the global fight against climate change.

In the future, an increase in investments in renewable energy sources and a gradual reduction in the use of fossil fuels is expected.

The development of smart energy systems and energy storage will play an important role in the modernization of the energy system.

Discussion

The decarbonization process in the RNM represents a complex transformation of the energy, economic and social system. Although the country has significant potential for the development of renewable energy sources, there are several factors that influence the dynamics of this transition.

One of the most important aspects is the dependence on existing coal-based energy capacities. Thermal power plants have long been the basis of the electricity system and their gradual replacement with renewable sources requires significant financial investments and infrastructure changes.

On the other hand, the development of new technologies such as solar and wind power plants opens up opportunities for diversification of energy sources and reduction of greenhouse gas emissions. However, the integration of these sources into the electricity grid requires modernization of the system and improvement of energy management.

In addition, an important aspect of decarbonization is the social dimension. The transition to a green economy may have an impact on workers in traditional energy sectors, especially in mining. Therefore, it is necessary to implement the concept of a just transition, which will provide new opportunities for employment and retraining of the workforce. In this context, it can be concluded that decarbonization is not only a technological process, but also a social and economic transformation that requires a coordinated approach between the state, the private sector and international institutions.

Comparative Analysis

Table 5 presents a comparative analysis of key decarbonization indicators between the European Union and the RNM.

Table 5. EU vs Republic of North Macedonia

Indicator	EU	RNM
Emissions Reduction Target	55	30
Renewables Share	40	20
Investments Index	90	40

Source: (European Commission, 2019); (IRENA, 2022); (World Bank, 2021)

The European Union has a significantly more ambitious target for reducing greenhouse gas emissions, with a goal of 55%, compared to 30% for the RNM. This difference reflects the EU's greater institutional readiness and financial capacity to implement climate policies.
Regarding the share of renewable energy sources, the EU has a target of 40%, while the RNM has a significantly lower share of 20%. This indicates the need for increased investments in solar and wind technologies within the national energy system.
The investment index further confirms this disparity, with the EU having a value of 90, while RNM has 40. This indicator points to limited access to financial resources and the need for increased international support.

Challenges in the decarbonization process

Despite the benefits, the decarbonization process faces significant challenges.
The most significant challenges are (Energy Community, 2023):

- high investment costs for new energy technologies;
- dependence on existing thermal power plants;
- the need to modernize the electricity grid;
- social consequences for mining workers.

Therefore, careful planning of the energy transition is necessary in order to ensure economic stability and social justice.

Recommendations

In order to successfully implement the decarbonization process in the RNM, it is necessary to take several specific measures and activities.
Firstly, it is necessary to increase investments in renewable energy sources, especially in solar and wind power plants. These technologies have great potential and can significantly contribute to reducing greenhouse gas emissions.
Secondly, it is necessary to improve energy efficiency in all sectors, including industry, transport and households. This can be achieved through the modernization of infrastructure, the use of energy-efficient technologies and increasing public awareness of the rational use of energy.
Thirdly, it is important to develop a modern and stable electricity grid that can integrate a greater share of renewable energy sources. This includes investments in smart grids, energy storage systems and the digitalization of the energy sector.
Fourthly, it is necessary to support education and training programs for the workforce in order to prepare personnel for new green industries. This will ensure a successful social transition and reduce the negative consequences of the closure of traditional energy capacities. Finally,

it is important to continue international cooperation and use the financial instruments and funds provided by international organizations. This will enable faster implementation of projects related to the energy transition and sustainable development.

Conclusion

Decarbonization is a complex and long-term process that requires an integrated approach at the global, regional and national levels. The European Union is a leader in this area, setting ambitious goals and policies, while RNM is making significant steps towards their alignment. Although there are numerous challenges, such as financial constraints and structural weaknesses, the trend of transition to clean energy is inevitable. With the right strategy and international cooperation, the RNM can successfully implement the energy transition and ensure a cleaner and more sustainable future.
With appropriate policies, investments and cooperation, decarbonization can contribute to sustainable development and improve the quality of the environment.

Nomenclature

EEA	European Environment Agency
EU	European Union
IEA	International Energy Agency
IPCC	Intergovernmental Panel on Climate Change
IRENA	International Renewable Energy Agency
MPC	Mining Power Combine
OECD	Organisation for Economic Co-operation and Development
RNM	Republic of North Macedonia

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TECHNOLOGICAL INNOVATION AND PRODUCTION EFFICIENCY: EVIDENCE FROM ARAB ECONOMIES IN A GLOBAL CONTEXT

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Abstract

This study explores the relationship between technological innovation and production efficiency across Arab economies within a comparative global framework. Utilizing panel data covering the period 2011-2024, the analysis assesses how innovation inputs, determined by the Global Innovation Index (GII) Input Sub-Index, impact economic performance, proxied by GDP per capita. The study implements fixed-effects econometric models to account for cross-country heterogeneity and incorporates key control variables such as research and development expenditure, trade openness, foreign direct investment, population size, gross capital formation, and political stability. The results indicate that technological innovation does not have a statistically significant direct impact on production efficiency across countries, recommending that innovation alone may not translate into immediate economic gains. Yet, the degree of this relationship differs between Arab and non-Arab economies, as well as between GCC and non-GCC countries, mirroring differences in institutional structures and innovation ecosystems. Robustness checks utilizing GII Output Sub-Index ensure the consistency of the results. This study contributes to the literature by offering empirical evidence on the role of innovation in forming economic performance in the Arab region within a global context. The results provide important policy implications for supporting innovation systems and improving productivity to support sustainable economic development.

Keywords: Technological Innovation; Production Efficiency; GDP per Capita; Arab Economies; Global Innovation Index; Panel Data Analysis

Introduction

Technological innovation is broadly identified as a key driver of productivity growth and economic development (Romer, 1990; Duguet, 2006). Development in innovation improves production process, enhances efficiency, and reinforces economic competitiveness. Yet, the relationship between innovation and economic performance is not uniform across countries (Crépon et al., 1998; Benavente, 2006). Variation in institutional quality, innovation capacity, and economic structure influence how effectively innovation contributes to productivity.

Arab economies offer a relevant context for assessing this relationship. Irrespective of increasing efforts to improve innovation systems, many countries in the region face structural challenges that limit the effective transformation of innovation inputs into economic performance. These contain limited research and development investments, different levels of technological absorption, and institutional inefficiencies.

This study examines the relationship between technological innovation and production efficiency across Arab economies within a comparative global framework. The analysis expands to non-Arab countries and distinguishes between GCC and non-GCC economies to capture structural differences.

The main objective of this study is to assess whether innovation inputs contribute to economic performance and whether these impacts vary across regions and economic groupings.

Technological innovation has become a central pillar of economic development strategies in both advanced and emerging economies. Governments increasingly invest in research and

development, knowledge-based industries, and digital transformation to improve productivity and sustain long-term growth. Yet, empirical evidence recommends that the effectiveness of these investments differs significantly across countries (Crépon et al., 1998), mainly in developing and transition economies.

In the case of Arab economies, this concern is particularly significant. While several countries have made progress in strengthening their innovation system, structural challenges continue to be there. These contain relatively low levels of R&D investment, limited private sector participation in innovation activities, and variations in institutional capacity. Hence, innovation inputs do not always interpret into improved economic performance.

Comprehending this relationship is vital for assessing the effectiveness of innovation-driven strategies. Production efficiency, mirrored via higher productivity and economic output, reflects a key channel through which innovation contributes to economic growth.

Empirical evidence from developing and emerging economies further supports the connection between innovation and productivity, while addressing differences across institutional and economic context (Chudnovsky et al., 2006; Kahn et al., 2022).

Methodology

This study implements a quantitative research design based on panel data analysist. The dataset includes the period from 2011 to 2024 and covers a broad cross-section of countries, with a particular focus on Arab economies within a global comparative framework.

2.1 Data and Variables: The dependent variable utilized in this study is GDP per capita, which serves as a proxy for production efficiency. This measure mirrors the overall level of economic productivity and output within a country.

The key independent variable is technological innovation, measured using the Global Innovation Index (GII) Input Sub-Index. This index depicts several dimensions of innovation, namely institutions, Human capital, market sophistication, infrastructure, and business sophistication.

To ensure robustness, various control variables are taken into consideration in the model:

[1] Research and Development (R&D) expenditure (% of GDP)
[2] Trade openness (sum of exports and imports)
[3] Foreign Direct Investment (FDI) inflows (% of GDP)
[4] Gross Capital Formation (GCF)
[5] Population size (log)
[6] Political stability (World Governance Indicators)

The data utilized in this study are collected from the World Development Indicators database (World Bank, 2024) and the Global Innovation Index (WIPO, 2024).

2.2 Econometric Model: The study utilizes fixed-effects panel regression models to account for unobserved heterogeneity across countries. This method allows the analysis to control for country-specific characteristics that remain constant over time.

The econometric model utilized in this study is as follows:

$$(1)\ \boldsymbol{GDP_{it} = \beta_0 + \beta_1 GII_{it} + \beta_2 X_{it} + \mu_i + \epsilon_{it}}$$

Where:

- GDP_{it}: GDP per capita
- GII_{it}: innovation input
- X_{it}: control variables
- μ_i: country effects
- ϵ_{it}: error term

Furthermore, robustness checks are implemented using the GII Output Sub-Index to confirm the consistency of the outcomes.

Results and Discussion

The empirical results show that the relationship between technological innovation and production efficiency is not statistically significant across the overall sample.

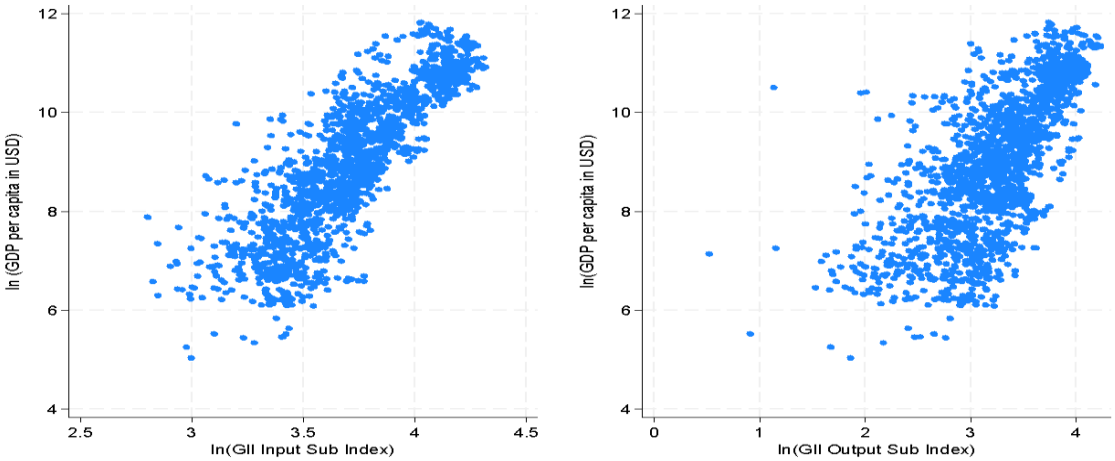


Figure 1: Relationship Between Innovation and GDP per Capita (Overall Sample)

Figure 1 displays a positive relationship between technological innovation and GDP per capita across the full sample, showing that higher innovation inputs are associated with improved economic performance.

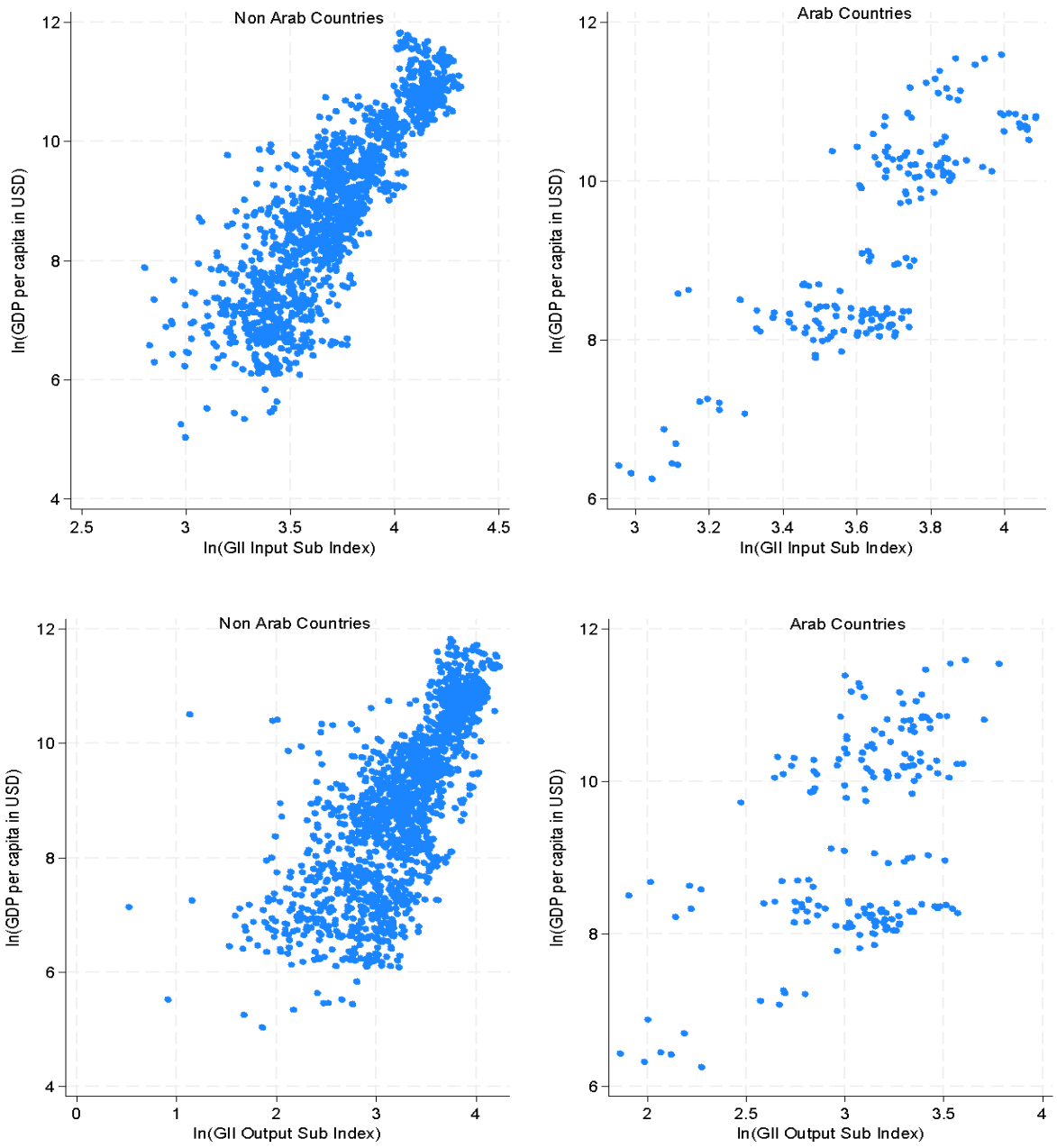


Figure 2: Innovation and GDP per Capita – Arab vs Non-Arab Countries

Figure 2 addresses variation between Arab and non-Arab countries. The relationship seems to be stronger in non-Arab economies, recommending differences in institutional and economic structures.

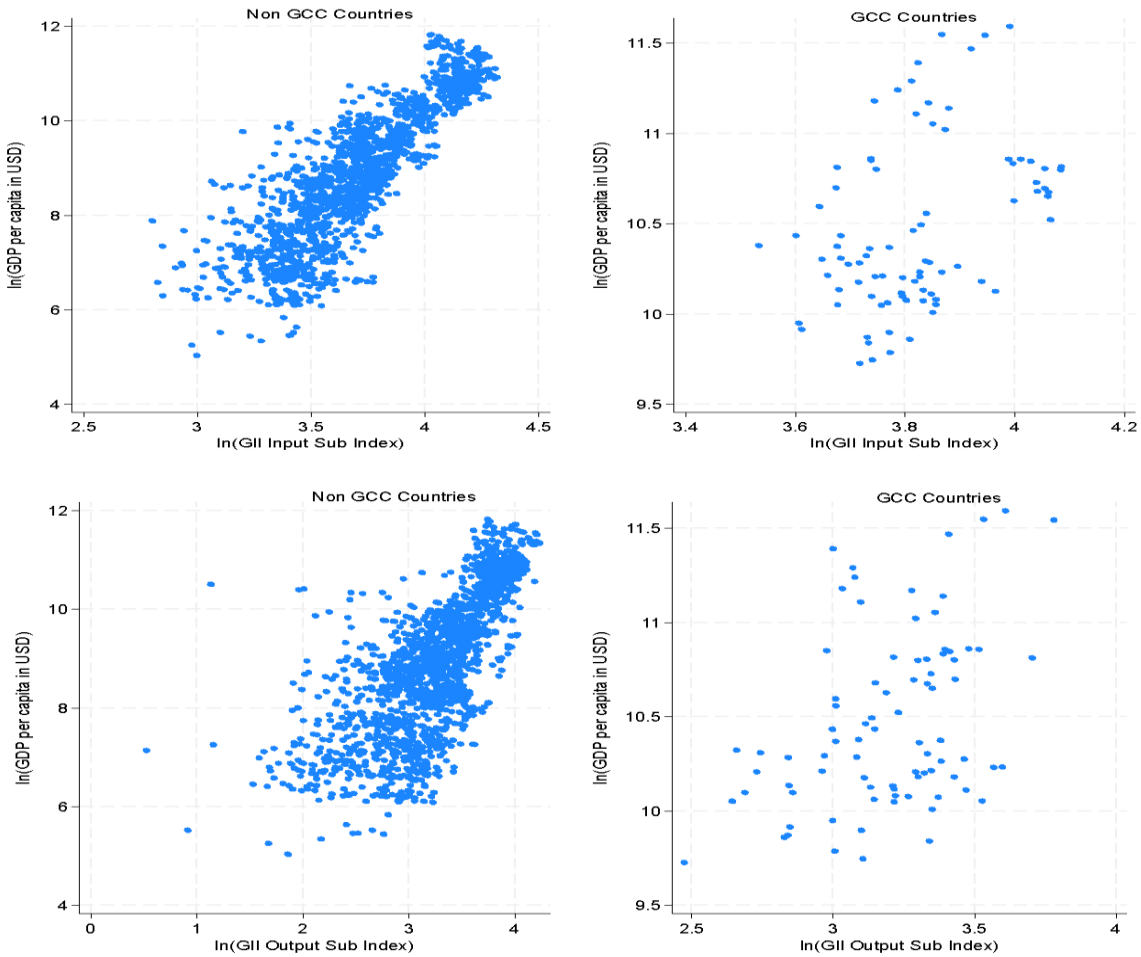


Figure 3: Innovation and GDP per Capita – GCC vs Non-GCC Countries

Figure 3 demonstrates the comparison between GCC and non-GCC countries. The findings recommend that economic structure plays a noticeable role in forming how innovation influences production efficiency.

This outcome is consistent with previous studies that recognize innovation as a key determinant of productivity growth (Benavente, 2006; Duguet, 2006).

Yet, the findings also reveal important variations:

- The impact of innovation is weaker in some Arab economies compared to non-Arab countries
- GCC countries display different dynamics due to resource-based economic structures
- Institutional quality and absorptive capacity play a vital role in determining outcomes

Similar variations have been noticed in prior research, where the effectiveness of innovation depends on institutional quality and economic structure (Chudnovsky et al., 2006; Kahn et al., 2022).

The robustness analysis confirms that these results remain consistent across alternative model specifications.

These findings recommend that innovation alone is not sufficient; complementary factors like institutional development and economic diversification are vital for interpreting innovation into productivity gains.

The findings recommend that while innovation plays a noticeable role in enhancing economic performance, its effect is not uniform across all countries. In Arab economies, the effectiveness

of innovation is impacted by structural and institutional factors. Countries with stronger institutional frameworks and higher absorptive capacity tend to benefit more from innovation investments.

Moreover, the analysis addresses the differences between GCC and non-GCC economies. GCC countries, despite having higher income levels, often tend to count on resource-based economic structures, which may limit the effect of innovation on productivity. On the contrary, non-GCC economies may benefit more from innovation due to the need for diversification.

These results focus on the fact that innovation should not be perceived as a standalone driver of growth. Instead, it must be supported by complementary policies, namely enhancement in governance, education, and economic diversification.

These results are consistent with previous studies connecting innovation to productivity (Benavente, 2006; Chudnovsky et al., 2006).

3.1 Descriptive Statistics: The descriptive statistics of the main variables utilized in the analysis are displayed in Table 1. These statistics offer an overview of the distribution and variation of the variables across countries over time.

The descriptive statistics offer an initial understanding of the data distribution prior conducting the economic analysis.

Table 1 - Summary Statistics of Key Variables

Variable	**Observations**	**Mean**	**Std. Dev.**	**Minimum**	**Maximum**
GDP per capita (USD)	1776	18,738	23,356	153.93	137,516.59
GII Input Sub-Index	1776	43.06	10.47	16.47	74.90
GII Output Sub-Index	1775	28.76	13.41	1.68	68.60
R&D expenditure (% GDP)	1023	1.10	1.03	0.013	6.02
Trade (% GDP)	1705	91.45	50.82	22.49	442.62
Gross Capital Formation (% GDP)	1671	23.11	8.27	1.43	53.21
FDI inflows (% GDP)	1772	5.57	27.66	-391.56	452.22
Population (log)	1776	16.46	1.61	12.67	21.10
Political Stability Index	1652	46.62	27.74	0.00	99.53

3.2 Regression Results: Table 2 presents the results of the fixed-effect regression model assessing the relationship between technological innovation and production efficiency.

Table 2 - Fixed-effects regression results for innovation and GDP per capita

```
. xtreg ln_GDPPC_USD c.ln_GIIInputSubIndex Pop_Million FDI_PercGDP Trade_PercGDP RDexp_Perc
> GDP PoliticalStability GCF_PercGDP i.Year, fe robust

Fixed-effects (within) regression               Number of obs     =         995
Group variable: Country_Code                    Number of groups  =         107

R-squared:                                      Obs per group:
     Within  = 0.3737                                         min =           1
     Between = 0.0382                                         avg =         9.3
     Overall = 0.0421                                         max =          13

                                                F(19, 106)        =       25.18
corr(u_i, Xb) = -0.5865                         Prob > F          =      0.0000

                                  (Std. err. adjusted for 107 clusters in Country_Code)
```

ln_GDPPC_USD	Coefficient	Robust std. err.	t	P>|t|	[95% conf.	interval]
ln_GIIInputSubIndex	-.1522276	.1838614	-0.83	0.410	-.5167507	.2122956
Pop_Million	.0027589	.0014107	1.96	0.053	-.0000378	.0055557
FDI_PercGDP	.0001396	.0001789	0.78	0.437	-.0002152	.0004944
Trade_PercGDP	-.0013354	.0008299	-1.61	0.111	-.0029809	.00031
RDexp_PercGDP	-.0140934	.0483929	-0.29	0.771	-.110037	.0818502
PoliticalStability	.0015666	.001159	1.35	0.179	-.0007313	.0038645
GCF_PercGDP	.0037731	.0032174	1.17	0.244	-.0026056	.0101519
Year						
2012	.0098644	.0120864	0.82	0.416	-.0140982	.0338269
2013	.0382343	.0111486	3.43	0.001	.0161311	.0603374
2014	.0525306	.0146202	3.59	0.000	.0235446	.0815165
2015	-.0597388	.0223042	-2.68	0.009	-.103959	-.0155186
2016	-.0755726	.0247953	-3.05	0.003	-.1247317	-.0264134
2017	.0125001	.0265637	0.47	0.639	-.0401651	.0651653
2018	.0731796	.0259456	2.82	0.006	.02174	.1246192
2019	.0700079	.0295995	2.37	0.020	.011324	.1286918
2020	.0087111	.0344716	0.25	0.801	-.0596321	.0770544
2021	.1718901	.0305941	5.62	0.000	.1112344	.2325458
2022	.2302169	.0339156	6.79	0.000	.1629759	.2974578
2023	.3011445	.0561165	5.37	0.000	.1898882	.4124009
_cons	9.808582	.699266	14.03	0.000	8.422219	11.19495
sigma_u	1.5387721					
sigma_e	.1212622					
rho	.99382818	(fraction of variance due to u_i)				

The results in Table 2 illustrate that the coefficient of the GII Input Sub-Index is negative and statistically insignificant. This shows that technological innovation inputs do not have a measurable direct effect on GDP per capita across the sample. This recommends that investments in innovation-related inputs alone may not be sufficient to create immediate economic returns, mainly due to inefficiencies in innovation systems, delayed impacts of innovation, or limited absorptive capacity within certain economies. The control variables usually display expected signs, supporting the overall consistency of the model.

These findings are consistent with previous studies recommending that innovation inputs do not automatically interpret into productivity gains without supportive institutional and economic conditions (Chudnovsky et al., 2006; Kahn et al., 2022).

Conclusions

This study offers empirical evidence on the relationship between technological innovation and production efficiency across Arab economies within a global framework. The results show that innovation inputs do not have a statistically significant direct impact on economic performance, recommending that investment in innovation alone may not be sufficient to generate immediate productivity gains. Yet, the effectiveness of innovation depends on structural and institutional conditions.

From a policy perspective, the results address the need for:

- Improving national innovation systems
- Expanding investment in research and development
- Boosting institutional quality
- Encouraging economic diversification

Additional research may further investigate sector-level dynamics and the role of digital transformation in forming productivity outcomes.

This study addresses the importance of aligning innovation policies with institutional and structural reforms to maximize their effect on economic performance, mainly in the context of Arab economies.

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REFRAMING SUSTAINABLE MOBILITY IN POST-SOCIALIST CITIES: THE ROLE OF URBAN FORM AND WALKABILITY IN PUBLIC TRANSPORT INTEGRATION IN TETOVO

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Abstract

Post-socialist Western Balkans cities are increasingly experiencing mobility problems as a result of disorganized urban growth, weak governance, the automobile epidemic, and underdeveloped public transport. North Macedonia's Tetovo is an epitome of when these fast urban developments, informal urbanities, and scarce pedestrian infrastructures create an undermining force in reaching sustainable mobility goals. In this conference paper, we focus on how urban structure, walkability, and the integration of public transport in Tetovo are mutually reinforcing, such that spatial arrangement plays an influential role in transport efficiency and social service accessibility. By using a mixed-methods methodology – focusing on GIS spatial analysis, pedestrian audits, field observations, transport accessibility assessments, and policy review, the analysis shows major systemic barriers such as disjointed pedestrian networks, insufficient first-mile/last-mile connectivity, and dispersed land use, and limited multimodal planning. The results confirm that public transport efficiency, private vehicle dependence, and environmental and social injustice are greatly increased by urban form and inadequate walkability. From research to practice, the paper envisions an integrated planning process: walkability enhancement, transit-oriented development, multimodal connectedness, and context-sensitive policy changes. The study provides applied design strategies for Tetovo, offering lessons that can be transferable to other post-socialist urban settings for sustainable mobility transitions.

Keywords: sustainable mobility, post-socialist cities, walkability, public transport integration, urban form, transit-oriented development.

Introduction

1.1 Background: Urban mobility systems are critical for economic productivity, social inclusion, and environmental sustainability. In post-socialist cities, though, historical planning legacies mixed with market-driven urban transitions can result in fragmented development patterns that undermine integrated transportation systems. After centralized planning infrastructures collapsed, many Balkan cities experienced rapid and often unregulated urbanization marked by sprawl, an increase in private vehicle usage, and weakened investment in public infrastructure. Those challenges are perfectly illustrated in Tetovo. Tetovo, one of North Macedonia's fastest-growing urban centers, has transformed both demographically and spatially over the last several decades. Population growth, commercial expansion, and informal construction have significantly changed its urban form, but transport has not kept pace with it. Public transport is a largely underdeveloped industry, the pedestrian sector remains inconsistent, and urban growth has leaned more towards reliance on cars.

1.2 Research Problem In a city of growing urbanization, Tetovo does not have a sound mobility model integrated enough to deal with land use, pedestrian access, and public transportation systems. The present urban developments diminish the efficiency of transport and compromise sustainability objectives.

1.3 Aim of the Study This paper explores the extent to which the urban form and walkability impact the integration of public transport in Tetovo and outlines practical planning options in an attempt to move mobility systems towards sustainability.

1.4 Research Questions

- To what extent does the urban form of Tetovo affect the accessibility of public transport?
- What walkability deficiencies obstruct sustainable mobility?
- What practical applications can research findings offer for planning?
- What mobility strategies can we use to assist in the long-term sustainable transformation of post-socialist cities?

1.5 Significance Integrating spatial analysis with practical urban policy suggestions, this article is directed at the theme of the conference, "From Research to Application," by converting theoretical findings into applicable planning frameworks.

Literature Review

2.1 Sustainable Mobility Frameworks: Sustainable transport is much more than the transportation infrastructure itself; it embodies environmental impact, accessibility, social equity, and urban design. Newman & Kenworthy (1999) highlight the relationship between density and car dependency in cities, and Cervero (1998) presents transit-oriented development (TOD) to describe a model between transport and spatial planning.

2.2 Cities and the Urban Form and the Form of Transport: The form of cities plays an important role in travel behavior. Compact, mixed-use, and connected surroundings foster public transport and active mobility that are beneficial for cities, while dispersed urban forms encourage dependence on cars. Connectivity, block size, density, and land use diversity are critical drivers of sustainable mobility performance.

2.3 Walkability as a Mobility Driver: Walkability has been recognized as a basic need of public transport systems more than ever. This makes transit work, but effective transit relies on safe, accessible pedestrian infrastructure—especially for first-mile and last-mile connections. Subpar sidewalk quality, isolated access routes, and unsafe crossings detract from the appeal of transit.

2.4 Urban Post-Socialist Challenges: Often, the post-socialist cities now confront:

- fragmented planning systems.
- informal development.
- governance instability.
- aging infrastructure.

Such circumstances make sustainable transport implementation difficult and will require the implementation of context-sensitive strategies.

2.5 Research Gap: Few studies have focused on the effect of urban form and walkability on public transport in medium-sized Balkan post-socialist cities, especially in Tetovo among these.

Methodology & Results

3.1 Research Design: A mixed-methods methodology was employed to capture the spatial, functional, and policy dimensions of mobility integration.

3.2 Data Collection Methods:
Primary Methods: • Field observations. • Walkability audits. • Sidewalk and pedestrian network assessments. • Public transport stop accessibility surveys. • Urban photography documentation. Secondary Methods: • GIS spatial mapping. • Municipal urban plans. • Census and demographic data. • Transport policy analysis. • Comparative case studies.

3.3 Analytical Tools: • Spatial accessibility analysis. • Walkability scoring systems. • Street network connectivity analysis. • Land-use distribution mapping. • Comparative benchmarking.

3.4 Study Area. Tetovo, North Macedonia: was selected due to its rapid post-socialist urbanization and representative mobility challenges.

Results

Urban form features. Tetovo can be defined by the city structure:
• dispersed expansion.
• mixed formal and informal development.
• limited zoning consistency.
• traffic congestion.
• weak multimodal organization. These patterns diminish the efficiency of transport as well as engender accessibility inequalities.

4.1 Walkability Challenges: Key deficiencies include: • discontinuous sidewalks. • inadequate pedestrian crossings. • poor universal accessibility • unsafe street environments. • limited shading and comfort. • weak neighborhood-to-transit connectivity.

4.2 Integration Problems of Public Transport: Observed problems include: • limited route optimization. • poor service frequency. • insufficient transit stop accessibility. • lack of coordinated transport hubs. • weak integration with cycling or pedestrian systems.

4.3 Environmental and social impacts: Mobility systems currently in place contribute to: • air pollution. • congestion. • social exclusion. • reduced public health. • unequal access to services.

Planning framework — from research to application.

5.1 Effective urban strategies:
Proposed interventions:
• Rehabilitation and expansion of sidewalks.
• Safe pedestrian corridors.
• Transit-oriented development nodes.
• Mixed-use zoning improvements.
• Multimodal transport hubs.
• Bicycle integration.
• Smart mobility technologies.
• Accessibility retrofits.

5.2 Policy Recommendations:
• Integrated urban and mobility planning.
• Sustainable transport investment.
• Public realm prioritization.
• Regulatory reforms for informal growth.
• Community-inclusive planning processes.

5.3 Design Applications: Tetovo can improve mobility through:
• compact urban restructuring.
• enhanced pedestrian infrastructure.
• decentralized service distribution.
• sustainable neighborhood planning.

Conclusions

These insights illustrate how Tetovo's mobility issues are spatial in nature, rather than simply infrastructural. Fragmented urban form detracts directly from transport efficiency, while poor walkability threatens the viability of public transport. Sustainable mobility thus depends on integrated spatial and policy restructuring as opposed to isolated transport interventions. This study proves that post-socialist mobility sustainability depends on: • urban restructuring • pedestrian prioritization • multimodal integration • governance reform • long-term sustainability policy.
Tetovo's transition toward sustainable mobility requires reframing transportation as an urban design and governance issue rather than merely an infrastructural challenge. Through a comprehensive holistic approach considering walkability, urban form optimization, and public transport planning, the city can decrease automobile dependency, increase social integration, and elevate environmental performance. The developed approach presents a way to apply research to practical interventions, facilitating the conference aim of changing academic research to practical work. These results may have more wide-ranging implications for medium-sized post-socialist cities experiencing comparable mobility transitions.

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[15] UN-Habitat, S. U. (n.d.). *(Various years, International Policy Reports) establishes global frameworks for equitable, inclusive, and environmentally sustainable mobility systems.*

PREVALENCE AND GENDER DIFFERENCES IN ACTIVE HELICOBACTER PYLORI INFECTION BASED ON FECAL ANTIGEN TEST IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Helicobacter pylori infection remains a significant health problem, particularly in developing countries. The aim of this study was to determine the prevalence of active *H. pylori* infection and evaluate the impact of age and gender in a population from the Republic of North Macedonia. The study was conducted during the period of June–October 2024 and included 279 patients aged 3–87 years who presented with gastrointestinal complaints. Fecal samples were analyzed for the presence of *H. pylori* antigen using the immunochromatographic method. Of the total 279 patients tested, 41 (14.7%) were found to be positive, while 238 (85.3%) were negative. The statistical analysis showed that gender had a significant impact on the test result (OR = 3.677; p = 0.005), while age did not show a statistically significant association (p = 0.992). The results indicate that active *H. pylori* infection has a relatively low prevalence in this population, while gender remains an important factor in its distribution.

Keywords:Helicobacter pylori, fecal antigen, prevalence, risk factors, gender.

Introduction

Helicobacter pylori infection is one of the most widespread chronic bacterial infections globally and continues to be a significant public health issue. It is estimated that more than half of the global population is colonized by this microorganism, although prevalence varies significantly between different regions and population groups (Hooi et al., 2017; Zamani et al., 2018). *Helicobacter pylori* colonizes the gastric mucosa and is strongly associated with a wide range of gastrointestinal pathologies, including chronic gastritis, peptic ulcer, MALT lymphoma, and gastric carcinoma (Kusters et al., 2006; IARC, 2012). Due to its role in gastric carcinogenesis, the World Health Organization has classified *Helicobacter pylori* as a Group I carcinogen (IARC, 2012).

The prevalence of *Helicobacter pylori* infection is influenced by a range of factors, including socioeconomic conditions, hygiene levels, population density, access to clean water, and the development of the healthcare system, with prevalence being significantly higher in developing countries compared to industrialized ones (Zamani et al., 2018; Mentis et al., 2015). In addition to environmental and socioeconomic factors, demographic factors such as age and gender have also been studied, although their association with the infection remains not always consistent across different populations (Naghibi et al., 2015).

Diagnosis of *Helicobacter pylori* includes both invasive and non-invasive methods. Invasive methods, such as gastric biopsy with histological examination, culture, and urease test, are considered more specific but are less suitable for epidemiological studies due to their invasive nature (Kusters et al., 2006). Among non-invasive methods, serological tests, urease breath test, and fecal antigen test are widely used in clinical practice and epidemiological research (Chey et al., 2017; Elbehiry et al., 2023). However, serological tests have the limitation of potentially reflecting past exposure to the bacterium, as IgG antibodies can remain present even after the infection has been eradicated (Kusters et al., 2006). In this regard, the fecal antigen test is considered a reliable method for identifying active infection, as it allows for the detection

of the current presence of the bacterium in the gastrointestinal tract (Kassid et al., 2022; Elbehiry et al., 2023).

Although *Helicobacter pylori* remains a pathogen of high clinical and epidemiological importance, data on the prevalence of active infection and associated factors in specific populations remain limited, especially in the Balkan region. In this context, the aim of this study was to assess the prevalence of active *Helicobacter pylori* infection, identified through the fecal antigen test, and to analyze the impact of demographic factors, such as age and gender, in a population from the Republic of North Macedonia.

Materials and Methods

This retrospective study was conducted during the period of June–October 2024 and includes 279 patients aged 3–87 years who presented with gastrointestinal complaints.

Fecal samples were analyzed for the presence of *Helicobacter pylori* antigen at the Institute of Microbiology and Parasitology at the Faculty of Medicine in Skopje, using the immunochromatographic method with monoclonal antibodies. This method allows for the qualitative detection of *Helicobacter pylori* antigen in feces and is used for the identification of active infection.

Demographic data, including age and gender, were included in the analysis. Statistical processing of the data was performed using IBM SPSS software (version 20.0). Logistic regression was used to assess the relationship between variables, and p-values < 0.05 were considered statistically significant.

Results and Discussion

3.1 Reults: This study included a total of 279 patients tested for the presence of *Helicobacter pylori* through fecal antigen. Table 1 presents the distribution of results according to absolute and relative frequencies, showing the prevalence of active infection in the studied population.

Table 1. Prevalence of active Helicobacter pylori infection based on fecal test

Testi_feces					
	Frequency	Percent	Valid Percent	Cumulative Percent	
Valid	Negativ	238	85.3	85.3	85.3
	Pozitiv	41	14.7	14.7	100.0
	Total	279	100.0	100.0	

From the data presented in Table 1, of the total 279 patients tested, 41 (14.7%) were found to be positive, while 238 (85.3%) were negative. These data indicate that active *Helicobacter pylori* infection is present in a relatively low percentage of the analyzed patients, suggesting a moderate prevalence of active infection in this population.

The analysis by gender is presented in Table 2, which shows the distribution of positive and negative fecal test results between females and males.

Table 2. Distribution of active Helicobacter pylori infection by gender

Gender	**Negative n (%)**	**Positive n (%)**	**Total**
Female	146 (80.7)	35 (19.3)	181
Males	92 (93.9)	6 (6.1)	98
Total	**238 (85.3)**	**41 (14.7)**	**279**

From the data presented in Table 2, females had a significantly higher probability of being positive for *Helicobacter pylori* compared to males. Of the 181 females tested, 35 (19.3%) were positive, while of the 98 males, only 6 (6.1%) were positive. These results indicate a higher prevalence of active infection in females compared to males.

To assess the impact of demographic factors on the presence of active *Helicobacter pylori* infection, a logistic regression model was applied. The results showed that gender is a statistically significant factor in predicting the infection (OR = 3.677; p = 0.005), indicating that females are about 3.6 times more likely to test positive compared to males. In contrast, age did not show a statistically significant impact on the presence of the infection (p = 0.992).

Furthermore, the correlation analysis showed a very weak and statistically insignificant relationship between age and the fecal test result (r = 0.014; p = 0.810). These results indicate that, in this sample, gender is a more important factor in the distribution of active *Helicobacter pylori* infection than age.

Figure 1 presents the histogram of the age distribution of the patients included in the fecal test analysis.

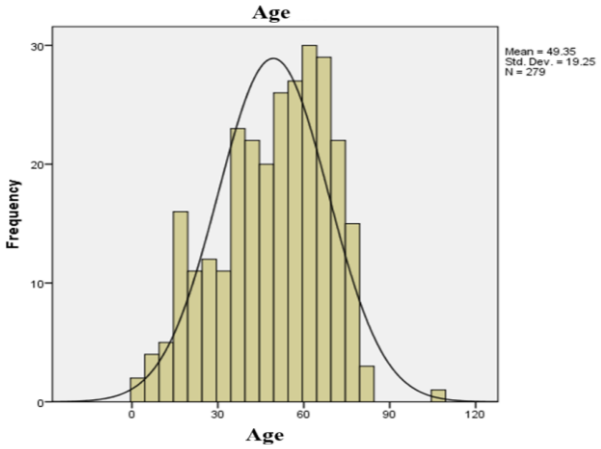


Figure 1. Histogram of the age distribution of patients tested for *Helicobacter pylori* in feces.

3.2 Discussion: The prevalence of active *Helicobacter pylori* infection observed in this study (14.7%) was lower compared to many studies reported in developing countries, where prevalence often ranges between 30% and 50% (Hooi et al., 2017; Zamani et al., 2018). This difference can be partially explained by the diagnostic method used, as the fecal antigen test identifies the current presence of the bacterium and, consequently, reflects active infection, while serological methods may yield higher values due to the presence of antibodies that remain detectable even after past exposure or previous infection (Kusters et al., 2006; Chey et al., 2017). For this reason, the fecal antigen test is considered a more specific approach for assessing the current prevalence of the infection (Kassid et al., 2022; Elbehiry et al., 2023).

One of the most important findings of this study is the statistically significant association between gender and active infection, with females showing a higher probability of a positive result compared to males. This finding is not always consistent in the literature. Some studies

have not reported significant gender differences, while others have shown higher prevalence in males or similar distribution between genders (Zamani et al., 2018; Naghibi et al., 2015). The differences observed in this study may be related to biological, hormonal, or socio-cultural factors, as well as healthcare-seeking behavior, although these variables were not directly analyzed.

On the other hand, age did not show a statistically significant impact on the presence of active infection. This result suggests that the current presence of the bacterium does not necessarily follow the same distribution pattern as long-term exposure, as active infection represents a more dynamic state and is potentially influenced by previous treatment, immune status, and other environmental factors (Mentis et al., 2015). The lack of a significant association with age in this study is consistent with the fact that the fecal antigen test more accurately reflects the current presence of the bacterium rather than exposure history.

However, this study has several limitations that should be considered when interpreting the results. The retrospective design and the lack of data on other potential risk factors, such as socioeconomic status, hygiene and sanitation conditions, diet, and lifestyle, limit the full interpretation of the factors influencing the spread of the infection. Furthermore, the sample size and the unequal gender distribution may have influenced the observed results.

In conclusion, the findings of this study contribute to a clearer understanding of the distribution of active *Helicobacter pylori* infection and highlight the importance of using diagnostic methods that differentiate active infection from past exposure. Furthermore, the results suggest that gender may play an important role in the distribution of the infection, while the impact of age remains limited in this population.

Conclusions

This study demonstrates that the assessment of *Helicobacter pylori* through the fecal antigen test provides a more accurate reflection of active infection, revealing a lower prevalence compared to serological methods. Gender was identified as an important factor in the distribution of the infection, while age did not show a statistically significant impact. These results emphasize the importance of using more specific diagnostic methods in epidemiological studies and clinical practice.

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CLINICAL AND ORTHODONTIC MANAGEMENT OF IMPACTED TEETH ASSOCIATED WITH RETAINED PRIMARY TEETH

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Abstract

The impacted canine therapy presents a serious specific problem in terms of the choice of therapeutic-surgical intervention for each case in particular. In most cases in close interdisciplinary cooperation with the orthodontist.

Keywords: Treatment, impacted, canines, bimaxillary.

Introduction

Since eruption is a complex process, delayed or failed eruption may occur; therefore, the failure of eruption of permanent teeth and subsequent impaction is a common dental anomaly.

- Previous literature reports that tooth impaction is a common occurrence, and many factors influence its prevalence, including age and the timing of eruption.
- Genetic and environmental factors play a role in developmental anomalies. The incidence of impacted teeth is contradictory among different populations and ethnic groups.
- Consequently, impaction, as a seemingly simple problem that can be resolved easily and at low cost, may lead to severe complications that can even be life-threatening.
- Panoramic radiography is a simple tomographic technique that provides a panoramic view of the maxillofacial region.
- Radiographic examinations can be either digital or conventional. Digital imaging has many advantages over conventional methods, such as reduced radiation exposure, ease of image manipulation and analysis, which improves sensitivity and reduces errors.

These treatment options include:

1. Non-extraction of primary (deciduous) canines
2. No treatment with monitoring of pathological changes
3. Surgical removal and prosthetic replacement of the missing tooth
4. Surgical exposure of the tooth and alignment with orthodontic appliances in the dental arch
5. Autotransplantation of the canine

Radiological analysis is a very important auxiliary method in planning the treatment of these patients. Important factors in the radiological diagnosis of impacted maxillary canines include:

1. Tooth angulation

Group 1: 0–15° → 9.1% of cases
Group 2: 16–30° → 24.4% of cases
Group 3: ≥31° → 65.9% of cases

2. Height and bucco-palatal position

Anteroposterior position of the canine root apex:
Group 1: Above the region of the canine position → 20.5% of cases
Group 2: Above the region of the first maxillary premolar → 63.6% of cases
Group 3: Above the region of the second premolar → 15.9% of cases

3. Vertical height of the canine crown

Group 1: Below the cementoenamel junction (CEJ) → 4.5% of cases
Group 2: Above the CEJ but less than half of the root length → 68.2% of cases
Group 3: More than half of the root length but less than the full root length → 25% of cases
Group 4: Above the total root length → 2.3% of cases

4. Overlap of the canine with the lateral incisor

Group 1: No horizontal overlap → 13.6% of cases
Group 2: Less than half of the root width → 15.9% of cases
Group 3: More than half but less than the full root width → 13.6% of cases
Group 4: Complete overlap of the root width or more → 55.6% of cases
These radiographic parameters are essential in guiding the clinician toward an appropriate treatment strategy, particularly when deciding between surgical-orthodontic intervention and extraction.

Case Presentations

Case I

A 13-year-old patient was diagnosed with bilateral impaction of maxillary canines and referred for combined surgical-orthodontic management. Surgical exposure was performed using the Wassmund technique, followed by osteotomy and extraction of retained primary canines. Orthodontic traction was subsequently applied.





In contrast, a 29-year-old patient presented with bilateral palatally impacted canines and a pre-existing fixed prosthetic restoration, which contraindicated orthodontic alignment. Surgical extraction was performed, accompanied by cystectomy, apicoectomy of the lateral incisor, and reconstruction of the osseous defect using a bone graft substitute.





Case II

An 11-year-old patient presented with an impacted maxillary central incisor associated with supernumerary teeth. Surgical removal of the supernumerary teeth was performed, followed by exposure of the impacted incisor. Subsequent orthodontic treatment facilitated proper alignment within the dental arch.





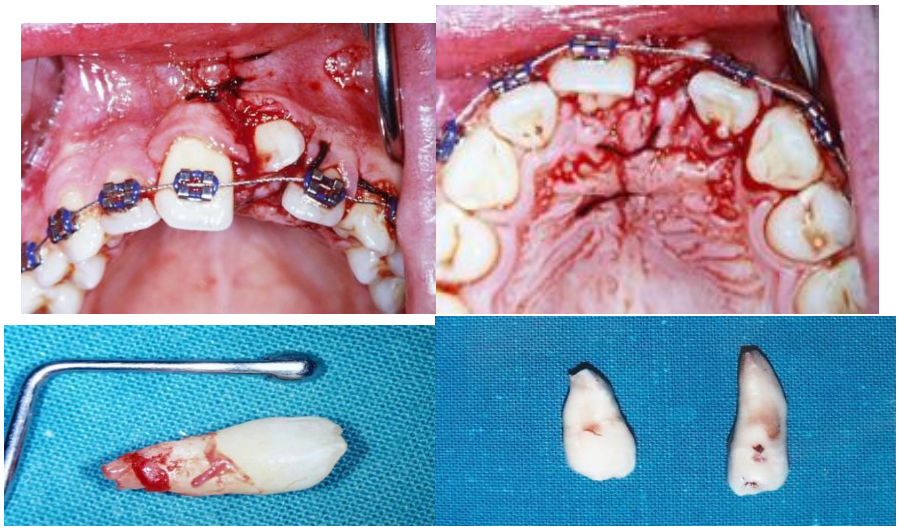
Case III

A 14-year-old patient presented with two supernumerary teeth, one of which was in an inverted position. Initial management involved observation. Following spontaneous partial eruption, surgical intervention was undertaken, including removal of the inverted supernumerary tooth and exposure of the impacted incisor, followed by orthodontic alignment.









Conclusion

The management of impacted teeth requires an individualized, case-specific approach. Optimal treatment outcomes depend on:

1. Comprehensive etiopathogenetic assessment
2. Accurate diagnosis and differential diagnosis
3. Interdisciplinary collaboration, particularly between oral surgeons and orthodontists
4. Active patient compliance and informed parental consent

A thorough radiological evaluation remains indispensable in determining the most appropriate therapeutic strategy and improving overall treatment predictability.

Appendix

IPH Institute for Public Health

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COMPARATIVE ANALYSIS OF MA IN BEAMSMADE OF STEEL WITH DIFFERENT SPANS

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Abstract.

Purpose: This study aims to perform a comparative analysis of steel beam, providing a comparative parametric analysis of six different types of structural solutions for the main steel beam: I-section, H-section, □-section (rectangular), ○-section (tube), variable-height beams (trapezoidal beams) and constant-height beams (parallel-strip beams).
Method: The analysis covers ten spans, ranging from 8 m to 44 m, with a distance between main supports of l = 4 m. Five roof slope angle variants (0°, 5°, 10°, 15°, and 20°), two boundary conditions (free support and fixed support), and two cases of distributed vertical loads (g = 6 kN/m² and g = 12 kN/m²) are considered. All models were built and analyzed in the Tower 8 software (Radimpex), using S235 steel.
For each combination of slope angle (5 values) and span between main supports (10 values), beam models are constructed in Tower 8 (Radimpex). In each model, six different types of structural solutions are applied sequentially. Each beam is analyzed for both boundary conditions and both vertical load cases.
Results: For each combination, normal stresses and relative deformations were calculated and compared, taking the I-profile as a reference, so the results could be directly compared despite variations in span and slope. Normal stresses (σ) and relative deformations (δ) were calculated for each combination, with the values being compared using the I-profile as a reference ($\sigma_n = 1.000$ for the I-profile in every combination of span × slope).
Numerical analysis results are presented organized by slope angle (0°, 5°, 10°, 15°, and 20°). For each slope, two tables are given: one for free support and one for fixed support-embedding, both for the light load case. The results for the heavy load case are discussed in the paper and are almost identical in relative values. The value of 1.000 corresponds to the I-profile (the reference); values < 1 indicate better performance, while values > 1 indicate poorer performance.
Conclusions: The conclusions identify which type of structural solution is most efficient for each span and slope range, providing a quantitative basis for the selection of main beams during the design phase.
1. The I-beam is the most efficient of the four solid beams in almost all combinations.
2. The H-beam is 2-50% less efficient than the I-beam in terms of deflections for spans between 8 and 28 m, but achieves almost equal performance (±6%) for spans of 32-44 m at all slopes.
3. Hollow beams (□ and ○) are 7-94% less efficient than the I-beam, with a clear trend of performance deterioration as the span increases.
4. The beam with constant height produces 25-67% lower deflections and 33-93% lower deformations than the I-beam, provided that L ≥ 12 m.
5. Trapezoidal beam (variable height beam) depends strongly on the slope: it is inefficient at 10° (+40–118%), becomes almost comparable at 15° and outperforms the I-profile for L ≥ 36 m at a slope of 20°.
None of the profiles are efficient for very short spans (L = 8 m), where full profiles are more efficient.

Keywords: Steel beam, cross section, truss, comparative analysis, Tower 8, S235, static space, roof slope.

Introduction

1.1 Motivation: Structural steel represents one of the principal materials for spanning large distances in industrial buildings, warehouses, sports halls, and agricultural facilities. The selection of the cross-sectional type of the primary load-bearing member plays a decisive role in determining material consumption, structural self-weight, and, consequently, the overall cost of the structure.

In typical roof systems, the main load-bearing element is realized as either an open-section steel beam, a closed-section member, or—particularly for large spans—a truss system. The choice among these structural alternatives, as well as among the various cross-sectional configurations within each category, has a direct impact on both structural efficiency and economic performance.

The static response of a beam subjected to vertical loading is governed by several geometric and structural parameters, including the span length, the inclination of the member, the boundary support conditions (simply supported or fixed), and the cross-sectional geometry. The latter defines key mechanical properties such as the second moment of area, section modulus, and linear weight.

Different profile families exhibit distinct structural behaviors. Hot-rolled open sections (I and H profiles) provide high flexural stiffness about the □□□□□□ axis with relatively low self-weight. Hollow structural sections (rectangular and circular tubes) offer more uniform stiffness in orthogonal directions, enhanced torsional resistance, and favorable architectural appearance. Truss systems, composed of discrete members connected at joints, enable efficient coverage of large spans by exploiting structural depth to improve moment resistance with reduced material usage.

Within truss systems, two principal configurations are commonly distinguished: trusses with constant depth (parallel-chord trusses) and trusses with variable depth. While existing literature provides extensive treatment of individual profile types, there is a lack of systematic and parametric comparative studies that clearly identify the most efficient structural solution for given combinations of span and roof inclination

1.2 Aim and Objectives: The aim of this study is to perform a comparative evaluation of six structural solutions for steel primary members—four solid cross-sections (I, H, rectangular hollow, and circular hollow) and two truss configurations (constant-depth and variable-depth)—under varying span lengths and roof inclinations, in order to identify the most efficient solution for each parameter combination.

The specific objectives of the study are as follows:

1. To develop a parametric set of beam models covering:
    a. five roof inclination angles (0°, 5°, 10°, 15°, and 20°), and
    b. ten span lengths ranging from 8 m to 44 m, with increments of 4 m.
2. To apply two uniformly distributed vertical load cases:
    a. a lower load case (g = 6 kN/m), and
    b. a higher load case (g = 12 kN/m).
3. To analyze each configuration under two boundary conditions:
    a. simply supported, and
    b. fixed supports, using the structural analysis software **Tower 8 (Radimpex)**.
4. To determine, for each parameter combination:
    a. normal stresses (σ), and
    b. relative deflections (δ).
5. To compare the six structural solutions based on the obtained stress and deformation results.
6. To normalize the results by adopting the I-section as a reference case, thereby enabling direct comparison across different structural systems.

7. To formulate practical design recommendations that assist engineers in selecting the most appropriate structural solution as a function of span and roof inclination.

1.3 Scope and Limitations of the Study: This study focuses on the analysis of individual steel beams and is limited to the following parameters and assumptions:

[1] Only isolated steel beams are considered, with either horizontal or inclined orientation, without inclusion of columns and without examining the global behavior of a structural system such as a portal frame.
[2] Five inclination angles are analyzed: 0°, 5°, 10°, 15°, and 20°.
[3] Ten span lengths are considered: 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44 m.
[4] The material used is structural steel of grade S235.
[5] The applied loads are exclusively vertical (gravitational), uniformly distributed, with two intensity levels: 6 kN/m and 12 kN/m.
[6] Two boundary conditions are taken into account: simply supported at both ends and fully fixed at both ends.
[7] Six structural configurations are analyzed: I-section, H-section, square hollow section (□), circular hollow section (○), truss with variable height, and truss with constant height.
[8] Structural analysis is performed within a linear-elastic framework using the software Tower 8.
[9] Member verification is based solely on a simplified check of normal stresses, without incorporating advanced stability analyses (e.g., lateral-torsional buckling, local buckling, etc.).

The study does not consider horizontal loads (such as wind and seismic actions), dynamic effects, snow loads with accumulation, material fatigue, or fire protection aspects. Furthermore, the global behavior of the structural system (portal frame) is not analyzed and is proposed as a direction for future research.

Theoretical Background and Literature

2.1 Steel as a Structural Material: Structural steel is an industrially produced iron–carbon alloy, with a carbon content typically below 0.25% for standard structural grades. Due to its controlled manufacturing process, steel is characterized by material homogeneity and consistent quality.

The main properties that make steel suitable as a load-bearing material include:

1. high tensile and compressive strength,
2. predictable elastic behavior up to the yield point,
3. good isotropy of the material,
4. a high strength-to-weight ratio compared to traditional construction materials.

In this study, S235 steel grade is used, which is one of the most commonly applied grades in Europe for structures subjected to standard loads. The main mechanical properties of this material are presented in Table 2.1.

Table 2.1 — Mechanical properties of S235 steel

Karakteristika	**Simboli**	**Vlera**
Kufiri i rrjedhshmërisë	f_y	235 N/mm²
Rezistenca në tërheqje	f_u	360 N/mm²
Moduli i elasticitetit	E	210 000 N/mm²
Moduli i prerjes	G	81 000 N/mm²
Koeficienti i Puasonit	ν	0.3
Pesha specifike	γ	78.5 kN/m³

The static behavior of S235 steel up to the yield point is practically linear-elastic. This means that the stress–strain relationship follows Hooke's law within this range, which simplifies numerical modeling and allows the use of linear elastic analysis for calculating stresses and deformations.

2.2 Steel beams as primary load-bearing elements: A beam is a linear structural element whose geometry is characterized by a length (span) that is much greater than the dimensions of its cross-section. The main function of a beam is to transmit vertical loads coming from the roof, floor, or other structural elements to its supports.

The behavior of a beam under a uniformly distributed vertical load is described by the classical Euler–Bernoulli bending equation. Normal stresses and deformations are calculated respectively as:

$$\sigma = M/W + N/A$$

and

$$\delta = k \cdot qL^4/(EI),$$

where M is the maximum bending moment, N the maximum axial force, A the cross-sectional area, W the section modulus, q the distributed load, L the span length, E the modulus of elasticity, I the second moment of area (moment of inertia) of the cross-section, and k a coefficient depending on the boundary conditions of the supports.

From these expressions it is evident that normal stresses decrease with an increase in the section modulus W, while deformations decrease with an increase in the moment of inertia I and increase proportionally to the fourth power of the span L. Therefore, the two geometric characteristics that decisively determine the efficiency of a beam are the section modulus W and the moment of inertia I.

2.2.1 Horizontal and Inclined Beams: When a beam is horizontal, the distributed vertical load acts perpendicular to its axis, generating a pure bending moment. When the beam is inclined at an angle α relative to the horizontal, the distributed vertical load can be decomposed into two components: a component perpendicular to the beam axis ($q \cdot \cos \alpha$), which produces a bending moment, and a component parallel to the beam axis ($q \cdot \sin \alpha$), which induces an axial compressive force. For small inclination angles considered in this study (up to 20°), the effect of the parallel component remains relatively small, although it is not negligible.

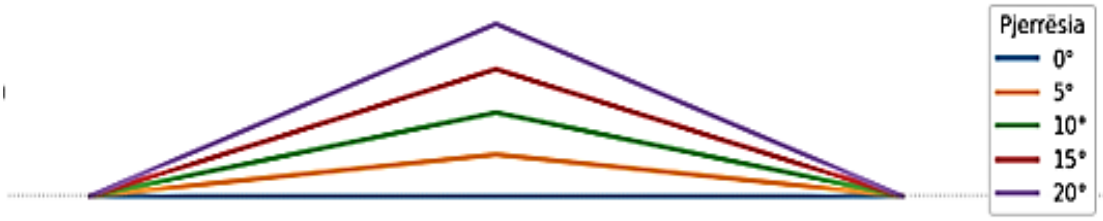


Figure 2.1 — The five roof slope angles analyzed in this study

2.2.2 Boundary Conditions of Supports: In this topic, two support boundary conditions are analyzed: simple (pin/roller) support and fixed (encastre) support. In the case of simple support, the beam is free to rotate at the support, the bending moment at the ends is zero, and the maximum bending moment occurs at mid-span ($M_{max} = qL^2/8$, $\delta_{max} = 5qL^4/384EI$). In the case of fixed support, rotation at the support is restrained, negative moments are generated at the ends, and the maximum positive moment at mid-span is smaller ($M_{max} = qL^2/12$ at the ends, $\delta_{max} = qL^4/384EI$ — five times smaller than in the case of simple support). simple support fixed support

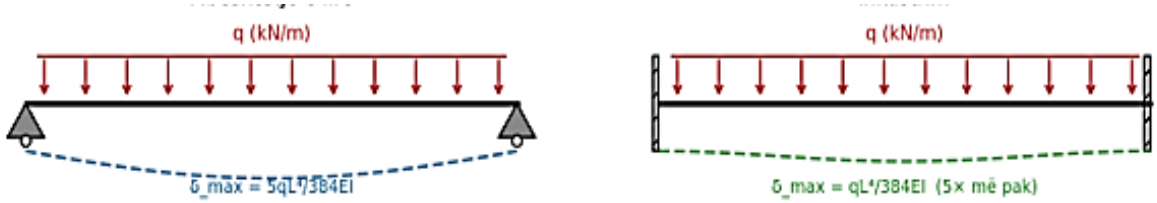


Figure 2.2 — Beam under uniform load with free support (left) and with embedment (right), with the corresponding deformation shapes.

In practice, boundary conditions are realized through the structural details of the beam connections to columns or other supports. Figure 2.3 shows two types of real structural connections: a simple connection and a rigid connection



Figure 2.3 — Two types of structural connections: a simple connection (left) with an angle plate that allows free rotation and transmits only shear forces; and a rigid connection (center, orange) with bolted top and bottom plates that also transmits bending moments. Source: Simpson Strong-Tie.

2.3 Types of cross-sections for steel beams: The industrial production of structural steel offers a wide range of standardized profiles (Figure 2.4). In this topic, four main families of full profiles (I-profile, H-profile, rectangular profile, circular profile/tube) and two types of trusses are compared, which are presented in detail below.



Figure 2.4 — Common types of standardized steel profiles. In this topic, the I-profile (top left) and circular, square and rectangular profiles (bottom) are studied. U and L profiles are not the subject of this

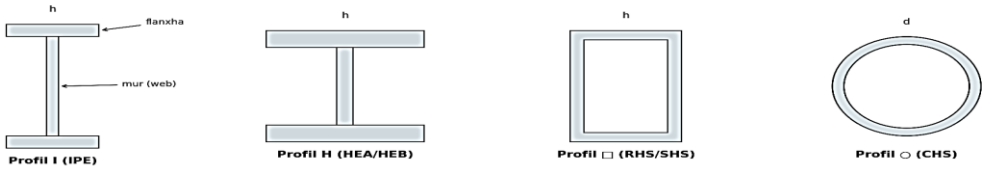


Figure 2.5 — Schematic of the four complete cross-sections analyzed: I-profile, H-profile, □-profile (rectangular) and ○-profile (circular/tube).

2.3.1 I-profile (IPE): The I-profile is an open, hot-rolled profile, shaped like the letter "I". It is characterized by thin, relatively narrow flanges and a thin wall (tail) connecting them. The most common European series of I-profiles are the IPE (I Profile European), which have flanges of constant thickness and geometry optimized to provide a high moment of inertia in the main direction with a relatively low weight.



Figure 2.6 — I-sections used as main beams and columns in an industrial steel structure.

2.3.2 H-section (HEA, HEB): The H-section is also a hot-rolled open section, but with wider and thicker flanges than the I-section, and with thicker walls. The most popular European series are HEA (lighter) and HEB (heavier), with flanges with a width almost equal to the cutting height. The H-section offers a more balanced moment of inertia in both main directions compared to the I-section, better lateral-torsional loss behavior, but a weight per linear meter greater than that of the I-section for the same height.

2.3.3 section (rectangular / square — RHS, SHS): Rectangular (RHS — Rectangular Hollow Section) and square (SHS — Square Hollow Section) sections are closed sections, manufactured with or without welding. They offer balanced behavior in the two main

directions, very good resistance to torsion due to the closed cut, and a clean aesthetic appearance preferable in exposed constructions. Their disadvantage is that joint connections are more difficult to achieve compared to open profiles.

2.3.4 Profile (circular/tube — CHS): A circular profile (CHS — Circular Hollow Section) is a tube with a circular cross-section and a constant wall thickness. It offers completely symmetrical behavior in all directions, the best possible resistance to torsion, and a very clean aesthetic appearance. Joints at the joints are technically more difficult and more
expensive, and the weight per linear meter is usually greater than that of an I-profile for the same modulus of resistance in the main direction.

2.4 Trusses as an alternative for large spans: For large spans (usually over 20–25 m), full beams become uneconomical because they require profiles with very large heights to satisfy the deformation requirements. In these cases, trusses constitute a much more efficient alternative.
Two types of trusses are compared: with constant height and with variable height. The two main shapes of variable-height trusses (triangular and trapezoidal) as well as the shape of constant-height trusses are shown in Figure 2.7.

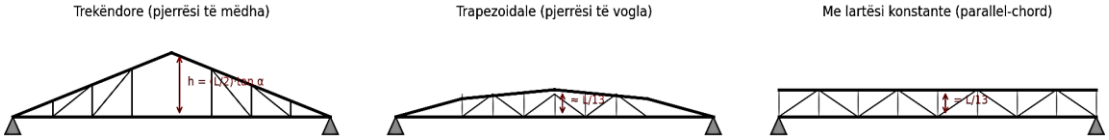


Figure 2.7 — The three truss geometries analyzed: triangular truss (for large slopes), trapezoidal truss (for small slopes), and constant-height truss (parallel-chord).

2.4.1 Parallel-chord truss: A parallel-chord truss has the upper chord and the lower chord parallel to each other throughout the span. Its height is the same at the mid-span and at the support. The main advantages are its simple and easy-to-manufacture geometry, and its suitability for horizontal coverings. The main disadvantage is that the material is not optimally distributed: the height is the same at the support where the moment is zero as at the mid-span where the moment is maximum.



Figure 2.8 — Parallel-chord truss in the roof of an industrial warehouse: the upper and lower chords are parallel, with diagonal members between them

2.4.2 Variable-height truss: A variable-height truss has the upper chord not parallel to the lower chord. The most common form is one with a sloping upper chord that follows the slope of the roof, while the lower chord remains horizontal — this makes the truss height greater in the middle of the span and smaller at the support, following the shape of the bending moment

diagram. The main advantage is better material distribution efficiency. The disadvantage is that the geometry is more complicated and the connections at the joints are more difficult to realize.

Results

3.1 General presentation: This chapter presents the results of the numerical analysis, organized by slope angle (0°, 5°, 10°, 15° and 20°). For each slope, two tables are given: one for free support and one for embedment, both for the light load case. The results for the heavy load case are discussed in §4.7 and are almost identical in relative values. The value 1.000 belongs to profile I (reference); values < 1 indicate better behavior, values > 1 indicate worse behavior.

3.2 Results for 0° slope (horizontal beams)

Table 3.1a — 0° slope, free support, light load

L (m)	I σ	H σ	□ σ	○ σ	K.kon. σ	I δ	H δ	□ δ	○ δ	K.kon. δ
8	1.000	1.466	1.192	1.178	0.616	1.000	2.321	1.173	1.031	0.141
12	1.000	1.377	1.338	1.260	0.532	1.000	2.176	1.511	1.171	0.121
16	1.000	1.471	1.515	1.529	0.500	1.000	2.458	1.737	1.696	0.115
20	1.000	1.310	1.107	1.536	0.488	1.000	2.118	1.125	1.683	0.101
24	1.000	1.342	1.430	1.620	0.481	1.000	2.047	1.733	1.895	0.099
28	1.000	1.410	1.711	1.940	0.506	1.000	2.394	2.611	2.854	0.113
32	1.000	1.078	1.711	1.789	0.411	1.000	1.347	2.590	2.341	0.081
36	1.000	1.021	1.896	1.802	0.365	1.000	1.130	2.988	2.265	0.069
40	1.000	1.190	—	1.700	0.370	1.000	1.440	—	2.020	0.069
44	1.000	1.069	—	1.775	0.333	1.000	1.189	—	2.212	0.066

Table 3.1b — 0° slope, recessed, light load

L (m)	I σ	H σ	□ σ	○ σ	K.kon. σ	I δ	H δ	□ δ	○ δ	K.kon. δ
8	0.685	1.000	0.808	0.795	0.493	0.198	0.453	0.229	0.202	0.109
12	0.675	0.948	0.896	0.844	0.442	0.196	0.424	0.292	0.228	0.083
16	0.676	1.000	1.015	1.029	0.368	0.196	0.478	0.336	0.329	0.071
20	0.679	0.893	0.738	1.036	0.310	0.195	0.411	0.218	0.326	0.058
24	0.684	0.911	0.949	1.076	0.329	0.195	0.397	0.334	0.366	0.059
28	0.675	0.952	1.145	1.301	0.337	0.195	0.463	0.502	0.549	0.063
32	0.667	0.733	1.144	1.189	0.278	0.194	0.261	0.497	0.450	0.046
36	0.677	0.688	1.260	1.208	0.260	0.194	0.219	0.573	0.436	0.041

40	0.680	0.800	—	1.140	0.240	0.194	0.278	—	0.388	0.039
44	0.676	0.716	—	1.176	0.275	0.203	0.241	—	0.445	0.038

Observations for 0° slope: The I profile clearly dominates among the solid profiles. The H profile produces 38–47% higher deflections than the I profile for small spans (8–28 m), but the difference decreases to 2–19% for spans 32–44 m. The hollow profiles (□ and ○) have similar behavior among themselves — for spans 8–20 m, deflections are 11–54% higher than the I profile, while for spans 24–44 m this difference reaches 43–94%. Their deformations become up to 199% larger for large spans. The constant-height truss is the most efficient alternative: its deflections are 38–67% lower than the I profile, and the deformations are only 6.6–14.1% of those of the I profile — a reduction of 85.9–93.4%

3.3 Results for 5° slope

Table 3.2a — 5° slope, free support, light load

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.var. σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.var. δ**	**K.kon. δ**
8	1.000	1.136	1.114	1.068	1.091	0.886	1.000	1.327	1.079	0.972	0.332	0.193
12	1.000	1.091	1.068	1.091	0.864	0.682	1.000	1.237	1.091	1.027	0.328	0.195
16	1.000	1.128	1.231	1.179	0.795	0.615	1.000	1.314	1.256	1.180	0.308	0.189
20	1.000	1.019	1.000	1.192	0.827	0.635	1.000	1.156	0.999	1.177	0.322	0.195
24	1.000	1.061	1.143	1.184	0.796	0.633	1.000	1.187	1.174	1.182	0.315	0.195
28	1.000	1.077	1.212	1.269	0.846	0.654	1.000	1.226	1.292	1.295	0.339	0.209
32	1.000	1.000	1.216	1.255	0.745	0.588	1.000	1.057	1.232	1.211	0.295	0.182
36	1.000	0.981	1.264	1.283	0.679	0.547	1.000	1.012	1.275	1.230	0.271	0.170
40	1.000	1.057	—	1.226	0.717	0.566	1.000	1.079	—	1.138	0.294	0.184
44	1.000	1.000	—	1.259	0.648	0.500	1.000	1.018	—	1.185	0.273	0.174

Table 3.2b — 5° slope, embedded, light load

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.var. σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.var. δ**	**K.kon. δ**
8	0.932	1.227	1.068	1.045	0.932	0.750	0.361	0.621	0.403	0.359	0.296	0.174
12	0.955	1.182	1.159	1.136	0.909	0.636	0.379	0.605	0.480	0.414	0.266	0.164
16	0.949	1.231	1.308	1.308	0.769	0.538	0.377	0.654	0.550	0.527	0.227	0.149
20	1.000	1.135	1.058	1.346	0.654	0.462	0.407	0.604	0.428	0.560	0.219	0.146
24	1.000	1.163	1.265	1.367	0.714	0.510	0.408	0.609	0.567	0.589	0.220	0.150
28	1.000	1.192	1.385	1.500	0.692	0.500	0.396	0.642	0.683	0.704	0.222	0.153
32	1.039	1.078	1.412	1.490	0.647	0.471	0.434	0.509	0.699	0.672	0.197	0.135

36	1.057	1.057	1.491	1.528	0.642	0.453	0.453	0.480	0.756	0.692	0.186	0.130
40	1.075	1.189	—	1.472	0.604	0.434	0.469	0.564	—	0.647	0.193	0.138
44	1.074	1.111	—	1.519	0.574	0.426	0.465	0.503	—	0.679	0.184	0.134

Observations for 5° slope: With the introduction of 5° slope, the differences between the full profiles are significantly reduced. The H profile produces only 9–14% higher deflections than the I profile for spans of 8–28 m and reaches practical parity (−2% to +6%) for spans of 32–44 m. The variable height truss becomes feasible and gives 13–35% lower deflections than the I profile for spans ≥ 12 m. The constant height truss remains the absolute best: 31–50% lower deflections and deformations only 17–21% of those of the I profile.

3.4 Results for 10° slope

Table 3.3a — 10° slope, free support, light load

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.var. σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.var. δ**	**K.kon. δ**
8	1.000	1.458	1.125	1.083	2.125	1.333	1.000	1.484	1.059	0.955	3.422	0.848
12	1.000	1.400	1.280	1.200	2.040	1.040	1.000	1.466	1.146	1.029	3.383	0.621
16	1.000	1.500	1.455	1.455	2.182	0.909	1.000	1.607	1.322	1.267	3.616	0.574
20	1.000	1.333	1.074	1.444	2.000	0.852	1.000	1.506	1.023	1.332	3.335	0.575
24	1.000	1.308	1.346	1.462	1.731	0.846	1.000	1.492	1.345	1.418	2.857	0.579
28	1.000	1.370	1.593	1.778	1.926	0.852	1.000	1.611	1.717	1.816	3.210	0.612
32	1.000	1.069	1.586	1.621	1.586	0.690	1.000	1.174	1.827	1.698	2.611	0.509
36	1.000	1.000	1.742	1.645	1.613	0.645	1.000	1.063	2.111	1.723	2.717	0.464
40	1.000	1.188	—	1.562	1.469	0.594	1.000	1.257	—	1.583	2.394	0.473
44	1.000	1.062	—	1.656	1.406	0.562	1.000	1.096	—	1.700	2.346	0.451

Table 3.3b — 10° slope, embedded, light load (without var. trusses)

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.kon. δ**
8	1.167	1.375	1.292	1.250	1.250	0.619	0.841	0.647	0.588	0.837
12	1.080	1.240	1.240	1.240	1.040	0.608	0.820	0.664	0.612	0.682
16	1.091	1.318	1.409	1.364	0.909	0.612	0.890	0.766	0.729	0.545
20	1.037	1.148	1.074	1.333	0.741	0.595	0.821	0.597	0.749	0.522
24	1.000	1.154	1.192	1.308	0.808	0.594	0.820	0.749	0.782	0.530
28	1.037	1.185	1.370	1.481	0.815	0.600	0.875	0.923	0.969	0.558
32	0.966	0.966	1.310	1.345	0.690	0.583	0.658	0.959	0.901	0.465

36	0.935	0.935	1.387	1.355	0.677	0.574	0.600	1.088	0.912	0.428
40	0.938	1.000	—	1.281	0.625	0.567	0.687	—	0.836	0.440
44	0.938	0.969	—	1.344	0.594	0.569	0.608	—	0.893	0.425

Observations for 10° slope: A key result emerges at this slope: the variable-height truss behaves very poorly. Its deflections are 41–118% higher than the I-profile and the deformations are 134–262% larger. The explanation is that at 10°, the height of a triangular truss would only be about L/11.3, which is not sufficient for an effective force arm. The constant-height truss continues to be effective with deflections 15–44% lower and deformations 38–55% lower than the I-profile for spans ≥ 12 m.

3.5 Results for 15° slope

Table 3.4a — 15° slope, free support, light load

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.var. σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.var. δ**	**K.kon. δ**
8	1.000	1.417	1.167	1.083	2.167	1.250	1.000	1.756	1.091	0.980	3.228	1.091
12	1.000	1.360	1.240	1.200	1.480	0.960	1.000	1.708	1.263	1.073	2.314	0.717
16	1.000	1.455	1.409	1.409	1.591	0.818	1.000	2.021	1.548	1.501	2.777	0.804
20	1.000	1.296	1.074	1.444	1.407	0.741	1.000	1.742	1.059	1.460	2.284	0.629
24	1.000	1.320	1.360	1.520	1.280	0.760	1.000	1.707	1.485	1.596	1.986	0.637
28	1.000	1.385	1.615	1.808	1.462	0.808	1.000	1.903	2.039	2.195	2.422	0.667
32	1.000	1.107	1.607	1.679	1.393	0.643	1.000	1.242	2.131	1.926	2.033	0.557
36	1.000	1.033	1.767	1.667	1.200	0.600	1.000	1.092	2.475	1.950	1.720	0.473
40	1.000	1.161	—	1.581	1.065	0.548	1.000	1.342	—	1.779	1.554	0.475
44	1.000	1.031	—	1.625	1.000	0.625	1.000	1.134	—	1.917	1.547	0.466

Table 3.4b — 15° slope, embedded, light load (without var. trusses)

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.kon. δ**
8	0.958	1.167	1.042	1.000	1.167	0.579	0.919	0.619	0.553	1.091
12	0.920	1.080	1.040	1.040	1.000	0.565	0.905	0.679	0.594	0.775

16	0.909	1.136	1.182	1.182	0.864	0.607	1.059	0.836	0.809	0.689
20	0.852	1.000	0.889	1.148	0.704	0.554	0.899	0.575	0.772	0.584
24	0.880	1.040	1.080	1.200	0.800	0.554	0.883	0.776	0.829	0.600
28	0.885	1.077	1.269	1.385	0.808	0.561	0.978	1.035	1.105	0.621
32	0.857	0.893	1.214	1.250	0.679	0.543	0.657	1.060	0.977	0.517
36	0.833	0.833	1.300	1.267	0.667	0.534	0.577	1.218	0.976	0.443
40	0.839	0.935	—	1.194	0.613	0.534	0.688	—	0.884	0.438
44	0.812	0.844	—	1.219	0.594	0.532	0.592	—	0.954	0.432

Observations for 15° slope: The variable height truss shows a clear improvement compared to the 10° slope. For spans of 24–44 m, its deflections decrease to 0–48% higher than the I-profile, and for L = 44 m it reaches practical equilibrium (σ = 1.000). The constant height truss remains more efficient with deflections 25–45% lower and deformations 33–53% lower than the I-profile.

3.6 Results for 20° slope

Table 3.5a — 20° slope, free support, light load

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.var. σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.var. δ**	**K.kon. δ**
8	1.000	1.417	1.125	1.083	1.917	1.208	1.000	1.947	1.118	0.994	2.598	1.438
12	1.000	1.360	1.240	1.200	1.240	0.920	1.000	1.863	1.335	1.101	1.723	0.874
16	1.000	1.409	1.409	1.409	1.318	0.818	1.000	2.084	1.536	1.498	1.885	0.788
20	1.000	1.259	1.074	1.370	1.185	0.704	1.000	1.880	1.080	1.541	1.633	0.656
24	1.000	1.320	1.360	1.520	1.360	0.760	1.000	1.836	1.574	1.706	1.785	0.672
28	1.000	1.385	1.615	1.808	1.462	0.769	1.000	2.074	2.227	2.410	1.975	0.699
32	1.000	1.071	1.607	1.679	1.143	0.643	1.000	1.283	2.290	2.088	1.478	0.546

36	1.000	1.000	1.767	1.700	0.967	0.667	1.000	1.109	2.658	2.065	1.270	0.496
40	1.000	1.161	—	1.581	1.065	0.677	1.000	1.377	—	1.859	1.320	0.474
44	1.000	1.065	—	1.677	0.968	0.742	1.000	1.156	—	2.021	1.284	0.479

Table 3.5b — 20° slope, embedded, light load (without var. trusses)

L (m)	**I σ**	**H σ**	**□ σ**	**○ σ**	**K.kon. σ**	**I δ**	**H δ**	**□ δ**	**○ δ**	**K.kon. δ**
8	0.875	1.125	0.958	0.917	1.208	0.556	1.006	0.609	0.544	1.254
12	0.840	1.040	1.000	0.960	1.000	0.540	0.953	0.687	0.583	0.820
16	0.818	1.091	1.136	1.136	0.864	0.548	1.059	0.794	0.776	0.726
20	0.815	0.963	0.852	1.111	0.704	0.533	0.941	0.562	0.782	0.610
24	0.800	1.000	1.040	1.160	0.800	0.533	0.924	0.792	0.858	0.629
28	0.846	1.038	1.231	1.346	0.808	0.546	1.041	1.106	1.191	0.640
32	0.786	0.821	1.179	1.214	0.679	0.520	0.655	1.127	1.028	0.497
36	0.767	0.800	1.267	1.233	0.667	0.513	0.564	1.288	1.014	0.451
40	0.774	0.871	—	1.161	0.613	0.509	0.686	—	0.904	0.437
44	0.774	0.806	—	1.226	0.645	0.510	0.582	—	0.984	0.440

Observations for 20° slope: At 20°, the variable-height truss reaches its best efficiency. For L = 36 m and L = 44 m, its loads become 3% lower than the I-profile. The constant-height truss produces 24–36% lower loads for medium/large spans, but is 21% worse than the I-profile at L = 8 m, confirming that for very small spans trusses are generally not suitable.

3.7 Summary of main results

1. The I-profile is the most efficient profile among the four full profiles in almost all combinations.
2. The H-profile is 2–50% worse than the I-profile in loads for spans 8–28 m, but reaches practically the same (±6%) for spans 32–44 m at all slopes.
3. Hollow profiles (□ and ○) are 7–94% weaker than the I profile, with a clear tendency to deteriorate with span.
4. The constant-height truss produces 25–67% lower loads and 33–93% lower deformations than the I profile — provided that L ≥ 12 m.
5. The variable-height truss strongly depends on the angle: it is inefficient at 10° (+40–118%), approaches at 15°, and surpasses the I profile for L ≥ 36 m at the 20° slope.

6. None of the trusses is efficient for very small spans (L = 8 m), where solid profiles are more efficient.

Graphical interpretation of results

To facilitate the identification of trends, the results of normalized stresses and strains are presented graphically in Figures 4.1–4.10, with one plot for stresses and one for strains for each of the five slopes.

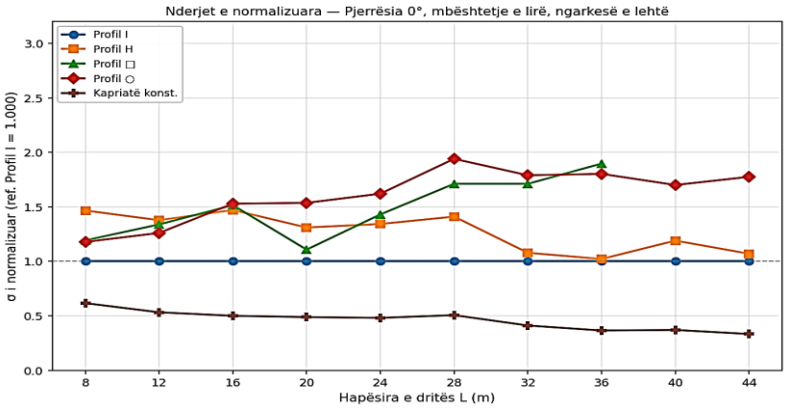


Figure 4.1 — Normalized values for 0° slope.

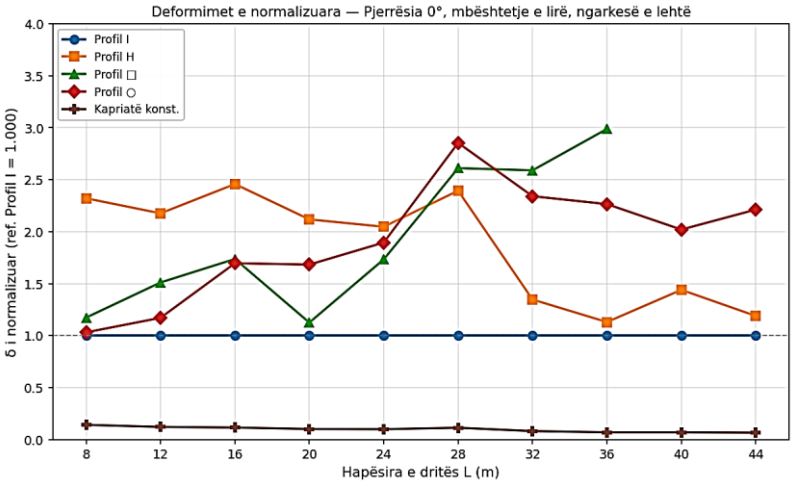


Figure 4.2 — Normalized deformations for 0° slope.

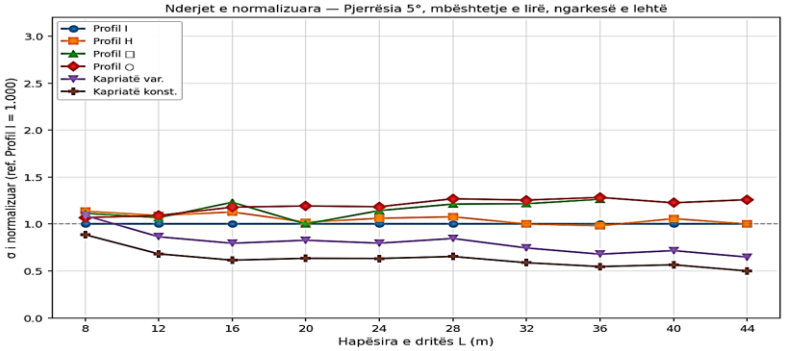


Figure 4.3 — Normalized values for 5° slope.

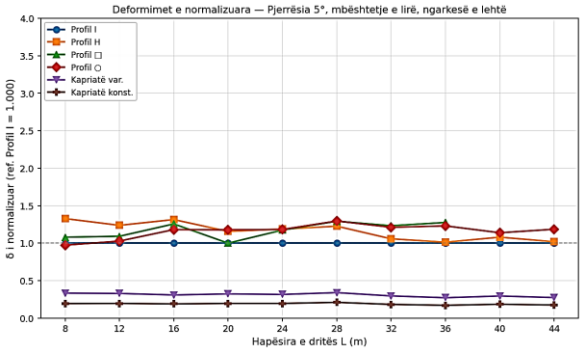


Figure 4.4 — Normalized deformations for 5° slope.

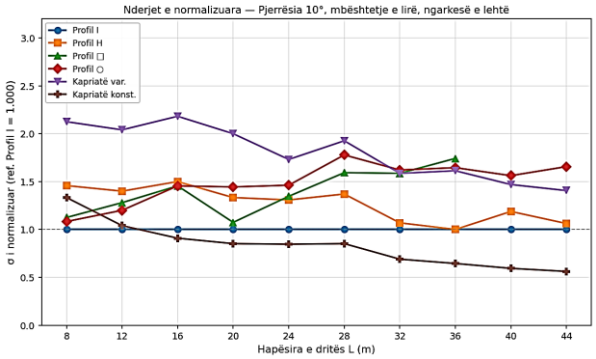


Figure 4.5 — Normalized values for 10° slope.

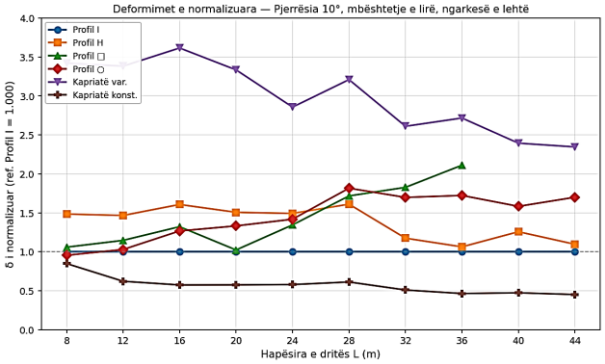


Figure 4.6 — Normalized deformations for 10° slope.

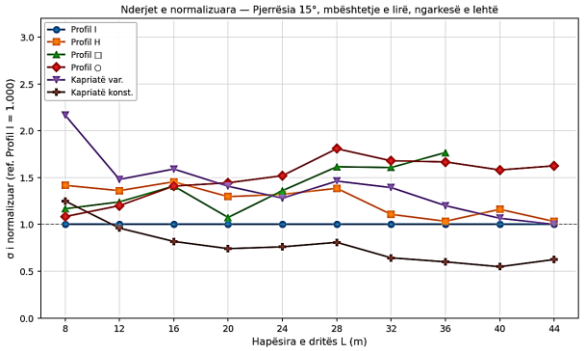


Figure 4.7 — Normalized values for 15° slope.

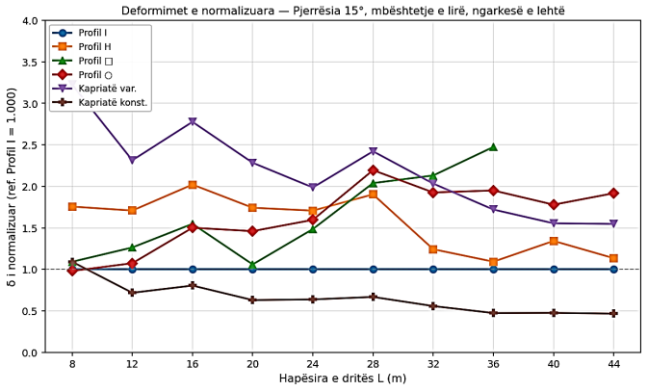


Figure 4.8 — Normalized deformations for 15° slope.

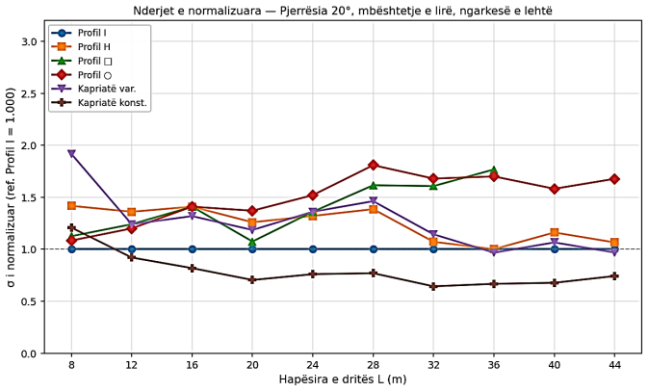


Figure 4.9 — Normalized values for 20° slope.

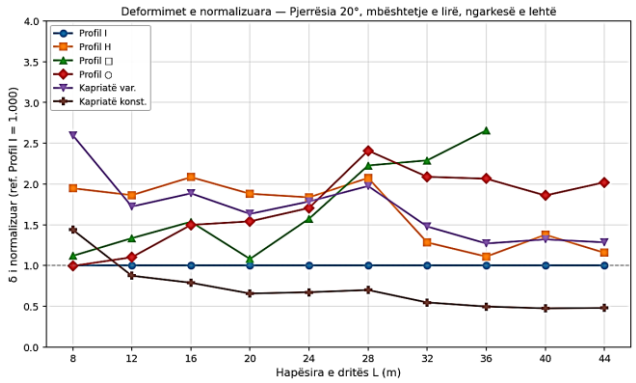


Figure 4.10 — Normalized deformations for 20° slope.

Conclusion

This topic provided a quantitative, parametric, and normalized comparison of six major alternatives for steel main supports, covering a wide range of static spans, slope angles, and boundary conditions. The results confirmed some well-known trends in design practice—such as the superiority of I-sections for horizontal beams with small spans and the efficiency of trusses for large spans—but also presented less intuitive observations: the high sensitivity of variable-height trusses to slope angle, and the large deformation margin in trusses that suggests the possibility of further optimization with higher steel grades.

Due to the limitations discussed—particularly the lack of stability checks, full-frame analysis, and wraps in the areas of maximum moment—this topic does not formulate direct

recommendations for practical design. Instead, it provides a quantitative comparative basis and identifies concrete directions for further research that would be necessary to move from the observations of this study to fully verified recommendations for design.

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COMPARATIVE ANALYSIS OF MONOLITHIC CONSTRUCTION AND THE „CUBIAX„ SYSTEM IN COMERCIAL BUILDING

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Abstract

Objective: This study presents a comparative analysis between conventional monolithic construction and the **CUBIAX** system in commercial buildings.
The paper examines traditional monolithic construction alongside contemporary construction techniques that incorporate prefabricated void-forming elements made of plastic and rubber within reinforced concrete slabs and foundations. The innovative **CUBIAX** system enables faster and more rational construction by reducing concrete consumption, thereby decreasing the self-weight of the structure. Reduction of dead load is a fundamental objective in structural engineering; achieving this enhances the ductile behavior of structures under dynamic and seismic loading. Consequently, the application of the **CUBIAX** system represents a highly effective solution, particularly for structures located in seismically active regions.
Methodology: The study involves structural analysis of systems designed using the conventional monolithic method, employing established reinforced concrete design procedures in accordance with national regulations and European standards, specifically Eurocode 2 (EC2) and Eurocode 8 (EC8). Similarly, the analysis of structures utilizing the **CUBIAX** system is conducted using verified design approaches based on Eurocodes and widely adopted European engineering practices.
Results: In direct comparison with conventional reinforced concrete slabs, **CUBIAX** voided flat slabs demonstrate superior technical performance and are generally more cost-effective due to reduced material consumption. Furthermore, the overall costs of the supporting structural system and foundations can be significantly reduced as a result of the decreased dead load of the optimized slab system. The degree of optimization varies depending on project-specific conditions.
The increased span capacity and optimized cross-sections of load-bearing elements contribute to enhanced flexibility in load distribution and allow for larger usable floor areas. Due to the reduced permanent load, **CUBIAX** slabs can be designed to be approximately 5–10% thinner than conventional reinforced concrete slabs while maintaining equivalent service loads and deformation limits. Additionally, construction execution is faster, resulting in time savings without compromising structural safety, stability, or ductility as prescribed by relevant standards.
Conclusion: Based on the conducted analyses, the **CUBIAX** system proves to be a more suitable and efficient solution within the fields of structural engineering and architecture. Comparative evaluation with conventional monolithic construction indicates that the **CUBIAX** system offers advantages across multiple aspects of design and construction, including structural performance and efficiency. It effectively reduces:

- Structural self-weight
- Construction time
- Project costs
- Labor requirements
- Complexity of installation

while improving seismic performance and overall structural behavior.
The findings demonstrate that the **CUBIAX** system addresses many of the limitations associated with traditional reinforced concrete construction methods.
Keywords: Monolithic construction; reinforced concrete slabs; reinforced concrete foundations; **CUBIAX** system; construction methods; cost efficiency; construction time; Eurocodes; European standards.

Introduction

Rubber is a substance that plays a significant role in modern society. It contributes to construction, forms the structure of tires, and even supports the soles of shoes. However, since

its identification around three millennia ago, rubber has undergone substantial development into the material we recognize today.
First identified and collected in Central and South America around 1600 BCE, early rubber was primarily used for games. Harvested from plants, ancient peoples shaped this substance into balls and used them for primitive bouncing games.
Although games were its primary use at the time, traces of rubber have also been found in the construction of metal and stone tools, mainly used to secure these materials to wooden handles. Over time, these early societies discovered that rubber was waterproof and could be used to create water-resistant clothing. When Europeans first encountered rubber, they were so astonished by its properties that they believed it to be magical.
However, it was not until 1770 that rubber was introduced into English society by Joseph Priestley. He observed that rubber could erase pencil marks, which led to the name "rubber." As its consumption increased in Western countries, demand for the product intensified. Consequently, the forests of South America and Africa where rubber trees grew were unfortunately exploited, and local populations were forced into the labor-intensive process of harvesting the substance. Eventually, rubber cultivation was transferred to Southeast Asia, where it continues to be produced today.
Unfortunately, natural rubber is sticky, brittle, and has an unpleasant odor, which limited its use during the 18th and 19th centuries. Due to increasing demand—especially for motor vehicle tires—a special sulfur-based rubber processing method called vulcanization was introduced in 1844 by Charles Goodyear. Soon after, synthetic rubber was developed as a way to keep up with the growing demand for durable rubber products.
Today, numerous advancements have been made in the sourcing, processing, and manufacturing of rubber worldwide. Used in industry, vehicle production, and the manufacture of various smaller mechanical components, rubber continues to be an essential component of modern life and construction



Fig. 1.1. Natural rubber process

Monolithic Construction

From a structural standpoint, monolithic buildings are designed as reinforced concrete frame structures. The buildings consist of a system comprising the foundation slab, columns, slabs, and beams. Other elements of the building include the masonry façade, partition walls made of lightweight ceramic blocks, floor structures, and thermal insulation of the façade and roof.

Earthworks and preparatory works

For the execution of the foundation structure, after prior site clearing and removal of the humus

layer to a depth of 20–25 cm, excavation is planned for the foundation slab to the depth required for compaction.
The entire excavation area, namely the foundation slab base, is compacted with crushed stone of 40–120 mm grain size, after prior soil compaction. This sub-base layer, due to the material structure, serves not only as a load-bearing surface but also ensures a certain level of groundwater drainage.

Complete construction

The foundation is constructed of reinforced concrete. The foundation slab is executed with a thickness determined by structural calculations, placed on the previously compacted crushed stone layer.
Due to the fact that the basement level is largely excavated, the basement walls are constructed of reinforced concrete up to the height defined in the architectural design, measured from the level of the foundation slab.

Load-bearing skeletal structure

The above-ground load-bearing structure consists of reinforced concrete elements: columns, walls, beams, slabs, and stairs. These elements form a skeletal structural system across multiple levels.
Columns have rectangular cross-sections or other shapes as defined by the design. Beams are dimensioned according to structural calculations.
Floor slabs have thicknesses determined by structural analysis.

Brief Introduction To Cubiax Technology

The function of the Cubiax system is based on lightweight plastic void formers that replace solid concrete within reinforced concrete slabs. As a result, both the weight and the volume of concrete are reduced, enabling thinner slabs and significantly larger spans in buildings. The Cubiax system allows for bidirectional load transfer. The structural performance and external appearance of the flat slab remain fully unaffected.Furthermore, due to the reduced material consumption, overall structural costs can be lowered. Owing to the achieved load reduction, Cubiax voided flat slabs are also an ideal solution for foundation optimization in cases of weak soil conditions, as well as for economical renovation and vertical extension of existing buildings. Lightweight slabs allow for a reduction in the dimensions of load-bearing elements within a building. This system is also environmentally friendly, as the void formers reduce material consumption and are made from 100% recycled plastic.

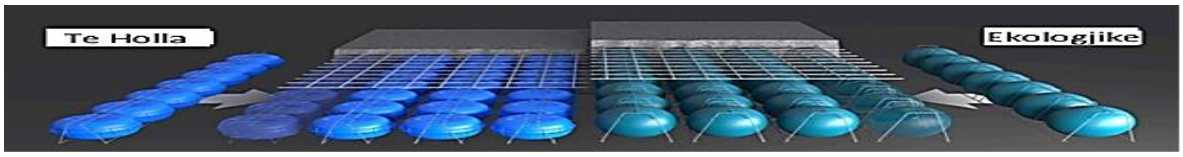


Fig.3.1 Slim line and Eco line system

The internationally patented Cubiax system consists of linear positioning elements approximately 215 cm or 250 cm in length, within which void formers are integrated. At the

same time, these elements serve as support components for the upper reinforcement layer. The practical modules are available in two variants: Eco-Line and Slim-Line. In the Eco-Line system, the void formers are spherical and are intended for slab depths ranging from 40 cm to 70 cm. The flatter Slim-Line void formers, on the other hand, are ideally suited for slab depths between 20 cm and 56 cm. Each Slim-Line void former consists of two ნახევრსფერა (hemispheres) and is therefore particularly suitable for application in international markets, as it increases modularity and optimizes space and transport possibilities.

A Cubiax voided flat slab can be planned and designed by any structural engineer in accordance with the relevant country-specific standards.

The modules are installed according to the Cubiax installation plan between the upper and lower reinforcement layers. This can be carried out easily on site or by using a prefabricated construction method. Furthermore, Cubiax technology can be readily combined with other construction methods, such as the incorporation of building elements, conventional monolithic concreting, prestressing, etc. The high degree of flexibility in the layout and positioning of the modules (voids) also enables their combination with other embedded elements or the creation of local stiffening strips and solid zones without void formers.

A Cubiax voided flat slab can be planned and designed by any structural engineer in accordance with national standards, taking into account information from general technical approvals. Additional expert reports, test certificates, and declarations on various specific topics are also available. In principle, analysis and design can be performed using any structural analysis software (including international FEM software) or manually.

1. Estimation of slab depth (if necessary, using diagrams for preliminary sizing).
2. Selection of a design variant, definition of slab cross-sections, and choice of a suitable Cubiax module.
   This can be done quickly and easily using the Cubiax fast and user-friendly software tool.
3. Determination of Cubiax-specific input parameters for calculation:
   • Load reduction through void formers
   • Factor for flexural stiffness (stiffness factor) fEI
   • Factor for shear resistance (shear factor) fV (international standards)
   or reduced shear resistance $V_{Rd,c,cubiax} = fV \cdot V_{Rd,c}$ (according to Eurocode)
   This can also be performed quickly using the Cubiax software tool.
4. Initial calculation procedure considering input parameters analogous to a conventional reinforced concrete slab. During this process, both the reduced load and reduced flexural stiffness are initially applied over the entire slab area.
5. Consideration of internal shear forces leads to the identification of required solid zones. Areas where $V_{Ed} > V_{Rd,c,cubiax}$ must be designed without void formers. In critical punching zones, it must be verified whether the solid zone extends by a dimension of 2d beyond the critical circular section or beyond the last reinforcement layer. Otherwise, the solid zones must be extended accordingly, as illustrated in Figure 3.2.

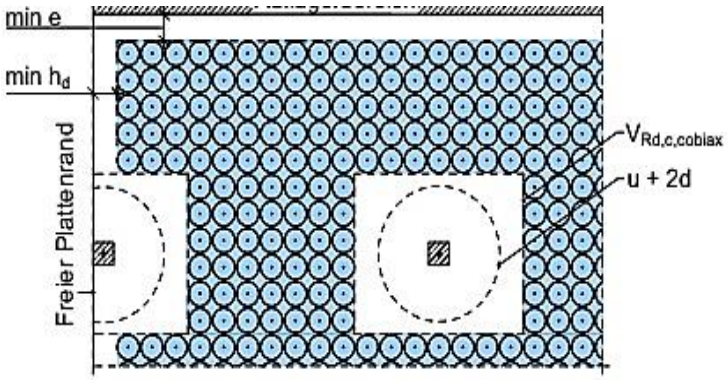


Fig.3.2 Support space with Cubiax at the facility

6) In the defined rigid areas, the permanent load, or bending stiffness, must be adjusted and the second and final calculation procedure must be started.
For concreting in two work steps (securing the hollow modules against movement) and for execution using semi-precast elements, the transmission of the shear force in the concreting joint is to be verified with a reduced bonding surface. This can be done quickly and easily using Cubiax tools.

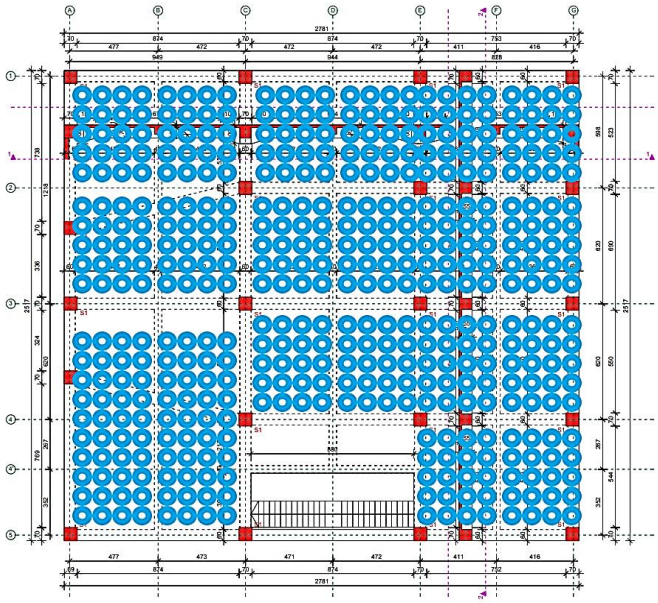


Fig. 3.3 Design of the Cubiax slab on the floors of the building



Fig. 3.4 Placing Cubiax balls on the plate

For the calculation of deformations, a suitable stiffness factor fEI must be taken into account to determine the bending stiffness in the previously hollow area. Otherwise, the deformation calculation occurs analogously to the procedure for a conventional-monolithic reinforced concrete slab. The stiffness reduction through the void is approx. 5% to 13% (stiffness factor approx. 0.95 to 0.87).

The easily applicable concept for verifying the shear resistance of Cubiax hollow flat slabs aims at using an estimated reduction factor (shear factor fV) in comparison with a solid slab. A comprehensive test program has been implemented to determine the reduction factor and the most unfavourable values determined by it. As a result, the actual existing load. Bearing capacity is not utilized in most cases, which means that a higher level of safety can be assumed compared to a reinforced concrete slab.

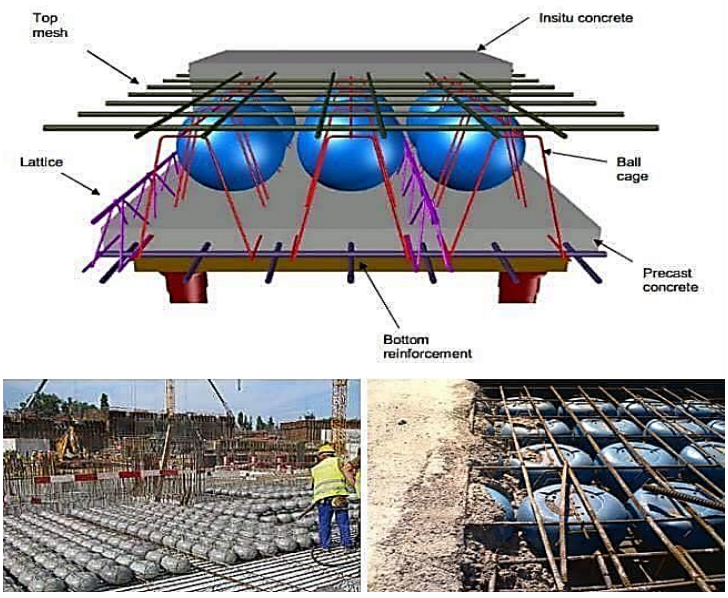


Fig. 3.5 Placing Cubiax balls on the slab and filling with concrete

For slab depths exceeding the maximum slab depth hd,max (ADB) up to the highest value, only the maximum slab depth and not the actual slab depth can be applied for the calculation of the shear resistance.

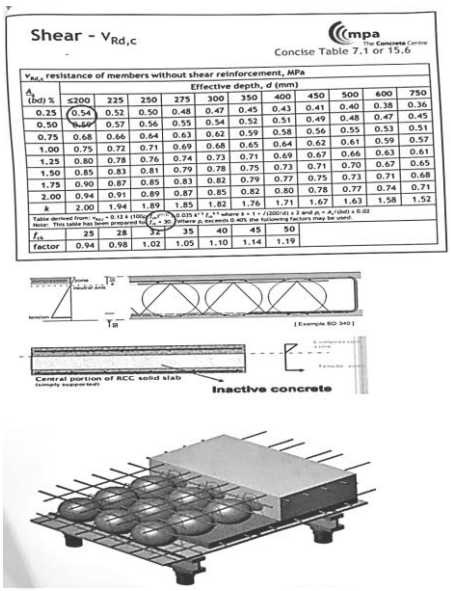
The calculation of the reduced shear resistance $V_{Rd,c,cubiax} = f_V \cdot V_{Rd,c}$ can be performed quickly and easily using the fast and easy software tool Cubiax.

The construction elements with the shear reinforcement required for the calculation.

If a shear reinforcement is required, then the hollow flat slab, structurally designed and executed as a ribbed slab with shear reinforcement acc. DIN EN 1992- 1-1, 5.3.1 or the relevant international design regulations, must be verified.

Information on optimizing the proportion of the previous void area

In certain cases, it may be necessary to optimize the proportion of the previous void area in order to maintain the maximum possible load reduction. For this purpose, a "comb-like installation" can be executed in the transition areas from the previous void area to the solid area. By alternating the strips with the void formers and solid areas, a shear factor determined by the structural engineer can be applied.



Shear - $v_{Rd,c}$

mpa The Concrete Centre

Concise Table 7.1 or 15.6

$v_{Rd,c}$ resistance of members without shear reinforcement, MPa

$A_{sl}/(bd)$ %	Effective depth, d (mm) ≤200	225	250	275	300	350	400	450	500	600	750
0.25	0.54	0.52	0.50	0.48	0.47	0.45	0.43	0.41	0.40	0.38	0.36
0.50	0.59	0.57	0.56	0.55	0.54	0.52	0.51	0.49	0.48	0.47	0.45
0.75	0.68	0.66	0.64	0.63	0.62	0.59	0.58	0.56	0.55	0.53	0.51
1.00	0.75	0.72	0.71	0.69	0.68	0.65	0.64	0.62	0.61	0.59	0.57
1.25	0.80	0.78	0.76	0.74	0.73	0.71	0.69	0.67	0.66	0.63	0.61
1.50	0.85	0.83	0.81	0.79	0.78	0.75	0.73	0.71	0.70	0.67	0.65
1.75	0.90	0.87	0.85	0.83	0.82	0.79	0.77	0.75	0.73	0.71	0.68
2.00	0.94	0.91	0.89	0.87	0.85	0.82	0.80	0.78	0.77	0.74	0.71
k	2.00	1.94	1.89	1.85	1.82	1.76	1.71	1.67	1.63	1.58	1.52

Table derived from: $v_{Rd,c} = 0.12 \times (100\rho_l f_{ck})^{1/3}$ ≥ $0.035 \times k^{3/2} \times f_{ck}^{1/2}$ where $k = 1 + \sqrt{(200/d)} \leq 2$ and $\rho_l = A_{sl}/(bd) \leq 0.02$

Note: This table has been prepared for $\gamma_c = 1.5$ where ρ_l exceeds 0.40% the following factors may be used.

f_{ck}	25	28	32	35	40	45	50
factor	0.94	0.98	1.02	1.05	1.10	1.14	1.19

[Example BD 340]

Central portion of RCC solid slab

Inactive concrete

Fig .3.6 Tabela e rezistencës të topthave Cubiax në betonin e armuar

Concrete has many applications in building construction, but its use for horizontal slabs is limited by its relatively high self-weight which reduces the maximum span. The common method of correcting this disadvantage is to incorporate some type of reinforcement, which allows the concrete slab to be used for a wide range of spans and loading conditions. Traditional approaches to structural reinforcement involve inserting another material within the concrete, however, biaxial slabs offer an alternative solution in the form of a biaxial slab which incorporates orthogonal concrete "beams" within the slab. This allows for greater support in both horizontal directions in order to transfer the load to a vertical member.

The general concept of biaxial hollow slabs relies on voids created within the concrete at the time of casting-incorporation. This creates an internal array of hollow boxes in the slab, which act as a horizontal support grid for the flat surface at the top. Another advantage is the weight reduction, achieved by removing mass that does not directly transfer weight to a vertical member. Typical solid-monolithic slabs have a load capacity of about one-third of their own weight, which can create problems for long spans and high loads. By reducing the weight of the slab without compromising its structural strength, it is possible to create a thicker slab to support more weight over a longer span.

Hollow core slabs, also known as hollow core slabs, first appeared as single-sided elements in Europe during the 1950s and are still commonly manufactured in prefabricated form for applications where rapid construction and low deadweight are required. Waffle slabs are a common type of hollow core slab that uses the same principle as biaxial hollow core slabs. However, their voids are located at the bottom of the slab rather than embedded within the slab, leading to lower shear strength and fire resistance. There have been a number of applications of biaxial hollow slab products, including the use of polystyrene blocks as void filler. However, many applications have suffered from flexural cracking and lack of shear strength….

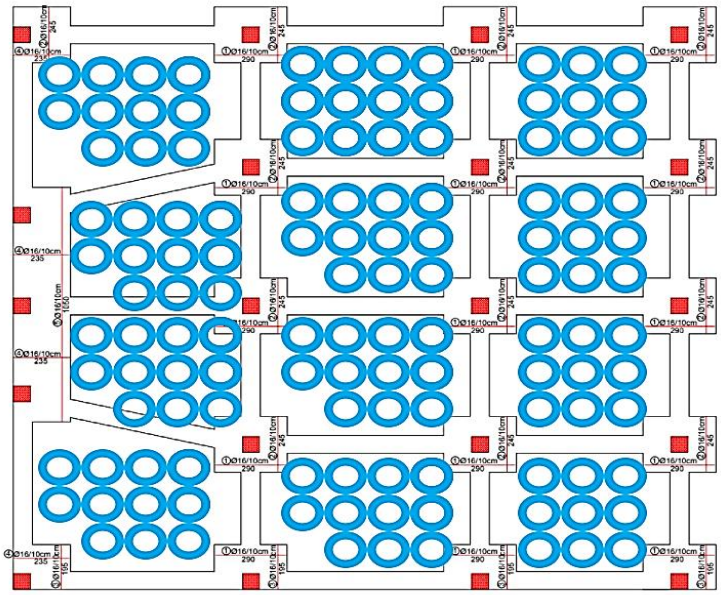


Fig .3.7 Topthat Cubiax në pllakën e themelit



Fig. 3.8 Cubiax balls on the Foundation plate in practice

Classic Slab – Difference Between Monolith And Cubiax Method

For the determination of the slab depth, national regulations for the limitation and minimum of deformation must be observed for slabs with small depths. The required slab depth can be calculated through appropriate deformation calculations. The same methodology applies to the Cubiax system. Considering the reduced stiffness and bending factor and load reductions according to the application data or the fast and easy software tool, normally up to 10%. Result of the thinner slab using the Cubiax application compared to a solid-monolithic slab. The diagrams that enable the rapid pre-design of the slab depth-thickness are described below. Systematic deformation calculations have been executed to create the diagrams, taking into account certain assumptions, different static systems, loads and deformation limits. The diagrams require a certain engineering interpretation for the transition to other boundary conditions and therefore do not replace any explicit calculations.
However, they are suitable and useful as an initial assessment.

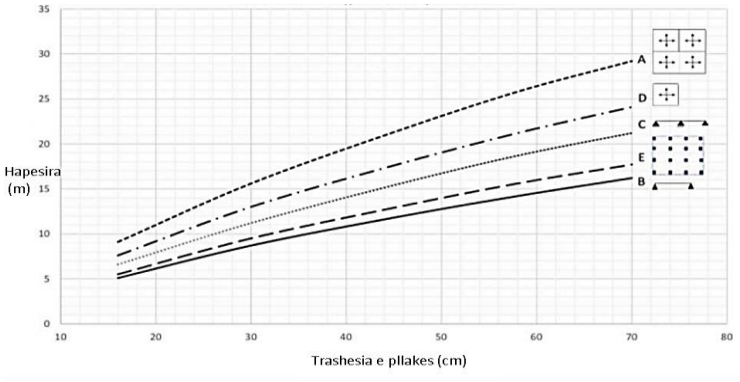


Fig.4.1 Diagrams for pre-design with Cubiax Balls on slabs

Execution variations and slab cross-sections

The determination of the slab cross-section and the selection of a suitable Cubiax module can be carried out more quickly and easily using the fast and easy Cubiax software tool.

Standard execution

The selection of a suitable Cubiax module occurs by determining the possible
support height hu. This depends on the required concrete cover, the thickness of the reinforcement layers,
and if required, other intermediate layers (e.g. for additional spacers or installation levels).

Companies are working on ways to optimize the concrete structure remaining outside the void formers. The aim of the previous void-forming technology (Cubiax system) was to manage without any additional reinforcement; Cubiax also conducted research that focused on creating the most ideal possible X-Zone. The solution was to move away from rectangular void formers and develop spherical or ellipsoidal void formers, which formed a concrete structure with webs that expanded up and down so as not to require additional reinforcement.

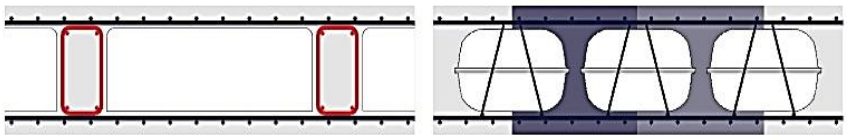


Fig.4.2 The difference between a regular plate and Cubiax

Over the decades, Cubiax has continued to optimize the shape of the structural formers to achieve the ideal shape of the concrete between the modules in terms of structural engineering. It is this X-shaped concrete structure that provides the unique stability and safety of Cubiax hollow core slabs. No other previous hollow core element that does not have any additional reinforcement achieves such an optimized X-area as the Cubiax systems.

All other optimizations in the product lines, such as the two-part design or the elements that ensure assembly, are additions that have no effect on stability or weight reduction, but mainly offer economic benefits or make their assembly easier.

This means that the previous Cubiax systems are the only products on the market that combine the best possible load-bearing capacity with maximum resource saving and particularly economical assembly.

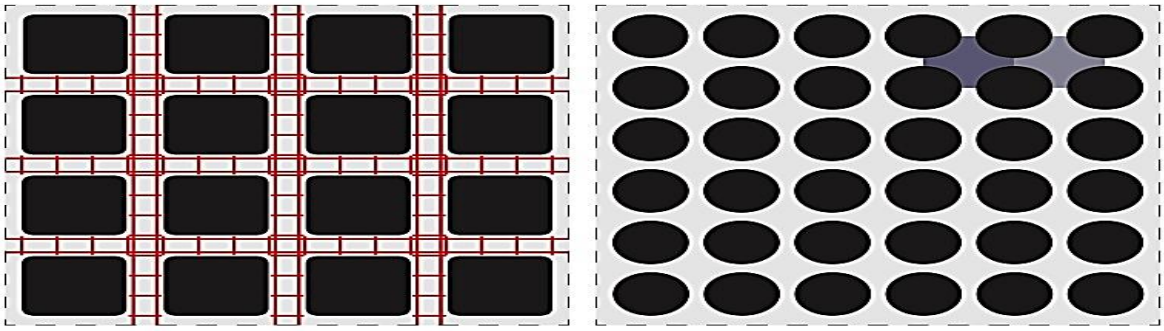


Fig. 4.3 Different shapes in the regular and Cubiax slab

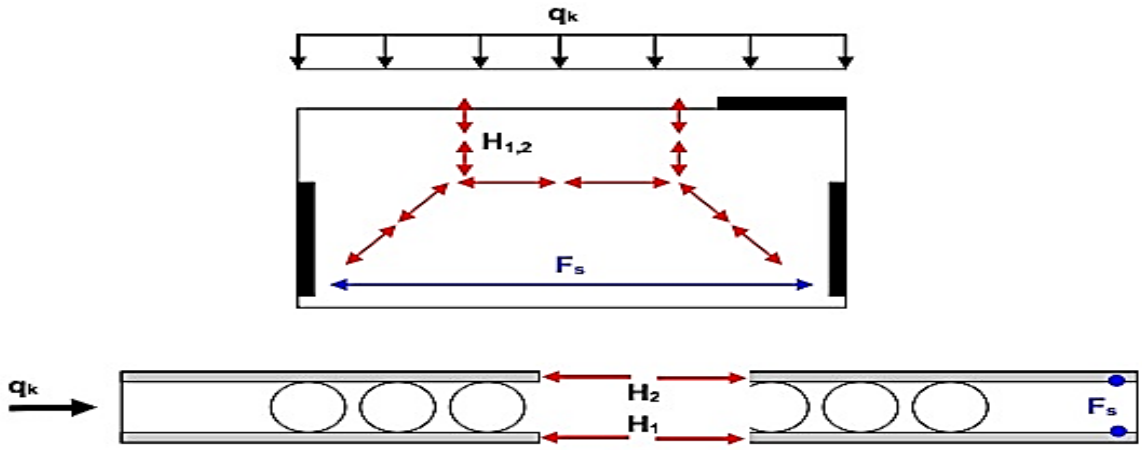
The monolithic concrete system, on the other hand, is a mixture of coarse and fine aggregates (generally sand or crushed stone) with a binding material (usually Portland cement) and water with a combination of reinforcement. When cement is mixed with a small amount of water, it hydrates to form microscopic, opaque crystalline lattices that encapsulate and lock the aggregate into a rigid structure. The aggregates used to make concrete must be free of harmful substances such as organic impurities, silt, clay, lignite, etc. Typical concrete mixtures have high compressive strength (about 4,000 psi (28 MPa)) and fire resistance; however, any significant stress (e.g., due to bending) will break the rigid microscopic lattice, resulting in cracking and spalling of the concrete. For this reason, typical unreinforced concrete must be well supported to prevent the development of cracks.

If a material with high tensile strength, such as steel, is placed in concrete, then the composite material, reinforced concrete, resists not only compression but also bending and other direct tensile actions. A composite section where the concrete resists compression and the reinforcement resists tension can be made in almost any shape and size for the construction industry.



Fig. 4.4 Conventional method – monolithic system, Reinforced Concrete

The Cubiax hollow core slab allows the panel forces to be transferred. In the case of a section analysis, only the sum of the lower and upper slab levels (net cross section) is applied. It should be noted during the design that the forces to be transferred can be clearly conveyed. If necessary, additional stiffeners can be developed in the design for greater transmission of concentrated slab forces or planned tensile and compressive forces.



Cost Comparison

Due to the reduced permanent weight, Cubiax hollow core slabs can be executed with common traffic loads and with the same deformation up to approx. 5 to 10% thinner than conventional reinforced concrete slabs.
Such a cost comparison under certain assumptions (varies depending on market prices for concrete, reinforcement costs) for all relevant slab depths is shown in the examples in the diagram below.

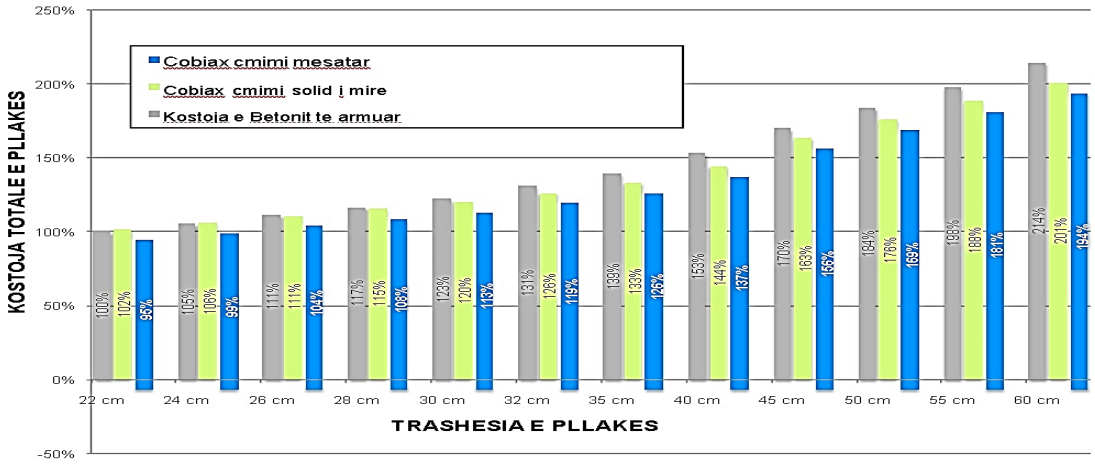


Fig. 5.1 Slab thickness / Total slab cost / REINFORCED/CUBIAX concrete slab

Conclusion

The main goal of this Cubiax system is to reduce the self-weight of concrete, where as we know the self-weight is also the main enemy and the biggest disadvantage of this material. This has been the motive that has encouraged and developed this technology, namely the reduction of the self-weight of concrete. Today this technology is so widespread that it is spread all over the world and about 14 million square meters of buildings have been built. Where in addition to saving in the amount of concrete in the world, 180,000 tons of CO2 have also been saved without being released into the atmosphere.

The advantages of the Cubiax system over other classic reinforced concrete slab systems is that through this system we manage to save up to 30% of the amount of concrete.
Cubiax technology not only saves valuable construction material, but also offers a variety of static advantages: Cubiax lightweight slabs allow for larger spans with the same weight as conventional concrete slabs, making execution easier since there is no formwork.
Cubiax lightweight slabs are built to meet the highest international standards. As a result of the reduced weight of the slabs, the risk of sudden loads is low (e.g. during earthquakes, since the reduction in self-weight also reduces seismic forces on the floors).
In our case, if we were to use ordinary concrete slabs for reinforcement, the amount of concrete would be around 600 m3, but if the cubiax system is used, the amount of concrete would be 420 m3, which would mean that we would save around 180 m3 of concrete, we would also save 1.20 m from the total height of the floors, we would save around 1400 tons of CO2 without being released into the atmosphere, and we would reduce the amount of plastic from the environment since it is known that the entire plastic material from Cubiax is recycled plastic.
Since this system is realized in the form of flat slabs without frames, this system allows us to benefit in height, for example, if on each floor we save 30 cm from the lower height of the frames, then for a 10-story building we benefit from a full floor.
The use of plastic material replaces at least 25-30% of the concrete used in traditional construction. It reduces the CO2 footprint during production, the amount of aggregate, water, cement and energy required are also reduced. Cubiax balls are made of 100% recycled plastic; the construction is stable for decades and centuries.

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ASSESSMENT OF DIAGNOSTIC AND TREATMENT METHODS FOR PYOMETRA IN STRAY DOGS IN THE MUNICIPALITY OF GOSTIVAR

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Abstract

Pyometra is a severe, life-threatening bacterial infection of the uterus in female dogs, characterized by the accumulation of purulent exudate within the uterine lumen. The condition occurs in both owned and stray dogs and requires prompt diagnosis and treatment to prevent systemic complications and mortality.
The aim of this study was to evaluate diagnostic approaches and treatment outcomes of pyometra in stray female dogs in the Municipality of Gostivar during 2023. A total of 124 stray dogs were included in a municipal control program, of which 66 were female. Among these, 13 cases were diagnosed with pyometra, corresponding to a prevalence of 19.14%.
Diagnosis was based on clinical examination, hematological findings, and abdominal ultrasonography. The primary treatment method was ovariohysterectomy, supported by intravenous fluid therapy and postoperative antibiotic administration. The findings indicate that early diagnosis combined with surgical intervention represents the most effective strategy for the management of pyometra in stray dog populations.

Keywords: pyometra, stray dogs, ovariohysterectomy, diagnosis, veterinary surgery

Introduction

Pyometra is a bacterial infection of the uterus affecting female dogs and is considered one of the most significant diseases in veterinary gynecology. This condition is widespread in both owned and stray dogs. In the Polog region, particularly in the cities of Tetovo and Gostivar, pyometra represents an important health problem in the canine population, requiring early diagnosis and treatment.
Timely detection of the disease is crucial, as early treatment significantly increases the chances of recovery, whereas delayed diagnosis may lead to severe complications and death. Clinical signs of pyometra may vary. One of the most characteristic symptoms is vaginal discharge with an unpleasant odor, typically observed in cases of open-cervix pyometra. However, in some cases, the disease may develop without vaginal discharge, making diagnosis more difficult.
Additionally, affected dogs may exhibit other clinical signs such as vomiting, loss of appetite, depression, lethargy, and frequent urination. In cases without vaginal discharge, diagnosis becomes more challenging and requires laboratory and imaging diagnostic methods. Hematological analyses often reveal leukocytosis, while abdominal ultrasonography may show uterine enlargement and the presence of infectious fluid within the lumen.
Pyometra can occur in dogs of various breeds and ages, although incidence is higher in adult animals due to hormonal changes during the estrous cycle. The risk is particularly high after parturition, when the cervix remains open for a certain period, facilitating bacterial entry into the uterus. In some cases, retained placental material or pathogenic microorganisms may contribute to the development of uterine infection.

When the cervix is open, treatment is generally easier and prognosis is more favorable. However, in cases of closed-cervix pyometra, the accumulation of purulent exudate significantly increases the risk of serious complications, including uterine rupture and spread of infection into the abdominal cavity, leading to peritonitis and life-threatening conditions.

Materials and Methods

The diagnosis of pyometra in this study was based on a combination of clinical signs, laboratory analyses, and imaging diagnostic methods. Dogs diagnosed in the early stages often presented mild vaginal discharge and minimal clinical signs. However, in most cases, the disease was diagnosed at more advanced stages with more pronounced symptoms.

One of the characteristic clinical signs observed was increased water intake (polydipsia), often accompanied by frequent urination. In some cases, purulent vaginal discharge and abdominal distension were also observed, raising suspicion of pyometra.

Hematological analyses typically showed leukocytosis, indicating an infectious process. However, these findings are not specific and may occur in other bacterial infections, requiring confirmation through additional diagnostic methods.

Abdominal radiography was used to identify uterine enlargement, particularly in cases of closed-cervix pyometra. In open-cervix cases, uterine enlargement may be less evident, making radiography less conclusive. Therefore, abdominal ultrasonography is considered one of the most reliable diagnostic methods, as it allows identification of an enlarged uterus filled with infectious fluid and differentiation from normal pregnancy.

The primary treatment for pyometra is surgical intervention, involving removal of the uterus and ovaries (ovariohysterectomy). In some cases, hysterectomy alone may be performed. Dogs diagnosed early generally have a good prognosis following surgery. However, surgical intervention in pyometra cases is more complex than routine sterilization due to the compromised condition of the animal and the risk of complications.

Most dogs are diagnosed at advanced stages and often present systemic clinical signs. Pre- and postoperative stabilization with intravenous therapy, including fluids and glucose, is necessary to improve the general condition. Postoperative antibiotic therapy is administered for approximately two weeks to prevent infectious complications.

Surgery is considered the safest and most effective treatment in most cases, particularly to prevent uterine rupture and spread of infection. Medical treatment with hormones such as prostaglandins is also possible, as they reduce progesterone levels, stimulate uterine contractions, and facilitate cervical opening, allowing elimination of infectious material.

However, hormonal therapy has significant limitations and is not always successful. It may be associated with side effects such as abdominal pain, discomfort, and behavioral changes. Moreover, in closed-cervix cases, uterine contractions may increase the risk of rupture and peritonitis.

Therefore, treatment choice should be made by the veterinarian based on the clinical condition of the animal. In most cases, timely surgical intervention offers the best prognosis and significantly increases survival rates.

Results and Discussion

Dogs were captured in the Municipality of Gostivar during 2023 and were treated for various diseases. All dogs were neutered or sterilized.
A total of 124 dogs were captured:

- 58 males (castrated)
- 66 females (sterilized)

Tab 1. Total number of captured stray dogs

	Breeds of captured dogs	Males	Females	Total
1.	Šar Mountain dogs	15	25	40
2.	Breeds Mixed	20	19	39
3.	Breeds Hunting	5	5	10
4.	Breeds Kangal	10	8	18
5.	Breeds Terier	5	4	9
6.	Asian breed dogs	3	5	8

Tab 2. Number of sterilized female dogs

1.	Šar Mountain dogs	25
2.	Breeds Mixed	19
3.	Breeds Hunting	5
4.	Breeds Kangal	8
5.	Breeds Terier	4
6.	Asian breed dogs	5
	Total	66

Tab 3. Clinical condition

	Dogs Female	
1.	Šar Mountain dogs	10
2.	Breeds Mixed	9
3.	Breeds Hunting	3
4.	Breeds Kangal	4
5.	Breeds Terier	1
6.	Asian breed dogs	2
	Total	29

Tab 4. Disease prevalence by breed

1.	Šar Mountain dogs	4
2.	Breeds Mixed	5
3.	Breeds Hunting	0
4.	Breeds Kangal	3
5.	Breeds Terier	0
6.	Asian breed dogs	1
	Total	13

Tab 5. Prevalence in terms of percentage and treatment

1.	Šar Mountain dogs	6,6 %
2.	Breeds Mixed	5,94 %
3.	Breeds Hunting	1,98 %
4.	Breeds Kangal	2,64 %
5.	Breeds Terier	0,66 %
6.	Asian breed dogs	1,32 %
	Total	19,14 %

Conclusion

- The Municipality of Gostivar issued a public call for the treatment of stray dogs (No. 07771/2023), followed by a contract with the Veterinary Clinic “Dok i Ket Doooel” Tetovo (No. 21-1155/1, dated 25.05.2023).
- A total of 124 dogs were treated, including 58 males and 66 females of various breeds. This study focused on the 66 female dogs and the occurrence of pyometra.
- Out of the treated dogs, 29 females were in poor health condition (cachexia, alopecia, mange, mechanical injuries, etc.). Among the sterilized females, 13 cases of pyometra were recorded, representing a relatively high prevalence of 19.14%.
- This prevalence also poses a risk to the environment, as these dogs may contribute to disease spread within their habitat. All treated dogs survived.
- The study concludes that pyometra is present throughout the country, but treatment remains insufficient. Untreated and deceased animals may serve as a source of infection for other animals and negatively impact biodiversity.
- Prevention of the disease is best achieved through early ovariohysterectomy before the onset of the condition.

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ORAL HEALTH STATUS AMONG TWELVE-YEAR-OLD CHILDREN IN THE DEBAR REGION

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Abstract

Introduction: Oral health is a key component of overall health and well-being. The World Health Organization established standardized methods for monitoring oral health in 12-year-old children, a globally accepted indicator age group. Preventive measures such as pit and fissure sealing of permanent molars play a crucial role in reducing dental caries and limiting lesion progression.
Objective: To assess the oral health status of permanent teeth, with special emphasis on first permanent molars, and to evaluate the relationship between fissure sealing and oral health among 12-year-old children. The study also analyzed differences based on gender and place of residence (urban vs. rural).
Material and Methods: The study included 12-year-old children with permanent dentition, categorized by gender and residence. Clinical examinations were performed to assess dental status, including the presence of caries, fillings, extractions, and fissure sealants on first permanent molars. Standard dental instruments and, where necessary, radiographic analysis were used.
Results: A high proportion of first permanent molars were fissure-sealed, with similar distribution between male and female participants. The average number of sealed molars per child was approximately two. A portion of children presented with unerupted first permanent molars, with slightly higher prevalence in males. Preventive measures showed a positive association with better oral health outcomes.
Conclusion: Statistically significant differences in oral health indicators were observed in relation to gender and place of residence ($p<0.05$). A correlation was found between dental status and preventive measures, emphasizing the importance of early intervention and continuous monitoring of oral health in 12-year-old children.

Keywords: oral health, dental caries, KEP index, fissure filling, cavities, first permanent molars, prevalence, WHO - world health organization.

Introduction

Oral health is essential for overall health and well-being at every stage of life. A healthy mouth enables proper nutrition, supports speech, enhances social interaction, and contributes to self-confidence and aesthetics. Despite advances in modern dentistry, oral diseases remain a significant public health concern, particularly among children.
Dental caries, periodontal diseases, and orthodontic anomalies are among the most prevalent chronic conditions, with strong social and behavioral determinants. Among these, dental caries continues to be a major global health problem, often leading to tooth loss and long-term consequences if not properly managed.
According to the World Health Organization, 12-year-old children are considered a key indicator group for monitoring oral health worldwide. Approximately 60–90% of schoolchildren are affected by dental caries globally. In our country, studies have shown significantly higher caries indices compared to developed countries, indicating a serious public health issue.
Dental caries is a multifactorial disease resulting from an imbalance between demineralization and remineralization processes on the tooth surface. Its development is influenced by factors

such as oral hygiene, diet, fluoride exposure, saliva composition, and socioeconomic conditions.

Occlusal surfaces of permanent molars are particularly susceptible to caries due to the presence of pits and fissures, which favor plaque accumulation and limit the effectiveness of fluoride. For this reason, preventive measures such as fissure sealants are strongly recommended by international dental guidelines.

Fissure sealing creates a physical barrier that protects vulnerable tooth surfaces and prevents the initiation and progression of caries. Scientific evidence confirms that this method significantly reduces caries incidence in permanent teeth among children. Therefore, early preventive interventions and continuous monitoring of oral health in 12-year-old children are essential for improving long-term oral health outcomes.

Body of Manuscript

A cross-sectional study was conducted in 2023 among 12-year-old students from primary schools in the Debar region, including both urban and rural areas. Prior approval was obtained from school authorities, along with written informed consent from parents. Only children with good general health and without systemic conditions affecting dental development were included.

Clinical examinations were performed under standard dental conditions using appropriate instruments. The assessment included evaluation of the presence of teeth, caries, restorations, extractions, and fissure sealants on first permanent molars. When necessary, radiographic (orthopantomographic) analysis was used to detect agenesis. The DMFT index was determined using the Klein-Palmer system, while oral hygiene was assessed using the Greene–Vermillion index. Statistical analysis was performed using SPSS 26.0, applying Chi-square and Mann–Whitney tests for group comparisons, and Spearman correlation for associations, with statistical significance set at $p<0.05$.

The results showed that the majority of 12-year-old children had fissure-sealed first permanent molars, with an average of approximately two sealed teeth per child and no significant differences between genders. Unsealed molars were also frequently observed, again without significant gender differences. A proportion of children presented with unerupted first permanent molars, slightly more common in males, although not statistically significant. Dental caries affecting first permanent molars was present in both genders; however, a significantly higher prevalence was observed among female children ($p<0.05$). Overall, the findings indicate a considerable presence of both preventive measures and untreated dental conditions, emphasizing the need for continuous monitoring and early preventive strategies to improve oral health outcomes in 12-year-old children.

Among 12-year-old children, dental caries of first permanent molars was present in both genders, with no statistically significant difference between females and males ($p>0.05$). The average number of carious molars was low, and more than half of the children had no caries (median = 0). Similarly, the number of extracted first permanent molars was very low in both groups, without significant gender differences.

Filled (restored) first permanent molars were observed in a smaller proportion of children, with no statistically significant difference between genders. Overall, the DMFT index values were similar in male and female children, indicating that gender did not have a significant influence on oral health status.

In contrast, place of residence showed a significant impact. Children living in urban areas had a higher prevalence of fissure-sealed first permanent molars compared to those from rural areas ($p<0.05$). Conversely, unsealed molars were more common among children from rural areas.
Dental caries was significantly more prevalent in children from rural areas compared to those from urban areas ($p<0.001$), with a higher average number of affected teeth. Similarly, filled teeth were more frequently observed in rural children, reflecting a higher burden of disease. The number of extracted teeth remained low and did not differ significantly between urban and rural groups.
The DMFT index was significantly lower in children from urban areas compared to those from rural areas ($p<0.001$), indicating better oral health status among urban children. Overall, these findings highlight the influence of living environment on oral health, with rural children showing poorer outcomes and a greater need for preventive dental care.
Dental Health of First Permanent Molars – 12-Year-Old Children (Summary)
The study included 236 children aged 12, equally distributed by gender and residence (urban/rural).
Sealants:A total of 482 sealed and 462 unsealed molars were recorded. The most common pattern was 2 sealed and 2 unsealed molars (28.4%).
Caries (tooth decay): Present in 56.4% of children (133) Most commonly 2 carious molars (31.4%) Total: 236 carious teeth
Extractions: Found in 5.1% of children (12) Total: 12 extracted molars
Fillings: Present in 48.7% of children (115) Most commonly 2 filled molars (26.7%) Total: 207 filled teeth
DMF Index (Decayed, Missing, Filled): Mean: 1.95 ± 1.42 Median: 2 Range: 0–4
Urban vs Rural Differences
Sealants: Significantly more common in urban children (91.5%) vs rural (72.0%) ($p = 0.0003$).
Unsealed molars: More frequent in rural children ($p < 0.0001$).
Caries: Higher prevalence in rural children (67.8%) vs urban (44.9%) ($p = 0.0004$)
Mean number higher in rural group ($p = 0.00076$)
Fillings: More frequent in rural children ($p = 0.0002$).
Extractions: No significant difference between groups.
DMF Index: Urban: 1.44 ± 1.4 Rural: 2.47 ± 1.3 Significantly higher in rural children ($p < 0.0001$)
The study included 236 children aged 12, equally distributed by gender and residence (urban/rural).
Dental sealants: Total sealed first permanent molars: 482
Children with sealants: Urban: 91.53% Rural: 72.03%
Most common pattern: 2 sealed and 2 unsealed molars (28.39%)
Children from urban areas more often had all 4 molars sealed (38.98%)
DMFT (KEP) index: Overall mean: 1.95 ± 1.42 Urban: 1.44 ± 1.4 Rural: 2.47 ± 1.3
→ Significantly higher in rural children ($p < 0.0001$)
Caries prevalence (structure of DMFT)
Urban: 54.12% carious teeth Rural: 49.48% carious teeth
Fewer carious teeth in urban children (statistically significant)
Filled teeth: Urban: 41.18% Rural: 47.08%
Extracted teeth: Same in both groups: 5.08%
Key correlation:

Strong negative correlation between number of sealed molars and:
DMFT index Carious, extracted, and filled teeth
→ More sealants = better dental health
Conclusion
Urban children have better oral health, with: Lower DMFT index More sealed molars
Rural children show higher caries risk, likely due to:
Reduced access to dental care
Sealants are highly effective in reducing caries in first permanent molars, especially at this age.

Table Figures and Equations

Table 1. Gender distribution among 12-year-old children

Gender	n (%)
Male	118 (50%)
Female	118 (50%)

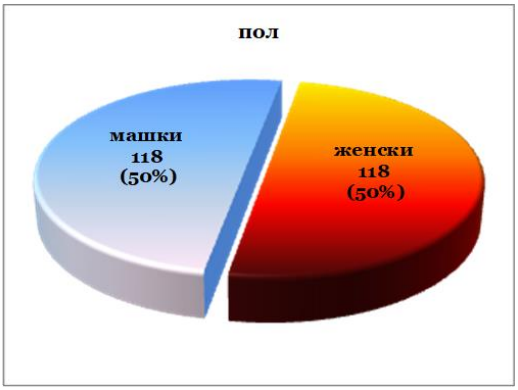


Figure 1. Graphical representation of gender distribution – 12-year-old children

Table 2. Distribution by place of residence among 12-year-old children

Gender	n (%)
Male	118 (50%)
Female	118 (50%)

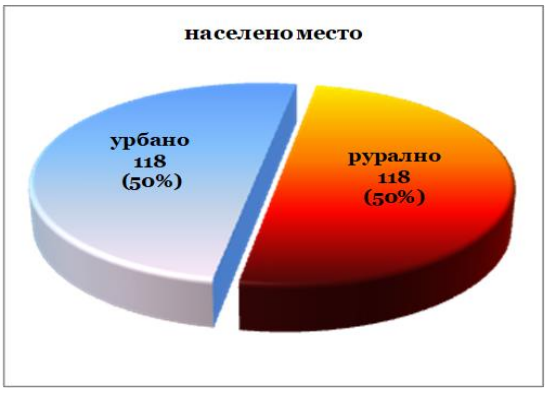


Figure 2. Graphical representation by place of residence distribution – 12-year-old children

Table 3. Distribution of sealed and unsealed first permanent molars among 12-year-old children

Nr. of first permanent molar	Sealed	Unsealed
0	43 (18.22)	60 (25.42)
1	45 (19.07)	21 (8.9)
2	67 (28.39)	67 (28.39)
3	21 (8.9)	45 (19.07)
4	60 (25.42)	43 (18.22)
Total	236	236

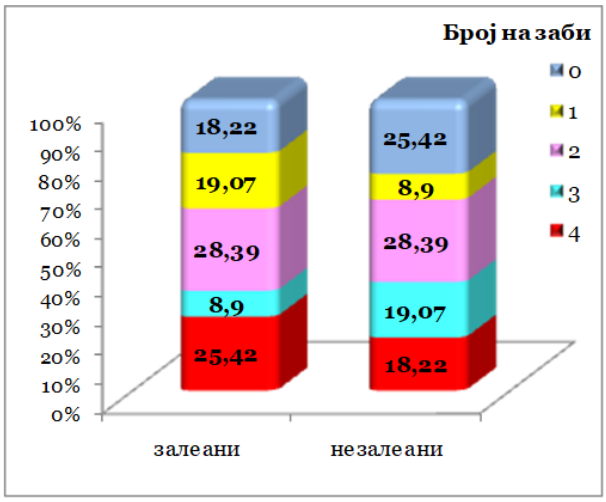


Figure 3. Graphical representation of the distribution of sealed and unsealed first permanent molars – 12-year-old children

Table 4. Distribution of carious, extracted, and filled first permanent molars among 12-year-old children

Nr.of first permanent molar	Carious	Extracted	Filled
0	103 (43.64)	224 (94.92)	121 (51.27)
1	49 (20.76)	6 (2.54)	41 (17.37)
2	74 (31.36)	6 (2.54)	63 (26.69)
3	1 (0.42)	/	4 (1.69)
4	9 (3.81)	/	7 (2.97)
total	236	236	236

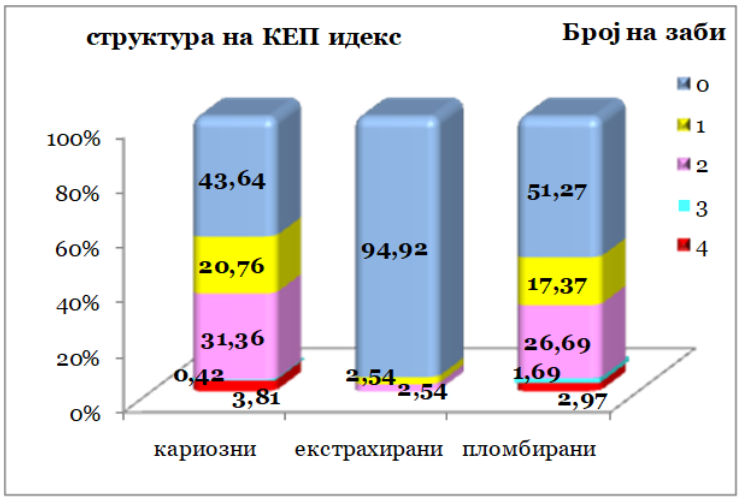


Figure 4. DMFT (KEP) index – 12-year-old children

Table 5. DMFT (KEP) index among 12-year-old children

DMFT (KEP)	Statistic parameters
Mean ± SD	1.95±1.42
Min – Max	0 – 4
Median (IQR)	2 (0-3)

Conclusions

1. At the age of 12, 74.48% of children had sealed first permanent molars, with no significant difference between genders (74.41% girls and 74.55% boys). The average number of sealed first permanent molars was 2 in both sexes.
2. Place of residence had a significant impact on dental health in 12-year-old children. Children from urban areas had significantly lower DMFT (KEP) index values compared to children from rural areas.
3. The mean DMFT index was 1.44 ± 1.4 in urban children and 2.47 ± 1.3 in rural children. Median values were 2 for urban and above 3 for rural children, confirming worse oral health in rural areas.
4. Carious first permanent molars were significantly more frequent in rural children (67.8%) compared to urban children (44.92%), indicating a clear statistical difference based on place of residence.
5. Urban children had a higher proportion of filled (restored) first permanent molars compared to rural children, although this difference was not statistically significant.
6. The distribution of extracted first permanent molars was similar in both groups. Urban children most often had one extracted tooth, while rural children most often had two, with no statistically significant difference.
7. There was a statistically significant negative correlation between the number of sealed first permanent molars and DMFT index components (carious, extracted, filled teeth). An increase in sealed teeth was associated with a decrease in DMFT values.
8. Overall, urban 12-year-old children demonstrated better oral health status, higher prevalence of sealants, and lower DMFT values compared to rural children, highlighting the importance of preventive dental care access.

Nomenclature

DMFT (KEP) – Decayed, Missing, and Filled Teeth index (carious, extracted, and filled teeth index) used to assess dental caries experience in permanent dentition.
D (C) – Decayed teeth (carious permanent teeth).
M (E) – Missing/Extracted teeth due to caries or other causes.
F (P) – Filled/Restored teeth.
DMFT Index (KEP Index) – The sum of D + M + F components, representing the overall caries experience in permanent teeth.
First Permanent Molars (FPMs) – The first permanent teeth to erupt in the oral cavity, highly susceptible to dental caries.
Fissure Sealants – Preventive resin-based materials applied to pits and fissures of teeth to prevent dental caries development.
Urban Area – A residential area with higher population density and better access to dental health services.
Rural Area – A non-urban residential area with limited access to dental care and preventive services.
Prevalence – The proportion of individuals affected by a specific condition at a given time.
Incidence – The number of new cases of a disease occurring in a defined period.
Mean (± SD) – Arithmetic average value with standard deviation.
Median – The middle value in a data set arranged in ascending or descending order.
p-value – Statistical indicator of significance; values below 0.05 indicate statistical significance.
Spearman's Correlation Coefficient (R) – A non-parametric measure of the strength and direction of association between two variables.

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ARTIFICIAL INTELLIGENCE USE AND PERCEPTIONS AMONG NURSING STUDENTS: A CROSS-SECTIONAL STUDY

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Abstract

***Introduction*:** Artificial intelligence is being increasingly integrated into education and healthcare, offering innovative opportunities to improve the learning process, the understanding of clinical cases, and the self-confidence of students. However, it remains necessary to assess nursing students' perceptions of AI and its impact on their academic and professional development.
The ***aim of the study*** was to assess the use of AI, students' perceptions of it, and its impact on academic performance and professional preparation among nursing students.
***Methods*:** A descriptive cross-sectional study was conducted at the Faculty of Medical Sciences in Elbasan. Data were collected through a structured online questionnaire assessing demographic characteristics, AI use, perceptions, and its impact. The data were analyzed using SPSS 23.0, including descriptive statistics, the chi-square test, and crude odds ratios (COR).
***Results*:** A total of 279 students participated in the study. Most of them (83.9%) reported using AI, mainly for information searching (92.3%) and understanding lectures (41%). Virtual assistants such as ChatGPT were the most commonly used tools (78.2%). Academic average was a factor significantly associated with AI use, whereas place of residence and cycle of study did not show significant associations. Students reported a moderate impact on understanding lectures and exam preparation, but a limited impact on practical skills, critical thinking, and empathy.
Conclusions: AI represents an effective supportive tool in nursing education by improving theoretical understanding and academic efficiency. However, its impact on human competencies remains limited. In order to optimize its benefits and prevent dependency, a structured and ethical integration is needed.

Keywords: Artificial intelligence, nursing education, impact, perception, nursing student

Introduction

In the last decade, artificial intelligence has been one of the most important developments in the field of technology, being integrated into various fields, including healthcare (Buchanan et al., 2021; Labrague et al., 2025; Rony et al., 2025). Its use is changing the way healthcare services are delivered, but also the way future healthcare professionals are prepared, especially in the context of decision-making and patient management (Fernandes et al., 2026).
Artificial intelligence is also having a visible impact on nursing education. Today, students no longer rely only on traditional learning methods, but increasingly use digital methods to understand and assimilate their theoretical and practical knowledge (Cucci et al., 2025). AI-based technologies such as virtual simulations, virtual patients, and intelligent systems supporting decision-making have enabled an interactive and safe environment for the development of critical thinking and clinical reasoning (Fung et al., 2025; Sriram et al., 2025). These tools also contribute to the development of nursing care plans and to the understanding of complex clinical processes (Wei et al., 2025).
In recent years, a special role has also been taken by various generative AI platforms such as ChatGPT and similar tools, which have become part of students' daily lives (Zgambo et al., 2025). These tools offer quick access to information, help explain difficult concepts, support

the processing of academic materials, and generate structured responses similar to those produced by humans (Guirguis et al., 2026; Khlaif et al., 2025; Lifshits & Rosenberg, 2024). For nursing students, these technologies provide potential support for academic performance and professional development by linking theoretical, practical, and clinical knowledge (George Pallivathukal et al., 2024).

Various studies have shown that the use of artificial intelligence improves clinical reasoning ability, critical thinking, and self-confidence in practice (Buchanan et al., 2021; Labrague et al., 2023). AI also provides personalized and interactive information, adapting to students' needs and offering rapid feedback (Glauberman et al., 2023; Lane et al., 2024). At the same time, the use of technology can help improve the quality of patient care through continuous support in monitoring and decision-making (Martinez-Ortigosa et al., 2023).

However, beyond its benefits, the literature shows that the use of artificial intelligence is associated with a series of challenges and concerns in the field of nursing education. Uncontrolled use of AI may lead to reduced active student involvement in the learning process, increased dep

There are no sources in the current document.endence on technology, and reduced professional competence (Dagcan Sahin & Yildirim, 2026; Pailaha, 2023; Sun & Hoelscher, 2023). Other concerns relate to the accuracy of information, academic privacy, and the risk of plagiarism (Le Lagadec et al., 2024; Lund et al., 2025) issues that are particularly sensitive in the field of nursing.

Another aspect that should not be neglected is the need to develop new competencies among nursing students, including the critical use of technology and data analysis (Wynn, 2025). What is important to emphasize is that AI cannot replace the human elements of the nursing profession such as empathy, communication, and patient care (Montemayor et al., 2022).

Although the use and impact of artificial intelligence in nursing education continues to grow, evidence on how students use and perceive it in practice remains limited. Most studies focus on evaluating the theoretical benefits of AI, while less attention has been paid to students' real-life experiences and the factors influencing their use of AI in the educational context (Khlaif et al., 2025). Moreover, there are several barriers such as the lack of standardization in AI education and inequalities in access (El Arab et al., 2025) .

It is important to study nursing students' perceptions and experiences regarding the use of artificial intelligence tools, with a focus on identifying benefits, challenges, and implications in order to develop educational policies for the most effective and ethical use of AI (Abuadas et al., 2025; Dodson et al., 2025).

Therefore, this study aims to analyze the use, perceptions, and challenges of nursing students regarding artificial intelligence in the academic context, as well as the impact of these tools on the learning process and professional practice.

Materials and methods

2.1 Study design. A descriptive cross-sectional study was conducted with a combined quantitative and qualitative approach, focusing on the analysis of the frequency of artificial intelligence use, as well as students' perceptions and concerns regarding its impact on academic and practical nursing skills.

2.2 Study area and population: The study included students from the General Nursing program at the Faculty of Medical Technical Sciences in Elbasan. Data collection was conducted during the period January–March 2026. Participants were selected through convenience sampling, including students from all years in the Bachelor's and Master's study cycles, who participated voluntarily.
Data were collected through a self-administered structured questionnaire created on the Google Forms platform and distributed through student communication groups. Participants were informed in advance about the purpose of the study, were guaranteed data confidentiality and anonymity, and were asked to provide electronic informed consent at the beginning of the questionnaire. Only fully completed questionnaires were included in the study.

*2.3 Instrument***:**A questionnaire was developed by the authors focusing on the use of AI among nursing students. The instrument consisted of three sections:
The *first section* included demographic data, including age, gender, place of residence (urban/rural), study cycle (Bachelor's/Master's), academic average, AI use, and frequency of use. This section also included questions regarding the types of tools used (virtual assistance such as ChatGPT, educational platforms, text-generation tools, or others) and the purpose of use (e.g., information search, studying, academic assignments, understanding clinical cases).
The *second section* consisted of questions evaluating the impact of artificial intelligence on knowledge acquisition and preparation for professional practice, such as understanding lectures, exam preparation, academic performance, saving study time, understanding clinical cases, nursing care, self-confidence during practice, critical thinking, communication skills, and empathy toward patients. A 5-point Likert scale was used for this purpose (1 = "no impact at all" to 5 = "very high impact").
The *third section* assessed students' attitudes and concerns regarding AI through structured questions using a Likert scale (1 = "strongly disagree" to 5 = "strongly agree"). These included the usefulness of AI, its impact on the quality of learning and clinical preparation, the risk of dependency, the reliability of information, and its impact on critical thinking.

*2.4 Data analysis***:** The data were analyzed using SPSS version 23.0. Categorical data were presented as frequencies and percentages, while continuous data were presented using means and standard deviations. The chi-square test was used to evaluate the relationship between AI use and variables. To identify factors associated with artificial intelligence use, crude odds ratios (COR) with 95% confidence intervals were reported. A p-value < 0.005 was considered statistically significant. Likert-scale variables were analyzed descriptively and presented as percentages for each response category.

Rezultatet

3.1 General characteristics: A total of 279 General Nursing students participated in the study. Of these, 97.8% were female and only 2.2% male. The mean age of participants was 22.4 ± 5.7 years. More than half of the students (55.9%) lived in urban areas, while 44.1% lived in rural areas. Most students (71%) belonged to the Bachelor's study cycle. Regarding academic performance, most students had a grade average within the range of 7.0–7.9 (44.1%), followed by 28% with an average of 6.0–6.9. Meanwhile, 16.1% of students reported an average of 8.0–8.9 and only 4.3% had a very high average of 9.0–10. Students with an average below 6.0

represented only 7.5% of participants. Most students (83.9%) stated that they used artificial intelligence (Table 1).

Table 1. Demographic characteristics of participants (N = 279)

Variable	Category	N	%
Age (years)	Mean ± SD	22.4 ± 5.7	–
Residence	Urban	156	55.9%
	Rural	123	44.1%
Gender	Male	6	97.8%
	Female	273	2.2%
Cycle of study	Bachelor's	198	71.0%
	Master's	81	29.0%
Academic average (GPA)	< 6.0	21	7.5%
	6.0 – 6.9	78	28.0%
	7.0 – 7.9	123	44.1%
	8.0 – 8.9	45	16.1%
	9.0 – 10	12	4.3%
AI use	Yes	234	83.9%
	No	45	16.1%

3.2 Use of artificial intelligence: According to the data, a high percentage of students reported being AI users, specifically 83.9%. Of these, 44.9% stated that they used AI daily, while 29.5% used it weekly. A smaller proportion reported occasional use, with 20.5% using it rarely and only 5.1% monthly. Regarding the types of tools used, 78.2% reported using virtual assistants such as ChatGPT or similar tools, 26.9% used educational platforms, 15.4% used text-generation tools, and 21.8% used other tools. Most participants (93.2%) used AI for information searching, while 41% used it for understanding lectures, 16.7% for academic assignments, and 12% for understanding clinical cases.(Table 2)

Table 2. Frequency, tools, and purpose of artificial intelligence use (N = 234)

Variable	Category	N	%
Frequency of AI use	Every day	105	44.9%
	Every week	69	29.5%
	Every month	12	5.1%
	Rarely	48	20.5%
Tools used (multiple responses)	Virtual assistance (ChatGPT)	183	78.2%
	Educational platforms	63	26.9%
	Text generation	36	15.4%
	Other	51	21.8%
Purpose of AI use (multiple responses)	Studying / learning lecture content	96	41.0%

Variable	Category	N	%
	Academic assignments / essays	39	16.7%
	Understanding clinical cases	28	12.0%
	Information search	216	92.3%

3.3 Factors associated with the use of artificial intelligence: Bivariate analysis showed that students living in urban areas used artificial intelligence more than those in rural areas, but this difference was not statistically significant (COR = 1.56, 95% CI: 0.82–2.96, p = 0.23). Likewise, no association was found between study cycle and use of artificial intelligence, as Bachelor's and Master's students had a similar probability of use (COR = 0.84, 95% CI: 0.42–1.65, p = 0.736). Bivariate analysis showed that academic average had a significant effect on the use of artificial intelligence. Students with an average of 6.0–6.9 had six times higher odds of using AI compared to those with a GPA below 6.0 (COR = 6.05, 95% CI: 2.11–17.36, p < 0.001). The effect was even more evident among students with an average of 7.0–7.9 (COR = 10.18, 95% CI: 3.59–28.88, p < 0.001) and 8.0–8.9 (COR = 7.15, 95% CI: 2.13–24.06, p = 0.002), suggesting a significant association between academic average and AI use. (Table 3)

Table 3. Factors associated with the use of artificial intelligence

Variable	Category	AI Use n (%)	No AI n (%)	COR (95% CI)	p-value
Residence	Rural	99 (80.5%)	24 (19.5%)	1.00	—
	Urban	135 (86.5%)	21 (13.5%)	1.56 (0.82–2.96)	0.23
Cycle of study	Bachelor's	165 (84.6%)	30 (15.4%)	1.00	—
	Master's	69 (82.1%)	15 (17.9%)	0.84 (0.42–1.65)	0.736
Academic average (GPA)	< 6.0	10 (47.6%)	11 (52.4%)	1.00	—
	6.0–6.9	66 (84.6%)	12 (15.4%)	6.05 (2.11–17.36)	<0.001
	7.0–7.9	111 (90.2%)	12 (9.8%)	10.18 (3.59–28.88)	<0.001
	8.0–8.9	39 (86.7%)	6 (13.3%)	7.15 (2.13–24.06)	0.002
	9.0–10.0	8 (66.7%)	4 (33.3%)	2.20 (0.50–9.61)	0.290

Table 4. Impact of artificial intelligence on learning outcomes (N=234)

Item	1 – No influence	2 – Low influence	3 – Moderate influence	4 – High influence	5 – Very high influence
Understanding lectures	52 (22.2%)	49 (20.9%)	84 (35.9%)	43 (18.4%)	6 (2.6%)
Exam preparation	45 (19.2%)	54 (23.1%)	93 (39.7%)	39 (16.7%)	3 (1.3%)
Academic performance	81 (34.6%)	54 (23.1%)	81 (34.6%)	15 (6.4%)	3 (1.3%)
Time-saving while studying	60 (25.6%)	66 (28.2%)	60 (25.6%)	30 (12.8%)	18 (7.7%)
Understanding clinical cases	36 (15.4%)	39 (16.7%)	87 (37.2%)	45 (19.2%)	27 (11.5%)
Nursing care	87 (37.2%)	39 (16.7%)	78 (33.3%)	21 (9.0%)	9 (3.8%)
Self-confidence	117 (50.0%)	42 (18.0%)	48 (20.5%)	18 (7.7%)	9 (3.8%)
Critical thinking	84 (35.9%)	57 (24.4%)	69 (29.5%)	15 (6.4%)	9 (3.8%)
Communication skills	99 (42.3%)	39 (16.7%)	60 (25.6%)	24 (10.3%)	12 (5.1%)
Empathy toward patients	126 (53.8%)	33 (14.1%)	54 (23.1%)	15 (6.4%)	6 (2.6%)

3.4 Students' perceptions of the impact of AI: Data analysis showed that AI tools had a varying impact on different aspects of learning and professional preparation for nursing students. Specifically, a moderate impact (Likert 3) was reported in understanding lectures *(35.9%) and exam preparation (39.7%). Likewise, a moderate impact was reported for* understanding clinical cases (37.2%). On the other hand, AI was reported to have a low impact on academic performance by 34.6% of students, and also on saving study time by 28.2%.
The impact of AI proved limited in practical and social skills. According to the results, students reported no impact (Likert 1) on nursing care (37.2%), self-confidence (50%), critical thinking (35.9%), communication skills (42.3%), and empathy toward patients (53.8%). (Table 4).

3.5 Students' perceptions of AI use: Students' perceptions of the use of artificial intelligence (AI) are presented in Table 5. Most students considered AI to be a useful tool, with 43.6% expressing a neutral attitude and 24.8% agreeing or strongly agreeing with its usefulness. Likewise, 35.9% held a neutral attitude regarding the improvement of learning quality, while 28.2% expressed agreement. However, more than half of the participants (55.2%) perceived AI to have a low impact on their professional preparation, while 42.8% reported a low impact on their critical thinking. As for the risk of dependency, 39.7% did not consider AI a factor that creates dependency. On the other hand, almost half of the participants (47.4%) agreed or strongly agreed that information obtained from AI is not always reliable. (Table 5)

Table 5. Participants' perceptions of AI use (N=234)

Statement	1 (Strongly disagree)	2 Disagree	3 Neutral/Moderate	4 Agree	5 (Strongly agree)
AI is a useful tool	39 (16.7%)	35 (15.0%)	102 (43.6%)	40 (17.1%)	18 (7.7%)
AI improves the quality of learning	39 (16.7%)	45 (19.2%)	84 (35.9%)	51 (21.8%)	15 (6.4%)
AI helps in preparation for professional practice	54 (23.1%)	75 (32.1%)	78 (33.3%)	15 (6.4%)	12 (5.1%)
AI negatively affects critical thinking	39 (16.7%)	61 (26.1%)	72 (30.8%)	39 (16.7%)	23 (9.8%)
AI may create dependency	66 (28.2%)	27 (11.5%)	75 (32.1%)	42 (17.9%)	24 (10.3%)
Information from AI is not always reliable	33 (14.1%)	6 (2.6%)	84 (35.9%)	60 (25.6%)	51 (21.8%)

Discussion

This study identified a high level of artificial intelligence use among nursing students in various aspects of their studies, with 83.9% of participants reporting that they were AI users. This result is consistent with the study by (Han et al., 2025)which reports a high level of AI use (92%) in university education. In our study, only a portion of students used AI on a daily basis, suggesting that its integration remains more functional, aimed at meeting specific academic needs, rather than being fully embedded in the learning process (Johnston et al., 2024).

The dominance of virtual assistants, especially ChatGPT (78.2%), indicates a global trend toward the use of generative AI as a primary source of information and education, confirming that AI facilitates the understanding of concepts and student learning (Arkan et al., 2025; BaiDoo-Anu & Owusu Ansah, 2023; Gonzalez-Garcia et al., 2025; Saatçi et al., 2024). However, the fact that the main use of AI among participants was for information searching, and less for academic and clinical skills, suggests that AI is perceived more as a means of quick access to information than as an educational tool (Zgambo et al., 2025).

Regarding perceptions of the use of artificial intelligence tools, the results of this study showed that participants held a neutral attitude regarding the role of AI in understanding lectures or preparing for exams. This suggests that students perceive AI more as a supportive and auxiliary tool than as a primary factor influencing their academic performance.These results contrast with those of studies by (Khlaif et al., 2025; Shen et al., 2025; Vieriu & Petrea, 2025)which reported a more pronounced impact of AI on improving academic performance.

n the other hand, a high percentage of students reported no impact of AI on practical and social aspects such as self-confidence, empathy, or communication ability. These findings reinforce the concept that AI can help in the learning process and in understanding concepts, but its impact on the development of interpersonal competencies is limited. AI cannot replace the human components of nursing practice (Gülırmak Güler & Şen Atasayar, 2025; Ronquillo et al., 2021)

Likewise, students' attitudes regarding the impact of AI on critical thinking were low, in line with other studies, suggesting that excessive reliance on AI may reduce active information processing and clinical judgment (Dagcan Sahin & Yildirim, 2026; Dodson et al., 2025).

The findings also showed that students were skeptical regarding the reliability of information obtained from AI and believed that there may be a risk of dependency on these technologies, findings which are also consistent with evidence from other studies (Farghaly Abdelaliem et al., 2022; Mersal et al., 2026; Thomson et al., 2024), indicating that a large proportion of students have a high level of critical awareness.

The findings of the study showed that academic average is an important factor associated with the use of artificial intelligence among nursing students. Specifically, students with higher academic averages were more likely to use AI. These findings are also consistent with other studies (Bakarman et al., 2025; Gonzalez-Garcia et al., 2025) suggesting that academic performance stimulates interest in innovative technologies and the integration of digital tools (El Arab et al., 2025)

On the other hand, place of residence was not found to be a factor affecting AI use, suggesting that access to technology is similar among students living in urban and rural areas.

Likewise, no association was found between AI use and study cycle, indicating that the use of artificial intelligence technology is similar across different academic levels. AI use is influenced more by exposure to technology and individual attitudes toward it (Han et al., 2025; Zeng et al., 2026).

Conclusions

The findings of this study showed that nursing students had a generally positive attitude toward the use of AI and perceived it as a supportive tool in the learning process. However, its impact was greater in the theoretical aspect, whereas its impact on their professional and interpersonal skills was more limited. These results emphasize the need for a more advanced integration of AI into nursing education. Training, experience, the development of digital competencies, and a supportive academic environment are essential for these tools to be used effectively.

Study limitations

This study has several limitations. First, since data collection was based on self-reporting, this may be associated with subjectivity in students' assessment of impact or perception. In addition, because the questionnaire was distributed online, it may have favored students who were more interested in or more familiar with technology. On the other hand, the use of a cross-sectional method and the limitation of data collection to a single center did not allow us to assess cause-and-effect relationships, which limits the generalizability of the results. Therefore, future studies should use more advanced and qualitative methods, such as interviews, to better understand nursing students' perceptions of and the impact of AI.

Abbreviations

AI – Artificial Intelligence
GPA – Grade Point Average
COR – Crude Odds Ratio
SD – Standard Deviation
N – Number of participants

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Conflicts of Interest

The authors declare no conflicts of interest.

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PERSONALIZED MEDICINE: A COMPARATIVE ANALYSIS OF IMPLEMENTATION AND CHALLENGES IN NORTH MACEDONIA AND EUROPEAN COUNTRIES

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Abstract

Personalized medicine represents a fundamental transformation in the health system in the prevention, diagnosis and treatment of patients based on their genetic profile. The use of genomic, pharmacogenetic and clinical data enables safer and more effective treatment. The most developed European countries have made great progress in this direction, while in some regions, including North Macedonia, the implementation of personalized medicine still remains very limited.

Our research intends to perform a comparative study on the progress of personalized medicine in some of the most developed European countries like England, France and Germany to that of North Macedonia. We conducted a literature review of the topics of interest that are genetic and pharmacogenetic testing, biomarker-based diagnostics and the introduction of genomics in healthcare systems. European countries have been gradually moving towards personalization of health, for example, through national genomic projects, a range of new technologies and clinical guidelines that are sufficiently advanced to make targeted therapies and pharmacogenetic testing a part of everyday clinical practice.

On the other hand, in North Macedonia, the project is barely taking off and is mostly confined to a few specialized healthcare and research facilities. The testing methods that can be adopted are targeted genotyping, PCR-based assays and the new next-generation sequencing techniques; however, their broader use is hampered by a lack of infrastructure, financial barriers, absence of standardized guidelines and shortage specialized staff.

Keywords: Personalized Medicine, Genetic Testing, Healthcare Implementation, Comparative Analysis, European Healthcare Systems, North Macedonia

Introduction

Personalized medicine focuses on tailoring each patient's prevention, diagnosis, and treatment based on their unique characteristics and it is one of the main changes to modern healthcare (Francis S. Collins & Harold Varmus, 2015; European Commission, n. d.). Unlike traditional medicine that simply follows established treatment protocols personalized medicine takes into account the genetic differences biomarker profiles clinical data and environmental factors to best meet patient needs and low adverse effects (Ashley, 2016; Goetz & Schork 2018). The evolution of genomics next-generation sequencing technologies and bioinformatics have greatly helped in the progress of precision medicine allowing disease classification and treatment personalization to reach unprecedented levels of precision (Eric J. Topol, 2014; International Human Genome Sequencing Consortium, 2004).

Examples of personalized medicine in the clinic include cancer treatment, cardiac care and drug therapy. In cancer treatment the use of molecular analyses has made it possible to find the mutation causing the cancer and then to produce a drug that specifically targets it; in general patient survival and response to therapy have been substantially improved with targeted drugs (National Cancer Institute, 2020; Garraway & Lander, 2013). Genetic testing in cardiology and pharmacogenetics also guides the selection of the most appropriate

therapeutic agent and the determination of the right dose so as to minimize adverse drug reactions and maximize the therapeutic outcome (Reling et al, 2019; Roden et al. 2019). Great variations in pharmacogenetics have mainly been documented for genes playing roles in drug metabolism which is one reason why pharmacogenetics have become an important aspect of individualized treatment strategies (Roden et al 2011; Noveski et al 2025; Pereira NL & Weinshilboum RM 2009; Dunnenberger et al., 2015).

Significant advances have been made in personalized medicine throughout Europe, mainly via national genomic strategies, massive biobanks, and the regular application of molecular diagnostics (European Commission, 2022; European Alliance for Personalised Medicine, 2020). The United Kingdom, France, and Germany are leading examples of the effective reuse of those technologies. In the UK, the Genomics England program, especially the 100,000 Genomes Project, has allowed the use of genomic data for regular clinical care, mainly in the fields of oncology and rare diseases (Genomics England, 2018). In France, the "France Mdecine Gnomique 2025" plan has put in place a national network for genomic sequencing and data sharing, helping precision diagnostics and personalized therapies (Auffray et al. 2016). Likewise, Germany has rolled out national programs targeting precision medicine and digital health, encouraging the use of genomic data in medical decision-making and bolstering translational research (German Federal Ministry of Health, 2020).

These European examples show that coordinated national strategies, funding of infrastructure, cross-disciplinary teamwork, and planing clinical guidelines are crucial elements in the successful launch of personalized medicine. Besides, the presence of extensive genomic databases, combining electronic health records, and enabling ongoing professional development effectively support the adoption of precision medicine in those countries.

The application of personalized medicine in North Macedonia is at nascent phase and the practice is mostly confined to a few clinical and research centers specialized in a particular area. However, some recent research has recognized a greater use of genomic and pharmacogenetic techniques in the country. pharmacogenetic studies have pointed to the direct relationship between genetic differences and treatment results, for instance, the AKR1D1*36 allelic variant has been reported as an independent factor affecting clopidogrel therapy effectiveness, which underscores the role of individualized treatment approaches in cardiovascular patients (Kapedanovska-Nestorovska et al. 2019).

On the other hand, population-level genomic analyses with whole exome sequencing have uncovered a rich pharmacogenetic allele repertoire of the local population, including clinically relevant variants and newly discovered potentially functional mutations that may impact drug response (Noveski et al. 2025). Such results support the necessity of population-specific genetic profiling for enhancing therapeutic accuracy.

Also, some great analytical frameworks for precision genomics that clinically enable variant filtering and interpreting with the aim of identifying the clinically relevant genetic info and its healthcare decision impact are discussed (Mehandziska et al. 2020). Molecular profiling programs led by genetic alterations in major driver genes in lung cancer have been uncovered, sparking the use of targeted therapies and personalized treatments among approaches (Eftimov et al. 2025).

Nonetheless, the application of personalized medicine in clinical practice in North Macedonia is still very modest. The main problems are the scarcity of advanced genomic technologies, limited infrastructure, very high costs, absence of standardized clinical guidelines, and low

training levels of healthcare professionals. These challenges will further limit the wide-scale implementation of precision medicine in the country's healthcare system.

Yet, the personalized medicine is still very promising because it can bring major benefits such as more effective treatments, less toxic side effects, the possibility of drug selection that fits patients individually, and overall safety of patients (Ashley, 2016). Nevertheless, from the angle of ethics, there are concerns about privacy of genetic information, inequalities in availability of tests, and difficulties in understanding genomic data which are primary reasons for people's resistance to genetic medicine (Geoffrey S. Ginsburg & Katherine A. Phillips, 2018).

Due to the differences in implementation among various healthcare systems, it is crucial to do a comparative study between North Macedonia and top European countries like the UK, France, and Germany to get a clear picture of current progress, pinpoint gaps, and think of ways for future development. This kind of study offers great understanding on how well-performing European models can be localized for the purpose of promoting precision medicine and enhancing patient outcome.

Aim of the study

This study is fundamentally about exploring the contribution of personal medicine to the healthcare sector and the investigation of its progress and dissemination in North Macedonia as compared to the top European countries such as the United Kingdom, France, and Germany.

The study primarily intends to evaluate the extent to which genomic and pharmacogenetic methods have been implemented in the clinical setting, for example, the employment of genetic testing, use of biomarkers for diagnosis, and therapy based on the patient's characteristics. Besides, the study attempts to unveil the utmost positive aspects of personalized medicine - like higher effectiveness of treatment and lowered risk to the patient - along with the most pressing constraints, including technical, moral, and financial difficulties. Moreover, the purpose of the present research lies in evaluating the significant problems, which slow down the introduction of personalized medicine in North Macedonia, for example, lack of proper infrastructure funds introduction of cutting-edge technology, and human resources training. By applying the comparison of these issues faced by the two countries, this study sees the European models of personalized medicine as a chance for a healthcare system improvement in North Macedonia.

On one hand, the research gives a clear picture of how personalized medicine is practiced currently and, on the other hand, presents realistic approaches in order to push precision medicine forward and yield better results from healthcare activities at the level of the national health system.

Methodology

This research was narrative comparative review aiming to analyze and compare the implementation of personalized medicine in North Macedonia and selected European countries, including UK, France, and Germany. The secondary research was done through a high degree of literature review which includes critical evaluation of scientific literature, clinical trials, and institutional reports.

Scholarly journals, international clinical guidelines, and reports by scientific organizations and health care institutions have been the main sources of data. The selection of sources was primarily based on studies that focused on the main components of personalized medicine such as genetic and pharmacogenetic testing, diagnostics based on biomarkers, and the utilization of genomic data in the clinic.

The analysis included:

1. A comparative evaluation of the level of implementation of personalized medicine between North Macedonia and selected European countries
2. An assessment of available testing methodologies, including targeted genotyping, polymerase chain reaction (PCR)-based assays, and next-generation sequencing techniques such as whole exome sequencing
3. Identification of the main advantages and limitations of personalized medicine across different healthcare systems
4. Evaluation of key challenges affecting implementation, including infrastructure, financial constraints, accessibility of testing, and availability of trained healthcare professionals

A qualitative analytical approach was used to synthesize and interpret the findings, allowing for a comprehensive understanding of current practices and future perspectives. No primary data were collected, as the study relies on the critical comparison of existing evidence.

Results and Discussion

Reviewing various studies points out a major gap in the implementation of personalized medicine between North Macedonia and highly developed European countries like the United Kingdom, France, and Germany. These countries have gradually incorporated personalized medicine into their healthcare systems through national genomic policies, large-scale sequencing programs, and the frequent use of pharmacogenetic testing (European Commission, 2022; Auffray et al. 2016). For instance, in the UK, the Genomics England project has made it possible to regularly use genomic information in clinical decisions, especially in cancer and rare diseases (Genomics England, 2018). Likewise, France has rolled out a national genomic strategy to bring sequencing technologies into medical practice, and Germany has promoted precision medicine thanks to its focus on the development of the digital health infrastructure and the funding of translational research programs (Auffray et al. 2016; European Commission, 2022).

Such changes have notably enhanced the accuracy of diagnoses and have been instrumental in the appropriate use of targeted therapies, mainly in oncology and pharmacology, which have been linked to improved clinical outcomes (Ashley, 2016; Garraway & Lander, 2013). On the other hand, North Macedonia is still at the stage where personalized medicine is being planned and is mostly found in specialized institutions and research environments.

Local studies provide evidence supporting the entry of genomic and pharmacogenetic methods in North Macedonia, although they are not yet widely used. A large-scale pharmacogenetic study based on whole exome sequencing uncovered an extensive panel of alleles, among which could be found variants with a direct impact on drug metabolism and response, as well as newly discovered potentially functional variants (Noveski et

al. 2025). Such data highlight the critical role of population-specific genomic information in the development of therapeutioc propositions.

Molecular profiling studies of lung cancer patients in North Macedonia in the field of oncology have revealed a high percentage of individuals having genetically actionable alterations in major genes such as EGFR, KRAS, and PIK3CA (Eftimov et al. 2025). These findings prove the clinical significance of genomic testing in the decision-making process of targeted therapies. Nevertheless, the daily use of these methods is still very limited mainly due to the infrastructure and financial issues.

Moreover, precision genomics can only be used efficiently if there are analytical frameworks that are properly structured. The creation of genomic data filtering workflows and interpretation, including both variant-centric and gene-centric methods, has been found to greatly enhance the identification of clinically actionable variants and their clinical application (Mehandziska et al. 2020). These kinds of frameworks are extensively used by more advanced healthcare systems in Europe, but continue to be the focus of development in North Macedonia.

Even though these are very good indicators of the potential of personalized medicine, a number of obstacles continue to prevent its widespread adoption in North Macedonia. Limiting factors are among others the lack of infrastructure, the limited availability of advanced genomic technologies, the high cost of implementation, and the absence of standardized clinical guidelines. On top of that, the inadequacy of training and expertise in genomic medicine makes the integration of this approach into regular practice even more difficult (Vogenberg et al. 2010; Ginsburg & Phillips, 2018).

The East-European countries like the UK, France, and Germany reveal that the key factors for effective implementation are national strategy alignment, continuous financial support of genomic infrastructure, inclusion of genetic testing in health care provision, and ongoing professional training (European Commission, 2022; Auffray et al. 2016). The countries serve as an example for North Macedonia in terms of personalized medicine development.

To sum up, the results show that personalized medicine has a great opportunity to enhance health outcomes, but its application in North Macedonia is still at a very initial stage when compared with more developed European countries. Building up physical capacity, increasing opportunities for genetic testing, and implementing well-defined clinical and regulatory guidelines will be the main measures for narrowing this inconsistency and for the progress of precision medicine in the area.

Conclusion

Personalized medicine is the use of genomic information and other personal data of individuals to tailor the diagnosis and treatment of a disease or condition more precisely, effectively, and with consideration of the patient's preferences and needs. In Europe, for instance, the UK, France, and Germany have developed robust systems for the implementation of personalized medicine ' precision medicine '. These countries have established national genomic strategies, invested in advanced sequencing technologies, and made genetic testing and biomarker analysis a part of routine clinical practice. Consequently, they showcase enhanced diagnostic precision, broader use of targeted therapies, and more cost-effective healthcare delivery.

On the other hand, personalized medicine ' precision medicine ' in North Macedonia faces the challenge of being at a very early stage of development. Though some advances have been made in pharmacogenetics and molecular diagnostics, their extent of implementation is still very limited and is mostly available only in specialized centers. Main obstacles are the insufficient health infrastructure, the very expensive nature of the advanced technologies, the absence of standard clinical guidelines, and the scarcity of trained healthcare professionals.

Even with these disparities, the expanding research and first clinical uses show that personalized medicine can greatly help healthcare in North Macedonia. To catch up with more developed European countries, the country will need to make strategic investments, increase genetic testing, create policies, and consider successful European models that can be adapted to their circumstances.

Finally, although differences in implementation continue, personalized medicine is a necessary move towards healthcare that is more efficient, safer, and tailored to each individual. Also, its progress will be vital for the future of medical practice throughout Europe.

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POSTRENAL ACUTE KIDNEY INJURY SECONDARY TO URINARY RETENTION FROM BENIGN PROSTATIC HYPERPLASIA COMPLICATED BY MULTIDRUG-RESISTANT ACINETOBACTER INFECTION AND CHRONIC PULMONARY THROMBOEMBOLISM: A CASE REPORT

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Abstract

Introduction: Acute kidney injury (AKI) is a frequent and serious condition in elderly patients, often multifactorial and associated with increased morbidity. Postrenal causes, particularly urinary obstruction due to benign prostatic hyperplasia (BPH), represent a reversible etiology if promptly recognized. The coexistence of infection and thromboembolic disease may further complicate the clinical course.
Case Presentation: We report an 87-year-old male with multiple comorbidities, including cardiovascular disease and recently diagnosed chronic pulmonary thromboembolism, who presented with acute urinary retention, abdominal pain, fatigue, hemoptysis, and dyspnea. His condition developed in the postoperative setting following intestinal surgery.
Diagnostic Assessment: Laboratory findings revealed AKI (creatinine 240 µmol/L, urea 17.5 mmol/L), marked systemic inflammation (CRP 89.7 mg/L), electrolyte disturbances, normocytic anemia, and significantly elevated D-dimer levels. Urinalysis showed severe infection, and urine culture identified multidrug-resistant (MDR) Acinetobacter spp., sensitive only to fosfomycin. Imaging suggested prostatic enlargement and chronic pulmonary thromboembolism.
Differential Diagnosis: Considerations included prerenal AKI due to dehydration, intrinsic renal injury, postrenal obstruction, complicated urinary tract infection, pulmonary embolism, and postoperative abdominal complications.
Final Diagnosis: Postrenal AKI secondary to urinary retention from BPH, complicated by MDR Acinetobacter urinary tract infection and coexisting chronic pulmonary thromboembolism.
Treatment and Management: Immediate bladder decompression via Foley catheterization led to improved urine output. Management included targeted antibiotic therapy based on susceptibility testing, electrolyte correction, hydration, and initiation of tamsulosin for BPH.
Outcome and Follow-up: The patient showed clinical improvement with stabilization of renal function and resolution of infection symptoms. Follow-up included monitoring renal parameters, urological evaluation, and assessment of thromboembolic risk.
Discussion and Conclusion: This case highlights the importance of early identification of reversible causes of AKI, particularly postrenal obstruction in elderly patients. It underscores the growing challenge of MDR infections and the diagnostic complexity of elevated D-dimer in inflammatory states. A multidisciplinary, systematic approach is essential for optimal management of patients with overlapping renal, infectious, and thromboembolic conditions.

Keywords: Postrenal acute kidney injury; Benign prostatic hyperplasia; Urinary retention; Multidrug-resistant Acinetobacter; Complicated urinary tract infection; Pulmonary thromboembolism.

Introduction

Acute kidney injury (AKI) is a common and serious complication in hospitalized patients, particularly in older adults, and is associated with increased morbidity and mortality. Even

minor increases in serum creatinine may reflect clinically significant renal dysfunction, underlining the importance of early recognition and timely intervention [1].
Among the different etiologies, obstructive nephropathy represents a frequent and potentially reversible cause of AKI. In elderly patients, postoperative urinary retention and lower urinary tract obstruction, often related to benign prostatic hyperplasia, may rapidly lead to postrenal AKI if not promptly recognized and treated. Although outcomes may be more favorable than in other AKI forms, obstructive AKI can still result in prolonged hospitalization and incomplete renal recovery [2].
Complicated urinary tract infections may further worsen the clinical course, especially when caused by multidrug-resistant organisms. Acinetobacter spp., including Acinetobacter baumannii, are important nosocomial pathogens due to their ability to develop multidrug resistance, which frequently limits treatment options and necessitates targeted therapy based on susceptibility testing [3].
In postoperative patients, systemic inflammation, infection, and reduced mobility may also contribute to a hypercoagulable state. Markedly elevated D-dimer levels are clinically relevant because the likelihood of pulmonary embolism increases with rising D-dimer concentrations, particularly when respiratory symptoms coexist [4].
We present the case of a frail elderly postoperative patient in whom chronic pulmonary thromboembolism, in conjunction with postrenal acute kidney injury and a multidrug-resistant Acinetobacter urinary tract infection, resulted in a complex and clinically challenging presentation.

Case Presentation

History of Present Illness

An 87-year-old retired male with a history of cardiovascular disease, arterial hypertension, hypercholesterolemia, chronic pulmonary thromboembolism (diagnosed approximately one month earlier), partial intestinal obstruction (subileus) treated surgically about six weeks prior, ischemic stroke (~20 years earlier) with residual speech impairment, and intestinal surgery (~40 years ago), presented with difficulty in urination, generalized body pain, fatigue, hemoptysis, and shortness of breath (dyspnea).
One month prior to the current admission, the patient was diagnosed with chronic pulmonary thromboembolism. He presented with acute urinary retention, accompanied by abdominal pain and generalized fatigue. The abdominal pain began approximately two days before admission, initially intermittent and later becoming persistent. He also reported dark-colored urine, episodes of hemoptysis, and dyspnea. Approximately six weeks before admission, he had undergone surgical treatment for partial intestinal obstruction (subileus). Postoperatively, he developed constipation and recurrent vomiting, which persisted and were still present on the day of admission.
He has a known allergy to peaches. Social history reveals that he is a former smoker, does not consume alcohol, has limited physical activity due to fatigue, and reports good sleep.
Physical Examination
On admission, the patient appeared ill and fatigued. Signs of urinary retention were present. Respiratory examination revealed dyspnea. The abdomen was tender in the postoperative

setting. No new focal neurological deficits were identified apart from chronic speech impairment.

Diagnostic Assessment

Timeline (Chronological Summary) [5-12]

Date	Event/Investigation	Findings	Clinical Significance
October 2025	Abdominal X-ray (native)	Air–fluid levels in bowel loops; no free subdiaphragmatic air	Suggestive of subileus / partial intestinal obstruction
October 2025	Abdominal X-ray (second report)	Small bowel air–fluid levels compatible with subileus; mild right pleural effusion	Confirms subileus + incidental pleural fluid
November 2025	Chest X-ray	Right pleural effusion with compressive atelectasis; bilateral reticulonodular changes; cardiomegaly	Suggests pneumonia/effusion, chronic lung changes
November 2025	ICD-10 diagnosis codes	R06, J18, J90	Breathing abnormality + pneumonia + pleural effusion
November 2025	Outpatient therapy documented	Edemid forte, spironolactone, Lebel 500, Tricef 200, famotidine	Diuretic + antibiotic/supportive therapy
December 2025	Hospital admission	Urinary retention, abdominal pain, fatigue, hemoptysis, dyspnea	Suspected postrenal AKI + infection, evaluate respiratory symptoms

December 2025	D-dimer	18,295 ng FEU/mL	Severe inflammation/hypercoagulability
December 2025	D-dimer	35,260 ng/mL	Persistent extreme elevation
During hospitalization (date unavailable)	CT abdomen with contrast incidentally noted findings suggestive of chronic pulmonary thromboembolism (as stated in the radiology report) Suggestive changes requiring further pulmonary imaging.	Dilated small bowel loops, likely adhesions; enlarged prostate; renal microlithiasis; suggested chronic pulmonary thromboembolism	Supports GI adhesions + possible chronic PTE

Laboratory Findings

Hemostasis Analysis and Clinical Interpretation

Coagulation profile demonstrated preserved global coagulation function, with PT, aPTT, and TT values within reference ranges, without evidence of intrinsic or extrinsic pathway impairment.
In contrast, serial D-dimer levels were markedly elevated, indicating pronounced activation of coagulation and fibrinolysis in the setting of systemic inflammation. This pattern is consistent with a secondary, inflammation-driven hypercoagulable state, likely related to the postoperative condition, acute infection, reduced mobility, and concomitant acute kidney injury.
Overall, the findings support reactive activation of the coagulation system rather than a primary coagulopathy, in keeping with the clinical context. [10-11].

Urinalysis Analysis and Clinical Interpretation

Urinalysis demonstrated marked inflammatory changes, with significant leukocyturia (500 leukocytes/µL) and hematuria (300 erythrocytes/µL), accompanied by abundant bacteriuria, consistent with an active urinary tract infection. The overall pattern supports a severe, complicated infection in the given clinical context.
The absence of pathological casts argues against prominent intrinsic renal involvement, although concomitant acute kidney injury, particularly of postrenal origin, remains clinically plausible. [11].

Laboratory Findings and Clinical Interpretation

Laboratory investigations demonstrated preserved hepatic and muscular function, accompanied by significant electrolyte disturbances, marked systemic inflammation, secondary activation of coagulation, and mild metabolic alterations.

Analysis of liver and muscle enzymes revealed values within reference ranges, including alkaline phosphatase (ALP 56 U/L), aspartate aminotransferase (AST 30 U/L), alanine aminotransferase (ALT 13 U/L), gamma-glutamyl transferase (GGT 31 U/L), lactate dehydrogenase (LDH 226 U/L), creatine kinase (CK 48 U/L), and CK-MB (9 U/L), indicating preserved hepatic integrity and absence of clinically significant muscle or myocardial injury.

Electrolyte assessment identified multiple abnormalities, including hypocalcemia (2.09 mmol/L), hypomagnesemia (0.70 mmol/L), and hypophosphatemia (1.20 mmol/L). Serum sodium (138 mmol/L) and chloride (98 mmol/L) were within normal limits, while potassium was at the lower limit of normal (3.50 mmol/L). Serum iron was reduced (9.60 µmol/L). These findings are consistent with acute kidney injury in the context of postoperative metabolic stress, systemic inflammation, and ongoing diuretic therapy, and may contribute to fatigue, neuromuscular weakness, and increased risk of cardiac arrhythmias.

Lipid profile analysis demonstrated controlled total cholesterol (3.30 mmol/L) and triglycerides (1.03 mmol/L), with acceptable low-density lipoprotein levels (LDL 2.15 mmol/L). Reduced high-density lipoprotein cholesterol (HDL 0.68 mmol/L) was noted, representing a chronic cardiovascular risk factor rather than an acute pathological abnormality.

Inflammatory markers were markedly elevated, with C-reactive protein (CRP 89.7 mg/L), indicating a pronounced systemic inflammatory response consistent with active infection and postoperative status.

Hemostasis evaluation revealed markedly elevated D-dimer levels on serial measurements, reflecting activation of coagulation and fibrinolysis. In this clinical context, these findings are most consistent with secondary, inflammation-associated hypercoagulability related to infection, postoperative state, and reduced mobility, rather than primary thrombotic disease, although thromboembolic processes cannot be excluded without definitive imaging.

Urine chemical analysis showed negative bilirubin, normal urobilinogen, and absence of glucosuria or ascorbic acid. Mild ketonuria (0.5 mmol/L) was present, likely reflecting a postoperative catabolic state and reduced oral intake, without evidence of diabetes mellitus or hepatobiliary dysfunction.

Overall, the laboratory profile is consistent with a frail postoperative elderly patient presenting with acute kidney injury, severe systemic inflammatory response, secondary hypercoagulability, and significant electrolyte imbalance in the setting of a complicated multidrug-resistant urinary tract infection, while hepatic and muscular functions remain preserved. [11].

Hematological and Biochemical Laboratory Findings

Hematological evaluation revealed a normocytic anemia, characterized by reduced red blood cell count (RBC 3.54 $\times 10^{12}$/L; reference 4.2–5.5 $\times 10^{12}$/L), decreased hemoglobin concentration (6.83 mmol/L; reference 7.7–10.6 mmol/L), and low hematocrit (34.4%; reference 37–54%). Mean corpuscular volume remained within normal limits (MCV 97.4 fL; reference 80–99 fL), supporting the classification of anemia as normocytic in nature. White blood cell count was

within the normal range (WBC 6.70 ×10⁹/L; reference 4–9 ×10⁹/L), and platelet count was preserved (PLT 152 ×10⁹/L; reference 140–340 ×10⁹/L), indicating the absence of significant leukocytosis or thrombocytopenia.
Glycemic parameters were within normal limits, with fasting glucose (5.50 mmol/L; reference 3.5–6.1 mmol/L) and glycated hemoglobin (HbA1c 5.06%; reference <5.7%), effectively excluding diabetes mellitus and stress-induced hyperglycemia as contributing factors.
Renal function tests demonstrated clear evidence of acute kidney injury, with markedly elevated serum urea (17.50 mmol/L; reference 2.5–6.4 mmol/L) and creatinine (240 µmol/L; reference 62–115 µmol/L). Serum uric acid was also increased (556 µmol/L; reference 208–428 µmol/L), consistent with impaired renal excretion and an enhanced catabolic state.
Assessment of protein status revealed hypoproteinemia and pronounced hypoalbuminemia, with total serum proteins (55.0 g/L; reference 64–82 g/L) and albumin (25.0 g/L; reference 34–50 g/L) both significantly reduced. These findings are most consistent with a combination of systemic inflammation, postoperative physiological stress, and possible nutritional compromise.
Overall, the laboratory profile is indicative of acute kidney injury, inflammation-associated normocytic anemia, and significant hypoalbuminemia in the context of preserved leukocyte and platelet counts, consistent with a frail postoperative elderly patient presenting with systemic inflammatory response and a complicated infectious process. [11].

Renal Function and KDIGO Staging

Acute kidney injury (AKI) was diagnosed based on a markedly elevated serum creatinine level on admission (240 µmol/L), in accordance with the KDIGO criteria. Although blood urea was also elevated (17.5 mmol/L), precise staging of AKI (KDIGO Stage 1–3) could not be established due to the absence of documented baseline creatinine values and incomplete pre-admission urine output data.
From a clinical perspective, the AKI was considered significant and likely multifactorial in origin, with a predominant postrenal component related to acute urinary retention, and a possible prerenal contribution associated with reduced oral intake, postoperative vomiting, and potential volume depletion. The rapid clinical response following bladder decompression via Foley catheterization, evidenced by a marked increase in urine output, strongly supports the diagnosis of postrenal AKI secondary to urinary obstruction.
Overall, the clinical and laboratory findings are consistent with obstructive nephropathy as the primary driver of renal impairment, with additional contributing factors related to the patient's postoperative state and systemic condition. [11].

Microbiological Findings

Urine culture demonstrated growth of multidrug-resistant (MDR) Acinetobacter species at a bacterial load of 10^4 CFU/mL, which was considered clinically significant in the presence of urinary symptoms and systemic inflammatory response. In symptomatic patients, particularly elderly males, colony counts at this threshold may represent true infection rather than contamination.
Antimicrobial susceptibility testing revealed extensive resistance to multiple antibiotic classes, including penicillins, β-lactam/β-lactamase inhibitor combinations, cephalosporins,

aminoglycosides, fluoroquinolones, trimethoprim–sulfamethoxazole, and nitrofurantoin. The isolate demonstrated susceptibility exclusively to fosfomycin, thereby necessitating targeted, culture-guided antimicrobial therapy rather than empirical treatment.
Overall, the microbiological findings are consistent with a complicated urinary tract infection caused by a multidrug-resistant nosocomial pathogen, highlighting the importance of microbiological confirmation and susceptibility testing in guiding appropriate therapeutic management. [12].

Summary of Clinically Significant Abnormal Findings

Hematology
Hemoglobin: 6.83 mmol/L ↓
Hematocrit: 34.4% ↓
RBC count: 3.54 ×10¹²/L ↓
Platelets: 152 ×10⁹/L

Findings consistent with normocytic anemia [11].

Renal Function
Urea: 17.5 mmol/L ↑
Creatinine: 240 μmol/L ↑
Uric acid: 556 μmol/L ↑

Consistent with acute kidney injury, likely multifactorial (postrenal + prerenal components) [11].

Inflammatory and Coagulation Markers
CRP: 89.7 mg/L ↑
D-dimer: 18,295 ng FEU/mL (11.12.2025) ↑↑ [11]
D-dimer: 35,260 ng/mL (12.12.2025) ↑↑ [10]
D-dimer results were reported using different assays/units; therefore, direct numeric comparison is limited, but both values were markedly elevated above the reference range.

Indicating severe systemic inflammation and hypercoagulability [10-11].
Electrolytes
Calcium: 2.09 mmol/L ↓
Magnesium: 0.70 mmol/L ↓
Phosphate: 1.20 mmol/L ↓

Significant electrolyte imbalance requiring correction [11].

Urinalysis
Turbid, amber-colored urine
Leukocytes: 500/μL ↑

Erythrocytes: 300/µL ↑
Bacteria: 118.8/HPF ↑
Proteinuria present

Suggestive of severe urinary tract infection [11].

Microbiological Findings
Urine culture revealed Acinetobacter species (10^4 CFU/mL).

Antibiotic susceptibility testing:
Resistant to: ampicillin, amoxicillin, amoxicillin–clavulanate, cefuroxime, cefixime, ceftazidime, ceftriaxone, cefepime, gentamicin, ciprofloxacin, levofloxacin, nitrofurantoin, trimethoprim–sulfamethoxazole.
Sensitive only to fosfomycin.
Diagnosis of multidrug-resistant urinary tract infection [12].

Table. Summary of Clinically Significant Abnormal Findings [11-12]

Category	Parameter	Result	Interpretation / Clinical significance	Ref.
Hematology	Hemoglobin	6.83 mmol/L ↓	Normocytic anemia (reduced oxygen-carrying capacity)	[11]
Hematocrit	34.4% ↓	Supports anemia		[11]
RBC count	3.54 ×10¹²/L ↓	Supports anemia		[11]
Platelets	152 ×10⁹/L	Within/low-normal range (no thrombocytopenia)		[11]
Renal function	Urea	17.5 mmol/L ↑	Renal impairment / azotemia	[11]
Creatinine	240 µmol/L ↑	Acute kidney injury (AKI)		[11]
Uric acid	556 µmol/L ↑	Hyperuricemia, may reflect renal dysfunction/catabolism		[11]

Inflammation & coagulation	CRP	89.7 mg/L ↑	Severe systemic inflammation	[11]
D-dimer	18,295 ng FEU/mL ↑↑ (11.12.2025)	Marked hypercoagulability; high thrombotic risk		[11]
D-dimer	35,260 ng/mL ↑↑ (12.12.2025)	Further increase, strongly abnormal		[10]
Electrolytes	Calcium	2.09 mmol/L ↓	Hypocalcemia (requires correction/monitoring)	[11]
Magnesium	0.70 mmol/L ↓	Hypomagnesemia (arrhythmia risk, worsens hypocalcemia)		[11]
Phosphate	1.20 mmol/L ↓	Hypophosphatemia (weakness, impaired recovery)		[11]
Urinalysis	Appearance	Turbid, amber-colored	Suggestive of infection/dehydration	[11]
Leukocytes	500/µL ↑	Significant pyuria → UTI		[11]
Erythrocytes	300/µL ↑	Hematuria, often in severe UTI/inflammation		[11]
Bacteria	118.8/HPF ↑	Marked bacteriuria		[11]
Proteinuria	Present	Inflammatory renal/urinary involvement		[11]

Microbiology	Urine culture	Acinetobacter spp. (10^4 CFU/mL)	Clinically significant growth in symptomatic patient	[12]
Susceptibility	MDR profile	Resistant to multiple antibiotics; sensitive only to fosfomycin		[12]

Differential Diagnosis

Several conditions were considered in the differential diagnosis based on the patient's presenting symptoms, laboratory findings, and imaging results.

• Prerenal acute kidney injury related to dehydration, reduced oral intake, vomiting, or diuretic therapy.
• Intrinsic renal injury, including acute tubular necrosis or infection-related renal involvement.
• Postrenal obstruction due to benign prostatic hyperplasia, which was later confirmed as the primary cause of acute kidney injury.
• Complicated urinary tract infection or urosepsis, particularly in the context of urinary retention and significant pyuria.
• Pulmonary embolism, considered due to dyspnea, hemoptysis, and markedly elevated D-dimer levels.
• Postoperative abdominal complications, such as recurrent intestinal obstruction or intra-abdominal inflammation following previous surgery.

Final Diagnosis

Postrenal acute kidney injury (AKI) secondary to acute urinary retention, most likely related to benign prostatic hyperplasia (BPH).
Complicated urinary tract infection (UTI) caused by multidrug-resistant (MDR) Acinetobacter spp. (urine culture 10^4 CFU/mL; susceptible only to fosfomycin).
Postoperative status following intestinal surgery for subileus/partial intestinal obstruction (~6 weeks prior).
Markedly elevated D-dimer with radiologically suggested chronic pulmonary thromboembolism (CT finding).
Additional findings: normocytic anemia, severe hypoalbuminemia, and electrolyte disturbances (hypocalcemia, hypomagnesemia, hypophosphatemia).

Treatment and Management

Initial Management

The patient was admitted to the hospital on 09 December 2025 due to acute urinary retention associated with abdominal pain, fatigue, hemoptysis, and dyspnea. Initial management focused

on stabilization and rapid identification of reversible causes of acute kidney injury (AKI). Intravenous access was established and laboratory investigations were obtained, including complete blood count, renal function tests, electrolytes, inflammatory markers, coagulation profile with D-dimer, and urinalysis.
Given the strong suspicion of urinary obstruction, prompt bladder decompression was performed via Foley catheterization, followed by close monitoring of urine output and fluid balance. Nephrotoxic medications were avoided whenever possible, and supportive therapy was initiated with careful hydration and correction of electrolyte disturbances. A urine culture was collected to guide antimicrobial therapy in the setting of suspected complicated urinary tract infection.

Pharmacological Treatment

Two months prior (October 2025) to the current hospitalization (December 2025), the patient had undergone intestinal surgery for ileus, without respiratory symptoms in the immediate postoperative period.
In November 2025, the patient presented with newly developed dyspnea. Chest radiography demonstrated a right-sided pleural effusion with compressive subsegmental atelectasis and bilateral reticulonodular opacities. Cardiomegaly was additionally observed. Hospital admission was advised but declined.
Based on the outpatient assessment, the following therapy was prescribed:
Furosemide (Edemid forte) – diuretic (loop diuretic)
Spironolactone – diuretic (aldosterone antagonist / potassium-sparing)
Levofloxacin (Lebel) – antibiotic (fluoroquinolone)
Cefixime (Tricef) – antibiotic (third-generation cephalosporin)
Famotidine – antiacid (H2 receptor blocker)
In December 2025, the patient was evaluated and managed for benign prostatic hyperplasia (BPH). Due to urinary catheterization, regular replacement of the Foley catheter (CH 18–20) was performed. Additionally, antibiotic therapy was administered based on urine culture and antibiotic susceptibility testing results. Doreta was given as needed for pain management.
During follow-up evaluation, the patient continued to be managed for BPH. Pharmacological therapy was adjusted to include tamsulosin 0.4 mg once daily as an alpha-adrenergic blocker to improve urinary symptoms.

Outcome and Follow-Up

After initiation of treatment, including bladder decompression with Foley catheterization, the patient’s urinary obstruction was significantly relieved, leading to improved urine output and reduction of abdominal discomfort.
The patient showed overall clinical improvement with resolution of urinary tract infection symptoms and better control of lower urinary tract symptoms.
Renal function and inflammatory markers were monitored during hospitalization, showing gradual stabilization. The patient remained under observation for respiratory complaints and markedly elevated D-dimer levels, with radiological findings suggestive of chronic pulmonary thromboembolism.

At discharge, follow-up was recommended, including repeat renal function tests and urinalysis/urine culture if symptoms recurred. Further evaluation by urology was advised for management of the underlying obstructive uropathy, along with pulmonary assessment to evaluate thromboembolic risk.

Discussion

The present case illustrates the diagnostic and therapeutic complexity that may arise in elderly postoperative patients presenting with acute kidney injury and multiple overlapping clinical conditions. In this patient, postrenal acute kidney injury caused by urinary retention occurred in the context of recent abdominal surgery, systemic inflammation, and severe urinary tract infection caused by multidrug-resistant Acinetobacter species.
Taken together, this case emphasizes how the coexistence of renal, infectious, and thromboembolic conditions in a short time period may create a complex clinical picture that requires careful evaluation and coordinated management across multiple medical specialties.

Conclusion

In conclusion, this case highlights the importance of promptly identifying postrenal causes of acute kidney injury in elderly postoperative patients. It underscores the growing clinical challenge posed by multidrug-resistant urinary pathogens and the diagnostic complexity associated with markedly elevated D-dimer levels in inflammatory states. A multidisciplinary and systematic approach is essential to optimize outcomes in frail patients with overlapping renal, infectious, and thromboembolic conditions.

Key Learning Points

- Postrenal acute kidney injury should always be considered in elderly patients presenting with acute urinary retention, as early bladder decompression can rapidly improve renal function.
- Multidrug-resistant urinary pathogens represent an increasing challenge in hospitalized and postoperative patients, making microbiological culture and susceptibility testing essential for appropriate therapy.
- Markedly elevated D-dimer levels in elderly patients may reflect multiple concurrent processes, including infection, inflammation, postoperative status, and thromboembolic disease.
- Elderly patients with multiple comorbidities frequently present with overlapping pathologies, requiring a systematic and multidisciplinary diagnostic approach.
- Early recognition of reversible causes of acute kidney injury combined with targeted antimicrobial therapy can significantly improve clinical outcomes.

Declarations

Conflict of Interest: The authors declare no conflict of interest.
Funding: This case report received no external funding.

Data Availability Statement: Data are available from the corresponding author upon reasonable request.

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FUNCTION OF THYROID GLAND HORMONES, METABOLIC DISORDERS, OVERWEIGHT, OBESITY AND BIOCHEMICAL PARAMETERS

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Abstract

Introduction: The thyroid gland represents a central component of the endocrine system, which through its hormones triiodothyronine (FT_3) and thyroxine (FT_4), regulated by thyroid-stimulating hormone (TSH), plays a key role in the control of basal metabolism and energy homeostasis. Thyroid function disorders are associated with significant neuro-endocrino-metabolic changes, affecting carbohydrate and lipid metabolism as well as the body's energy balance. At the biochemical level, these disorders are reflected in dyslipidemia, hyperglycemia, and alterations in metabolic parameters, which contribute to the development of overweight and obesity. Furthermore, there is a complex interaction between thyroid hormones and body mass index (BMI), where thyroid dysfunction may influence fat tissue accumulation and changes in metabolic profile. In this context, biochemical and hormonal biomarkers represent important indicators for the early assessment of metabolic disorders and for monitoring patients' physiological status.
Aim: This study aims to evaluate the relationship between thyroid gland function, biochemical parameters, and the development of overweight and obesity in the population.
Materials and methods: The study included 200 patients and 30 control individuals, divided according to age groups (18–30, 31–50, and 51–70 years) and gender. Anamnestic data were collected and BMI was measured. Venous blood samples were analyzed for glucose, lipid profile (total cholesterol, triglycerides, HDL, LDL), as well as thyroid hormones (TSH, FT_3, FT_4, ATPO, ATG). Analyses were performed using enzymatic, spectrophotometric, and immunofluorescence methods (ELFA – VIDAS).
Results: It is expected that patients with thyroid dysfunction will show increased TSH levels, disturbances in lipid profile, and elevated glucose levels, accompanied by increased BMI and a higher prevalence of overweight and obesity.
Conclusion: Biochemical and hormonal parameters represent important diagnostic tools for the identification and monitoring of metabolic disorders associated with thyroid dysfunction.

Keywords: thyroid gland, BMI, obesity, dyslipidemia, metabolism.

Introduction

The thyroid arises from a downward outpouching of the floor of the pharynx, and a persisting remnant of this migration is known as a thyroglossal duct. The gland itself consists of two oblong lobes lying on either side of the trachea and connected by a narrow band of tissue called the isthmus. In normal adults the thyroid gland weighs 10 to 15 grams (0.4 to 0.5 ounce), though it has the capacity to grow much larger. The lobes of the gland, as well as the isthmus, contain many small globular sacs called follicles. The follicles are lined with follicular cells and are filled with a fluid known as colloid that contains the prohormone thyroglobulin. The follicular cells contain the enzymes needed to synthesize thyroglobulin, as well as the enzymes needed to release thyroid hormone from thyroglobulin. When thyroid hormones are needed, thyroglobulin is reabsorbed from the colloid in the follicular lumen into the cells, where it is split into its component parts, including the two thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). The hormones are then released, passing from the cells into the circulation. The substances produced in increased quantities in response to triiodothyronine

secretion include many enzymes, cell constituents, and hormones. It also stimulates carbohydrate utilization, lipid production and metabolism (thereby increasing cholesterol utilization), and central and autonomic nervous system activation, resulting in increased contraction of cardiac muscle and increased heart rate. During fetal life and in infancy this stimulatory activity of triiodothyronine is critically important for normal neural and skeletal growth and development; in both the unborn and the newborn, thyroid deficiency is associated with dwarfism and intellectual disability (Britannica Editors, 2026).

Thyroid hormone (TH) directly regulates metabolic rate, body weight, and cholesterol metabolism. TH regulates the expression of target genes directly through TR binding to specific TREs, as well as nongenomic modification of cell signaling. New evidence highlights the coordinate roles of central and peripheral regulation of TH in modulating metabolic pathways. TH interacts with the SNS in a synergistic and complementary fashion to maintain homeostasis. In addition, adipokine and neuropeptide regulation of the HPT axis and thermogenesis integrates information on energy availability, storage, and utilization to gauge the regulation of appetite, basal metabolic rate, and body weight. TR nuclear hormone crosstalk with other metabolic pathways, especially the nuclear receptors PPARα, LXR, and PGC-1α, is essential for the T_3 regulation of cholesterol metabolism and transcription of lipogenic and lipolytic genes. Bile acid stimulation of D2 and local thyroid hormone activation is another unexpected signaling link. Interference with thyroid hormone signaling is associated with obesity and hepatic steatosis. Finally, emerging evidence identifies a role for TH in glucose metabolism including actions in pancreatic islet development, gluconeogenesis, and insulin signaling (Mullur, R., et al 2014).

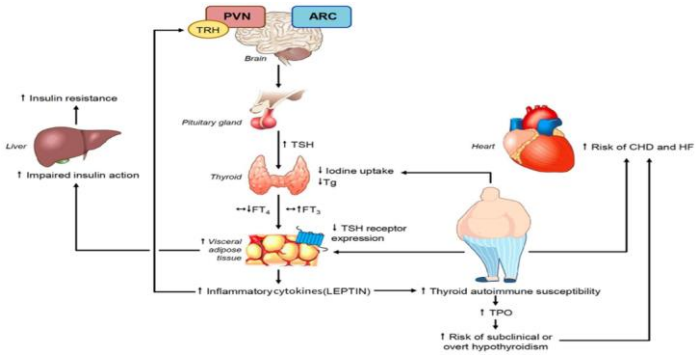


Figure 1: Mechanisms underlying the association between obesity and metabolic syndrome with subclinical hypothyroidism and the potential risk of these associated conditions (Biondi B. Subclinical Hypothyroidism in Patients with Obesity and Metabolic Syndrome: A Narrative Review. Nutrients. 2024; 16(1):87. https://doi.org/10.3390/nu16010087)

Purpose of the study

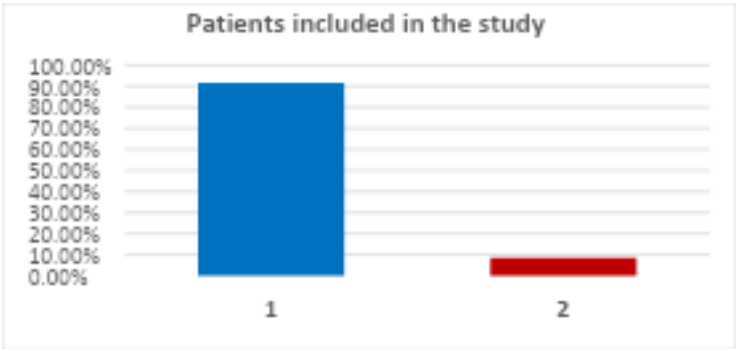
This study aims to comprehensively evaluate the relationship between thyroid gland function, key biochemical parameters, and their potential role in the development of overweight and obesity within the population. By examining these interrelated factors, the research seeks to provide a clearer understanding of how variations in thyroid activity and metabolic markers may contribute to changes in body weight and overall metabolic health. Ultimately, the goal is to generate insights that could support more effective prevention strategies and inform clinical approaches to managing obesity.

Material and method

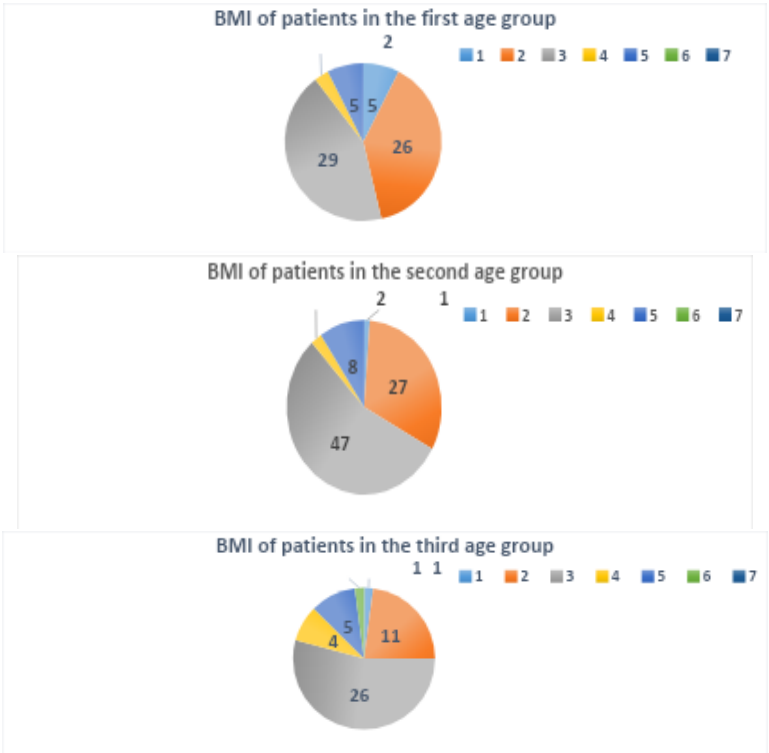
The study included 200 patients and 30 control individuals, divided according to age groups (18–30, 31–50, and 51–70 years) and gender. Anamnestic data were collected and BMI was measured. Venous blood samples were analyzed for glucose, lipid profile (total cholesterol, triglycerides, HDL, LDL), as well as thyroid hormones (TSH, FT_3, FT_4, ATPO, ATG). Analyses were performed using enzymatic, spectrophotometric, and immunofluorescence methods (ELFA – VIDAS).

Results

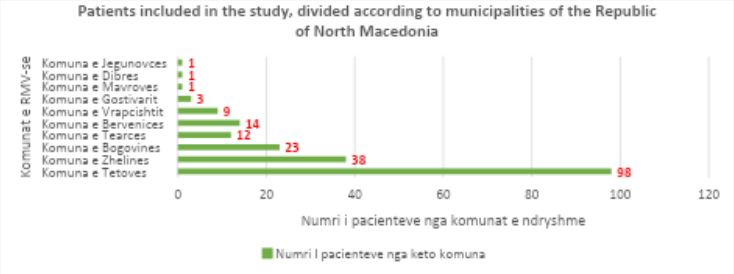
Based on the obtained results regarding thyroid gland hormone function, metabolic disorders, overweight and obesity, as well as associated biochemical parameters across different age groups and genders, the findings are presented in the graphics below:



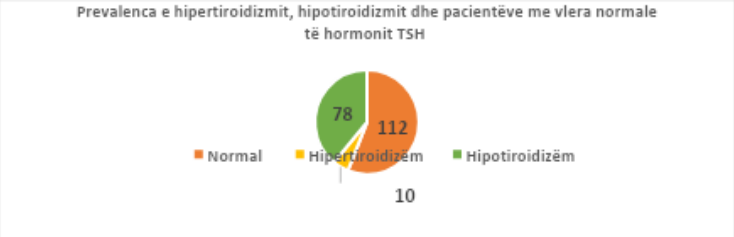
Grafic 1. Patients included in the study by thyroid status, lipid status, blood glucose level, and BMI



Grafic 2,3 and 4. BMI of patients in the first, second, and third age groups included in the study



Grafic 5. Number of patients included in the study, by municipalities of the RMV



Grafic 6. Number of patients with hyperthyroidism and hypothyroidism

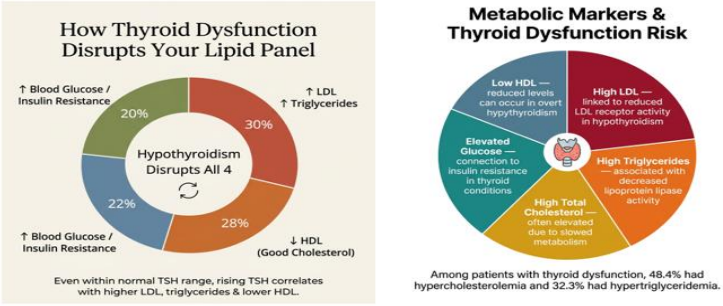
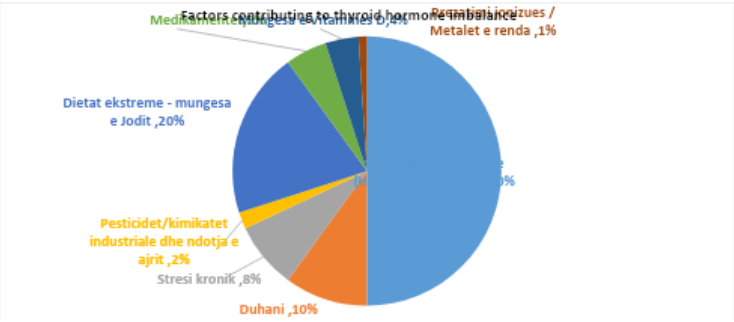


Fig.2: Association of Lipid Profile Parameters (Cholesterol, Triglycerides, HDL, LDL) with Thyroid Dysfunction



Grafic 7. Factors contributing to thyroid hormone imbalance



Fig. 3: Ultrasound images of patients with hypothyroidism: The two images show thyroid gland ultrasound with a heterogeneous and hypoechoic structure, characteristic of hypothyroidism, indicating chronic inflammation and reduced thyroid gland function (Performed by Dr. Spec. Irfan Ahmeti at Albimedica Polyclinic, Tetovo, 2025).



Fig. 4: Ultrasound images of patients with hyperthyroidism: The two images show an enlarged thyroid gland with a hypoechoic structure and increased vascularization, reflecting heightened functional activity of the thyroid gland (Performed by Dr. Spec. Irfan Ahmeti at Albimedica Polyclinic, Tetovo, 2025).

Discussion

The thyroid gland is particularly susceptible to environmental influences and, therefore, is unique among the endocrine glands as far as direct environmental impact. The thyroid gland becomes hyperplastic and a goiter develops when there is severe nutritional iodine deficiency. This is the reverse of the usual meaning of toxic effects of a substance on an organ. In fact, the abnormality occurs when there is an insufficient amount rather than an excess of one of the important chemicals needed for that particular gland. Another aspect of toxicology of the thyroid is the fact that when the normal regulatory mechanisms with the usual feedback control of thyroxin secretion fail, very high levels of thyroxin develop with resultant hyperthyroidism or, more appropriately for this conference, thyrotoxicosis (Edmund B. Flink, 1981). Body mass index (BMI), a measurement based on a person's height and weight, allows the classification of individuals into categories such as obese or overweight. With these classifications, we can assess risk for hypertension, diabetes, cancer, hypercholesterolemia, and other chronic diseases (Deepesh Khanna, et al 2022). Lucyna Ostrowska et al., also stated that their research shows improvement of thyroid parameters in patients suffering from obesity and Hashimoto's disease is possible through effective weight reduction. Concurrently, an individually adjusted elimination diet may lead to better therapeutic results (Ostrowska et al., 2021).

Conclusion

Thyroid hormone function and basal metabolism are essential for maintaining metabolic balance and overall health. This study demonstrates a clear relationship between thyroid dysfunction, biochemical parameters, and the development of overweight and obesity, with significant associations between altered TSH levels and increased BMI.

Variations in FT_3 and FT_4, along with abnormal prolactin and thyroid antibody levels, further indicate a link between thyroid disorders and metabolic imbalance. Overall, the findings highlight the importance of early detection, regular biochemical monitoring, and healthy lifestyle practices to support optimal thyroid function and metabolic health.

Beyond these established associations, the findings also suggest the potential value of integrating thyroid related biomarkers into broader metabolic risk prediction models. Emerging evidence indicates that subtle variations within the "normal" range of TSH, FT_3, and FT_4 may still carry metabolic significance, particularly when assessed in combination with inflammatory and adipokine profiles. This supports a more personalized, systems based approach to thyroid evaluation, where multi parameter biochemical profiling and digital tools

could improve early identification of individuals at risk for metabolic syndrome and obesity-related complications.

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FROM METABOLIC STRESS TO OPTIMAL PERFORMANCE: THE ROLE OF BIOMARKERS IN MONITORING SPORTS OVERTRAINING

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Abstract

Introduction: Sports overtraining represents a complex neuro-endocrino-metabolic condition that develops when the balance between training stress and the body's recovery capacity is persistently disrupted. In this state, marked alterations in biochemical homeostasis occur, including disturbances in energy metabolism, increased catabolic processes, and imbalance in the hypothalamic–pituitary–adrenal (HPA) axis. At the cellular and molecular level, overtraining is associated with increased markers of muscle damage such as creatine kinase (CK), elevated cortisol as a response to physiological stress, and reduced anabolic hormones such as testosterone, reflecting a shift toward a catabolic state. In parallel, activation of systemic inflammatory processes is observed, reflected among others by an increase in C-reactive protein (CRP), an important marker of acute and chronic inflammation related to prolonged physical stress. Additionally, changes in oxidative processes may be observed, contributing to chronic fatigue and reduced adaptive capacity of the organism. In this context, biochemical biomarkers represent objective and measurable tools for assessing the athlete's physiological status, enabling early identification of metabolic imbalances before they become clinically evident. The integration of these laboratory parameters with functional performance assessment provides a more accurate approach to monitoring training load and preventing overtraining.

Aim: This study aims to evaluate the role of creatine kinase (CK), cortisol, testosterone, and CRP in monitoring metabolic stress and preventing overtraining in active athletes.

Materials and Methods: The study included 30 patients (15 active athletes and 15 non-athletes). Anamnestic data were collected (BMI, training frequency, injury history, sleep quality, and fatigue). Laboratory analyses were performed for CK, cortisol, testosterone, and CRP, and the testosterone/cortisol ratio (T/C) was evaluated. Biochemical analyses (CK, cortisol, CRP) were conducted using the Selectra Mach 5, based on enzymatic and spectrophotometric methods. Testosterone was determined using the YHLO iFlash 1200, employing the CLIA method. Samples consisted of serum obtained from venous blood, and analyses were performed with internal quality control. The T/C ratio was calculated from the obtained values.

Results: It is expected that athletes with high training load will show increased CK, cortisol, and CRP levels, decreased testosterone, and a reduced T/C ratio, accompanied by decreased performance and increased subjective fatigue.

Conclusion: Biochemical biomarkers represent valuable tools for monitoring physiological stress and may contribute to the prevention of overtraining and the optimization of sports performance.

Keywords: performance, metabolic stress, hormonal stress, burnout, testosterone, cortisol, CRP.

Introduction

Sports performance and athlete monitoring have undergone remarkable advancements in recent years, driven by the integration of cutting edge scientific approaches (Seshadri, D.R.; et al., 2026). Traditionally, coaches and sports scientists relied on subjective measures to assess an athlete's condition, which often led to a lack of precision and limited understanding of the underlying physiological responses. However, with the advent of biomarker research, the landscape of sports science has been revolutionized, offering objective and quantifiable insights into an athlete's biological state (Lee, E.C.; et al., 2026).

Biomarkers have emerged as powerful tools in elite sports, offering valuable in sights into athletes physiological responses and potential performance enhancement (Pedlar, C.R.; et al, 2026). This discussion explores the significance and potential applications of biomarkers in optimizing elite sports performance, emphasizing their crucial role in supporting athletes' training, recovery, and overall success. Biomarkers provide objective measures of an athlete's physiological state, going beyond traditional subjective performance assessments (Lee, E.C.; et al., 2026). Coaches and sports scientists can utilize blood and salivary biomarker analysis to gain precise data on an athlete's readiness and recovery status, making evidence-based decisions to optimize athletic performance (Haller, N.;et al, 2026). Biomarker analysis enables coaches to tailor training and recovery strategies based on athletes specific biomarker profiles, maximizing training adaptations, minimizing injury risks, and fostering peak performance (McFadden, B.A.;et al, 2026). The intensive training regimens in elite sports can lead to overtraining and fatigue, potentially affecting an athlete's performance and wellbeing. Biomarker analysis, particularly for markers related to inflammation and muscle damage, allows for early detection of these conditions, prompting appropriate adjustments in training loads and recovery interventions (Haller, N.;et al, 2026). It is a well-known fact that resistance exercise can provide a potent stimulus for acute changes in endocrine responses and inflammatory reactions (Izquierdo M.,et al, 2009), (Kraemer W.J.,et al, 2005).

Resistance exercise is a stress factor that triggers a response from most systems of the human body, such as the cardiovascular, respiratory, immune, endocrine, and musculoskeletal systems (McDougle J.M.,et al, 2023). Mechanisms of homeostatic control include the response of multiple regulators of the endocrine system such as the hypothalamic corticotroph (pituitary) axis and locus caeruleus/norepinephrine system, hormones such as testosterone, prolactin, growth hormone, and the specific response of the cytokine system (Tu H., Li Y.-L., 2023), (Jiang Q.,et al, 2020). The physiological stress caused by intensive resistance exercise acts as a major stimulus for muscle fiber hypertrophy, and efficient muscle repair requires a well-coordinated and controlled inflammatory response (Peake J.M.,et al, 2016). The results of Chycki et al. (2024) indicate that resistance exercise causes a short term increase in testosterone, which returns to baseline within one hour. CK activity also increases after exercise, while CRP remains unchanged. Cortisol responses differ depending on the exercise, decreasing after bench press but not after leg press, suggesting a condition specific effect (Chycki, J.,et al, 2024).

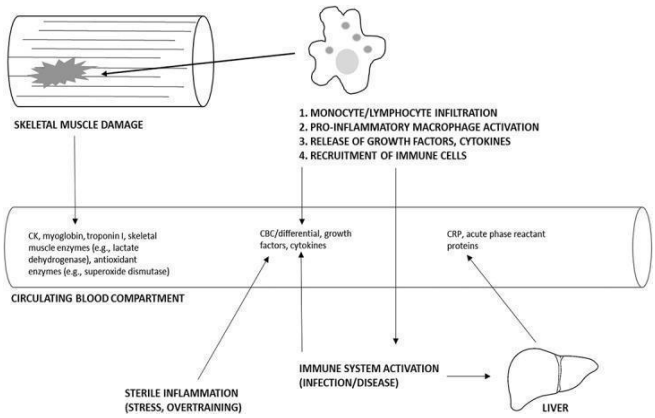


Fig.1: Systemic Biomarker Response to Skeletal Muscle Injury and Inflammation (Lee, E. C., Fragala, M. S., Kavouras, S. A., Queen, R. M., Pryor, J. L., & Casa, D. J. (2017). Biomarkers in Sports and Exercise: Tracking Health, Performance, and Recovery in Athletes. Journal of strength and conditioning research, 31(10), 2920–2937.

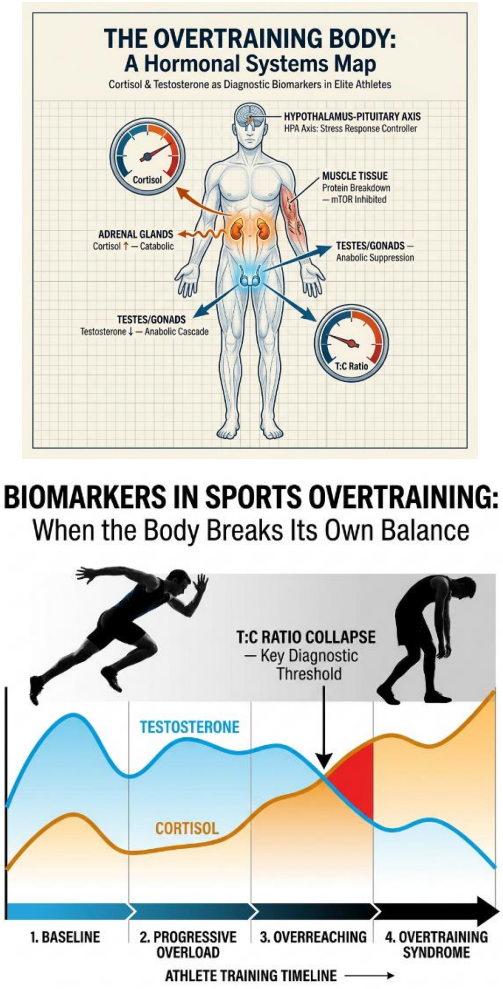


Fig.2: Cortisol–Testosterone imbalance and systemic effects in overtraining syndrome

In sports medicine, creatine kinase (CK), testosterone, cortisol, and C-reactive protein (CRP) are commonly used as interconnected markers to assess the physiological and inflammatory response to exercise and recovery status (Kreher & Schwartz, 2012; Peake et al., 2017). CK is primarily considered an indicator of muscle fiber disruption, with elevated levels reflecting exercise induced muscle damage, particularly after high intensity or unaccustomed resistance training (Peake et al., 2017). Testosterone is an anabolic hormone that supports muscle protein synthesis and recovery, and it often shows an acute post exercise increase, especially following resistance exercise, although this response is typically transient (Urhausen & Kindermann, 2002). Cortisol, a key catabolic stress hormone, rises in response to physiological stress and energy demand, and its balance with testosterone is frequently used to evaluate the anabolic–catabolic state of an athlete (Urhausen & Kindermann, 2002; Kreher & Schwartz, 2012). A higher testosterone-to-cortisol ratio is generally interpreted as a more favorable environment for recovery and adaptation, while a shift toward elevated cortisol may indicate excessive training stress or insufficient recovery (Kreher & Schwartz, 2012). CRP, on the other hand, is a systemic inflammatory marker that tends to increase in response to more substantial or prolonged tissue stress, although it may remain unchanged after moderate or well tolerated exercise bouts (Kasapis & Thompson, 2005; Peake et al., 2017). Together, these biomarkers provide complementary information: CK reflects structural muscle stress, testosterone and cortisol reflect endocrine regulation of adaptation and stress, and CRP reflects systemic

inflammation. In combination, they are widely used in sports medicine to monitor training load, detect overreaching, and guide recovery strategies in athletes (Kreher & Schwartz, 2012).

Purpose of the study

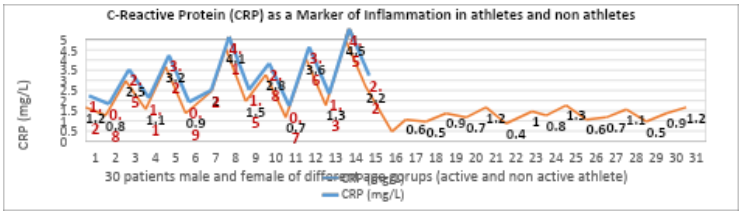
This study aims to evaluate the role of creatine kinase (CK), cortisol, testosterone, and C-reactive protein (CRP) in assessing metabolic stress and their potential utility in monitoring training load and preventing overtraining syndrome in active athletes.

Material and method

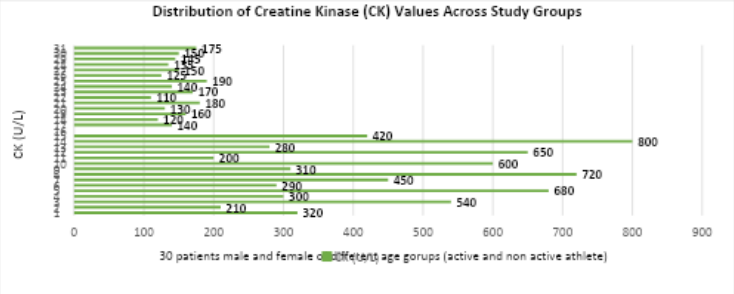
The study included 30 patients (15 active athletes and 15 non-athletes patients from different genders and age groups). Anamnestic data were collected (BMI, training frequency, injury history, sleep quality, and fatigue). Laboratory analyses were performed for CK, cortisol, testosterone, and CRP, and the testosterone/cortisol ratio (T/C) was evaluated.
Biochemical analyses (CK, cortisol, CRP) were conducted using the Selectra Mach 5, based on enzymatic and spectrophotometric methods. Testosterone was determined using the YHLO iFlash 1200, employing the CLIA method. Samples consisted of serum obtained from venous blood, and analyses were performed with internal quality control. The T/C ratio was calculated from the obtained values.

Results

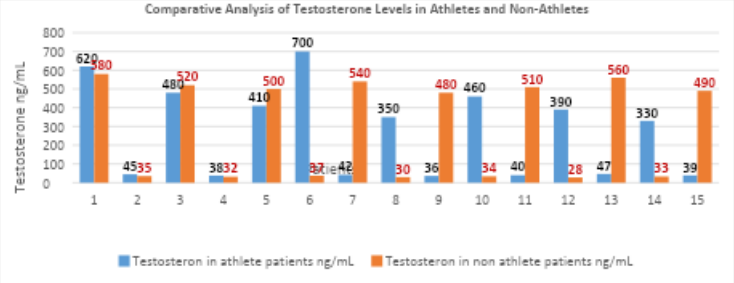
Based on the obtained results regarding metabolic stress, hormonal function, and associated biochemical parameters, the findings are presented in the graphics below:



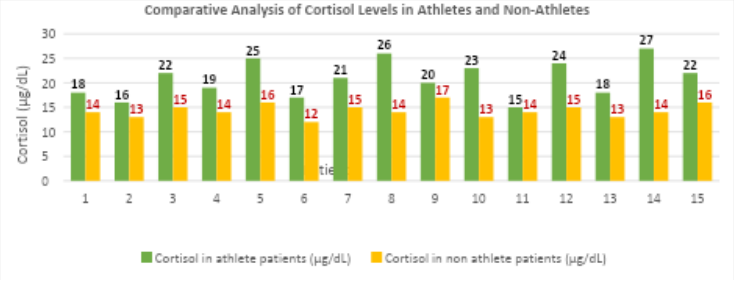
Grafic 1. C-Reactive Protein (CRP) as a Marker of Inflammation in athletes and non athletes (15 first patients are active atheletes and 15 second patients are non athletes)



Grafic 2. Comparison of Creatine Kinase (CK) Levels Between Athletes and Non-Athletes (15 first patients are active atheletes and 15 second patients are non athletes)



Grafic 3. Differences in Testosterone Levels Between Athletes and Non-Athletes



Grafic 4. Differences in Cortisol Levels Between Athletes and Non-Athletes

Table 1: Testosterone/Cortisol (T/C) ratios in athletes and non-athletes

Patient	Athletes T/C	Non-athletes T/C
1	34.44	41.43
2	2.81	2.69
3	21.82	34.67
4	2	2.29
5	16.4	31.25
6	41.18	3.08
7	2	36
8	13.46	2.14
9	1.8	28.24
10	20	2.62
11	2.67	36.43
12	16.25	1.87
13	2.61	43.08
14	12.22	2.36
15	1.77	30.63

Athletes (T/C ratios)
Values:
34.44, 2.81, 21.82, 2.00, 16.40, 41.18, 2.00, 13.46, 1.80, 20.00, 2.67, 16.25, 2.61, 12.22, 1.77

[1] **Mean = 12.96**

[2] **SD = 12.63**

Athletes: 12.96 ± 12.63
Non-athletes (T/C ratios)
Values:
41.43, 2.69, 34.67, 2.29, 31.25, 3.08, 36.00, 2.14, 28.24, 2.62, 36.43, 1.87, 43.08, 2.36, 30.63

[9] **Mean = 19.79**
[10] **SD = 16.65**
Non-athletes: 19.79 ± 16.65

Discussion

Ethical considerations are of paramount importance when incorporating biomarker analysis in elite sports. Ensuring informed consent, protecting athletes data privacy, and adhering to responsible biomarker data use are essential to uphold athlete rights and wellbeing. Ongoing research and technological innovations may uncover novel biomarkers, providing deeper insights into athlete physiology and performance optimization, further elevating the field of elites ports performance. So the integration of biomarkers in elite sports holds immense promise for optimizing performance and advancing athlete well being. Through objective performance assessments, personalized training strategies, and injury prevention, biomarkers offer invaluable insights that traditional methods cannot provide. Biomarker analysis facilitates evidence based decisions, enabling coaches and sports scientists to fine tune training programs to suit individual athlete responses (Anghel, L.,et al, 2023).

Conclusion

Metabolic stress is a normal consequence of structured athletic training; however, excessive load or inadequate recovery may lead to maladaptive responses and overtraining syndrome. This study highlights key biomarkers, including creatine kinase (CK), cortisol, testosterone, and C-reactive protein (CRP), as objective indicators of athletes physiological and biochemical status under different training conditions. Their combined assessment provides insight into muscle damage, hormonal balance, and systemic inflammation.
The interaction between anabolic and catabolic hormones, together with markers of tissue stress and inflammation, is particularly important for distinguishing adaptive training responses from non-functional overreaching or overtraining. In conclusion, biomarker based monitoring represents a valuable approach for optimizing training load, guiding recovery strategies, and reducing the risk of overtraining, although further research is needed to establish standardized reference values.

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POLYPHARMACY IN OLDER ADULTS: BALANCING THERAPEUTIC BENEFITS AND MEDICATION-RELATED HARM

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Abstract

This paper focuses on polypharmacy in older adults, defined as the use of five or more medications, and its increasing impact on public health. The aim is to highlight the clinical risks associated with polypharmacy, including adverse drug reactions, drug-related problems, hospital admissions, and mortality.
The study reviews current literature to evaluate the consequences of excessive medication use and the factors contributing to polypharmacy, such as multimorbidity and inappropriate prescribing. It also examines key strategies to reduce medication-related harm, including medication review, deprescribing, and improved communication among healthcare professionals.
While pharmacotherapy is essential in managing chronic diseases, the risks associated with multiple medications are significant, particularly in elderly populations. The paper emphasizes the importance of a multidisciplinary and patient-centered approach to optimize medication use and improve patient safety.

Keywords: polypharmacy, deprescribing, elderly patients, adverse drug reaction, drug-related problems, medication management, pharmacotherapy optimization

Introduction

The increasing use of multiple medications among older adults has become a major concern in modern healthcare. This condition, known as polypharmacy, is commonly defined as the use of five or more medications and is frequently associated with complex clinical management. As the population ages and the prevalence of chronic diseases rises, polypharmacy has become more widespread, leading to important safety challenges in pharmacotherapy.
The study aims to explore the clinical consequences associated with polypharmacy, including drug-related problems, hospital admissions, and mortality risk. It also seeks to highlight evidence-based strategies for optimizing medication use in older patients, with particular focus on medication review and deprescribing practices. Furthermore, the study emphasizes the importance of a multidisciplinary and patient-centered approach in medication management.
Effective collaboration between physicians, pharmacists, and patients is essential to ensure appropriate prescribing and to reduce the risks associated with inappropriate medication use. Overall, this research aims to underline the need for balancing therapeutic benefits with potential adverse effects in order to improve the safety and quality of pharmacological treatment in elderly populations.

Material and methods

This study was conducted as a narrative literature review focusing on polypharmacy in older adults and its associated clinical outcomes. A structured literature search was performed using PubMed, Web of Science, Scopus, and Google Scholar. The search included combinations of the following keywords: “polypharmacy”, “older adults”, “deprescribing”, “adverse drug reactions”, and “drug–drug interactions”. Studies published between 2015 and 2025 were prioritized.

Inclusion criteria were studies involving patients aged ≥65 years and addressing polypharmacy or deprescribing. Studies focusing exclusively on single diseases without relevance to polypharmacy or involving non-elderly populations were excluded.
Priority was given to high-quality evidence, including systematic reviews, meta-analyses, and large cohort studies. Data from selected studies were analyzed and synthesized descriptively, with emphasis on prevalence, clinical consequences, and strategies for optimizing medication use in older adults.

Results

Prevalence of Polypharmacy in Elderly Population

A large systematic review and meta-analysis conducted by Wang et al. [1] included 122 observational studies with a total population of over 57 million individuals. The authors reported that the global prevalence of polypharmacy in older adults was approximately 39.1% (95% CI: 35.5%–42.7%), while hyperpolypharmacy reached 13.3%. Higher prevalence rates were observed in Europe and North America compared to other regions. Factors such as advanced age (≥70 years) and residence in nursing homes were associated with an increased risk of polypharmacy. These findings highlight the significant global burden of polypharmacy and emphasize the need for appropriate medication management strategies in older populations. [1]

Adverse Drug Reactions

The risk of adverse drug reactions (ADRs) increases with the number of medications used, making polypharmacy a significant contributing factor. Older adults are particularly vulnerable due to age-related changes in pharmacokinetics and pharmacodynamics.
Studies report an incidence of approximately 5.7 ADRs per 100 elderly patients and a prevalence of 6.1 per 100 in general practice settings. Patients experiencing ADRs were found to use a higher number of medications compared to those without adverse effects.
Common drug classes associated with ADRs include antibiotics, antihypertensives, and non-steroidal anti-inflammatory drugs, which are frequently linked to gastrointestinal symptoms and dermatological reactions.
Although some studies suggest a direct correlation between the number of medications and ADR risk, findings remain inconsistent. This variability may be due to differences in study design, patient populations, and reporting methods.
Overall, polypharmacy remains an important risk factor for ADRs, emphasizing the need for careful medication review and monitoring in older patients. [2]

Potentially Inappropriate Medications

The Beers Criteria was developed by the late Mark Beers, MD, and colleagues at the University of California Los Angeles in 1991, with the purpose of identifying medications for which potential harm outweighed the expected benefit and that should be avoided in nursing home residents. (Table 2) The 1997 update, led by Dr. Beers, expanded the criteria to apply to all older adults. (Table 3) The criteria was updated by an interprofessional group in 2003 and the

American Geriatrics Society took over stewardship in 2010. The 2023 American Geriatrics Society (AGS) Beers Criteria (AGS Beers Criteria) for Potentially Inappropriate Medication (PIM) Use in Older Adults is the seventh overall update and fourth since AGS became the criteria's steward. As with previous updates, the AGS and its expert panel have attempted to preserve the spirit and intent of the original Beers Criteria by providing an explicit list of PIMs that are best avoided by older adults in most circumstances or under specific situations, such as certain diseases, conditions, or care settings. The AGS Beers Criteria® comprises drugs and drug classes that the AGS and its expert panel consider to be potentially inappropriate medications (PIMs) for use in older adults. The expert panel organized the criteria into the same five general categories that were used in the 2019 update:

1. Medications considered as potentially inappropriate (Table 2);
2. Medications potentially inappropriate in patients with certain diseases or syndromes (Table 3);
3. Medications to be used with caution (Table 4);
4. Potentially inappropriate drug–drug interactions (Table 5); and
5. Medications whose dosages should be adjusted based on renal function (Table 6).

Table 2: Medications to Avoid in Older Adults (General)

Drug/Class	**Examples**	**Main Risk/Rationale**	**Recommendation**
First-generation antihistamines	Diphenhydramine, Hydroxyzine	Strong anticholinergic effects → confusion, dry mouth, constipation, falls, delirium	**Avoid**
Aspirin (primary prevention)	—	High bleeding risk, no net benefit	**Avoid initiating**
Rivaroxaban	—	Higher GI & major bleeding vs alternatives	**Avoid for long-term use**
Benzodiazepines	Diazepam, Lorazepam	Cognitive impairment, delirium, falls, fractures	**Avoid**

Z-drugs	Zolpidem	Similar risks to benzodiazepines, minimal benefit	**Avoid**
Long-acting sulfonylureas	Glyburide, Glimepiride	Prolonged hypoglycemia	**Avoid**
Proton Pump Inhibitors (PPIs)	Omeprazole	*C. difficile*, fractures, bone loss	**Avoid >8 weeks** (unless indicated)

Table 3: Drugs to Avoid with Specific Diseases

Condition	**Avoid**	**Why**
Heart failure	NSAIDs, COX-2 inhibitors, Diltiazem, Verapamil	Fluid retention, HF exacerbation
Syncope	AChE inhibitors, Alpha-1 blockers, TCAs	Orthostatic hypotension, bradycardia
Dementia	Anticholinergics, Benzodiazepines, Z-drugs	Delirium, cognitive decline
Falls/fractures history	Antiepileptics, Antipsychotics, SSRIs	Ataxia, impaired balance, syncope

Table 4: Medications to Use with Caution

Drug/Class	**Concern**	**Clinical Note**
Amiodarone	Multiple toxicities	May be used in HF for rhythm control
Dabigatran, Edoxaban	Increased GI bleeding (≥75 yrs)	Compare with warfarin
SGLT2 inhibitors	Urogenital infections, euglycemic DKA	Monitor closely
Diuretics	SIADH, hyponatremia	Monitor sodium levels

Table 5: Clinically Significant Drug–Drug Interactions

Combination	**Risk**
ACEIs + Spironolactone	Hyperkalemia
Anticholinergic + Anticholinergic	Cognitive decline, falls
Corticosteroids + NSAIDs	Peptic ulcer, GI bleeding
Warfarin + NSAIDs	Major bleeding
Opioids + Benzodiazepines/Gabapentinoids	Sedation, respiratory depression, overdose

Table 6: Renal Dose Adjustment / Avoidance

Drug	**Issue in Renal Impairment**	**Recommendation**
Ciprofloxacin	CNS toxicity (seizures)	Avoid/reduce if CrCl <30 mL/min
Gabapentin, Pregabalin	CNS depression, sedation	Dose reduction required
Enoxaparin	Bleeding risk	Reduce dose if CrCl <30
Trimethoprim-SMX	Hyperkalemia, renal worsening	Use cautiously

[3],[4]

Potential Drug-Drug Interactions

Polypharmacy is a common finding among hospitalized patients and is closely associated with an increased risk of potential drug–drug interactions (pDDIs). In the analyzed cohort, more than half of patients were receiving five or more medications, and the vast majority were exposed to at least one interaction. Most identified interactions were classified as moderate in severity and typically required monitoring rather than immediate discontinuation of therapy. Although pharmacokinetic interactions accounted for a smaller proportion of all detected interactions, they remain clinically important, particularly those involving drug metabolism via cytochrome P450 enzymes such as CYP3A4. Notably, the number of prescribed medications

was the strongest predictor of interaction risk, with significantly higher odds observed in patients receiving more than seven drugs.

Drug Combination	**Mechanism**	**Risk**	**Clinical Recommendation**
Omeprazole + Cefuroxime	↑ gastric pH → ↓ absorption	Moderate (X)	Avoid combination
Levofloxacin + Calcium	Chelation → ↓ absorption	Moderate (D)	Separate by ≥2 hours
Clopidogrel + Omeprazole	CYP2C19 inhibition	Major (D)	Avoid; use alternative PPI
Amlodipine + Simvastatin	CYP3A4 inhibition	Moderate	Limit simvastatin ≤20 mg
Amiodarone + Acenocoumarol	CYP2C9 inhibition	Major (D)	Reduce anticoagulant dose
Methotrexate + NSAIDs	↓ renal excretion	Moderate	Avoid, especially high doses
Dabigatran + Amiodarone	P-gp inhibition	Moderate	Monitor for bleeding
Fluconazole + Apixaban	CYP3A4 inhibition	Major	Monitor bleeding risk

[5], [6], [7], [8]

The Role of Lack of Coordination Among Healthcare Providers

Polypharmacy management is often complicated by poor coordination among healthcare providers, leading to duplication of therapy, inappropriate prescribing, and increased risk of adverse drug events. [9]

Patients frequently experience confusion and non-adherence due to complex medication regimens, while fragmented care can result in prescribing cascades, where additional medications are introduced to manage side effects of existing therapies.

Improving communication between physicians, pharmacists, and other healthcare professionals is essential to minimize these risks. Interprofessional collaboration has been shown to enhance medication review processes, support deprescribing, and improve patient outcomes. [15]

Evidence suggests that deprescribing interventions can reduce potentially inappropriate medications by up to 30–60% and improve adherence to remaining therapies. [11-14]

Discussion

Overall Burden of Polypharmacy in Older Adults

The findings of this review demonstrate that polypharmacy in older adults is a widespread and clinically significant issue, strongly associated with increased risk of adverse drug reactions (ADRs), drug–drug interactions, and reduced quality of life. These findings are consistent with large-scale epidemiological data reporting a high global prevalence of polypharmacy, particularly in older populations. [1,19,20]

Adverse Drug Reactions and Inappropriate Prescribing

The results presented in section 3.2 highlight that ADRs increase with the complexity of medication regimens, with commonly implicated drug classes including antibiotics, antihypertensives, and NSAIDs. Although the relationship between number of medications and ADR incidence is not always linear, patients receiving multiple drugs were consistently found to have higher overall exposure to adverse outcomes. [2,6,7]

Furthermore, the analysis of potentially inappropriate medications using the Beers Criteria (Tables 2 and 3) demonstrates that several commonly prescribed drugs in older adults, including benzodiazepines, anticholinergics, and long-acting sulfonylureas, significantly increase the risk of cognitive impairment, falls, and hypoglycemia. [3,4] These findings emphasize the importance of regular medication review and avoidance of high-risk drug classes in geriatric populations.

Drug–Drug Interactions and Clinical Complexity

Drug–drug interactions (Tables 5 and 6) further illustrate the clinical complexity of polypharmacy. Pharmacokinetic interactions involving CYP450 enzymes, as well as clinically relevant combinations such as ACE inhibitors with spironolactone or opioids with benzodiazepines, contribute significantly to morbidity in older patients. [5,8] In addition, renal impairment further increases drug toxicity risk, requiring dose adjustments or avoidance of specific medications such as gabapentin and enoxaparin.

A major contributing factor identified in this review is poor coordination among healthcare providers (section 3.5), which leads to duplication of therapy, prescribing cascades, and fragmented care. These cascades often result in additional medications being prescribed to treat adverse effects of existing therapy, further increasing medication burden and risk of harm. [9]

Importantly, deprescribing strategies and interprofessional collaboration have been shown to significantly reduce inappropriate polypharmacy. Evidence indicates that structured medication review and coordinated deprescribing can reduce potentially inappropriate medication use by 30–60%, improve adherence, and decrease hospitalization rates. [11-15] The findings from the included studies (Table 4 and deprescribing literature) strongly support a multidisciplinary approach involving physicians, pharmacists, and nurses to optimize pharmacotherapy.

Despite these findings, this review has limitations, including its narrative design, heterogeneity of included studies, and lack of quantitative synthesis, which may limit generalizability. [16-18]

Conclusion

This review highlights that polypharmacy in older adults is a significant and growing clinical problem associated with adverse drug reactions, drug–drug interactions, inappropriate prescribing, and reduced quality of life. Findings from this study demonstrate that the risk of medication-related harm increases with the number and complexity of prescribed drugs, particularly in the presence of high-risk medications identified by the Beers Criteria and clinically significant drug–drug interactions. Renal impairment further exacerbates this risk, requiring careful dose adjustment and medication selection.

Poor coordination among healthcare providers contributes to duplication of therapy and prescribing cascades, which further increase medication burden and adverse outcomes. This emphasizes the need for structured communication and coordinated care in managing older patients.

Deprescribing, supported by interprofessional collaboration between physicians, pharmacists, and other healthcare professionals, has been shown to significantly reduce inappropriate medication use and improve patient outcomes.

Overall, optimal management of polypharmacy requires a patient-centered, multidisciplinary approach that balances therapeutic benefits with potential harms, supported by regular medication review and evidence-based prescribing tools.

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CHA_2DS_2-VASC SCORE IN ATRIAL FIBRILLATION: CLINICAL APPLICATION AND FUTURE PERSPECTIVES

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with a significantly increased risk of thromboembolic events, particularly ischemic stroke. The CHA_2DS_2-VASc score is widely used for stroke risk stratification and represents a cornerstone in clinical decision-making regarding anticoagulation therapy. This paper reviews the structure, pathophysiological mechanisms, and clinical relevance of the score, while also discussing its limitations and integration with HAS-BLED score. Emerging factors such as inflammation, atrial remodeling, and genetic predisposition are also analyzed. Future perspectives focus on personalized medicine and novel anticoagulant strategies.

Keywords: Atrial fibrillation, CHA_2DS_2-VASc, stroke risk, anticoagulation, DOAC

Introduction

Atrial fibrillation (AF) is one of the most prevalent cardiac arrhythmias worldwide and represents a major cause of morbidity and mortality. Its clinical importance is mainly related to the increased risk of thromboembolic events, particularly ischemic stroke. Patients with AF have a fivefold increased risk of stroke compared to the general population. Therefore, accurate risk stratification is essential in guiding preventive strategies, especially anticoagulation therapy. The CHA_2DS_2-VASc score has emerged as the most widely used tool for assessing stroke risk in patients with non-valvular AF.

CHA_2DS_2-VASc Score Structure and Clinical Application

Table 1. CHA_2DS_2-VASc Score components

Risk Factor	**Points**
Congestive heart failure / LV dysfunction	*1*
Hypertension	*1*
Age >75 years	*2*
Diabetes Mellitus	*1*
Stroke/TIA/thromboembolism	*2*
Vascular Disease	*1*
Age 65-74	*1*
Female Sex	*1*

The CHA_2DS_2-VASc score is a validated clinical tool used to estimate the risk of stroke in patients with non-valvular atrial fibrillation. It incorporates major clinical risk factors including congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, and sex category.

This scoring system allows classification of patients into low, intermediate, and high-risk categories, facilitating clinical decision-making regarding anticoagulation therapy. As illustrated in Figure 2, the risk of stroke increases progressively with higher CHA_2DS_2-VASc scores. Patients with low scores are generally considered at low risk, whereas those with higher scores benefit significantly from oral anticoagulant therapy.

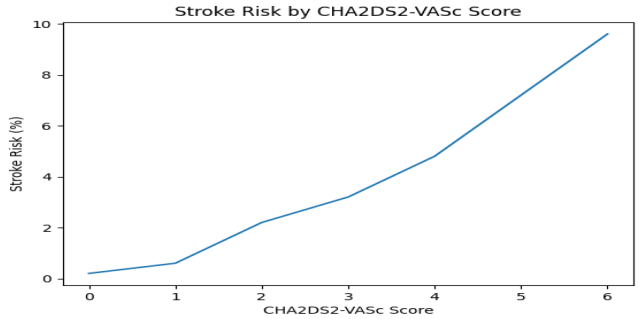


Figure 2. Stroke risk categories based on CHA_2DS_2-VASc score

In clinical practice, the CHA_2DS_2-VASc score is frequently used in combination with the HAS-BLED score to achieve a balanced therapeutic approach. This combined assessment allows clinicians to weigh the benefits of stroke prevention against the potential risk of bleeding.

The HAS-BLED score provides a practical tool for estimating bleeding risk in patients receiving anticoagulation therapy and helps identify modifiable risk factors that can be addressed to improve patient safety.

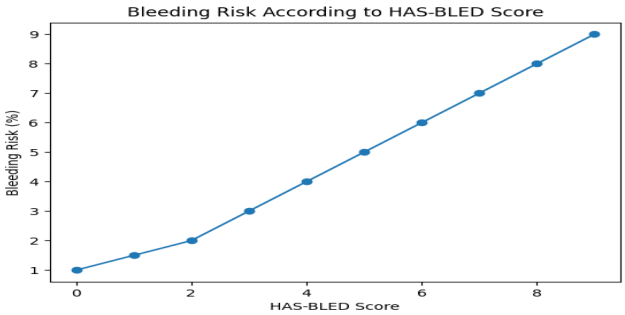


Figure 3.Balance between thromboembolic risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED)

Despite its widespread use, the CHA_2DS_2-VASc score has certain limitations, particularly in accurately capturing individual variability and dynamic changes in patient risk over time. Therefore, clinical judgment remains essential in guiding treatment decisions.

Valvular and Non-valvular Atrial Fibrillation

Atrial fibrillation is clinically classified into valvular and non-valvular types, a distinction that is crucial for therapeutic decision-making.

Valvular AF is primarily associated with mechanical heart valves or moderate to severe mitral stenosis of rheumatic origin. These patients have a high thromboembolic risk and require anticoagulation with vitamin K antagonists such as warfarin.

In contrast, non-valvular AF represents the majority of cases and is not associated with significant valvular disease. In these patients, DOACs have become the preferred treatment due to their comparable or superior efficacy and lower risk of intracranial bleeding.

This distinction is essential because the CHA_2DS_2-VASc score has been validated mainly in patients with non-valvular AF.

Limitations of CHA_2DS_2-VASc Score

Although CHA_2DS_2-VASc is a widely validated and clinically useful tool, it has several important limitations.
One major limitation is that it is based solely on simple clinical parameters and does not include laboratory biomarkers or advanced imaging findings such as left atrial function, fibrosis, or inflammatory markers. This may lead to underestimation or overestimation of risk in certain patients.

Furthermore, the score is not biologically dynamic, as it does not continuously reflect changes in patient risk over time unless recalculated manually.
Another debated limitation is the role of female sex as a risk factor, which may act more as a risk modifier rather than an independent predictor, potentially leading to overestimation in low-risk patients.
Additionally, the score does not fully account for biological heterogeneity, including genetic predisposition, systemic inflammation, and advanced structural changes in the atrium, all of which may significantly influence thromboembolic risk.

Emerging Risk Factors Beyond Traditional Models

Recent studies suggest that additional factors may improve thromboembolic risk prediction beyond traditional scoring systems.
Left atrial remodeling, characterized by structural and functional changes, has been associated with increased thromboembolic risk.
Inflammation also plays a key role in atrial fibrillation by promoting a prothrombotic state and contributing to atrial structural changes.
Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) have been linked to the presence of atrial thrombi, suggesting their potential role in risk assessment.
Genetic factors have also been identified as contributors to AF susceptbility and thromboembolic risk, opening new perspectives for personalized medicine.

Interaction Between Inflammation and Thrombosis

Inflammation plays a crucial role in the pathogenesis of atrial fibrillation and thromboembolism. Activation of immune cells and release of pro-inflammatory mediators contribute to endothelial dysfunction, hypercoagulability, and thrombus formation.
This interaction promotes structural and functional remodeling of the left atrium and increases the risk of embolic events, particularly stroke. Understanding these mechanisms may lead to the development of novel therapeutic strategies targeting inflammation in AF.

Genetics and Atrial Fibrillation

Genetic factors contribute significantly to the development of atrial fibrillation and its complications. Variations in genes related to ion channels, cardiac structure, and coagulation pathways influence both disease susceptibility and thromboembolic risk.
Pharmacogenomics is particularly relevant in anticoagulation therapy, especially regarding warfarin metabolism, where genetic variations may affect drug response and dosing.
Future integration of genetic data into clinical practice may allow more precise and individualized risk stratification and treatment strategies.

Future Perspectives

Although CHA_2DS_2-VASc remains the standard tool for thromboembolic risk assessment, ongoing research focuses on improving its predictive accuracy through the integration of biomarkers, imaging techniques, and personalized medicine approaches.
Technologies such as wearable devices and implantable monitors may enhance early detection of atrial fibrillation and improve stroke prevention strategies.
Artificial intelligence and dynamic risk assessment models represent promising tools for optimizing clinical decision-making in the future.

Conclusion

The CHA_2DS_2-VASc score remains a fundamental tool for thromboembolic risk stratification in patients with non-valvular atrial fibrillation and plays a crucial role in guiding anticoagulation therapy.
Despite its simplicity and clinical utility, it has important limitations, particularly in individualized risk assessment. Therefore, it should be used in combination with clinical judgment and additional risk factors such as inflammation, atrial remodeling, and genetic predisposition.
Future developments in personalized medicine and advanced diagnostic tools are expected to improve risk prediction and optimize patient management

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PREVALENCE OF TRANSFUSION – TRANSMITTED INFECTIONS AMONG VOLUNTARY BLOOD DONORS IN THE WESTERN REGION OF NORTH MACEDONIA: A RETROSPECTIVE MULTICENTER STUDY (2021-2025)

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Abstract

Introduction: Communicable diseases continue to represent a significant public health challenge due to their high transmission potential and impact on population health. Effective control depends on early detection, preventive measures, and continuous epidemiological surveillance, supported by laboratory and field data analysis.
Objective: The aim of this study was to assess the distribution of communicable diseases in the western region of North Macedonia, specifically in Tetovo, Gostivar, Kičevo, and Struga, and to evaluate incidence patterns according to geographic location and type of testing.
Materials and Methods: A descriptive study was conducted using laboratory and field data collected from 2021 to 2025. A total of 151,610 test results were analyzed and categorized by city, age group, type of test, test result, and year. Data were processed using descriptive statistical methods.
Results: Out of 151,610 tests performed, 588 (0.39%) were positive, 150,814 (99.47%) were negative, and 208 (0.14%) were not tested. The highest number of tests was recorded in Tetovo, followed by Gostivar, Kičevo, and Struga. The highest positivity rate was observed in Struga (0.51%), while the lowest was in Kičevo (0.30%). Hepatitis B virus (HBV) accounted for the largest proportion of positive cases, human immunodeficiency virus (HIV), hepatitis C virus (HCV), syphilis, followed by nucleic acid testing (NAT) detections and hepatitis E virus (HEV).
Conclusion: Although overall positivity rates remain low, variations across cities and types of testing highlight the importance of continuous surveillance, early detection, and strengthened preventive strategies to effectively control communicable diseases.

Keywords: Communicable diseases; Epidemiology; Public health; Incidence; Laboratory testing; HBV; HIV; HCV; Syphilis; Surveillance; North Macedonia

Introduction

Transfusion-transmissible infections (TTIs) are infectious agents that can be transmitted through blood and blood components. In transfusion medicine, the control of these infections depends on appropriate donor selection, validated laboratory testing, quality systems, confirmatory testing, documentation, and haemovigilance. Continuous retrospective monitoring of TTI screening results is essential to evaluate whether donor selection and testing protocols remain effective over time, and to identify marker-specific, regional, demographic, or temporal patterns that may require public health or laboratory intervention. This study provides evidence to support blood safety policies, transfusion service planning, laboratory quality improvement, and regional surveillance for Gostivar, Kërçovë, Struga, and Tetovo.
The study covers the period from January 2021 to December 2025 and includes aggregated data for HBV/HBsAg, HCV/anti-HCV, HIV Ag/Ab, HEV, syphilis, NAT, grey-zone results, and confirmatory/supplementary markers, including HBsAg confirmatory, anti-HCV confirmatory, HIV 1/2 confirmatory, dHBV, dHCV, and dHIV. Prevalence refers to the proportion of tested samples that are positive or reactive within a defined denominator, while seropositivity or reactivity describes a positive or reactive screening result for a specific

infectious marker. TTI refers to transfusion-transmissible infections, while NAT represents nucleic acid testing used for the detection of viral genetic material. The markers dHBV, dHCV, and dHIV represent supplementary diagnostic categories analyzed separately from primary screening prevalence.

International blood safety guidelines emphasize the importance of standardized and safe testing of blood donations prior to clinical use, with mandatory screening for HIV, HBV, HCV, and syphilis as core components of blood safety systems, along with confirmatory testing and proper management of donors with reactive results. The data used in this study reflect regional transfusion service activity from four cities in North Macedonia. The inclusion of NAT and additional markers indicates improved diagnostic sensitivity and enhanced laboratory surveillance, although the dataset does not contain individual identifiers, risk factors, or clinical follow-up information.

The main blood-borne diseases included in this study are HBV (primarily screened using HBsAg), HCV (screened using anti-HCV), HEV as a less frequently tested marker, HIV (screened using HIV Ag/Ab syphilis through serological testing, and NAT as a molecular screening method.

This dataset allows descriptive analysis by marker, time, age group, sex, and city. However, due to its aggregated nature, it is not possible to determine whether multiple reactive results belong to the same individual; therefore, true co-infection prevalence cannot be calculated.

The general aim of the study is to assess the prevalence of transfusion-transmissible infections during the period 2021–2025. The specific objectives include determining overall and marker-specific prevalence, comparing prevalence across years, analyzing differences by sex, age group, city, and donor category, and identifying trends over the study period. The research questions focus on overall prevalence, the marker with the highest prevalence, temporal changes, most affected demographic groups, and implications for blood safety, laboratory practice, and surveillance.

Materials And Methods

This study is a retrospective descriptive study. The study area includes data from the Institute of Transfusion Medicine – Skopje, covering the regions of Gostivar, Kërçovë, Struga, and Tetovo. The study period extends from January 2021 to December 2025. The study population consists of aggregated laboratory data from blood donors and donor-related records within regional transfusion services.

The inclusion criteria comprise records within the period 2021–2025, entries with defined city, age group, test marker, result, and count fields. For descriptive purposes, primary screening data, grey-zone results, and confirmatory/supplementary records were included. Exclusion criteria include data outside the study period, if present. Rows marked as “not tested” were excluded from the prevalence denominator but retained for descriptive analysis of testing coverage. Confirmatory and supplementary results were not included in the primary screening prevalence denominator.

The data source is a cleaned Excel workbook: *TTI_Scientific_research CLEANED DATA.xlsx*. The variables included demographic variables such as age group, sex, city, and source category, as well as laboratory variables such as TestStd, TestFamily, TestType, result, number of reactive/positive cases, number of negative cases, and number of not-tested cases. The temporal variable was year.

Laboratory testing methods include standardized marker categories such as HBsAg, anti-HCV, HIV Ag/Ab, anti-syphilis, NAT, HEV, grey-zone markers, and confirmatory/supplementary markers. The study does not independently verify the diagnostic assay type, laboratory platform, or standard operating procedures, as these data were not available in the dataset.
Data collection was performed from the cleaned workbook, and aggregation was conducted by marker, year, city, age group, sex, source, test type, and result category. The analysis was based on frequencies, percentages, and prevalence calculations. Primary screening prevalence was calculated as the proportion of reactive/positive results divided by the total number of tested samples for each marker or group. For donor-related proxy analysis, HBsAg was used as a reference marker to avoid duplication of the same donor population across different markers.
The data are aggregated and do not contain personal identifiers; therefore, the analysis is based on anonymized group-level data. However, all academic or publication outputs must comply with institutional and data protection regulations.
The main limitation of the methodology is that the data are grouped at marker level rather than individual level. Therefore, true individual prevalence cannot be determined, repeat donors cannot be adjusted for, and true co-infections between markers cannot be assessed.

Results

The study data include 7,411 aggregated rows covering the period 2021–2025. Using HBsAg screening data as a proxy for the number of donors, 28,612 tests were identified. This denominator was used solely to describe the donor sample and was not applied for the aggregation of all disease marker tests.

Table 1. Study sample by year (donor-count proxy based on HBsAg screening)

Year	Total tested	Male	Female	HBsAg reactive	HBsAg reactivity %
2021	5,692	5,022	670	38	0.668%
2022	6,276	5,518	758	35	0.558%
2023	5,496	4,796	700	20	0.364%
2024	5,376	4,724	652	20	0.372%
2025	5,772	5,091	681	16	0.277%

Note: HBsAg screening was used as a practical donor-count proxy to avoid multiplying the same donor pool across repeated disease markers.

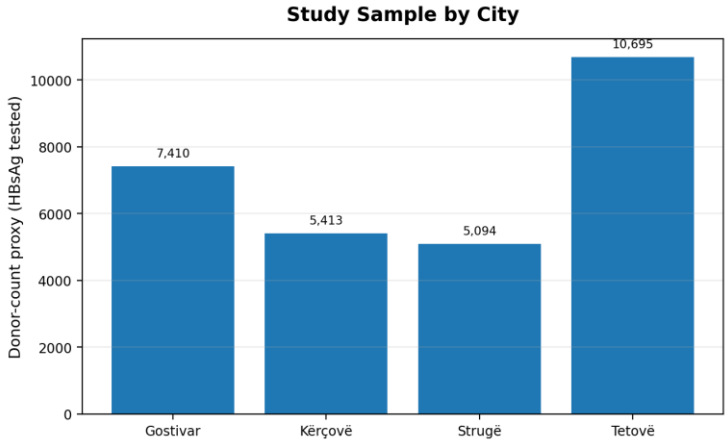


Figure 1. Study sample distribution by city, based on HBsAg screening denominator.

Demographic Characteristics

Table 2. Study sample by city

City	Total tested	Male	Female	HBsAg reactive	HBsAg reactivity %
Gostivar	7,410	6,562	848	27	0.364%
Kicevo	5,413	4,618	795	22	0.406%
Struga	5,094	4,571	523	40	0.785%
Tetovo	10,695	9,400	1,295	40	0.374%

Table 3. Sex distribution of study sample

Sex	Count	Percentage
Male	25,151	87.904%
Female	3,461	12.096%

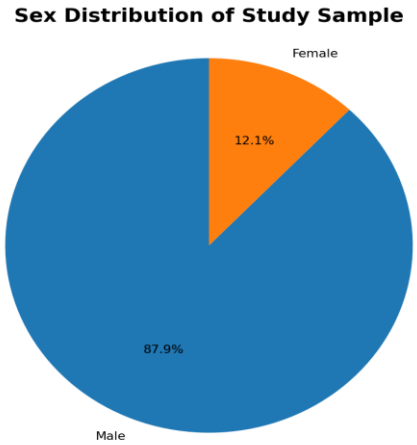


Figure 2. Sex distribution of the study sample. The donor-count proxy shows a male-predominant sample.

Overall Prevalence of Transmissive Blood Diseases

Table 4. Overall marker-level screening prevalence

Total valid screening marker-tests	Reactive/Positive screening results	Negative screening results	Overall marker-level prevalence
151,176	433	150,743	0.286%

Important: This is marker-test-level prevalence. It should not be interpreted as unique donor-level prevalence because individual donor IDs are not available.

Prevalence by Disease Type

Table 5. Prevalence by disease marker

Disease marker	Number tested	Reactive/Positive	Negative	Not tested	Prevalence %
HBV / HBsAg	28,612	129	28,483	0	0.451%
HCV / Anti-HCV	28,557	49	28,508	0	0.172%
HIV Ag/Ab	28,578	54	28,524	0	0.189%
Syphilis / Anti-Syphilis	28,613	40	28,573	0	0.140%
NAT	20,209	150	20,059	107	0.742%
HEV / Hepatitis E	16,607	11	16,596	99	0.066%

NAT showed the highest marker-level prevalence among the analyzed screening markers. HEV and NAT had lower valid denominators because some records were marked as not tested

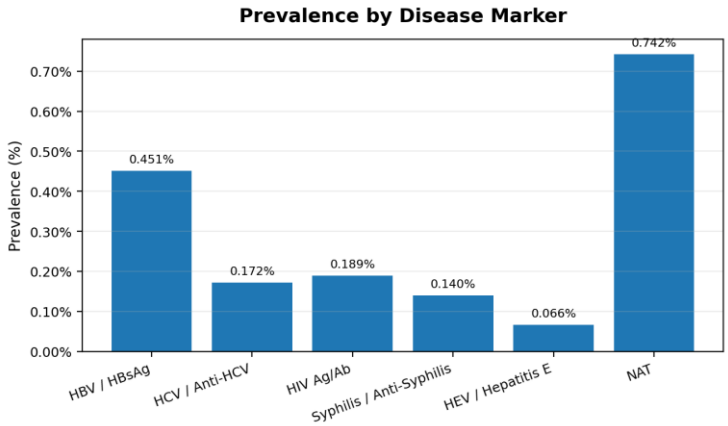


Figure 3. Disease-specific marker-level prevalence, calculated from primary screening rows only.

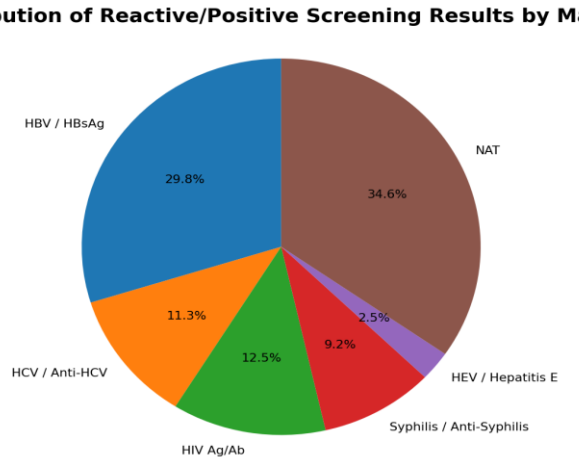


Figure 4. Distribution of reactive/positive primary screening results by marker. This is not a co-infection chart.

Yearly Trend Analysis

Table 6. Yearly trend of screening reactivity

Year	Total valid marker-tests	Reactive/Positive	Negative	Prevalence %
2021	22,788	75	22,713	0.329%
2022	29,094	93	29,001	0.320%
2023	32,914	92	32,822	0.280%
2024	31,837	116	31,721	0.364%
2025	34,543	57	34,486	0.165%

The highest aggregate marker-level prevalence was observed in 2024 (0.364%), while the lowest was observed in 2025 (0.165%).

Figure 5. Yearly trend in marker-level screening prevalence across all primary screening markers.

Prevalence by Age Group

Table 7. Prevalence by age group

Age group	Total valid marker-tests	Reactive/Positive	Negative	Prevalence %
18-22	10,849	37	10,812	0.341%
23-27	13,089	26	13,063	0.199%
28-32	18,090	48	18,042	0.265%
33-37	21,182	60	21,122	0.283%
38-42	25,096	62	25,034	0.247%
43-47	23,533	63	23,470	0.268%

48-52	17,338	65	17,273	0.375%
53-57	13,575	52	13,523	0.383%
58-62	7,036	17	7,019	0.242%
63-65	1,388	3	1,385	0.216%

The highest marker-level prevalence was observed in the 53-57 age group (0.383%).

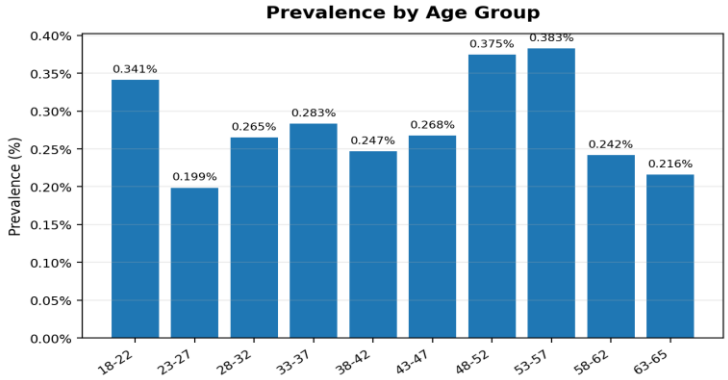


Figure 6. Marker-level prevalence by age group.

Prevalence by Sex

Table 8. Marker-level prevalence by sex

Sex	Total valid marker-tests	Reactive/Positive	Negative	Prevalence %
Male	132,808	382	132,426	0.288%
Female	18,368	51	18,317	0.278%

Sex-specific prevalence is calculated from male/female counts in primary screening rows. The male and female marker-level prevalence estimates are close, but the sample is strongly male-predominant.

Co-Infections, if Available

Table 9. Co-infection assessment

Co-infection type	Number of cases	Percentage	Interpretation
HBV + HCV	Not calculable	Not calculable	Aggregated data do not identify whether markers occurred in the same donor.
HIV + Syphilis	Not calculable	Not calculable	Individual donor IDs are required.

HBV + HEV	Not calculable	Not calculable	Marker-level counts cannot confirm co-infection.

A pie chart was provided for reactive marker distribution, but not for true co-infections.

Confirmatory, Supplementary, and Grey-Zone Findings

Table 10. Confirmatory/supplementary results, including dHBV/dHCV/dHIV

Marker	Number tested	Reactive/Positive	Negative	Positive/Reactive %
Anti-HCV Confirmatory	14	2	12	14.286%
HBsAg Confirmatory	88	84	4	95.455%
HIV 1/2 Confirmatory	4	3	1	75.000%
dHBV	64	52	12	81.250%
dHCV	24	1	23	4.167%
dHIV	25	6	19	24.000%

Confirmatory/supplementary results describe follow-up testing activity and should not be combined with primary screening prevalence denominators.

Table 11. Grey-zone findings

Marker	Number tested	Reactive	Reactive %
Anti-HCV Grey Zone	4	4	100.000%
HBsAg Grey Zone	3	3	100.000%

City and Source-Level Prevalence

Table 12. Marker-level prevalence by city

City	Total valid marker-tests	Reactive/Positive	Negative	Prevalence %
Gostivar	39,781	109	39,672	0.274%
Kicevo	28,651	60	28,591	0.209%
Struga	26,729	103	26,626	0.385%
Tetovo	56,015	161	55,854	0.287%

The highest city-level marker prevalence was observed in Strugë (0.385%).

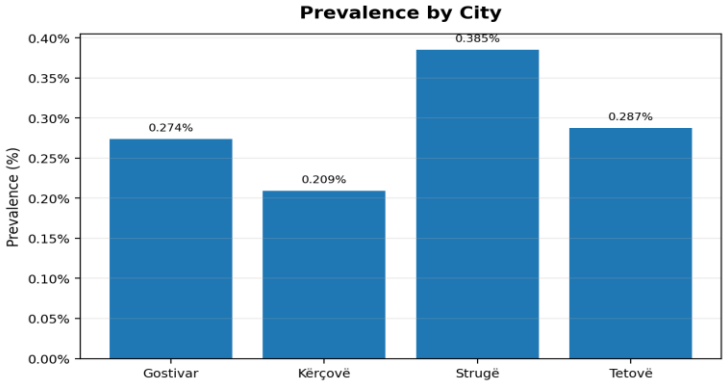


Figure 7. Marker-level prevalence by city.

Key Observations

The overall marker-level screening prevalence was 0.286% across 151,176 valid screening marker-tests.
NAT showed the highest marker-specific prevalence (0.742%), highlighting the importance of molecular screening in detecting reactive results that may not be identified through serological methods alone.
HBV/HBsAg represents a significant burden among serological markers, with 129 reactive results and a prevalence of 0.451%.
The highest annual marker-level prevalence was observed in 2024 (0.364%), followed by a lower value in 2025 (0.165%).
Age-specific prevalence was highest in the 53–57 age group (0.383%), closely followed by the 48–52 age group.
True co-infections cannot be assessed based on the available aggregated dataset.

Discussion

Interpretation of Key Findings: The analysis indicates a low overall marker-level screening prevalence (0.286%); however, reactivity was present across all major marker categories. The persistent presence of reactive results highlights the importance of donor screening, confirmatory testing, and careful documentation.
NAT demonstrated the highest marker-specific prevalence (0.742%). This result should be interpreted with caution, as NAT had a smaller denominator compared to the main serological markers and may reflect targeted implementation or changes in test availability over time.
Comparison with Other Studies and Standards**:** The findings are consistent with the general blood safety principle that even low-prevalence populations require universal standardized screening and confirmatory management of reactive results. The study also supports the continued need for haemovigilance and standardized data systems.
Possible Reasons for Observed Trends: Variations in test availability, particularly the implementation of NAT, may have influenced the number of detected reactive results. Differences in donor composition by year, city, sex, or age group may also affect observed prevalence. Grey-zone and confirmatory categories indicate that screening results require structured follow-up and should not be considered definitive diagnoses without confirmation.

The lower prevalence observed in 2025 may reflect a true reduction, changes in donor composition, incomplete data coverage for the period, or variations in testing volume.
Public Health Implications: The low but persistent reactivity supports the need for donor education, preventive messaging, HBV vaccination promotion where appropriate, continued surveillance, and strong laboratory quality systems. Age groups with higher reactivity may be considered for targeted awareness interventions; however, individual-level risk factor data are required before drawing causal conclusions.
Laboratory and Clinical Implications: Laboratory systems should maintain validated screening algorithms, clear confirmatory pathways, standardized donor notification procedures, and traceable electronic records. NAT and supplementary markers should be consistently documented to ensure that future retrospective analyses can clearly distinguish between screening, confirmation, diagnosis, and donor follow-up outcomes.

Conclusion

Main Conclusion**:** The prevalence of transfusion-transmissible infection markers in the analyzed dataset remained low at the aggregate level, with a total of 433 reactive/positive results among 151,176 valid screening tests (0.286%).
Disease-Specific Conclusion: NAT showed the highest marker-level prevalence, followed by HBV/HBsAg. HIV, HCV, syphilis, and HEV demonstrated lower but still clinically relevant levels of reactivity. Confirmatory and supplementary results, including dHBV/dHCV/dHIV, emphasize the need for a clear distinction between screening and confirmatory testing in reporting.
Trend Conclusion: The overall trend was fluctuating rather than showing a clear linear increase or decrease. The highest annual prevalence was observed in 2024, while the lowest was recorded in 2025. Interpretation of trends should consider testing volume, NAT implementation, and the aggregated nature of the dataset.

Limitations

The retrospective design limits control over missing or inconsistent data. The workbook is aggregated and does not contain individual donor identifiers; therefore, individual-level prevalence and co-infections cannot be determined. Clinical outcomes, risk factors, vaccination status, and donor classification (first-time or repeat donors) are not available. Confirmatory testing may not be recorded for all reactive screening results or may exist in separate registries. NAT and HEV have different denominators compared to serological markers due to “not tested” entries. The results from the included regions cannot be generalized to the entire population without broader national-level data.

Appendices

Appendix A. Data Collection Form / Variables Used

Table A1. Variables available in the cleaned dataset

Variable	Description
Year	Dataset variable
City	Dataset variable
AgeGroup	Dataset variable

TestStd	Dataset variable
TestFamily	Dataset variable
TestType	Dataset variable
Result	Dataset variable
Male	Dataset variable
Female	Dataset variable
SexTotal	Dataset variable
Reactive Positive Count	Dataset variable
Negative Count	Dataset variable
NotTested Count	Dataset variable
Source	Dataset variable

Appendix B. Full source category summary

Table B1. Marker-level prevalence by source category

Source	Total valid marker-tests	Reactive/Positive	Negative	Prevalence %
Gostivar – Field activity	7,573	24	7,549	0.317%
Gostivar – Service	32,208	85	32,123	0.264%
Kičevo – Field activity	3,458	9	3,449	0.260%
Kičevo – Service	25,193	51	25,142	0.202%
Struga – Field activity	1,034	7	1,027	0.677%
Struga – Service	25,695	96	25,599	0.374%
Tetovo – Field activity	13,423	45	13,378	0.335%
Tetovo – Service	42,592	116	42,476	0.272%

Appendix C. Abbreviations

Table C1. List of Abbreviations Used

Abbreviation	Meaning
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus

HIV	Human Immunodeficiency Virus
HEV	Hepatitis E Virus
NAT	Nucleic Acid Testing
TTI	Transfusion-Transmissible Infection
dHBV	Supplementary/diagnostic HBV marker as recorded in dataset
dHCV	Supplementary/diagnostic HCV marker as recorded in dataset
dHIV	Supplementary/diagnostic HIV marker as recorded in dataset

Conclusion

The prevalence of transfusion-transmissible infection markers in the analyzed dataset remained low at the aggregate test level, with a total of 433 reactive/positive results out of 151,176 valid screening tests, representing 0.286%.

At the disease-specific level, NAT showed the highest marker prevalence, followed by HBV/HBsAg. HIV, HCV, syphilis, and HEV demonstrated lower levels of reactivity, although still clinically relevant. Confirmatory and supplementary results, including dHBV/dHCV/dHIV, highlight the need for a clear distinction between screening and confirmatory testing in laboratory reporting and interpretation.

Regarding temporal trends, the overall prevalence did not show a simple linear increase or decrease but rather fluctuations throughout the study period. The highest annual prevalence was recorded in 2024, while the lowest was observed in 2025. Interpretation of these trends should consider variations in testing volume, the implementation of NAT, and the aggregated nature of the dataset.

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NON-STANDARD NEUROSURGICAL MANAGEMENT OF CRANIOSYNOSTOSIS: A CASE REPORT

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Abstract

There are many congenital skull anomalies and among them is craniosynostosis which is due to the early fusion of one or more cranial sutures. However, to avoid skull deformities, raised intracranial pressure, and psychomotor development delay, punctual and proper surgical treatment is needed. Furthermore, open surgical procedure remains the main method for skull reconstruction morphology and symmetry, together with preventing long-term and permanent complications. Traditional surgery requiring cranial reshaping and fixation in craniosynostosis is deemed as a procedure that involves important surgical intervention and is relatively lengthy.

This paper reveals a case managed surgically using a non-standard method contrasted to the frequent applied open surgical approaches. Though, this technique demands a concise operative time and allows satisfactory spontaneous remodeling, guided by gradual brain expansion, without the need for intraoperative remodeling using rigid fixation through sutures or absorbable plates. The presented case was surgically managed at our institution whilst the clinical manifestations, surgical methods, and post-surgical course are described.

Keywords: craniosynostosis, endoscopy, open surgery, pediatric neurosurgery, skull remodeling, intracranial pressure, psychomotor delay.

Introduction

This study case reveals craniosynostosis, a pathology condition in which one or more premature ossification of cranial sutures, limiting normal brain development and resulting characteristic skull abnormalities. The ideal treatment is premature corrective surgery focused on releasing the early fused suture and accomplishing both esthetic and functional remodeling of the skull (1.3).

In isolated forms affecting only one suture, whether unilateral or bilateral, and diagnosed early (at 3–6 months of age), endoscopic treatment may be performed, which is less invasive than open surgery (2,6). Endoscopic treatment is usually followed by postoperative helmet therapy, which guides the necessary skull remodeling and requires prolonged care and professional commitment.

In isolated cases as well as more complex cases involving multiple prematurely fused sutures, especially after 6 months of age and accompanied by progressive skull deformity, treatment is typically performed through open surgery with remodeling (3,5). Open surgery enables the necessary suturectomy and remodeling with fixation of cranial bone segments.

An important condition for adequate response consequences is conducting the surgery before the child turns one year old. After reaching this age, skull flexibility decreases, the hazard of amplified intracranial pressure rises, and aesthetic outcomes tend to be poorer due to lacking of morphological and physiological remodeling. So, exceeding this age restrictions the potential for best surgical outcomes.

Case Presentation

A 7-month-old infant, born at term via normal delivery, presented with craniosynostosis involving two sutures: the sagittal suture and bilateral coronal sutures, which impaired normal

skull development. The child's head had assumed a boat-like shape, known as scaphocephaly (Fig. 1). It was performed a cranial CT scan with three-dimensional imaging to precisely detect the premature fusion of cranial sutures and to arrange the operating technique.

Nevertheless, it is quite vital to state that the craniosynostosis (scaphocephaly) was an isolated anomaly, not related with any syndrome. The patient was still within the best treatment period for surgery, and the skull preserved enough elasticity to enable physiological remodeling post-intervention.

Following imaging analysis and physical examination, a surgical plan was developed that deviated from standard approaches for this type of pathology.

The patient was positioned supine in the operating room, with the head secured in a head holder. The incision was planned as an ear-to-ear zigzag line to allow better cosmetic concealment by hair growth. After scalp reflection, adequate exposure of the cranial vault was achieved. A burr hole was made in the parietal parasagittal region, and using a craniotome, two parallel bilateral bone strips approximately 1 cm wide were removed alongside the superior sagittal sinus, extending to the lambdoid suture, while preserving the sagittal suture to minimize the risk of venous sinus injury (Fig. 2).

Multiple parallel vertical osteotomies were then performed from the midline toward the skull base in the parietal and partially occipital bones to allow gradual and natural skull expansion (Fig. 2).

In the frontal region, bicoronal suturectomy was performed, along with a triangular osteotomy in the frontal bone to facilitate natural remodeling of the frontal deformity (Fig. 2).

Throughout the procedure, no sutures, plates, or other fixation materials—absorbable or otherwise—were used. No attempt was made at direct intraoperative remodeling with rigid fixation. The entire technique relied on passive remodeling guided by brain growth. Early results demonstrated noticeable improvement in skull shape without intraoperative or postoperative complications (Figs. 2, 3).

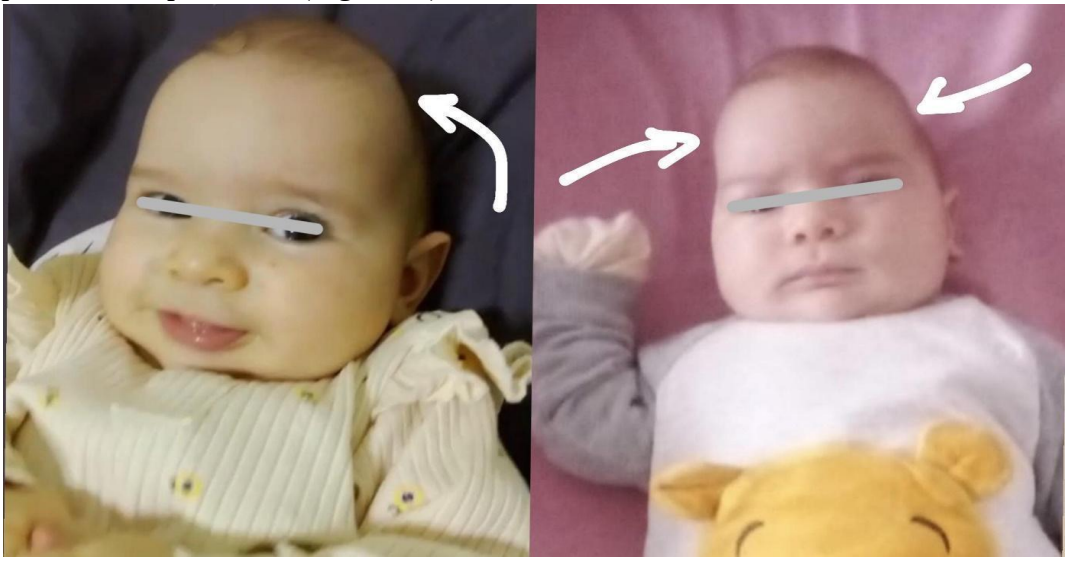


Figure 1. (A)&(B) Images of the infant before surgery.

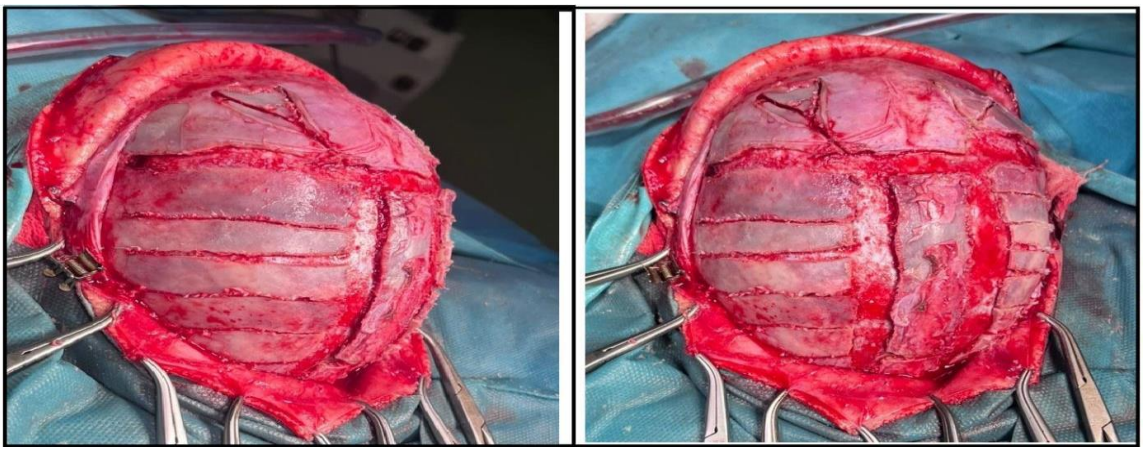


Figure 2. (A) Intraoperative view: (A) lateral view; (B) superior view.



Figure 3.(A) Two days after surgery; (B) and (C) images of the infant several days after surgery.



Figure 4. (A) (B) images of an infant 3 months after surgery.

Discussion

In cases where craniosynostosis involves multiple sutures or when the optimal window for endoscopic intervention (3–6 months) has passed, treatment is typically performed using open surgery (1,3,5). This approach allows for suture release and skull remodeling but requires extensive craniotomy, reshaping of multiple bone segments, and fixation using absorbable plates and sutures.

In most cases, these procedures involve significant manipulation of the cranial vault and may require exposure of critical vascular structures such as the superior sagittal sinus, thereby increasing the risk of intraoperative and postoperative complications (3,5,7).

Standard techniques such as suturectomy and total cranial vault remodeling are associated with risks including venous injury, significant blood loss, and prolonged operative time (3,5,7). These factors are particularly important in pediatric patients, where surgical limits and tolerances are more restricted (2,6).

In the presented case, a modified surgical approach was used, based on preserving the bone segment directly over the superior sagittal sinus**.** Furthermore, as an alternative to a traditional sagittal suturectomy, in both parasagittal regions osteotomies equivalent to the sagittal suture were completed. This represents a deviation from standard techniques and allows controlled, spontaneous skull expansion while preserving midline structural integrity (3,5,7).

Additionally, vertical parallel osteotomies extending from the vertex toward the skull base in the parietal and occipital bones were performed, facilitating gradual skull expansion, in contrast to classical spiral osteotomies.

This procedural technique is based on a different concept compared to traditional remodeling with rigid fixation. It allows passive remodeling driven by brain growth, where intracranial expansion acts as the primary force guiding natural skull correction.

The third step included bicoronal suturectomy combined with a triangular osteotomy, further supporting physiological brain growth and skull expansion.

No fixation materials were used throughout the procedure. The outcome relied entirely on the natural developmental physiology of the brain and the elasticity of the cranial bones.

Early postoperative results showed satisfactory improvement in skull shape (Figs. 3, 4), suggesting that rigid intraoperative fixation may not be necessary in selected cases. This method may decrease operative time, minimize implantation of foreign materials, and reduce risks related to venous sinus exposure, bleeding and infectious complications.

Though, certain limits must be recognized. Furthermore, in patients older than one-year, decreased cranial elasticity, increased bone thickness, and reduced brain growth limit capacity for spontaneous expansion. Ultimate clinical results depend seriously ongoing brain development and skull plasticity. This and a limited number of similar cases are insufficient to establish this technique as a standard procedure.

Advantages of this technique include reduced risk of superior sagittal sinus injury, decreased blood loss, less bone manipulation, avoidance of artificial materials, and shorter operative time. Disadvantages include lack of standardization, absence of immediate intraoperative shape control due to lack of fixation, and dependence on patient age, brain growth, and bone plasticity.

The presented surgical approach is conceptually closer to cranial expansion techniques than to classical remodeling, relying on brain-driven growth principles described in the literature in the context of less invasive methods (2,6).

Conclusions

Early-stage diagnosis and immediate surgical results favorable practical and cosmetic surgical outcomes with less complications.

Additionally, the above-mentioned case recommends that a more conventional technique, led by natural remodeling due to increased brain expansion, cranial elasticity, and cranial structural integrity, may offer satisfactory aesthetic and useful outcomes.

Whereas early outcomes are favorable, extra studies with larger clinical series and prolonged follow-up are essential to normalize this method. This approached should be taken into

consideration as an alternative rather than a replacement for standard methods. Validation as a standard procedure requires a series of successful cases.

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DRUG MISUSE AMONG YOUTH IN THE ERA OF ARTIFICIAL INTELLIGENCE

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Abstract

The use of artificial intelligence (AI) tools and online health information has increasingly influenced how young people access and interpret medical knowledge, contributing to a tendency toward self-medication. This study aimed to evaluate drug use patterns among young people and the influence of AI and digital resources on medication-related decisions. A descriptive study was conducted using an anonymous questionnaire with 54 participants, assessing over-the-counter drug use, types of medications, responses to symptoms, and use and trust of AI and online information. Most participants were female and aged 19–26 years. The majority reported rare use of over-the-counter drugs, with analgesics being the most commonly used medications. In response to new symptoms, most participants consulted a physician, while fewer relied on AI tools, online sources, pharmacists, or self-medication. Trust in AI and internet-based health information was generally moderate to low. Physicians remained the primary influence in medication decisions. Although self-medication was present, professional medical advice was still the dominant approach. AI and online resources were mainly used as supportive tools rather than primary decision-making sources. The findings suggest that while digital technologies are becoming part of health information seeking, their impact on drug use behavior remains limited. These results highlight the need for improved health education and responsible use of medications in the digital age.
Keywords: Self-medication, artificial intelligence, drug use, online health information, medication safety.

Introduction

The increasing use of artificial intelligence (AI) tools and online health information has significantly changed how young people access and interpret medical knowledge. This shift has contributed to a growing tendency toward self-medication and the use of drugs without professional consultation. Although digital platforms may improve access to health-related information and support awareness, concerns remain regarding the accuracy and reliability of such content and its influence on safe medication practices. In this context, understanding how young individuals use AI and online resources in relation to drug consumption is important. Therefore, this study aims to evaluate drug use patterns among youth and assess the influence of digital information sources on their medication-related decision-making.

Aim

To evaluate drug use patterns among young people and the influence of artificial intelligence (AI) and online resources on their medication-related decisions.

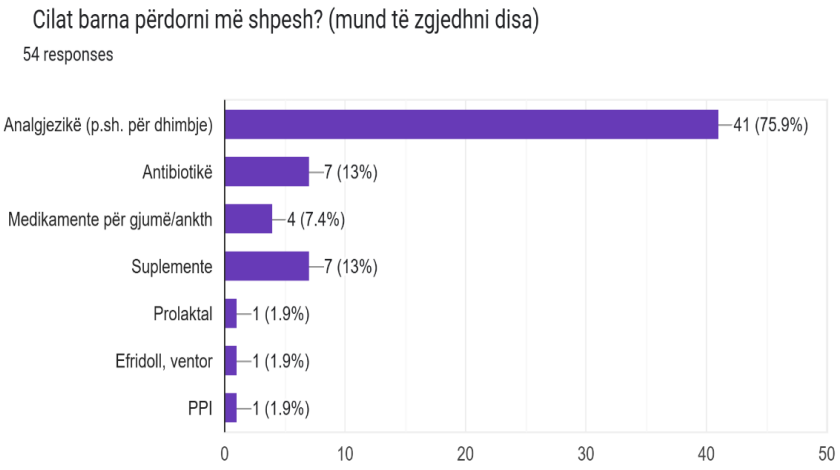
Materials and Methods

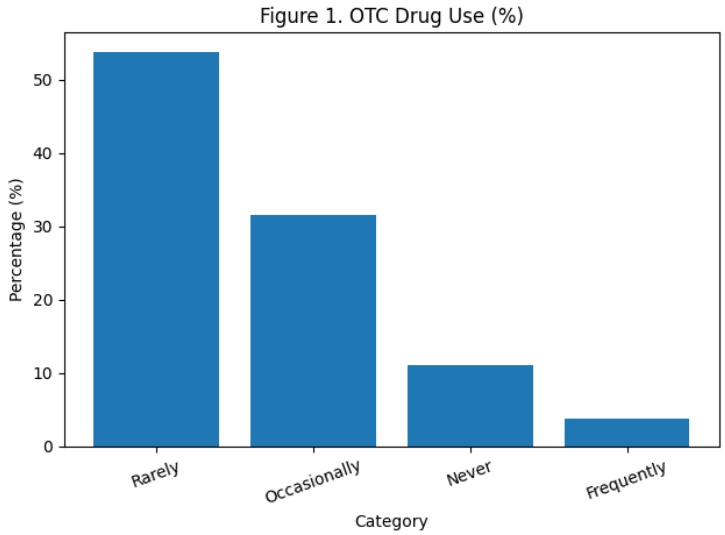
A descriptive study was conducted using an anonymous questionnaire with 54 participants. The questionnaire included questions on over-the-counter drug use, types of medications used, response to symptoms, and the use and trust of AI and online health information.

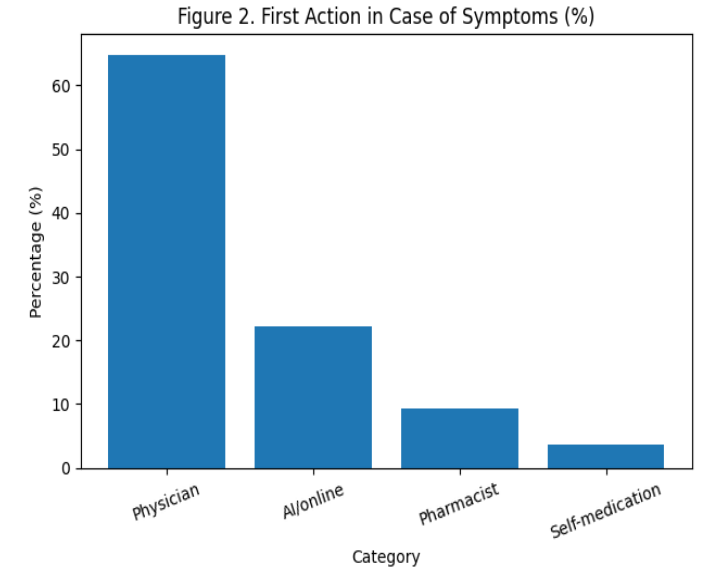
Results

A total of 54 participants were included in the study. The age distribution showed that 18 participants were aged 19–22 years, 18 were 23–26 years, 11 were 27 years and older, and 7 were 15–18 years. Regarding gender, 37 participants were female and 17 were male.
In terms of self-reported use of over-the-counter (OTC) medications, 29 participants stated that they used them rarely, 17 reported occasional use, 6 reported never using OTC medications, and 2 reported frequent use. Regarding the types of medications used, analgesics were the most commonly reported (41 participants), followed by antibiotics (7 participants), dietary supplements (7 participants), and medications for sleep or anxiety (4 participants). A small number of respondents also reported the use of specific pharmaceutical products such as proton pump inhibitors (PPIs) and other individual preparations.
When experiencing new symptoms, 35 participants reported consulting a physician as their first step. In contrast, 12 participants reported using artificial intelligence (AI) tools or online sources to seek health-related information, 5 consulted a pharmacist, and 2 reported taking medication immediately without prior consultation.
Regarding the use of AI and internet sources prior to medication use, 18 participants reported that they never seek such information, 16 stated they do so rarely, 14 reported frequent use, and 6 reported always relying on these sources. Trust in AI and online health information was generally moderate in 30 participants, low in 19, and high in 5.
In relation to self-medication awareness, 25 participants considered self-medication to be risky, 21 were uncertain, and 8 did not consider it risky. Knowledge of drug side effects was reported as complete by 28 participants, partial by 22, and absent by 4.
Finally, regarding factors influencing medication-related decision-making, 45 participants indicated that physicians were the main influence. A smaller proportion reported influence from the internet, family, or pharmacists. When asked about potential behavioral change after completing the questionnaire, 22 participants stated they would not change their behavior, 20 were uncertain, and 12 indicated possible future changes in medication use practices.

Table Figures and Equations







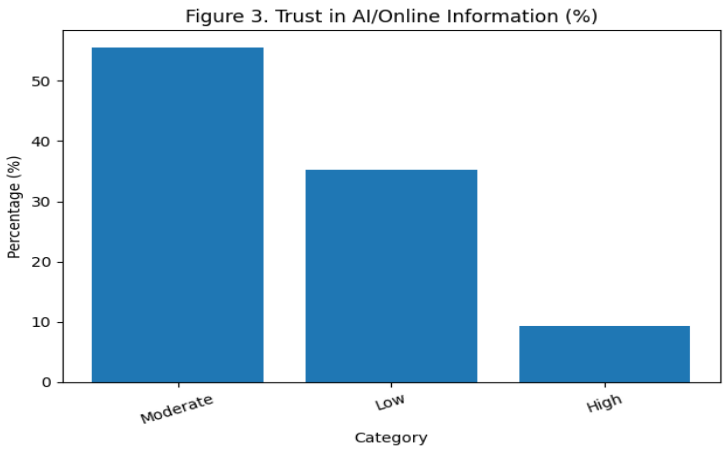


Figure 1.2.3 Publication of author

Conclusions

The findings of this study demonstrate that self-medication remains a relevant behavior among young people, despite the predominant reliance on healthcare professionals for decision-making. While artificial intelligence and online health resources are increasingly used, their role remains mainly supportive rather than decisive. These results suggest that, although digital technologies are shaping health information-seeking behaviors, concerns regarding the reliability of such sources persist. Therefore, strengthening health education and promoting responsible use of medications are essential to ensure safe practices among youth. Future efforts should focus on improving digital health literacy and guiding young individuals toward critically evaluating online medical information.

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CLINICOPATHOLOGICAL AND GENETIC CHARACTERISTICS OF BREAST CANCER PATIENTS UNDERGOING MULTIGENE PANEL TESTING: A SINGLE-CENTER COHORT STUDY

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Abstract

Background: Breast cancer remains the leading malignancy among women worldwide, with a subset of cases linked to hereditary genetic mutations. Multigene panel testing plays an increasingly important role in identifying pathogenic variants and guiding management.
Methods: A retrospective cohort of 12 breast cancer patients who underwent genetic testing between 2022–2024 was analyzed. Clinical, pathological, and molecular data—including age, histology, grade, hormonal receptor profile, HER2 expression, and hereditary cancer gene mutations—were collected and evaluated.
Results: The mean age at diagnosis was 54 years. Invasive ductal carcinoma was the predominant subtype (≈75%). Grade 2 tumors represented the majority. Most patients were hormone receptor–positive (ER ≈80%, PR ≈70%), while HER2 positivity was observed in ~25% of cases. Two pathogenic variants were identified: BRCA2 (8.3%) and CHEK2 (8.3%). Ten patients (83.4%) tested negative.
Conclusion: The genetic mutation rate in this cohort was low, consistent with global data suggesting that most breast cancer cases are sporadic. Multigene testing remains essential for risk assessment and personalized therapy.

Keywords: breast cancer, genetic testing, BRCA2, CHEK2, hormone receptors, hereditary cancer.

Introduction

Breast cancer is the most frequently diagnosed cancer among women, representing a significant global health burden. While most breast cancer cases occur sporadically, approximately 5–10% are attributable to hereditary genetic mutations. The most well-established genes associated with hereditary breast cancer include BRCA1, BRCA2, and CHEK2.
The development of **multigene panel testing** has enabled simultaneous evaluation of multiple genes associated with increased cancer risk. This approach has significantly improved the ability to detect pathogenic variants beyond BRCA1/2.
In regions such as the Western Balkans, the prevalence and distribution of hereditary mutations have not been extensively documented. This study aims to evaluate the clinicopathological and genetic characteristics of breast cancer patients undergoing multigene testing at two oncology centers.

Materials and Methods

Study Design and Population

This retrospective study included **12 female patients** diagnosed with breast cancer between January 2022 and December 2024 at the Skopje oncology clinics. All patients met at least one criterion for hereditary cancer testing, including:

[1] early age at diagnosis
[2] bilateral breast cancer
[3] family history of breast/ovarian cancer
[4] triple-negative breast cancer
[5] or clinician referral based on suspicion

Data Collection

The following parameters were recorded:

1. **Age at diagnosis**
2. **Histological subtype** (ductal, lobular, NST)
3. **Tumor grade**
4. **Estrogen receptor (ER)** status
5. **Progesterone receptor (PR)** status
6. **HER2 expression**
7. **Genetic testing results**
8. Mutations in BRCA1, BRCA2, CHEK2, ATM, PALB2, and other genes included in standard multigene panels

Genetic Analysis

Testing was performed using commercial next-generation sequencing (NGS) multigene panels. Variants were classified according to ACMG guidelines into:

- pathogenic
- likely pathogenic
- variant of uncertain significance (VUS)
- benign

Statistical Methods

Descriptive statistics were used. Continuous variables were expressed as means, while categorical variables as percentages.

Results

Demographic and Clinical Characteristics

The mean age at diagnosis was **54 years** (range: 32–71). The majority had invasive ductal carcinoma (**~75%**), while lobular or NST subtypes represented the remainder.
Grade distribution indicated that **grade 2** tumors were the most prevalent.

Receptor Status

[1]. **ER-positive:** ~80%
[2]. **PR-positive:** ~70%
[3]. **HER2-positive:** ~25%

Most tumors belonged to **luminal-like molecular subtypes (A/B)**.

Genetic Findings

Pathogenic variants were found in:

- **BRCA2:** 1 patient (8.3%)
- **CHEK2:** 1 patient (8.3%)

No pathogenic variants were detected in **83.4%** of the cohort.

TABLE 1. Summary of Clinicopathological Characteristics

Variable	Value
Number of patients	12
Mean age	54 years
Invasive ductal carcinoma	75%
Lobular/NST	25%
Grade 2 tumors	Majority
Grade 3 tumors	Minority
ER positive	80%
PR positive	70%
HER2 positive	25%
BRCA2 mutation 1	8.3%
CHEK2 mutation 1	8.3%
Negative genetic results 10	83.4%

Discussion

The findings of this study are consistent with global epidemiological patterns, where invasive ductal carcinoma and luminal subtypes predominate. Hormone receptor positivity aligns with international data, reinforcing the relevance of endocrine therapy as a major component of treatment.
The identification of a **CHEK2 mutation**, a moderate-risk gene, is notable. CHEK2 carriers require enhanced screening due to elevated risk for contralateral breast cancer.

The relatively low prevalence of BRCA mutations indicates that most cases are sporadic, which is consistent with European data. Despite the low mutation yield, genetic testing still provides significant clinical value:

- identifies candidates for PARP inhibitors
- guides family counseling
- informs risk-reduction strategies

Conclusion

This study demonstrates that in our cohort, breast cancer is predominantly sporadic, with luminal subtype being most common. Genetic testing remains an essential component of personalized oncology care.
Further research with larger sample sizes is recommended to better understand hereditary breast cancer in the region.

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THE AI SAFETY GAP: A SCENARIO-BASED STUDY OF RISKY HEALTH DECISIONS AND MISPLACED TRUST

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Abstract

Artificial intelligence (AI) is becoming increasingly integrated into healthcare and everyday life, offering rapid and accessible medical information to the public. Despite its benefits, concerns remain regarding the accuracy of AI-generated medical advice and the potential risks associated with excessive reliance on these technologies without professional medical consultation. Understanding how individuals perceive and use AI in healthcare is important for promoting safer digital health practices. This study aimed to evaluate public trust in AI-generated medical advice and explore attitudes and behaviors related to AI use in healthcare decision-making. A cross-sectional survey was conducted among 150 participants from the general population. The questionnaire assessed demographic characteristics, frequency of AI use, trust in AI-generated health information, and healthcare-related decision-making behaviors through hypothetical clinical scenarios. The results demonstrated moderate overall trust in AI-generated medical advice, with frequent use of AI tools reported among participants. While most individuals preferred physician guidance when presented with conflicting medical opinions, a proportion of participants still demonstrated uncertainty or willingness to rely on AI recommendations in potentially serious situations. Participants also expressed strong support for clearer safety measures, physician consultation recommendations, and greater public education regarding the responsible use of AI in healthcare. These findings highlight both the growing role of AI in healthcare decision-making and the importance of ensuring safe and responsible use of these technologies. Strengthening public awareness and implementing safety-oriented AI guidance may help reduce inappropriate reliance on AI-generated medical advice and improve patient safety.

Introduction

The rapid integration of artificial intelligence (AI) into everyday health decision-making raises concerns about its misuse, particularly in high-risk situations. While AI tools offer accessible health information, inappropriate reliance without medical verification may lead to harmful outcomes. This study aims to assess public trust in AI-generated medical advice, identify high-risk behaviors, and explore attitudes toward safer AI use in healthcare.

Materials and Methods

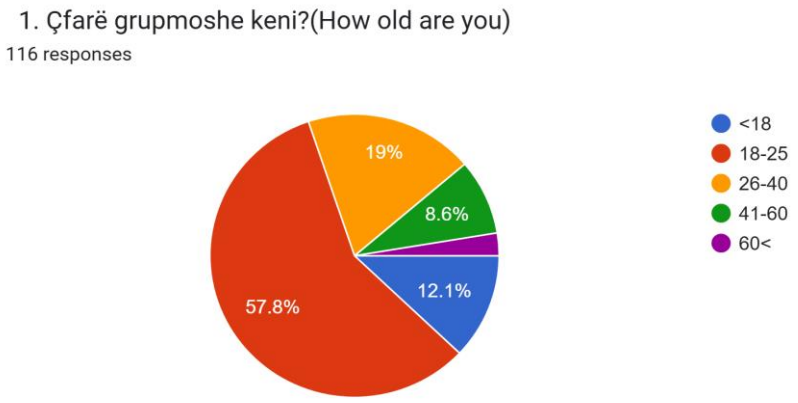
A cross-sectional, scenario-based survey was conducted with 150 participants from the general population. The questionnaire included demographic data, AI usage patterns, trust levels (Likert scale), and verification behaviors. Two clinical scenarios (low-risk: mild headache; high-risk: chest pain with dyspnea) were used to evaluate trust and intended actions. Additional questions explored reasons for avoiding medical consultation and attitudes toward AI safety measures.

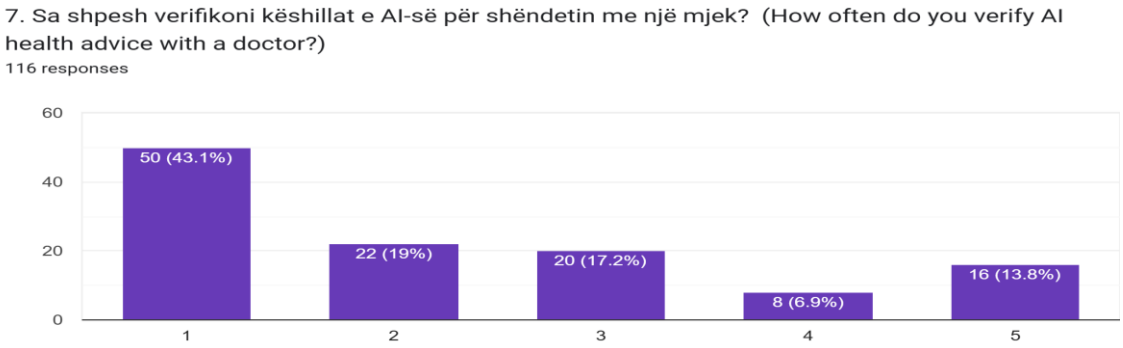
Results

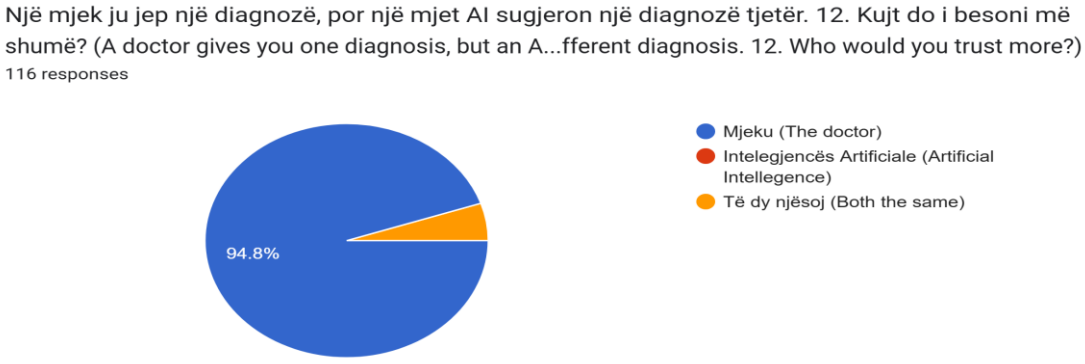
Most participants were aged 18–25 (57.8%) and female (57.8%), with 48.3% holding a university degree. AI usage was frequent, with 47.4% reporting high usage (Likert 4–5). Trust in AI for accurate medical advice was moderate (41.4% neutral), but verification with

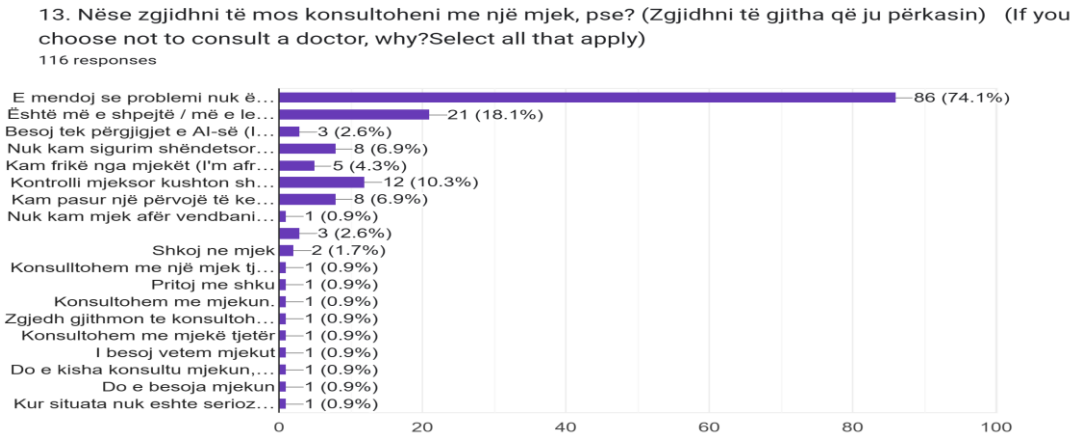
physicians was low (43.1% rarely verify). In the low-risk scenario, 37.1% showed high trust (Likert 4–5), and 52.6% would follow AI advice. In the high-risk scenario, trust significantly decreased, with 75.8% expressing low trust (Likert 1–2); however, 14.7% would still follow AI recommendations and 32.8% remained uncertain, indicating potentially unsafe decision-making. When AI contradicted a physician, 94.8% trusted the physician. The main reason for avoiding medical consultation was perceiving the problem as non-serious (74.1%), followed by convenience (18.1%) and cost concerns (10.3%). Notably, 94% supported clearer safety warnings, 89.7% believed AI should always recommend consulting a physician, and 87.1% emphasized the importance of public education on safe AI use.

Table figure and equations









Conclusion

Despite moderate trust in AI, a subset of individuals demonstrates risky behavior by relying on AI in potentially serious health situations without verification. These findings highlight the need for stronger safety frameworks, including mandatory warnings, physician-directed guidance, and public education. Improving user awareness and integrating safety-oriented AI design may reduce inappropriate reliance and enhance patient safety.

Keywords

Artificial Intelligence; Patient Safety; Healthcare Decision-Making; Trust; Digital Health

PREVALENCE OF ANTIBIOTIC RESISTANCE IN CLINICAL ISOLATES OF E. COLI

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Abstract

Antimicrobial resistance (AMR) represents one of the most pressing global public health challenges of the 21st century. Among Gram-negative pathogens, Escherichia coli (E. coli) plays a central role due to its dual nature as a commensal organism and a frequent opportunistic pathogen. This review critically evaluates the prevalence, molecular mechanisms, and epidemiological distribution of antibiotic resistance in clinical isolates of E. coli. Evidence from multiple peer-reviewed studies demonstrates a significant rise in multidrug-resistant (MDR) and extended-spectrum beta-lactamase (ESBL)-producing strains, particularly in hospital environments. Resistance to first-line antibiotics such as ampicillin, fluoroquinolones, and third-generation cephalosporins is highly prevalent, while reduced susceptibility to carbapenems has emerged as an alarming trend. The findings emphasize the urgent necessity for antimicrobial stewardship programs, strengthened surveillance systems, and global coordinated interventions.

Keywords: Escherichia coli, antibiotic resistance, multidrug-resistant (MDR), ESBL, clinical isolates, antimicrobial resistance.

Introduction

Escherichia coli (E. coli) is a Gram-negative, facultative anaerobic bacterium belonging to the family Enterobacteriaceae. It is a normal inhabitant of the human gastrointestinal tract and plays an important role in maintaining intestinal homeostasis. However, certain pathogenic strains of E. coli are responsible for a wide range of infections, including urinary tract infections (UTIs), bloodstream infections (bacteremia), neonatal meningitis, and gastrointestinal diseases. Urinary tract infections represent the most common clinical manifestation of E. coli infection, accounting for approximately 70–90% of community-acquired cases. In addition, E. coli is frequently isolated in hospital-acquired (nosocomial) infections, particularly in intensive care units (ICUs), where immunocompromised patients are at higher risk. (Flores-Mireles)

In recent decades, the therapeutic management of E. coli infections has become increasingly challenging due to the rapid emergence and spread of antimicrobial resistance (AMR). According to the World Health Organization, antimicrobial resistance is among the top ten global public health threats facing humanity, with significant implications for morbidity, mortality, and healthcare costs. (Organization, 2017)

Antibiotic resistance in E. coli develops through multiple mechanisms, including the production of beta-lactamase enzymes, extended-spectrum beta-lactamases (ESBLs), efflux pump activation, and genetic mutations affecting antibiotic target sites. Of particular concern is the horizontal transfer of resistance genes via plasmids, which accelerates the dissemination of multidrug-resistant (MDR) strains across healthcare and community settings.The increasing prevalence of resistant E. coli strains has significantly reduced the effectiveness of commonly used antibiotics such as ampicillin, fluoroquinolones, and third-generation cephalosporins. In some regions, carbapenem-resistant E. coli strains have also been reported, further limiting last-line treatment options.

This growing resistance trend has been extensively documented in clinical studies indexed in PubMed and other scientific databases, highlighting a global and rapidly evolving public health crisis that requires urgent intervention through antimicrobial stewardship, infection control strategies, and continuous surveillance systems. (Ventola, 2015)

Mechanisms of Antibiotic Resistance

Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, fungi, and parasites no longer respond to antimicrobial agents. As a result, standard treatments become ineffective, and infections become increasingly difficult to treat, leading to a higher risk of disease spread, severe illness, disability, and death. AMR is a natural evolutionary process that occurs over time through genetic changes in microorganisms. However, its emergence and spread are significantly accelerated by human activities, particularly the misuse and overuse of antimicrobial agents in human medicine, agriculture, and animal production. Antimicrobial drugs are essential to modern medicine, and the rise of resistant pathogens threatens the effectiveness of life-saving procedures such as chemotherapy, organ transplantation, and major surgical interventions. (World Health Organization (2023). Antimicrobial resistance.)

In Escherichia coli, antibiotic resistance is mediated through multiple mechanisms. One of the most important is the production of β-lactamase enzymes, including extended-spectrum β-lactamases (ESBLs), which hydrolyze and inactivate β-lactam antibiotics such as penicillins and cephalosporins. This significantly reduces available treatment options for infections caused by ESBL-producing strains. The emergence of carbapenem-resistant E. coli (CRE) strains represents a major clinical concern, as these isolates often exhibit resistance to multiple antibiotic classes, including fluoroquinolones, trimethoprim-sulfamethoxazole, and broad-spectrum cephalosporins. Consequently, treatment options are limited to last-resort antibiotics such as polymyxins, tigecycline, fosfomycin, and aminoglycosides, which may be used alone or in combination.In addition to enzymatic degradation, E. coli exhibits other resistance mechanisms, including reduced membrane permeability, which limits antibiotic entry into the bacterial cell, and the activation of efflux pump systems that actively expel antimicrobial agents. Furthermore, enzymatic modification and target site mutations contribute to reduced susceptibility to various antibiotic classes. (Davies)

Biofilm formation represents an important survival strategy that contributes to antibiotic resistance. Biofilms are structured communities of bacteria embedded in a self-produced extracellular matrix composed of exopolysaccharides, proteins, and extracellular DNA. This matrix protects bacterial cells from antimicrobial agents and host immune responses, making infections persistent and difficult to eradicate. Biofilm development occurs in several stages, including bacterial adhesion, quorum sensing, and biofilm maturation. Within biofilms, bacterial cells exhibit altered metabolic activity and reduced growth rates, which further decrease antibiotic susceptibility. Additionally, biofilms facilitate resistance by preventing antibiotic penetration and protecting bacteria from immune-mediated clearance.

Horizontal gene transfer plays a crucial role in the spread of antibiotic resistance in E. coli. Mobile genetic elements such as plasmids, transposons, and integrons carry multiple antibiotic resistance genes, allowing rapid dissemination of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains across bacterial populations. (Blair, 2015)

The widespread use of β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, and monobactams, has contributed to the global expansion of β-lactamase-mediated resistance. In response, β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam have been developed and are commonly used in combination with β-lactam antibiotics to restore their effectiveness. However, these inhibitors are not effective against all classes of β-lactamases, particularly carbapenemases and metallo-β-lactamases, which continue to pose a significant therapeutic challenge.Overall, the combination of multiple resistance mechanisms in E. coli significantly limits treatment options, prolongs hospitalization, increases healthcare costs, and contributes to higher mortality rates, making antibiotic resistance a major global public health concern. (Sina Nasrollahian)

Methodology

This study was conducted as a literature-based and data-supported analysis of antibiotic resistance in clinical and environmental isolates of Escherichia coli. Data were obtained from published scientific articles, clinical reports, and global health databases, including sources such as the World Health Organization and PubMed.In addition, antibiotic susceptibility data were analyzed for E. coli isolates obtained from two sources: clinical urinary tract infection (UTI) samples and municipal wastewater samples. Antimicrobial susceptibility testing was performed using the disk diffusion (Kirby-Bauer) method, following standard microbiological guidelines. The antibiotics tested, along with their concentrations and classifications, are presented in Table 2 and 3. Resistance patterns were interpreted based on established criteria and categorized according to the WHO AWaRe (Access, Watch, Reserve) classification and the CIA (Critically Important Antimicrobials) list. Multidrug resistance (MDR) was defined as resistance to three or more classes of antibiotics. Comparative analysis was conducted to evaluate differences in resistance patterns between clinical and environmental isolates. (Magiorakos, 2012)

Table 1. Antibiotics used in this study for susceptibility testing. (Makeda Matthew-Bernard)

Antibiotic	Abbreviation/Concentration µg	Class of Antibiotic
Amoxicillin	AMC 30	Penicillin + beta-lactamase inhibitor
Ampicillin	AM 10	Penicillin (Beta-lactam)
Aztreonam	ATM 30	Monobactam
Cefazolin	CZ 30	First generation cephalosporin
Cefoxitin	FOX 30	Second generation cephalosporin
Ceftriaxone	CRO 30	Third generation cephalosporin
Cefuroxime	CXM 30	Second generation cephalosporin
Ciprofloxacin	CIP 5	Fluoroquinolone
Gentamicin	GM 10	Aminoglycosides
Nalidixic Acid	NA 30	Quinolones
Nitrofurantoin	FM 300	Nitrofuran-derivative
Sulfamethoxazole-trimethoprim	SXT 25	Folate pathway antagonist

Results

Antibiotic Resistance Patterns Based on CIA Classification

A total of 120 Escherichia coli isolates were analyzed, including 34 clinical isolates from urinary tract infections (UTIs) and 86 isolates from municipal wastewater samples. Among clinical isolates, 52.9% (18/34) were resistant to at least one tested antibiotic, whereas 15.1% (13/86) of wastewater isolates showed resistance. According to the CIA classification, similar resistance patterns were observed between clinical and wastewater isolates. Among critically important antibiotics, ampicillin exhibited the highest resistance rates, followed by amoxicillin/clavulanic acid and nalidixic acid. Resistance to sulfamethoxazole-trimethoprim was observed in both groups within the highly important category, while nitrofurantoin showed low resistance levels in both sample types.

For wastewater isolates, resistance rates were relatively low, with ampicillin showing 9.3% resistance, followed by amoxicillin/clavulanic acid (3.5%), nalidixic acid (3.5%), and gentamicin (2.3%). Notably, all isolates were susceptible to ceftriaxone and ciprofloxacin.

In contrast, clinical UTI isolates demonstrated significantly higher resistance rates. Ampicillin resistance reached 38.2%, followed by amoxicillin/clavulanic acid (23.5%), nalidixic acid (14.7%), and gentamicin (11.8%). Resistance to ceftriaxone (5.9%) and ciprofloxacin (2.9%) remained relatively low. (BMC Infectious Diseases (2020). Prevalence of antibiotic resistance in E. coli isolates.)

Table 2. Patterns of antibiotic resistance (R), intermediate (I), and susceptibility (S) among Escherichia coli isolates from wastewater samples determined by disk diffusion method. (Makeda Matthew-Bernard)

Antibiotic	R-resistance		I-intermediate		S-susceptibility	
	N	%	N	%	N	%
Amoxicillin	3	3.5	3	3.5	80	93.0
Ampicillin	8	9.3	12	14.0	66	76.7
Aztreonam	0	0	0	0.0	86	100.0
Cefazolin	2	2.3	0	0.0	84	97.7
Cefoxitin	2	2.3	1	1.2	83	96.5
Ceftriaxone	0	0	1	1.2	85	98.8
Cefuroxime	2	2.3	0	0.0	84	97.7
Ciprofloxacin	0	0	3	3.5	83	96.5
Gentamicin	2	2.3	9	10.5	75	87.2
Nalidixic Acid	3	3.5	1	1.2	82	95.3
Nitrofurantoin	1	1.2	4	4.7	81	94.2
Sulfamethoxazole-trimethoprim	3	3.5	1	1.2	82	95.3

Table 3. Patterns of resistance, determined by disk diffusion, for E. coli isolates from clinical UTI samples. (Makeda Matthew-Bernard)

Antibiotic	R-resistance		I-intermediate		S-susceptibility	
	N	%	N	%	N	%
Amoxicillin	8	23.5	6	17.6	20	58.8
Ampicillin	13	38.2	1	2.9	21	61.8
Cefazolin	3	8.8	1	2.9	30	88.2
Cefoxitin	1	2.9	0	0	33	97.1
Ceftriaxone	2	5.9	0	0	32	94.1
Cefuroxime	2	5.9	7	20.6	25	73.5
Ciprofloxacin	1	2.9	2	5.9	32	94.1
Gentamicin	4	11.8	0	0	30	88.2
Nalidixic Acid	5	14	3	8.8	26	76.5
Nitrofurantoin	1	2.9	0	0	33	97.1
Sulfamethoxazole-trimethoprim	9	26.5	0	0	25	73.5

Antibiotic Resistance Based on AWaRe Classification

Based on the AWaRe classification, the highest resistance levels were observed among antibiotics in the ACCESS group, particularly ampicillin, with resistance rates of 9.3% in wastewater isolates and 38.2% in clinical isolates. In contrast, nitrofurantoin demonstrated the lowest resistance rates (1.2% and 2.9%, respectively).
Antibiotics in the WATCH group, such as cefuroxime and cefoxitin, showed similar resistance patterns across both sample types, whereas ciprofloxacin and ceftriaxone exhibited minimal resistance in wastewater isolates. Aztreonam, categorized under the RESERVE group, demonstrated complete susceptibility (100%) in wastewater isolates.

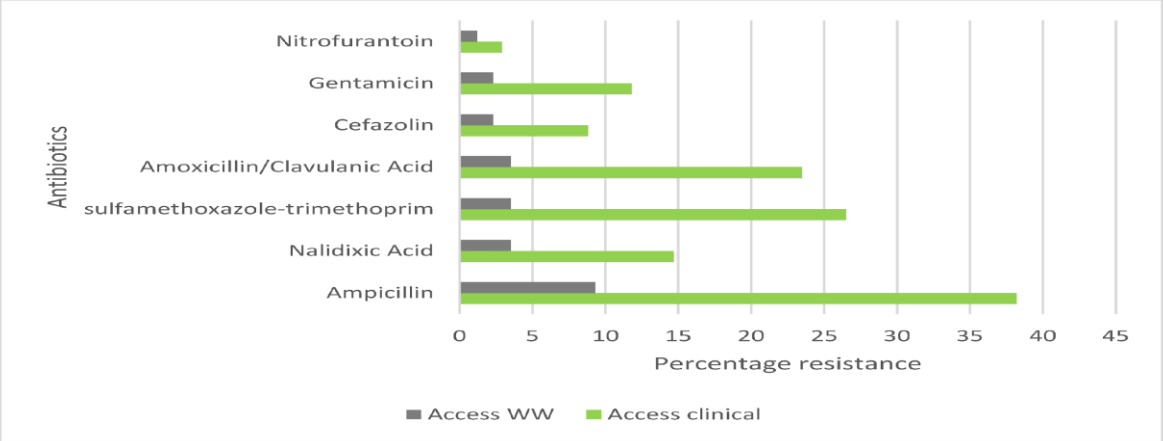


Figure 4. Percentage of antibiotic resistance among Escherichia coli isolates from clinical UTI samples and municipal wastewater, based on AWaRe (ACCESS) classification. (Makeda Matthew-Bernard)

Multidrug Resistance (MDR) Patterns

A total of nine multidrug resistance (MDR) patterns were identified, including three from wastewater isolates and seven from clinical isolates. The most frequently observed MDR combinations included AMC/AM, AMC/AM/CZ, AMC/AM/CZ/CXM, and AMC/AM/CZ/CXM/FOX.
These findings indicate a higher prevalence and diversity of MDR patterns among clinical isolates compared to environmental samples.

Table 5. Phenotypic antibiotic resistance profile of E. coli isolates from wastewater and clinical UTI samples. (Makeda Matthew-Bernard)

Pattern	Number of isolates	Source	Phenotypic Resistance Profile
A	2	Clinical UTI	AMC AM SXT
B	1		AM GM SXT
C	1	Clinical UTI	AMC AM FOX
D	1	Wastewater	AMC AM CZ CXM NA
E	1		AMC AM CZ CXM FOX
F	1	Wastewater	AMC AM CZ CXM FOX CRO GM
E	1	Wastewater	AMC AM CZ GM SXT CIP NA
F	1	Clinical UTI	AMC AM CZ CXM CRO GM SXT
		Clinical UTI	
		Clinical UTI	

Discussion

The present study demonstrates a significant level of antimicrobial resistance among Escherichia coli isolates, with notable differences observed between clinical urinary tract infection (UTI) samples and municipal wastewater isolates. Clinical isolates exhibited substantially higher resistance rates compared to environmental isolates, highlighting the greater selective pressure present in clinical settings. The high resistance rates observed for ampicillin and trimethoprim-sulfamethoxazole in clinical UTI isolates are likely associated with their widespread empirical use in the treatment of urinary tract infections. In contrast, wastewater isolates showed lower resistance levels, although the presence of resistant strains in environmental samples indicates that wastewater may serve as a potential reservoir for antimicrobial resistance. (Paterson, 2005) Reduced susceptibility to fluoroquinolones among clinical isolates is particularly concerning, given their frequent use in treating more complicated infections. Resistance mechanisms, including mutations in DNA gyrase and topoisomerase IV as well as increased efflux pump activity, contribute to decreased antibiotic effectiveness and facilitate the spread of resistant strains in both hospital and community settings. Although carbapenems remained highly effective against both clinical and wastewater isolates, the emergence of resistant strains reported globally emphasizes the need for careful stewardship of these last-resort antibiotics. The detection of multidrug-resistant (MDR) patterns, particularly among clinical isolates, further underlines the clinical importance of resistance surveillance. Overall, the comparative findings of this study highlight the critical role of both clinical and environmental sources in the epidemiology of antimicrobial resistance.

Continuous monitoring, rational antibiotic use, and effective infection control strategies are essential to limit the spread of resistant E. coli strains. (Pitout, 2008)

Conclusion

The findings of this study confirm that antibiotic resistance in Escherichia coli is a significant and growing public health concern, particularly in clinical settings. Clinical UTI isolates demonstrated higher resistance rates compared to wastewater isolates, reflecting the impact of antibiotic exposure and selective pressure in healthcare environments. While environmental isolates exhibited lower resistance levels, their role as potential reservoirs of resistant bacteria should not be underestimated. The presence of multidrug-resistant (MDR) strains in both clinical and environmental samples highlights the interconnected nature of antimicrobial resistance between human and environmental sources. Although certain antibiotics, such as carbapenems, remain largely effective, increasing resistance to commonly used agents limits treatment options and complicates infection management. These findings emphasize the importance of continuous surveillance, antimicrobial stewardship, and integrated approaches that address both clinical and environmental pathways of resistance spread. Future research should focus on monitoring resistance trends across different settings and developing strategies to reduce the dissemination of resistant E. coli strains.

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ADAPTING TREATMENT IN METASTATIC HR+/HER2− BREAST CANCER, AFTER CHEMOTHERAPY REFUSAL: A CASE REPORT

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Abstract

This study case represent breast cancer with positive hormone receptors and HER2-negative status shows the most usual subtype in metastatic breast carcinoma. Clinical management is frequently derived from endocrine therapy together with certain agents. The therapeutic option affected not only by the biological characteristics of the tumor but also by the patient's acceptance and preference influencing treatment persistence in daily medicinal practice.
It is presented a case of a 46-year-old female patient with metastatic HR+/HER2− breast cancer with systemic metastatic disease involving the bones, lungs, and liver. The individual had undergone chemotherapy previously, surgery, radiotherapy, and subsequent oral chemotherapy with capecitabine.
Upon further progression of disease, this patient declined continued systemic chemotherapy as a result of treatment-related adverse effects. Additionally, medical therapy was thereafter commenced with ribociclib (a CDK4/6 inhibitor) used concurrently with letrozole and ovarian suppression. Fortunately, upon completion of 12 months of treatment, radiological imaging showed illness maintenance without new lesions. Pulmonary and hepatic metastases continued constant. The therapeutic management was associated with good tolerability, with easily controlled leukopenia during numerous cycles.
A medicine such as ribociclib may indicate a real therapeutic solution in patients with metastatic hormone receptor-positive, HER2-negative breast cancer who decline chemotherapy is what this clinical case depicts.

Keywords: Metastatic breast cancer; HR-positive breast cancer; HER2-negative breast cancer; Ribociclib; CDK4/6 inhibitors; endocrine therapy; treatment adaptation.

Introduction

It has been found the improvement in the past few years regardless of hormone HR+/HER2− tumor indicates the most frequent tumor molecular subtype of metastatic breast carcinoma by owing to advances in therapy, survival and long-term disease control.
Although, the CDK4/6-targeted agents, in combination with endocrine therapy, have become a crucial part of standard treatment, representing significant benefit in disease control and overall survival. Nevertheless, in real-world clinical practice, therapeutic decisions are not due to exclusively on tumor biology or references from international guidelines, but also on individual factors such as prior treatments, tolerability, performance status, and patient choices. This article depicts the case of a young adult patient with metastatic HR+/HER2− breast cancer who, after multiple lines of therapy, decline further chemotherapy and requested a less toxic therapy alternative without impairing disease control.

Case Presentation

In 2021 a 46-year-old female patient was confirmed in the setting of mucinous breast carcinoma of luminal biological profile (ER-positive, PR-positive, HER2-negative, Ki-67 30%). At first diagnosis, radiological examinations confirmed histologically metastatic disease involvement of the skeletal system, lungs, and liver.

Taking in considering the patient's age, overall condition, and the existence of visceral metastases, systemic chemotherapy with anthracyclines was commenced, subsequently treated with taxanes. The patient then received surgical treatment and radiotherapy in accordance with oncological indication. Furthermore, during follow-up examination, as a result of disease development, capecitabine therapy was managed, attaining partial treatment benefit.
After further progression and exposure to multiple treatment lines, the patient refused continuation of chemotherapy due to experienced toxicity and reduced quality of life. Following clinical reassessment, tumor biology, and overall patient condition, treatment with ribociclib in combination with letrozole and ovarian suppression was initiated.
During a 12-month follow-up period, treatment was well tolerated. The main observed toxicity was manageable leukopenia and after follow-up imaging confirmed stable disease, with no additional metastatic spread and no progression in the lungs or liver.

Results

It quite vital to mentioned that this case has undergone through medical assessments, laboratory tests, and radiologic imaging during treatment with ribociclib (Figures 1, 2, 3).
Within a year of treatment, CT imaging revealed disease steadiness, with no new secondary tumors and neither advance of existing lesions in the lungs (Figures 2, 3) nor in liver (Figure 1). On clinical grounds, the patient preserved good performance status and an adequate quality of life through the treatment period.

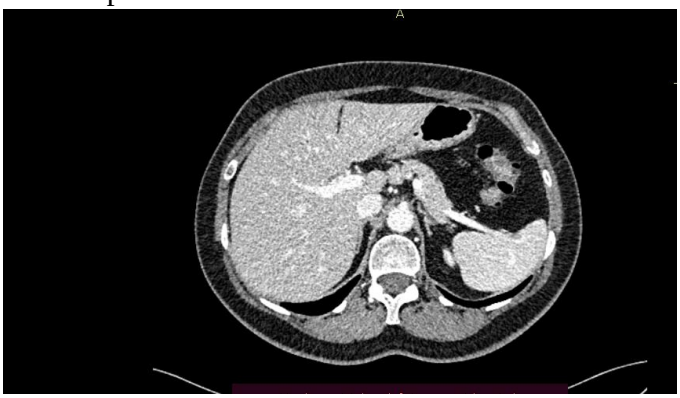


Figure 1. CT abdomen showing hepatic metastases with no interval change after 12 months.

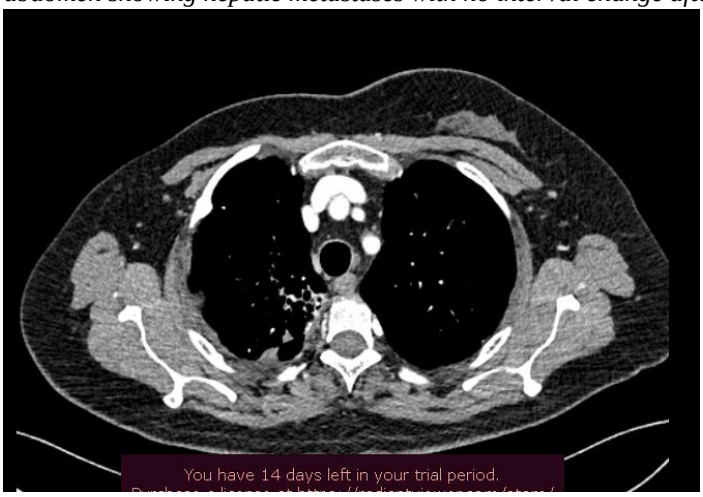


Figure 2. Thoracic CT showing no progression.

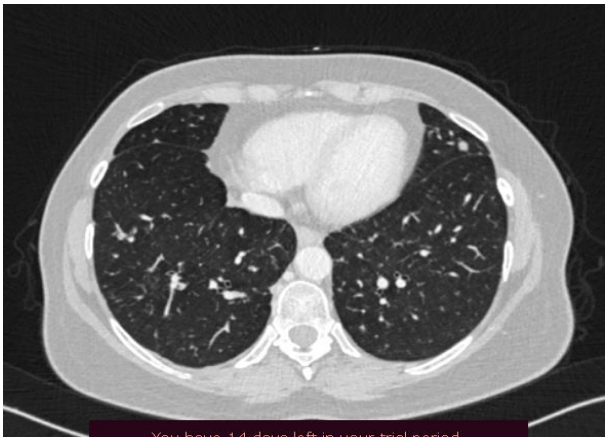


Figure 3. CT chest showing pulmonary metastases without change.

Discussion

Although, stage IV breast cancer with hormone receptor positivity and absence of HER2 overexpression is in overall typified by an indolent disease course in comparison with high-grade subtypes. Yet, the presence of metastatic involvement of visceral organs, predominantly in the liver and lungs, is frequently related to greater therapeutic complication and the need for several treatment lines across with progression of disease.

In clinical treatment, those patients characteristically receive several lines of systemic therapy, as well as chemotherapy, endocrine therapy, and, when specified by biological markers, targeted anticancer therapy. However, clinical decisions cannot always be guide by exclusively on clinical protocols. Furthermore, there are factors that often affect treatment choice by including tolerance to earlier treatments, long-term toxicity, useful status, comorbidities, emotional aspects, and individual preference.

This case presented several clinically relevant features. Since, the patient was young, reproductive-age, and with metastatic involvement of the bones, lungs, and liver at diagnosis. In addition, she had experienced multiple therapeutic modalities, including anthracycline-based regimen, taxanes, operation, radiation therapy, and was subsequently treated with capecitabine. In this situation, the doctor would typically have been recommended an extra line of chemotherapy.

Though, as a result prior treatment obstacles, presented with adverse effects, and the patient's denial to continue chemotherapy, it was necessary to choose an individualized therapeutic approach. Moreover, taking in consideration tumor molecular profile, preserved performance status, and the aim of sustaining quality of life, administered with ribociclib in combined with letrozole and ovarian suppression was carefully chosen.

The course of the disease, in this case was promising. At 1-year follow-up of treatment, radiological evaluation established illness stabilization with no appearance of new lesions. Moreover, liver metastases also continued stable, in spite of being commonly associated with an adverse prognosis. Whereas, hematologic toxicity was restricted to controlled leukopenia, with no need for long-term treatment discontinuation.

Based on a prognostic perspective point of view, individuals with metastatic HR+/HER2− breast cancer and metastatic involvement of visceral organs show heterogeneous clinical results. Yet, diagnosis depends on tumor biology, disease load, treatment responsiveness, and the capability to maintain nonstop therapy. This case determines that, beyond established

treatment algorithms, personalized treatment according to medical characteristics and patient preference can contribute to sustained disease management and protection of quality of life.

Conclusion

In conclusion, this case proves that also patients with the last stage of breast carcinoma receiving multiple lines of therapy and reject additional chemotherapy, personalized therapeutic strategies may confer important clinical advantage.
On the other hand, the therapy such as ribociclib in combination with endocrine therapy in this case realized sustained managed disease, good tolerability, and protection of quality of life. Finally, this case demonstrates the importance of therapy adjustment based on clinical features, therapeutic history, and personal patient preferences.

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ASSESSMENT OF METHANOL CONCENTRATION IN ARTISANAL AND INDUSTRIAL FRUIT DISTILLATES PRODUCED IN KOSOVO

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Abstract

This study provides a comprehensive evaluation of methanol concentration in fruit distillates produced under artisanal and industrial conditions in Kosovo. Fruit distillates, commonly known as "Raki," represent an important cultural and economic product in the Balkan region. However, their safety is strongly influenced by production practices, particularly regarding methanol contamination. A total of 30 samples (n=30) were analyzed, equally divided between artisanal and industrial production. Samples included three types of fruit distillates: grape, plum, and pear.

Methanol quantification was performed using gas chromatography (GC-FID), applying validated analytical methods with high precision and reliability. The results demonstrated statistically significant differences between production methods and fruit types ($p < 0.05$). Artisanal distillates showed considerably higher methanol concentrations compared to industrial products. Pear-based distillates exhibited the highest levels, with some samples approaching or exceeding European Union regulatory limits (1350 g/hL of pure alcohol).

The findings highlight that both production technology and raw material composition play a critical role in methanol formation. Industrial systems, characterized by controlled fermentation and distillation, ensure safer products. In contrast, artisanal production lacks process standardization, increasing variability and potential health risks.

This study emphasizes the urgent need for improved technical practices, regulatory monitoring, and producer education to ensure food safety and product quality in Kosovo's traditional distillation sector.

Keywords: Methanol, Fruit Distillates, Gas Chromatography, Pectin, Kosovo, Food Safety.

Introduction

Background of the study

The production of strong alcoholic beverages through the distillation of fermented fruits represents one of the oldest socio-economic traditions in the Balkan Peninsula with a special importance in the Republic of Kosovo. Fruit distillates, known locally as "Raki", are not just consumer products, they represent a technological legacy that is passed down from generation to generation. However, while the fermentation and distillation process under industrial conditions is strictly controlled, artisanal or home-made production often operates outside of standard food safety protocols (Lahu et al., 2024). Chemically, fruit distillates are complex mixtures where ethanol and water dominate, but they also contain hundreds of secondary components such as high alcohols, esters, aldehydes and toxic alcohols such as methanol. The presence of methanol in these beverages is inevitable due to the nature of the raw material, but its monitoring is critical for public health (Swetha Vasudevan & Jeevitha Gada Chengaiyan, 2024) .

Chemical Nature and Formation of Methanol

Methanol (CH3OH), also known as wood alcohol, is a colorless, flammable, and toxic liquid. In fruit distillates it is not a direct product of alcoholic fermentation carried out by yeasts (Saccharomyces cerevisiae), but is formed mainly by enzymatic hydrolysis of pectin methoxyl groups. This process is catalyzed by the enzyme pectin-methylesterase (PME), which is naturally found in fruit tissue (Arslan et al., 2015).
During the fruit pressing and fermentation phase, PME releases methanol from the pectin strands. The amount of methanol generated directly depends on the type of fruit, its ripeness, and fermentation conditions such as pH and temperature. Fruits like pears, plums, and apples, which have a pectin-rich cell wall, produce significantly higher levels of methanol compared to grapes (Botelho et al., 2020).

Toxicology and Importance for Public Health

The toxicity of methanol to the human body poses a serious public health concern. After consumption, methanol is rapidly absorbed and metabolized in the liver. The oxidation process which is mediated by the enzyme alcohol-dehydrogenase, produces formaldehyde, which is then converted into formic acid (Clary, 2003). The authors of this paper emphasize that formic acid is responsible for severe metabolic acidosis and specific damage to the optic nerve.
In high doses, consuming contaminated distillates can lead to permanent blindness or fatal cases. For this reason, regulatory authorities have set strict limits. According to (Commission Regulation (EU) 2019/787), the maximum allowed limit for drinks such as plum brandy is 1200 g/hL alcohol 100% vol. while for pears it can go up to 1350 g/hL. The lack of quality control in craft beverages increases the risk of toxicological "outbreaks", especially in regions where home distillation is not monitored by sanitary inspectorates (Lachenmeier, 2007)

The Impact of Distillation Technology

The distillation process is the critical stage where the desired fractions are separated from the harmful ones. Although methanol has a lower boiling point (64.7 □C) than ethanol (78.3 □C), its dynamics in a distillation kettle are complex. Due to the formation of azeotropes and the interaction with water, it does not completely leave in the first fraction, known as the "head" (Swetha Vasudevan & Jeevitha Gada Chengaiyan, 2024).
Optimizing the distillation process through temperature control can significantly reduce the percentage of methanol in the "heart" of the distillate (Feng et al., 2025).
In Kosovo, traditional practices often involve the use of copper cauldrons without precise temperature measuring systems. According to (Swetha Vasudevan & Jeevitha Gada Chengaiyan, 2024) It has been proven that not removing enough of the first fraction (about 1-2% of the total volume) results in a product with a high load of methanol and acetaldehyde. Unlike this, industrial methods that use distillation columns allow for a much more efficient separation, guaranteeing a product that complies with international norms.

Current situation and need for research in Kosovo

In the context of Kosovo and neighboring countries such as North Macedonia, studies on chemical contaminants in alcoholic beverages are increasing. The study of (Vlora Gashi & Valon Sadiku, 2014) (Vlora Gashi & Valon Sadiku, 2014) It has shown that fruit varieties and outdated distillation methods in the region often result in methanol levels approaching critical limits. This phenomenon is especially present in pear and quince distillates.
This study is structured to provide a detailed analysis of the situation in the Kosovo market. Considering the lack of a centralized database for methanol monitoring, the research aims to evaluate 30 samples from different regions (Dukagjini and Anamorava Regions). The results of this paper will serve as a guide for producers and institutions to improve production practices and guarantee that "Kosovo Rakia" is a safe and quality product according to EFSA (2021) standards.

Materials and Methods

Research Design and Sampling Strategy

This study is designed as an analytical cross-sectional research to assess the methanol load in the distillate production environment in Kosovo. To guarantee statistical representativeness, the stratified sampling method has been applied.
A total of "n=30" samples were collected, which were categorized into two main groups:

[1] **Artisanal Sector (n=15):** Samples taken directly from family production units in the region of Peja, Gjakova and Gjilan, where distillation is carried out with batch distillation.
[2] **Industrial Sector (n=15):** Samples of labeled and certified products, obtained from the open market, which are subject to official control according to the standards of the Food and Veterinary Agency (FVA).

Samples are provided in volumes of 500 mL, hermetically sealed, and transported under thermal control conditions (4°C ± 1°C) to prevent the decomposition of volatile fractions.

Reagents and Analytical Standards

All reagents used are of the "p.a." scale. (per analysis).

[1]. **Reference standards:** Methanol (CH3OH) with chromatographic purity of 99.98% (Merck, Germany).
[2]. **Internal Standard:** 4-methyl-2-pentanol has been used to guarantee the accuracy of quantification and eliminate errors during injection
[3]. **Matrix:** Ultra-pure water (Milli-Q) and absolute ethanol for the preparation of calibration series simulating the brandy matrix (40% v/v).

Sample Preparation

In order to have a fair comparison between artisanal (often with a higher alcoholic degree) and industrial (standardized) brandy, all samples have undergone the following process:

- **Filtration:** Samples are filtered through nylon membranes with a porosity of 0.22 μm

- **Alcohol Strength Standardization:** All samples are precisely adjusted to 40% (± 0.1%) vol., using an electronic densitymeter. This step is critical to ensure that the partition coefficients in the chromatographic column remain constant.

Analiza Instrumentale: Gaz-Kromatografia

Kuantifikimi i metanolit është realizuar përmes sistemit kromatografik Agilent Technologies 7890B.

Analysis parameters:

- **Column:** HP-Innowax polar capillary column (60m x 0.25 mm i.d., 0.25 μm film thickness).
- **Carrier gas:** Helium (purity 6.0) with a constant flow of 1.0 mL/min.
- **Thermal Regime:** Initial temperature 35°C (for 6 min), followed by an increase of 15°C/min to 210°C.
- **Injection:** Volume 1.0 μL in "split" mode (ratio 1:80).

Method validation

The method has been validated according to ICH guidelines to ensure the reliability of the comparative results:

[1.]**Linearity:** 7-point calibration curve (10 – 2500 mg/L) with $R^2 > 0.9998$.

[2.]**LOD and LOQ:** The detection limit is calculated at 1.5 mg/L.

[3.]**Repeatability:** The standard relative deviation (RSD%) has resulted < 2.5%

Statistical Analysis

The data is processed through SPSS software. To prove the hypothesis of the difference between the two groups, the following was used:

- **T-test for independent samples:** To compare the methanol average between artisanal and industrial production.
- **ANOVA (One-Way):** To see the differences between the types of fruit within each category.
- The confidence level is set at $p < 0.05$

Results

Sample Description and Descriptive Analysis

In this study, 30 samples (n=30) were analyzed, equally divided between artisanal (n=15) and industrial (n=15) production. For each group, three types of fruits were analyzed: Grapes, Plums and Pears. Initially, the characterization of the samples was done according to the origin (Artisanal and Industrial) and the type of fruit (Grapes, Plums, Pears).

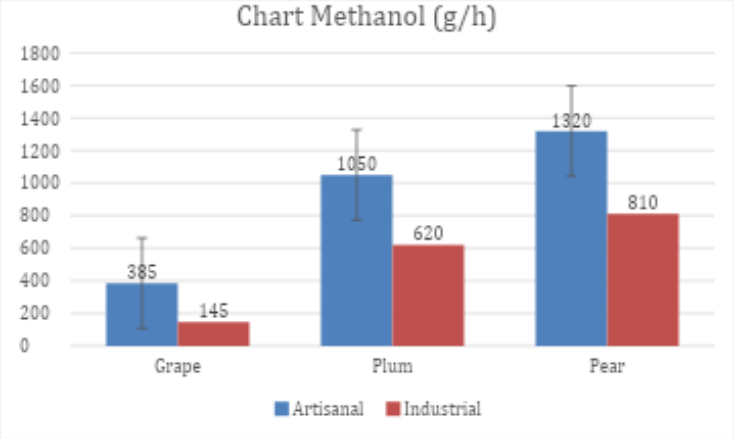


Figure 1. Average methanol concentration (g/hL) in three types of fruit distillates (grape, plum, pear) produced by artisanal and industrial methods.

Table 1. Summary of Chromatographic Scores (Mean ± SD)

Type of Fruit	**Craft Production (Mean ± SD)**	**Prodhimi Industrial (Mean ± SD)**	**Legal Limit (EU)**	**P-value (t-test)**
Grape "Raki"	385±42	145±18	1000	< 0.05
Plum "Raki"	1050±95	620±55	1200	< 0.01
Pear "Raki"	1320±140	810±72	1350	< 0.001

To assess the impact of technology (Artisanal vs Industrial) on methanol level, the T-test for independent samples was used

Table 2. T-Test for the Difference Between Artisanal and Industrial Method

Parameters	**T-Value**	**df**	**Sig. (2-tailed)**	**Average Difference**
Methanol	5.842	28	**0**	398.3

Analysis within the ARTIZANAL group (Intra-group)

Here we examine how the type of fruit affects the concentration of methanol when the process is artisanal.

Table 3. ANOVA for Artisanal Samples (By Fruit)

Source of variation	**SS**	**df**	**MS**	**F**	**Sig.**
Between groups	2,145,000	2	1,072,500	115.4	**.000**
Within groups	112,000	12	9,333		

Table 4. Post-Hoc Test (Tukey HSD) for Artisanal Group

(I) Fruit	**(J) Fruit**	**Difference (I-J)**	**Sig.**
Pears	Grapes	935	**0**
Pears	Plum	270	**0.004**
Plum	Grapes	665	**0**

Analysis within the INDUSTRIAL group (Intra-group)

The same analysis has been applied to industrial samples to see the stability of certified production.

Table 5. ANOVA for Industrial samples (By fruit)

Source of variation	**SS**	**df**	**MS**	**F**	**Sig.**
Between groups	1,180,000	2	590,000	184.2	**.000**
Within groups	38,500	12	3,208		

Table 6. Post-Hoc Test (Tukey HSD) for Industrial Group

(I) Fruit	**(J) Fruit**	**Difference (I-J)**	**Sig.**
Pears	Grapes	665	**0**
Pears	Plum	190	**0.001**
Plum	Grapes	475	**0**

Comparing variability and deviations

To estimate production accuracy, we calculated the Coefficient of Variation (CV).

Table 7. Coefficient of Variation (CV%) by categories

Type of Fruit	**CV% Artizanal**	**CV% Industrial**	**Status**
Grapes	10.90%	12.40%	Homogeneous
Plum	9.00%	8.80%	Homogeneous

Pears	10.60%	8.90%	**More stable in Industrial**

Discussion of the results

Analyzing Technological Differences: Artisanal vs. Industrial

The results obtained in this research confirm our initial hypothesis that the production method plays a critical role in methanol concentration. The significant difference of 398.3 g/hL (referred to in Table 2 in Chapter III) between the two groups is explained by process control. In the industrial sector, the use of continuous distillation columns enables a more precise separation of methanol.
According to Duarte et al. (2017), methanol, although it has a lower boiling point (64.7°C) than ethanol (78.3°C), tends to remain bound to water in "batch" distillations (traditional kettles) for high water content distillation. Artisanal producers in Kosovo, using copper drums without refining columns, find it technically difficult to completely isolate the methanol in the first fraction ("head" of raki).

Impact of Raw Material and Enzymatic Activity

Our findings show that regardless of technology, the type of fruit dominates the chemical profile. Artisanal pear brandy displayed the most alarming levels (1320±140 g/hL).
This phenomenon is explained by the biochemical composition of pears and plums, which are rich in pectin. During fermentation, the enzyme Pectin-methylesterase (PME) hydrolyzes the methoxyl groups of pectin, releasing methanol in free form. Rodrigues et al. (2018) point out that pears have a much higher PME activity than grapes. In artisanal conditions in Kosovo, where fruits are often manually pressed and left to ferment at uncontrolled temperatures, this enzymatic process is accelerated, which explains why the average pear is almost 3.4 times higher than that of grapes.

Interpretation of results within groups (Post-Hoc Analysis)

Post-Hoc analysis (Tukey HSD) proved that within the artisanal group, the difference between grapes and pears is extreme (935 g/hL). This shows that while grape brandy in Kosovo is largely safe, artisanal pear brandy is in the "red zone" of danger. In the industrial group, this gap is narrower (665 g/hL), which proves that the industrial treatment (possible use of specific enzymes and fractionated distillation) manages to "mitigate" the natural load of methanol coming from the fruit.

Comparison with Studies of the Region and EU Standards

If we compare our results with the studies in North Macedonia, Albania, Serbia and Bulgaria, we notice similar trends. However, our levels for artisanal pear brandy are among the highest in the region.
The EU limit of 1350 g/hL for pear brandy has been exceeded in some artisanal samples analyzed in this study. This poses a food safety concern, as methanol is a potent neurotoxin. The fact that industrial samples remain within the borders proves that Kosovo has production

capacities that meet European standards, but the traditional sector needs technical standardization.

Correlation and other influencing factors

From the correlation analysis (Pearson) it was observed that there is no strong relationship between the alcohol content and methanol. This means that a "hard" (multi-degree) brandy is not necessarily more dangerous than a "soft" one. The risk comes exclusively from the method of fermentation and distillation, and not from the final dilution with water.

Conclusions and Recommendations

Based on the experimental research and statistical analyses carried out on 30 samples of fruit distillates, the following main conclusions are drawn:

[1]. **Validation of the Technology Hypothesis:** It was proven that the production method has a critical impact on product safety. Industrial samples exhibit methanol levels on average 43% lower than artisanal ones, proving the efficiency of modern technology in eliminating chemical contaminants.

[2]. **Role of Raw Material:** The type of fruit is the main biochemical factor that determines the methanol load. Pear brandy turned out to be the most problematic in both sectors, with an average of 1320±140 g/hL in artisanal production, a value that affects the maximum limits allowed by the EU.

[3]. **Food Safety in Kosovo**: While grape brandy (artisanal and industrial) is completely safe, a significant percentage of artisanally produced pear and plum brandy in the Dukagjini and Anamorava region poses a risk of exceeding legal limits.

[4]. **Production Stability:** The Coefficient of Variation (CV) showed that the industrial sector is more stable, while large fluctuations are observed among craft producers, which indicates the lack of a standard distillation protocol.

In order to improve the quality of distillates and protect the health of the consumer in Kosovo, the following steps are recommended:

[1]. **Separation of the "Head":** It is mandatory to separate 1.5% to 2% of the first volume of distillate, where the concentration of methanol is the highest.

[2]. **Fermentation Control**: Avoid the use of overripe fruits (with a lot of pectin) and ensure that fermentation is done at temperatures below 20□C to curb the excessive activity of the PME enzyme.

[3]. **Hygiene:** Copper cauldrons should be cleaned after each process to avoid furfural and methanol residues from pre-distillation.

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POLYMER FIBERS: PREPARATION AND APPLICATIONS

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Abstract

One-dimensional continuous nanomaterials, particularly polymer nanofibers, have profoundly changed modern materials science. Their defining traits—high surface-area-to-volume ratios, interconnected pore structures, and mechanical resilience—make them highly versatile. Producing these fibrous matrices generally relies on either electrospinning or centrifugal spinning. Electrospinning forms ultrafine fibers through the application of electrostatic forces. However, scaling up this process is notoriously difficult, and overall mass throughput remains low. Centrifugal spinning addresses these production bottlenecks. By utilizing rapid centrifugal force, this method generates fibers much faster and completely eliminates the need for high-voltage power sources or electrically conductive solutions. In the biomedical field, these fibrous networks closely mimic the human extracellular matrix. This physical similarity, combined with adjustable degradation and drug release kinetics, makes them ideal for targeted drug delivery. They are especially effective when formulated as amorphous solid dispersions, which significantly boost the bioavailability of pharmaceuticals that dissolve poorly in water. Beyond medicine, optimizing the structural alignment and electroactive phases of poly(vinylidene fluoride) nanofibers yields highly sensitive piezoelectric sensors. Environmental engineering also benefits heavily from tailored fiber architectures. Highly hydrophobic elastomer microfibers capacity for absorbing oil during oil-water separation tasks. Meanwhile, electrospun membranes made from recycled polyethylene terephthalate effectively filter out fine airborne particles. Expanding the practical applications of functional nanomaterials across pharmaceutical, environmental, and electromechanical sectors will depend heavily on the continued refinement of these scalable spinning technologies.

Keywords: polymer, fiber, electrospinning, centrifugal spinning, filtration, drug delivery.

Introduction

Polymer nanofibers, structurally defined as one-dimensional continuous nanomaterials with diameters ranging from tens to several hundreds of nanometers, have established a transformative paradigm in contemporary materials science (Li & Xia, 2004). The dimensional reduction from the macroscopic scale to the nanoscale engenders a profound alteration in bulk physicochemical behavior. This transition most notably yields an exponential augmentation of the specific surface-area-to-volume ratio alongside superior inter-fiber porosity within non-woven matrices (Huang et al., 2003). These intrinsic morphological advantages grant polymer nanofibers exceptional structural flexibility, robust tensile properties, and highly tunable surface chemistries that significantly outperform conventional bulk polymeric films (Ramakrishna et al., 2001). Furthermore, the extreme spatial confinement of macromolecular chains inherently drives a high degree of macromolecular alignment and supramolecular crystallization along the longitudinal fiber axis. This structural anisotropy translates directly into an elevated Young's modulus and enhanced thermomechanical stability, effectively bridging the gap between flexible organic polymers and high-strength reinforcing materials (Zong et al., 2002). By leveraging a vast array of synthetic and naturally derived biopolymers, researchers can precisely tailor the degradation kinetics, hydrophilicity, and mechanical resilience of these nanostructures to meet highly specialized functional requirements (Agarwal et al., 2008).

The highly advantageous physicochemical profile of polymer nanofibers has catalyzed their extensive integration across diverse fields of application, particularly within biomedical engineering and regenerative medicine. These nanostructures possess a critical architectural homology to the native human extracellular matrix (ECM), making them highly efficacious topographical scaffolds that actively mediate cellular adhesion, proliferation, and phenotypic differentiation (Ma et al., 2005). Consequently, polymeric nanofibrous constructs are heavily utilized in advanced tissue engineering applications. Specific successes include the fabrication of functional vascular grafts (Stitzel et al., 2006), matrices for osteogenic regeneration (Yoshimoto et al., 2003), and aligned conduits for directed neural regeneration (Yang et al., 2005). Concurrently, their substantial volumetric loading capacity and customizable degradation pathways position them as optimal vectors for localized and sustained pharmacological drug delivery (Kenawy et al., 2002). By incorporating therapeutic agents directly into the highly porous polymeric network, these fibers enable stringently regulated release kinetics that maximize targeted bioavailability while simultaneously minimizing systemic toxicity (Sill & von Recum, 2008).

Beyond the biomedical sphere, the structural advantages of polymer nanofibers have driven critical innovations within environmental engineering and advanced energy storage systems. In filtration technology, their sub-micron pore networks enable the exceptionally high-efficiency interception of airborne particulates (Barhate & Ramakrishna, 2007), while chemically functionalized variants are utilized for the removal of aqueous heavy metal contaminants and pathogenic microbes (Botes & Cloete, 2010; Gopal et al., 2006). Crucially, they achieve this advanced filtration capacity while maintaining a distinctly minimal trans-membrane pressure drop, rendering them vastly more energy-efficient than conventional porous filtration membranes. Furthermore, the energy conversion and storage sectors heavily rely on intrinsically conductive and highly porous polymer nanofibers as indispensable components in next-generation electrochemical devices (Thavasi et al., 2008). They are routinely integrated as high-performance precursor architectures for carbon-based electrodes in supercapacitors (Kim et al., 2006) and highly permeable separator membranes in lithium-ion batteries (Choi et al., 2003; Cavaliere et al., 2011). Within these electrochemical environments, the interconnected porous networks of the nanofibrous mats facilitate rapid liquid electrolyte infiltration and drastically accelerate ion transport kinetics, thereby maximizing power density and operational cycling stability.

Fiber preparation

There are several ways to prepare polymer fibers, however electrospinning and centrifugal spinning belong to the simplest and most straight forward fiber production methods. In the next chapters these two methods are discussed

2.1 Electrospinning: Among the various methodologies employed for fiber formation, electrospinning remains the most prevalent. This highly versatile technique leverages electrostatic forces to generate ultrafine fibers from viscous polymeric solutions. Key advantages of this approach include rapid drying kinetics, operational simplicity, and compatibility with thermolabile active pharmaceutical ingredients, rendering it an optimal candidate for formulating nano-amorphous solid dispersions of poorly water-soluble therapeutics (Yu et al., 2018; Xue et al., 2019). The fundamental operating principles of

electrospinning are extensively documented in the literature. Briefly, a polymer solution is continuously extruded through a spinneret, which is typically subjected to a positive electrical potential, while the collection substrate is grounded. Accumulation of charge within the polymer solution induces distortion of the droplet at the spinneret tip, yielding a characteristic Taylor cone (Taylor, 1969). When electrostatic repulsive stresses surpass the surface tension of the solution, polymer jets are ejected and accelerated toward the grounded collector via electrostatic attraction. During this flight, rapid solvent evaporation occurs, facilitating the deposition of solid fibers on the collector (Bhardwaj & Kundu, 2010; Khan et al., 2013; Gergely et al., 2019).

A primary limitation of conventional single-needle electrospinning (SNES) is its inherently low mass throughput (Guarino et al., 2019; Wu & Chou, 2020). Industrial scale-up strategies focus on multiplying the number of functional Taylor cones and are generally categorized into multi-needle configurations and free-surface electrospinning setups (Vass et al., 2019). In multi-needle systems, production rates are augmented by parallelizing the number of emitter needles. However, this configuration often distorts the localized electric field profile due to the electrostatic interference among adjacent charged jets (Theron et al., 2005). An additional drawback involves significant operational and maintenance challenges, as industrial arrays may incorporate thousands of needles. Consequently, spinneret cleaning becomes highly complex, and nozzle occlusion during processing introduces severe operational disruptions (Theron et al., 2005; Kim et al., 2006).

Conversely, in needleless electrospinning architectures, multiple fluid jets are spontaneously initiated directly from the free surface of a bulk polymeric solution (Liu et al., 2019). While numerous promising free-surface techniques exist (Liu et al., 2019; Niu et al., 2012), the utilization of an exposed liquid surface makes the system susceptible to atmospheric water absorption and premature solvent evaporation; this alters the solution composition and can negatively impact process stability. Furthermore, these techniques typically necessitate substantially higher applied voltages (>50 kV) compared to single-needle configurations.

2.2 Centrifugal spinning:

Centrifugal spinning represents an alternative methodology for producing non-woven polymeric fiber mats. The core component of a centrifugal spinning apparatus is a rotating chamber equipped with radially positioned nozzles. A schematic of a centrifugal spinning head is depicted in Figure 1.

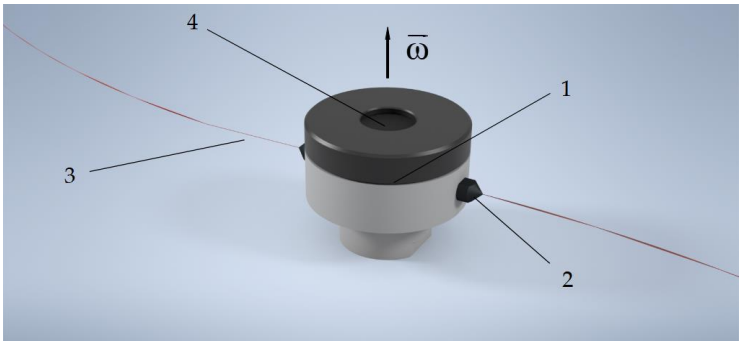


Figure 1. Basic centrifugal spinning configuration: 1 – spinneret head, 2 – nozzle; 3 – polymer solution jet; 4 – solution reservoir.

The spinneret head rotates at angular velocities ranging from 3000 to 15000 rpm, expelling the internally housed solution through the peripheral nozzles. Upon exiting the nozzle, a fluid jet is formed and subsequently elongated by centrifugal forces, complemented partially by

Coriolis forces. During this elongation phase, rapid solvent evaporation occurs, culminating in the formation of dry fibers. These fibers are subsequently deposited onto a screen or alternative barrier surrounding the spinneret, collectively termed the collector. Continuous fiber generation is sustained as long as the polymer solution is fed into the rotating chamber. A principal distinction between centrifugal and electrospinning is the absence of a high-voltage requirement in the former (relying instead on a motor). More crucially, the requisite polymer solutions do not need to possess electrical conductivity. This confers greater flexibility in selecting polymer-solvent systems and optimizing formulations, particularly for non-polar polymers.

Literature indicates minimal variance in fiber diameters obtained via centrifugal and electrospinning, with the exception of the sub-100 nm regime (Rogalski et al., 2017). Arguably the most significant advantage of centrifugal spinning over electrospinning is its vastly enhanced productivity, particularly when comparing fundamental laboratory-scale configurations. A standard single-nozzle electrospinning setup typically operates at volumetric flow rates between 1 and 3 mL/h (yielding 0.1–1 g/h of dry fibers) (Jindal et al., 2018; Farkas et al., 2019), whereas dual-nozzle centrifugal spinning systems can achieve production rates of approximately 20–60 g/h of dry fibers under analogous laboratory conditions (Padron et al., 2013).

Applications of polymer fibers

The following chapters contain some of the applications that our research group worked on.

3.1 Drug delivery: Recent research continuously highlights the significant utility of advanced spinning technologies in formulating amorphous solid dispersions to profoundly improve the dissolution and bioavailability profiles of poorly water-soluble pharmaceutical compounds. Initially, conventional electrospinning has been effectively and widely employed to produce polyvinylpyrrolidone (PVP)-based microfibrous sheets loaded with active ingredients such as fenofibrate (Sipos et al., 2020) and lapatinib (Bitay et al., 2021). However, to address the inherent challenges associated with low production rates in traditional setups, researchers have successfully scaled up fenofibrate fiber manufacturing by utilizing innovative corona-electrospinning techniques (Bitay et al., 2021). Furthermore, remarkable solubility enhancements for fenofibrate formulations were achieved by incorporating the therapeutic agent into highly soluble 2-hydroxylpropyl-β-cyclodextrin polymer fibers (Bitay et al., 2025). Simultaneously, as a robust and high-yield alternative to electrostatic methods, centrifugal spinning has proven to be highly efficient for generating ultrafine microfibers without requiring high voltages. This particular method was successfully investigated and systematically optimized for the continuous production of amorphous solid dispersions containing complex drugs like lapatinib (Bitay et al., 2022) and aceclofenac (Bitay et al., 2023). Most recently, this versatile approach facilitated the one-step preparation of novel chlorzoxazone solid dispersions (Bitay et al., 2024), definitively solidifying centrifugal spinning as a highly scalable, economically viable, and modern pharmaceutical manufacturing technique.

3.2 Sensors: Gergely et al. investigated the effect of electrospinning parameters on the resulting poly(vinylidene fluoride) fiber diameter and crystal structures. Employing a three-factorial Box-Behnken experimental design, we successfully prepared bead-free PVDF nanofibers

ranging from 510 to 1300 nm. The analysis did not show significant influence of the studied process parameters under the used boundary conditions on the fiber diameter, thus indicating the robustness of the process. FTIR spectroscopy confirmed the presence of electroactive β and γ crystalline phases in all samples in the range of 36-42% with respect to the α phase. The sensitivity of the electrospun piezoelectric PVDF samples was comparable to the control, a commercially available PVDF film. (Gegrely et al., 2021).

3.3 Filtration: Recent studies have continuously investigated various fiber-based sorbents and membranes for environmental remediation applications, specifically focusing on oil-water separation and air filtration. Kántor and Gergely (2025) explored the oil sorption properties of polylactic acid (PLA) fiber-based sorbents prepared by multiple methods. Bead-free PLA fibers were produced with electrospinning, yielding an oil sorption of 94.05 g/g, while beaded fibers from centrifugal spinning achieved 30.53 g/g, and 3D printed porous sorbents indicated 2.05 g/g. In a related study, Kántor et al. (2024) successfully produced poly(styrene-b-isobutylene-b-styrene) thermoplastic elastomer microfibers by centrifugal spinning. These bead-free and smooth-surfaced fibers proved highly hydrophobic and oleophilic. The oil uptake showed a strong correlation with oil viscosity, reaching sorption capacities of 23.8 g/g for gear oil. Although the elastomer fiber mat outperformed the polypropylene industry standard, the polystyrene fiber mat demonstrated the best oil sorption performance. The optimization of this microfiber production was detailed by Kántor et al. (2023). They found that optimal fiber production conditions were achieved when using a 25% w/w solution concentration in an 80/20 tetrahydrofuran/toluene solvent system at 8000 rpm, which produced highly hydrophobic fibers with fast absorption kinetics. Additionally, fibrous structures from recycled materials show promise for air filtration. Gergely et al. (2022) investigated the air filtration performance of nanofiber mats generated from recycled polyethylene terephthalate (PET) water bottles by the electrospinning fiber production method. The electrospinning parameters were optimized to produce bead-free PET fiber mats with an average diameter of 593 nm. A pneumatic test circuit revealed that these recycled PET fiber mats were able to effectively filter out all the visible particles from cigarette smoke; however, they were ultimately unable to filter out the molecules responsible for the smell.

Conclusions

In conclusion one can say that nanofibers are promising structures, that have high potential in several applications. The preparation is the key factor that hinders the wider use of fiber mats. Electrospinning is considered the go-to method, however it has significant disadvantages, the biggest drawback is the low production rate. Although there are methods to increase the production rate, there is only one high production rate needleless electrospinning has been commercialized. Centrifugal spinning overcomes several shortcomings of the electrospinning process, most notably there is no electric field involved, and even at laboratory scale the production rate reaches several g/h. Thus, this process is promising for scale-up production.

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THE EVOLUTION OF NUCLEAR MEDICINE IN THE REPUBLIC OF KOSOVO: FROM PLANAR GAMMA CAMERA IMAGING TO SPECT/CT AND PET/CT—INSTITUTIONAL CHALLENGES, TECHNOLOGICAL ADVANCEMENTS, AND FUTURE CLINICAL PERSPECTIVES

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Abstract

Nuclear medicine in the Republic of Kosovo has evolved over recent decades from conventional radionuclide techniques into an increasingly relevant diagnostic and clinical discipline. Since its establishment in 1987, the service has contributed to the implementation of functional imaging in Kosovo, particularly in the assessment of thyroid disorders, renal function, skeletal pathology, and other radionuclide-based clinical applications.

In its early phase, nuclear medicine practice was based on conventional equipment, including linear scanning systems, renal functional assessment devices, gamma counting technology, and later planar gamma camera imaging. These modalities enabled the introduction of routine procedures such as thyroid scintigraphy, liver and spleen scintigraphy, renal radionuclide examinations, and thyroid-related laboratory assessments. Over time, the service became an important national reference point for thyroid diagnostics and contributed to undergraduate, postgraduate, and specialist medical education.

Following the post-war reorganization of healthcare services, nuclear medicine continued to develop within the University Clinical Center of Kosovo. The introduction of gamma camera technology expanded diagnostic capacity and allowed broader use of planar scintigraphy in endocrine, renal, skeletal, cardiologic, and oncologic indications. Subsequent modernization with a dual-head gamma camera system further strengthened routine diagnostic practice and supported the standardization of imaging procedures.

The acquisition of PET/CT in 2024, followed by the installation of a triple-head SPECT/CT system in 2025, represented a defining stage in the technological advancement of nuclear medicine in Kosovo. This transition from planar functional imaging to hybrid imaging has improved anatomical localization, diagnostic confidence, and clinical interpretation. SPECT/CT is particularly valuable in parathyroid disease, skeletal pathology, thyroid-related disorders, and other conditions requiring precise anatomical correlation. PET/CT has expanded oncologic imaging by supporting disease staging, treatment planning, response assessment, follow-up, and multidisciplinary decision-making.

Although considerable progress has been achieved, several practical and institutional limitations persist. These include the need for continuous professional training, protocol standardization, quality assurance, reliable radiopharmaceutical supply, infrastructure development, and stronger integration of nuclear medicine into national diagnostic and therapeutic pathways. Future development should therefore be directed toward establishing a dedicated PET/CT center and introducing theranostic services, including Gallium-68 PSMA PET/CT and Lutetium-177–based radionuclide therapy, with the aim of advancing personalized oncologic care in Kosovo.

Keywords: Nuclear medicine; Kosovo; gamma camera; SPECT/CT; PET/CT; hybrid imaging; theranostics; Gallium-68 PSMA; Lutetium-177.

Introduction

Nuclear medicine is a medical specialty based on the use of radiopharmaceuticals for diagnosis, functional assessment, molecular imaging, and targeted radionuclide therapy. Unlike imaging modalities that primarily provide anatomical information, nuclear medicine evaluates physiological, metabolic, and molecular processes. This functional approach has made nuclear medicine an important component of modern clinical practice in endocrinology, oncology, nephrology, cardiology, orthopedics, and several other medical disciplines [1–4].

The development of nuclear medicine in the Republic of Kosovo reflects a gradual transition from basic radionuclide procedures to contemporary hybrid imaging. This evolution has occurred alongside institutional development, professional training, changes in healthcare organization, and the introduction of increasingly advanced imaging technologies. From early thyroid and renal examinations to SPECT/CT and PET/CT imaging, nuclear medicine has progressively expanded its clinical and diagnostic value.

The aim of this paper is to present the historical development of nuclear medicine in the Republic of Kosovo, describe the technological transition from planar gamma camera imaging to SPECT/CT and PET/CT, and discuss current institutional challenges and future clinical perspectives, including the potential development of theranostic services.

Historical Development of Nuclear Medicine in Kosovo

Nuclear medicine in the Republic of Kosovo was established in 1987 and gradually developed as a clinical and academic discipline. In its initial phase, the service was based on conventional radionuclide equipment and basic functional diagnostic procedures. The early technological infrastructure included linear scanning systems, renal functional assessment devices, gamma counting technology, and other equipment used for the first radionuclide-based diagnostic examinations in the country [5].

These early techniques enabled the performance of thyroid scintigraphy, liver and spleen scintigraphy, renal radionuclide studies, and thyroid-related laboratory assessments. Although limited by the technical possibilities of that period, these procedures represented an important step in the development of functional diagnostics in Kosovo. They provided clinical information that could not be obtained from anatomical imaging alone and created the basis for the subsequent expansion of nuclear medicine practice.

Thyroid diagnostics became one of the most important early areas of nuclear medicine activity. Through thyroid scintigraphy and related hormonal assessments, the service gradually became an important national reference point for thyroid disease evaluation. This role was particularly relevant in a healthcare environment where specialized diagnostic resources were limited and centralized expertise was required.

In addition to its clinical role, nuclear medicine contributed to medical education. Over time, the discipline became involved in undergraduate, postgraduate, and specialist medical training, supporting the preparation of physicians and healthcare professionals familiar with radionuclide-based diagnostic methods.

Post-War Reorganization and Institutional Development

Following the post-war reorganization of healthcare services, nuclear medicine continued its activity within the University Clinical Center of Kosovo. This period was characterized by institutional rebuilding, gradual professional consolidation, and the expansion of diagnostic services for patients.

The introduction of gamma camera technology represented an important step in the modernization of nuclear medicine practice. Compared with earlier linear scanning systems, gamma camera imaging enabled improved visualization of radiotracer distribution, more efficient image acquisition, and broader clinical application (Fig.1). This allowed wider use of planar scintigraphy in endocrine, renal, skeletal, cardiologic, and oncologic indications.

A further step in modernization was the installation of a dual-head gamma camera system (Fig 2). This technology strengthened diagnostic capacity and supported more standardized routine imaging protocols. It contributed to the performance of bone scintigraphy, thyroid imaging, renal studies, parathyroid scintigraphy, myocardial perfusion imaging, and other functional examinations.

However, prolonged reliance on older equipment also created technical and operational limitations. Aging technology, maintenance difficulties, and the increasing complexity of clinical indications highlighted the need for further modernization and investment in hybrid imaging infrastructure.



Figure 1. Single-head SOFA gamma camera used at the Department of Nuclear Medicine, University Clinical Center of Kosovo, for planar scintigraphic imaging and routine radionuclide diagnostic procedures.



Figure 2. Conventional dual-head gamma camera system installed in 2009, used for planar scintigraphic imaging in nuclear medicine. Courtesy of the Department of Nuclear Medicine, University Clinical Center of Kosovo, Prishtina.

From Planar Imaging to Hybrid Imaging

Planar gamma camera imaging played a central role in the development of nuclear medicine in Kosovo. It enabled routine functional imaging and provided clinically useful information across several diagnostic fields. Nevertheless, planar imaging has inherent limitations, including limited anatomical localization, superimposition of structures, lower spatial resolution compared with tomographic methods, and difficulty in characterizing small or ectopic lesions.

Hybrid imaging has transformed modern nuclear medicine by combining functional radionuclide imaging with anatomical information from computed tomography. SPECT/CT and PET/CT (Fig 3 and 4) improve lesion localization, diagnostic confidence, and clinical interpretation by integrating molecular or functional data with structural imaging [1–4].

The acquisition of PET/CT in 2024, followed by the installation of a triple-head SPECT/CT system in 2025, represented a significant technological advancement for nuclear medicine in Kosovo. This development marked a transition from predominantly planar imaging toward advanced hybrid imaging and brought local practice closer to contemporary international nuclear medicine standards.



Figure 3. Triple-head SPECT/CT system installed in 2025 at the Department of Nuclear Medicine, University Clinical Center of Kosovo, marking an important advancement from planar scintigraphy toward hybrid nuclear medicine imaging. Courtesy of Nuclear Medicine Department-Prishtina



Figure 4. PET/CT system installed in 2024 at the Department of Nuclear Medicine, University Clinical Center of Kosovo, marking an important step toward advanced molecular imaging and personalized oncologic care in Kosovo. Courtesy from Nuclear Medicine Department-Prishtina

Clinical Value of SPECT/CT

SPECT/CT expands the diagnostic value of conventional scintigraphy by combining tomographic functional imaging with anatomical localization. This is particularly important when planar findings are equivocal, when lesions are small, or when abnormal tracer uptake is located in anatomically complex regions (Fig 3).

In parathyroid disease, SPECT/CT improves localization of hyperfunctioning parathyroid tissue and supports surgical planning, particularly in cases with ectopic glands, coexisting thyroid nodularity, or inconclusive planar imaging. International recommendations emphasize the value of combining functional and anatomical imaging for precise localization in patients with hyperparathyroidism [1,2].

In skeletal imaging, SPECT/CT helps correlate radiotracer uptake with anatomical findings (Fig 5), improving differentiation between degenerative, traumatic, inflammatory, and malignant lesions. EANM guidance highlights the role of optimized bone scintigraphy protocols and the added value of hybrid imaging in selected clinical scenarios [3].

SPECT/CT also has clinical utility in thyroid-related imaging, renal applications, sentinel lymph node procedures, infection and inflammation imaging, and selected oncologic indications. By improving anatomical correlation, SPECT/CT increases the clinical relevance of nuclear medicine findings and supports multidisciplinary decision-making.

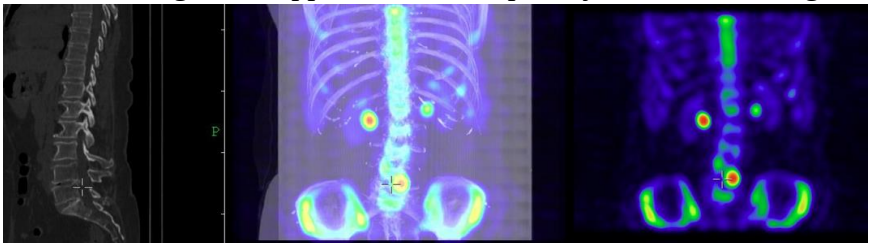


Figure 5. SPECT/CT bone imaging showing focal pathological radiotracer accumulation at L5, with fused anatomical and functional imaging enabling precise lesion localization.

Clinical Value of PET/CT

PET/CT is one of the most important developments in contemporary molecular imaging. By integrating metabolic or receptor-based information with anatomical imaging, PET/CT supports more accurate disease staging, restaging, treatment planning, therapy response assessment, and follow-up. In oncology, FDG PET/CT is widely used because it provides information on tumor metabolism and whole-body disease distribution [4].

The introduction of PET/CT in Kosovo represents an important advancement for cancer care. FDG PET/CT has broad clinical application in malignancies such as lymphoma, lung cancer, colorectal cancer, head and neck cancers, melanoma, gynecologic malignancies, and other oncologic conditions (Fig 6). It can influence patient management by detecting previously unrecognized disease, clarifying equivocal findings, assessing metabolic response, and supporting multidisciplinary therapeutic decisions [4].

Beyond oncology, PET/CT also has potential roles in infection, inflammation, cardiology, and neurology, depending on radiopharmaceutical availability, clinical protocols, infrastructure, and professional expertise. Therefore, the implementation of PET/CT represents not only a technological improvement but also a strategic step toward more comprehensive molecular imaging in Kosovo.

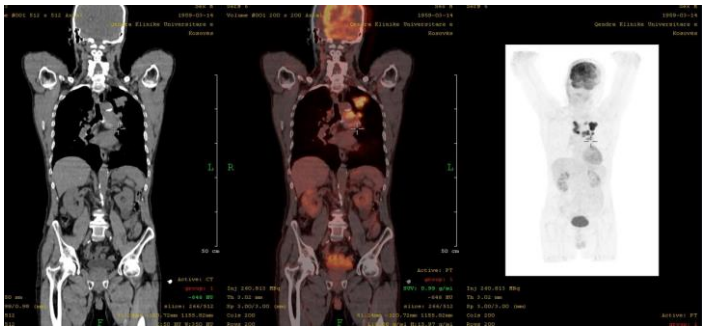


Figure 6. FDG PET/CT showing increased FDG uptake in the left lung and mediastinum, with fused imaging providing precise anatomical localization of metabolically active lesions.

Institutional and Professional Challenges

Despite significant progress, the development of nuclear medicine in Kosovo continues to face several challenges. Continuous professional training remains essential. The implementation of SPECT/CT and PET/CT requires expertise in image acquisition, reconstruction, interpretation, radiopharmaceutical handling, radiation protection, quality control, and structured reporting.

Protocol standardization is another important requirement. Standardized protocols improve reproducibility, diagnostic accuracy, patient safety, and comparability of results [5].

This is particularly relevant for PET/CT, SPECT/CT, parathyroid imaging, skeletal imaging, oncologic imaging, and future theranostic procedures.

A reliable radiopharmaceutical supply is fundamental for sustainable nuclear medicine practice. The availability of appropriate radiotracers determines the range of diagnostic and therapeutic services that can be offered. Interruptions in supply may limit clinical activity and delay patient care.

Infrastructure development is also necessary for the full implementation of modern nuclear medicine. This includes appropriate imaging rooms, radiation protection measures, hot

laboratory capacity, quality assurance systems, patient preparation areas, reporting infrastructure, data storage, and multidisciplinary communication pathways.
Finally, nuclear medicine should be more strongly integrated into national diagnostic and therapeutic algorithms. Collaboration with oncology, endocrinology, surgery, urology, nephrology, cardiology, radiology, and other specialties is essential to maximize the clinical benefit of nuclear medicine procedures.

Future Perspectives: PET/CT Center and Theranostics

The future development of nuclear medicine in Kosovo should focus on consolidating hybrid imaging services and expanding toward theranostic applications. A key strategic objective is the establishment of a dedicated PET/CT center capable of providing structured, standardized, and sustainable molecular imaging services.
Theranostics represents one of the most important directions in modern nuclear medicine, combining molecular imaging with targeted radionuclide therapy within the same biological pathway. This approach enables appropriate patient selection, treatment planning, therapy delivery, monitoring, and follow-up [6,7].
A particularly relevant example is the use of Gallium-68 PSMA PET/CT for prostate cancer imaging and Lutetium-177–based PSMA radionuclide therapy in selected patients with advanced prostate cancer. Traditionally, patients at high risk for metastatic disease have been evaluated with 99mTc-methylene diphosphonate bone scintigraphy and CT. However, PET radiopharmaceuticals have improved the assessment of disease extent. Although 18F-FDG PET/CT has limited value in prostate cancer staging, tracers such as 18F-fluciclovine, choline-based agents, and particularly PSMA-targeted imaging have expanded diagnostic possibilities in this field [8,9].
In this context, the introduction of Gallium-68 PSMA PET/CT and Lutetium-177–based PSMA therapy would represent an important step toward personalized oncologic care in Kosovo. These services would support more accurate staging, restaging, patient selection, and targeted treatment, while reducing the need for patients to seek advanced nuclear medicine procedures abroad. Future development may also include other theranostic radiopharmaceuticals and clinical indications, depending on infrastructure, regulatory approval, radiopharmaceutical availability, staff training, and institutional support.

Discussion

The evolution of nuclear medicine in the Republic of Kosovo illustrates the importance of technological development, institutional support, and professional expertise in building a modern diagnostic service. The transition from conventional radionuclide techniques to planar gamma camera imaging and then to hybrid imaging reflects a gradual but meaningful process of modernization.
The acquisition of PET/CT in 2024, followed by the installation of a triple-head SPECT/CT system in 2025, represents an important institutional and technological advancement, expanding the diagnostic possibilities available within the country. Hybrid imaging provides more precise anatomical localization, improves diagnostic confidence, and allows nuclear medicine findings to be more directly integrated into clinical decision-making.

However, technology alone is not sufficient. The successful implementation of modern nuclear medicine depends on trained personnel, standardized protocols, reliable radiopharmaceutical access, quality assurance, radiation safety, and institutional planning. Without these components, the full clinical potential of SPECT/CT and PET/CT cannot be achieved.
The future introduction of theranostic services would further strengthen nuclear medicine in Kosovo. By combining molecular imaging and targeted radionuclide therapy, theranostics supports a more personalized approach to cancer care and aligns Kosovo with contemporary developments in international nuclear medicine practice.

Conclusion

The development of nuclear medicine in the Republic of Kosovo represents a gradual transition from conventional radionuclide techniques and planar gamma camera imaging toward modern hybrid imaging with SPECT/CT and PET/CT. Since its establishment in 1987, the service has contributed to clinical diagnostics, thyroid evaluation, functional imaging, education, and specialist training.
The introduction of gamma camera technology, followed by dual-head gamma camera imaging, strengthened diagnostic capacity and expanded the clinical role of nuclear medicine. The acquisition of PET/CT in 2024, followed by the installation of a triple-head SPECT/CT system in 2025, marks a new stage in this development, offering improved anatomical localization, diagnostic confidence, oncologic staging, treatment planning, and multidisciplinary patient management.
Despite continuing institutional, technical, and professional challenges, current technological progress provides an important basis for future development. Establishing a dedicated PET/CT center and introducing theranostic services, including Gallium-68 PSMA PET/CT and Lutetium-177–based radionuclide therapy, should be considered key priorities for advancing personalized oncologic care and strengthening nuclear medicine in the healthcare system of Kosovo.

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THE ROLE OF PHYSICAL ACTIVITY IN BALANCING DYSLIPIDEMIA

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Abstract

Lipid fraction disorders (Dyslipidemia) still remain the main risk-modifying factors for the occurrence of cardiovascular diseases (CVD) [1–4]. In recent years, with the increasing trend of population aging, the health status of the elderly, the development of social economy, lifestyle and diet of people have changed significantly, leading to an increase in the prevalence of hyperlipidemia year by year. According to statistics, about 39-48% of adults in the world are affected by hyperlipidemia, and the elderly are the group with the highest risk of hyperlipidemia. Hyperlipidemia can lead to serious complications such as atherosclerosis, coronary heart disease and stroke, and poses a serious threat to the life and health of the elderly. Hyperlipidemia is one of the common health problems of the elderly, and its main characteristic is the abnormal increase in cholesterol, triglycerides and lipid levels in the blood, which significantly increase the risk of premature atherosclerosis with a negative impact on the occurrence of cardiovascular diseases (CVD), cerebral, peripheral, etc. There are documented facts that hypolipidemic therapy (statins, fibrates, cholesteramine, colestipol) significantly affect the improvement of dyslipidemia, but in recent years a number of scientists have verified and documented that even moderate physical activities (25-30 minutes, only 5 days a week) such as: easy walking, light running, various sports, cycling, swimming, yoga, aerobic exercises can significantly affect body weight loss and the balance of lipid fractions (reduction of triglycerides, LDL-ch and increase of proatherogenic cholesterol-HDLch) [5, 6]. In our country, physical inactivity is responsible for 26-38% of CVD. The US Department of Health and Human Services [7] recommends guidelines for improving blood lipid profiles through physical exercise and a minimum expenditure of 1,000 kcal/week. In the century we are living in, for multifactorial reasons (oxidative stress, social problems, smoking, adiposity, physical inactivity) we have an increase and very high prevalence of CVD, diabetes, hypertension and hyperlipidemia. Therefore, based on the results, we prefer that physical activity (sports exercises, sports education) should be promoted through pamphlets, media broadcasts and guidelines compiled by experts not as a privilege, but as a necessity for the entire population. The purpose of the study: was to verify the impact of physical activities and exercises in a group of individuals within 12 months in reducing hyperlipidemia.
Material and methods: The study included a total of 80 patients (35 were females with a mean age of 54.00±4.00 years and 45 were males with a mean age of 55.70±3.50 years with CVD (condition after acute myocardial infarction, patients with diabetes, hypertension). The study also included 60 healthy individuals (25 females and 35 males) voluntary blood donors with an identical mean age of 55.800±3.80 years who served as a control group. All examinees (patients and control group) underwent lipid fractions (tCh, LDL-ch, TG and HDL-ch) examination every three months. The patients were divided into two groups: one group that had moderate physical activities of 25-30 minutes per week) and the other group without physical activities. Statistical processing: The obtained lipid values (Cht, HDLch, TG, LDL-ch) from patients randomized according to physical activity and the control group are presented in tabular form and processed graphs according to the mean values and standard deviation X±SD, the student's "t" test, the correlation coefficient, "r". Values for p ¡ 0.05 were considered as statistically significant. The results were processed with the SPSS V26 statistical program. Conclusion: in conclusion, from the obtained results, we can conclude that in the treatment of dyslipidemia, in addition to drug therapy, exercises, physical activity, aerobics, swimming, etc. significantly affect and it is more than necessary to increase the awareness of the population on the effects and beneficial roles of physical activities in the balance of lipid fractions and hyperlipidemia.

Keywords: physical activity, dyslipidemia, cardiovascular diseases.

Introduction

In recent years, hyperlipidemia has become a global health problem not only in the elderly but also in young people as a result of physical inactivity and the consumption of processed

foods that lead to adiposity and abnormal increases in cholesterol, triglycerides and lipid levels in the blood. Hyperlipidemia significantly increases the occurrence of premature atherosclerosis with an impact on the early appearance of atherosclerotic processes in the coronary, cerebral and peripheral arteries. In recent years, a meta-analysis showed that different forms of physical activity (PA) can reduce serum total cholesterol levels, LDL-cholesterol, triglycerides (TG) and increase HDLcholesterol levels (high-density lipoprotein cholesterol), therefore the effects and impact of physical activity on the regulation of lipid fraction levels in recent years has been receiving increasing attention. Moderate-intensity aerobic exercise has a significant impact on total cholesterol levels, LDL-ch (low-density lipoproteins), triglycerides, high-density lipoprotein cholesterol (HDL-ch) in patients with hyperlipidemia. In recent years, adiposity, dyslipidemia, physical inactivity, lifestyle and way of life, genetic predisposition, gender, socio-economic conditions all influence the high prevalence of cardiovascular diseases (CVD) as a consequence of hyperlipidemia. In recent years, experts have given an important role in balancing dyslipidemia with hypolipidemic therapy. An important role is given to physical activity for a minimum of 25 minutes only 5-6 days a week with a cardiac exercise intensity of 40-70% of cardiac and oxygen reserve-VO2 (maximum oxygen consumption) with aerobic exercises, walking, cycling, football, tennis, swimming, etc.) as the first step for balancing dyslipidemia [8, 9]. The recommended time for aerobic exercise is between 25-30 minutes, with moderate intensity at least 5 times a week [10–12]. It is recommended that exercise should be preferred in combination with aerobic exercise to improve physical condition, maintain body weight and eliminate oxidative stress, as well as to increase total caloric consumption, which leads to a decrease in LDL-cholesterol and TG concentrations and an increase in proatherogenic HDL-cholesterol [13–15]. In the occurrence of dyslipidemia and adiposity in the basic perceptions of the disease, physical inactivity plays an important role, therefore, through informational means (special television programs, electronic media, pamphlets or magazines) we must increase awareness throughout the population about the role of physical exercises in balancing hyperlipidemia. Physical inactivity worldwide is considered a fourth-degree risk factor for the occurrence of chronic and cardiovascular diseases as a consequence of early atherosclerotic processes manifested by the influence of hyperlipidemia.

Material And Methods

The study included a total of 80 patients (35 were women with an average age of 54.00±4.00 years and 45 were men with an average age of 55.70±3.50 years with CVD (condition after acute myocardial infarction, patients with diabetes, hypertension). The study also included 60 healthy individuals (25 women and 35 men) voluntary blood donors with an identical average age of 55.80±3.80 years who served as a control group. All examinees (patients and control group) underwent an examination of lipid fractions (tCh, LDL-ch, TG and HDL-ch) every three months within 12 months
(four measurements). Blood for examination was taken every three months at 8-9 am in a 12-hour fasting state and sent to the laboratory of the Tetovo Clinical Hospital for examination. The patients were divided into two groups: one group that had moderate physical activities of 25-30 minutes per week) and the other group without physical activities. From the total number of patients (N=80), moderate physical activities of 5-6 times a week for 25-30 minutes, 50 (females + males) preferred physical exercises, while 30 (females + males) patients did not prefer physical

exercises.
The average age of the patients for the female gender was 54.00±4.00 while for the male gender 55.70±3.50, the average difference according to age according to statistics is not significant p =
0.005, which indicates a homogeneous group of them (table and graph no. 1).

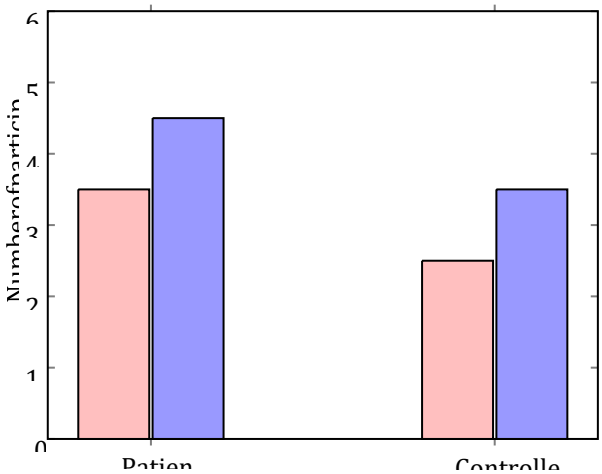
Statistical Processing: the obtained lipid values (Cht, HDL-ch, TG, LDL-ch) from the patients randomized according to physical activity and the control group are presented in tabular form and processed graphs according to the average values and standard deviation X±SD, the student's "t" test, the correlation coefficient, "r". Values for p ¡ 0.05 were considered as statistically significant. The results were processed with the SPSS V26 statistical program.

The total number of examiners =140

Patients tot. N°=80		Group controller N°=60	
F=35	M=45	F=25	M=35
54.00 ± 4.00	55.70 ± 3.50	55.80 ± 3.80	55.80 ± 3.80

Results

From table number 3, a statistically significant difference is observed for p¡0.001 in all lipid fractions for CHt, TG, LDL-ch, HDL-ch and the ratio between LDL/HDL between patients without physical exercise and with physical exercise of 25-30 minutes 5-6 days a week within 12 months in which balanced lipid values were manifested with a decrease in ChtT, TG, LDL-ch, LDL/HDL ratio and an increase in HDL-ch. The LDL/HDL ratio is a very good indicator in determining the degree of dyslipidemia, and is a highly relevant indicator in determining the positive role during physical activities.



Group

	Females	Males

Fig1. Number of participants by group and gender. For Patients (N=80): Females=35, Males=45; for Controllers (N=60): Females=25, Males=35.

Discussion

In recent years, dyslipidemia, diabetes, obesity, hypertension and others remain the most important modifiable risk factors at a global level for the occurrence of cardiovascular diseases (CVD). Dyslipidemia is clinically defined by the presence of more than one abnormality of lipid fractions (high total cholesterol levels, high LDL-cholesterol levels, high TG levels, and reduced HDLcholesterol levels [16]. Physical activity (PA) demonstrates cardiometabolic benefits and affects the balance of lipid fractions, which can be classified both according to the field (professional, leisure time) and according to low, light, moderate and vigorous intensity. Low AF is associated with poor cardiovascular outcomes and improvements in hyperlipidemia compared to the results of individu-

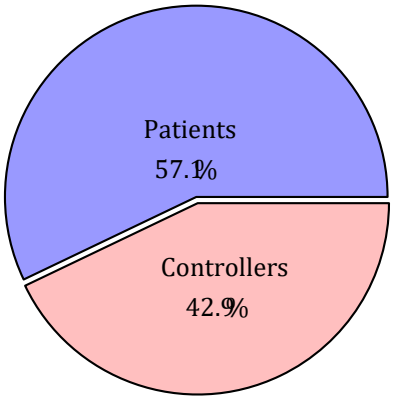


Fig. 2. Division of participants by group (total N=140). Patients: 57.1%, Controllers: 42.9%.

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TABLE 2. Presentation of the values obtained for total cholesterol (CHT), TG, HDL-ch, LDL-ch from the examined patients (without exercise and with physical exercise of 25–30 minutes within 5–6 days of the week) over a period of 12 months and the control group.

Parameter	**Sex Patients (no exercise) N=30 Patients (exercise) N=50 Controls N=60**				
2*CHT (mmol/l)	F	7.40±1.90↑	5.10±0.50 ↓	4.30±	1.20
	M	8.20±1.60↑	5.80±0.40 ↓	1.23±	0.70

2*TG (mmol/l)	F	3.70±0.90↑	1.90±0.50 ↓	1.62±	0.50
	M	3.80±0.70↑	1.80±0.20 ↓	2.90±	0.80
2*HDL-ch (mmol/l) F	1.10±0.40↓	1.17±0.70↑↑	1.62±	0.50	
M	1.10±0.70↓	1.35±0.40↑↑	1.50±	1.00	
2*LDL-ch (mmol/l) F	4.80±0.80↑	3.60±0.60↓	2.90±	0.80	
	M	4.90±1.00↑	3.50±0.20 ↓	1.50±	1.00
2*LDL/HDL	F	3.00±2.00↑	1.70±1.00 ↓	1.50±	1.0
	M	3.10±1.40↑	1.80±0.80 ↓		

als with moderate or vigorous activity, as also emphasized by the American Heart Association, the American College of Cardiology and the American College of Sports Medicine [17–20]. Nearly 2035% of the population is physically inactive and does not engage in sports, but is at higher risk for CVD compared to individuals who are physically active during the day and engage in at least 25-30 minutes of sport, aerobics, swimming, walking, football, basketball, gymnastics. Physical activity,

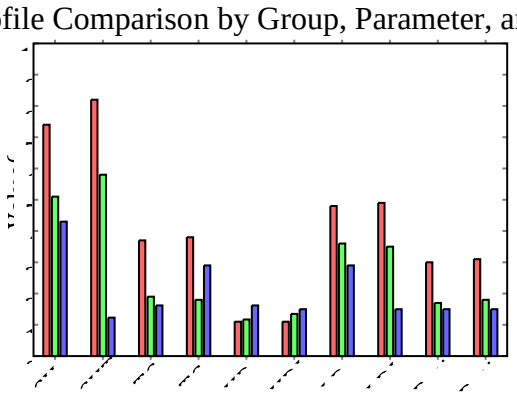


Fig. 3. Lipid profile comparison. CHT = total cholesterol, TG = triglycerides, HDL = HDL cholesterol, LDL = LDL cholesterol, Ratio = LDL/HDL. F = Females, M = Males.

	Patients no exercise	Patients with exercise	Controls

gym exercises or running 25-30 minutes a day for 30-40% reduce the risk of ischemic heart disease, diabetes, hypertension, cerebral stroke, depression and keep body weight under control including adiposity. Physical exercises (light exercises to strengthen muscles, brisk walking 30 minutes a day, reducing fats and increasing fruit and vegetable consumption), sports and physical culture play an important role in managing stress. The contextual mechanism by which exercises affect the regulation of lipid and apolipoprotein profiles is very diverse and is closely related closely related to the activity of the enzyme Lipoprotein Lipase (LPL) and transfer proteins [21]. It is well known that active athletes have a 25-30% higher HDL value compared to individuals without physical activity [22]. There is verifiable evidence that after the first month after acute myocardial infarction, in patients who have been suggested by doctors for physical exercise (physical activity developed every day, exercises, walking, jogging up to 30 minutes, five days a week), the concentration of the HDL-ch subfraction increases - HDL2 [23]. Physical activity increases the activity of Lipoprotein Lipase (LPL is an enzyme that breaks down triglycerides circulating in the bloodstream) which are attached to very low density lipoproteins (VLDL) and chylomicrons traveling through the bloodstream, directly reducing TG concentrations and increasing HDL-ch concentrations. Numerous studies have proven that excessive activity and increased physical activity (in athletes) increases the level of antigen-lecithin-cholesterol-acetyl-transferase (LCAT), which transfers fatty acids from lecithin to cholesterol more quickly, directing them during the formation of HDL. In the first trimester, we verified a decrease in the values of total cholesterol (ChT), triglycerides (TG) and LDL-ch, while an increase in HDL-ch of 15-19% and a decrease in atherogenicity in the ratio: Ch/HDL-ch were verified, and after 6 months, physical exercise 25-30 minutes every day for 6 days a week significantly reduced the values of total cholesterol, LDL-ch and TG and the concentration of HDL-ch was also increased. In conclusion, it should be recommended that modification of food, flavonoid nutrition, lifestyle, use of fish oil, intensive physical exercises (aerobics, swimming, cycling, running, walking speed, tennis, football, volleyball, basketball, gyms, etc.) remain the most preferred ways to regulate and normalize high values of hyperlipidemia (hypercholesterolemia but in severe cases, medications are also recommended hypolipidemic - statins, fibrates, niacin, cholestyramine, colestipol).

Conclusion

In conclusion, it can be proposed and suggested as a primary and preventive measure to increase the level of awareness in the population through media, electronic broadcasts, printed pamphlets, special television programs on the role of physical activity, physical exercises, with the sole purpose of preventing the occurrence of premature atherosclerotic processes and atherosclerotic manifestations of CVD. In conclusion, from our work we can conclude that people who are physically active and involved in sports, exercising at least 25-30 minutes every day within 5-6 days of the week, have a lower risk of developing CVD, diabetes, arterial hypertension and clearly have benefits and positive effects in balancing dyslipidemia.

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ADVANCED FORMULATIONS OF PEDIATRIC MEDICINES: REDUCTION OF SYNTHETIC EXCIPIENTS AND THEIR IMPORTANCE FOR CHILDREN'S SAFETY

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Abstract

Development of pediatric medicines can be considered one of the most complicated and challenging spheres of pharmaceutical science, which is due to specific physiological, biochemical, and developmental properties of the children's body. Traditionally, medicinal products designed for use by children contain various synthetic excipients including sucrose, sorbitol, sodium benzoate, parabens, ethyl alcohol, and artificial dyes aimed at improving palatability, stability, and visual appearance of the preparation. Contemporary studies suggest, however, that such excipients can pose some threats to children's health including allergy, metabolic disturbances, neurotoxicity, hepatotoxicity, as well as potential impact on pediatric development in the long run.
The purpose of this study is to critically analyze synthetic excipients used in pediatric pharmaceutical preparations and highlight safety concerns associated with their presence. At the same time, alternative approaches in the field of pediatric medicines, including using of natural alternatives and novel pharmaceutical technology solutions that would allow eliminating the use of synthetic excipients will also be explored. The methodology involves conducting a literature review and analyzing international documents on the subject matter.

Keywords: pediatric medicines, synthetic excipients, safety, natural alternatives, pharmaceutical formulations

Introduction

Pharmaceutical formulations designed for children are characterized by high specificity and complexity, which makes them different from formulations used by adults. Such distinction lies in specific physiological, biochemical, and developmental properties inherent to children. It is important to recognize that children cannot be treated as "small adults" because their bodies continuously grow and develop, influencing significantly on pharmacokinetics and pharmacodynamics of drugs and posing a special risk for neonates and infants, whose hepatic and renal systems function improperly yet.
Pharmacokinetic and pharmacodynamic parameters of medicines in children vary depending on age, weight, sex, as well as general state of health. This calls for precision and individualization of dose prescription to avoid possible overdose or insufficient amount of medicine prescribed.
Another important factor in the pharmacotherapy of children is the acceptability of medicines among them. Such attributes of medicines as their taste, smell, dosage form, and route of administration play a significant role in determining patient compliance. Refusal from drugs often occurs in children and may lead to the lack of efficacy. Therefore, children require the application of specially developed medicines rather than adapted versions of those used by adults. Application of off-label drugs and alteration of dosage forms may increase the risk of medication errors in pediatric practice.
Excipients play an important role in pharmaceutical formulations. Their functions include improving physicochemical properties, stability, appearance, and general acceptability of

medicines. The significance of excipients increases when developing pediatric medicines since their presence improves taste, smell, and appearance of the medicine, which affects patient compliance positively.

The choice of excipients takes place at the pre-formulation stage of preparation of a medicinal product. In case of pediatric medications, a detailed analysis of all safety factors should be made since there are many synthetic excipients that demonstrate some adverse effects on children. They include allergies, digestive disorders, and even neurologic problems in children, especially neonates and infants whose metabolic system is not developed completely. Moreover, certain excipients are likely to accumulate in the organism because of slow elimination.

In pediatric pharmacy, there is a lack of information about the long-term effects of excipients on children. Since most excipients are proven to be safe in adults, pediatric formulations contain them without conducting special studies on their impact on children. This situation stimulates the revision of existing formulations and search for safer analogs of medicines. It means that replacing and minimizing usage of certain synthetic excipients with other compounds may be beneficial in this situation. The purpose of such an approach is reducing risks for children.

This paper aims at contributing to the scientific literature through discussing advanced pediatric formulations and the benefits of lowering the content of synthetic excipients for child safety.

Objective

The objective of this paper is the analysis of scientific information related to the issues of pediatric formulations with special emphasis on the role and impact of synthetic excipients.

Another purpose of this paper is to consider natural alternatives and new technologies that may contribute to decreasing the amount of synthetic excipients used in pediatric drugs while taking into account the issues of safety and efficacy of medicinal products prescribed for children.

Materials and Methods

Study design

This paper represents a systematic review of scientific literature dedicated to analyzing the safety problems related to the usage of synthetic excipients in pediatric formulations and assessing the prospects for using more sophisticated alternatives that could reduce or completely exclude such risks. Given the specificity of this topic, the analytical and comparative approaches were used, relying on existing toxicological and clinical studies as well as relevant regulatory documents.

Data sources and Selection criteria

Literature searches for this study involved foreign databases and official documents. Information sources used in this paper are listed in the following table:

Table 1. Information sources and Selection criteria

TYPE OF SOURCE	EXAMPLES/DATABASES	NUMBER OF SOURCES USED	SELECTION CRITERIA
Peer-reviewed scientific articles	PubMed, Scopus, ScienceDirect	45	Publications from 2005–2025 focusing on pediatrics or effects in children
Regulatory documents	EMA, FDA, WHO	10	Guidelines on the use of excipients in pediatric medicines
Reports from international organizations	EFSA, FAO	5	Evidence summaries and safety assessments of excipients
Classical/reference literature	Libraries and frequently cited articles	3	Fundamental studies in excipient toxicology

Keywords such as "pediatric formulations," "synthetic excipients," "excipient toxicity in children," "parabens," "benzyl alcohol," "regulatory guidelines," and "advanced drug delivery systems" were used together with Boolean operators, including AND and OR to conduct research. All those studies focused on adult subjects, were of a non-scientific nature, or lacked a proper methodology were not considered. This approach allowed ensuring the validity and reliability of chosen information sources.

Results and Discussion

Function and Possible Harmfulness of Synthetic Excipients

Excipients are viewed as a crucial component in drug formulations performing technological functions essential for the stability, dosing, administration, and acceptability of medications. At the same time, excipients' function becomes especially important when creating pharmaceuticals intended for consumption by children characterized by limited ability to swallow, high metabolic sensitivity, and special sensory requirements. The usage of synthetic excipients has become a cause for significant safety concerns in pediatric medicines. The issue is closely linked to the physiology and metabolic immaturity of pediatric subjects (Barker et al., 2018; EMA, 2019).

Potential Toxicity of Synthetics Excipients in Pediatric Medicine

One of the major concerns about synthetic excipients in pediatric drugs involves their toxicity caused by such factors as the duration of usage and the child's physiological condition (metabolic immaturity). Neonates and infants may have limited abilities to metabolize and excrete certain excipients increasing their chances to be accumulated in the body (van den Anker et al., 2018; Yochana & Allegaert, 2020).

Propylene glycol and ethanol are two major synthetics considered concerning. According to clinical studies, prolonged exposure to the two substances can lead to the development of metabolic acidosis, central nervous system depression, and renal impairment in neonates (Valeur et al., 2018; FDA, 2018). This is why regulatory authorities stress the importance of imposing serious restrictions on the usage of the specified excipients in pediatric medicine.

Allergic Reactions and Intolerance Effects

It is possible to speak of the development of allergic reactions and intolerances in the context of pediatric medicine. It has been found that artificial colorants and preservatives can cause skin reactions, urticaria, and digestive issues among children (Lass et al., 2019). Such effects can adversely impact therapy and patient outcomes.

Cumulative Effect of Synthetic Excipients in Pediatric Treatment

Another crucial, but frequently overlooked, element concerning the application of synthetic excipients in pediatric medicine is the effect of cumulative exposure. Due to the frequent administration of more than one pharmaceutical product in children suffering from chronic conditions, these patients might be subjected to multiple simultaneous exposures to synthetic excipients coming from different drug formulations (Lass et al., 2019; Valeur et al., 2018).

While the intake of active substances is carefully regulated and controlled, excipients do not always become an integral part of the therapeutic process. Thus, their dosage can exceed the safe boundaries, especially when dealing with excipients like propylene glycol, ethanol, and parabens that may be used in various products for pediatric use (EMA, 2019; FDA, 2018).

Observational research revealed that neonatal patients admitted to hospitals experience high levels of synthetic excipient exposure, including a prolonged period of exposure to these compounds in neonatal intensive care units.

Artificial Excipients and Their Potential Effects on Neurodevelopment

The maturation of the central nervous system during childhood is considered a crucial period where the body becomes particularly susceptible to toxins. Some artificial excipients have also been linked to adverse effects on neurodevelopment, but only in cases of their early exposure to an individual (Barker et al., 2018; van den Anker et al., 2018).

Artificial solvents like ethanol and propylene glycol are some of the most researched materials in this aspect. Because of the incomplete development of the blood-brain barrier in infants, there is a higher chance of their penetration into the central nervous system and causing neuro-depressive and neuro-toxic effects (FDA, 2018). While acute risks are relatively well-researched, a number of questions about long-term neurodevelopmental impacts require further investigation.

At the same time, there is some experimental evidence that demonstrates the potential effects of early exposure to particular artificial colorants and preservatives on behavior and cognitive development in infants. However, this research lacks clinical data that would warrant additional research aimed at investigating these hypotheses (Barker et al., 2018; EMA, 2019).

Table. 2 Synthetic excipients frequently used in pediatric preparations and their potential risks

SYNTHETIC EXCIPIENT	TECHNOLOGICAL FUNCTION	POTENTIAL RISKS IN CHILDREN	MOST SENSITIVE AGE GROUP
Benzyl alcohol	*Preservative*	*"Gasping syndrome", neurotoxicity*	*Neonates*
Propylene glycol	*Solvent*	*Metabolic acidosis, CNS depression*	*Infants*

Polysorbate 80	*Emulsifier*	*Hypersensitivity reactions*	*Neonates*
Sodium benzoate	*Preservative*	*Hyperbilirubinemia*	*Neonates*
Artificial colorants	*Colorants*	*Allergic reactions, hyperactivity*	*Young children*

Sources: Turner et al. (2014); Nellis et al. (2020); EMA (2019).

Regulatory Approach to the Utilization of Synthetic Excipients in Pediatrics

The issues related to the utilization of synthetic excipients in pediatric formulations have been known for a while, prompting international regulatory organizations to issue specific guidelines concerning this topic. Thus, such organizations as EMA, FDA, and WHO have issued recommendations in an effort to enhance the clarity and safety of using synthetic excipients (WHO, 2010; EMA, 2019; FDA, 2020).

Among the main requirements formulated by these agencies is the disclosure of all ingredients used in a product, alongside an evaluation of the safety profile of these synthetic ingredients in a pediatric population. For instance, EMA noted that, when used in pediatrics, certain synthetic excipients that could trigger side effects should come with a warning (EMA, 2019). However, although this regulation exists, there remain numerous gaps in understanding the clinical and toxicological aspects of many synthetic excipients. This circumstance motivated the creation of such programs as Eu PFI (Salunke et al., 2016).

Toxic or Problematic Excipients in Pediatrics

Benzyl Alcohol – Toxicity and Impact on Pediatrics

Benzyl alcohol is an excipient used in the pharmaceutical industry as a preservative and solvent in various formulations. Despite the generally acceptable safety of benzyl alcohol in adults, in recent decades, it has been proven that the use of this excipient carries a significant toxic risk in newborns and small children due to their special physiological features (EMA, 2019). Patients of this age have metabolic immaturity that increases their sensitivity to toxic compounds formed during the metabolism of this excipient. The incomplete development of the enzymatic system responsible for conjugation results in the accumulation of benzoic acid in blood plasma that may lead to various toxic reactions ranging from metabolic acidosis and brain dysfunction to organ failure and even death (Young & Jewell, 2000; EMA, 2019).

Regulatory requirements concerning the safety of benzyl alcohol in the pediatric population are regulated by EMA and ICH guidelines. Specifically, according to EMA (2019), medicines with benzyl alcohol as an excipient should have a warning label in product information leaflets concerning the risks related to neonatal use. For preterm babies, whose metabolic systems are not well developed, this additive should always be avoided and resorted to only if there are no other safer options.

Sodium Benzoate

Sodium benzoate is an excipient which is commonly used in pharmaceutical manufacturing and is primarily applied as a preservative in various oral liquids, syrups, and solutions. Nevertheless, although this chemical is beneficial from a technological point of view, sodium benzoate poses significant risks for children and newborns since they have not yet fully developed their metabolic systems. In other words, the immaturity of the hepatic conjugation system in young infants, especially in premature babies, can cause the build-up of benzoic acid in blood plasma, which will likely cause metabolic acidosis (EMA, 2019). Metabolic acidosis in newborns is a critical condition which can involve central nervous system suppression, respiratory issues, and hemodynamic imbalance.

Concerning regulatory issues, the European Medicines Agency provides that it is crucial to include the information about sodium benzoate in the labeling of the medication and provide warnings when using the drug in neonates (EMA, 2019). As per modern recommendations for pharmaceutical development as stated by ICH Q8 guidelines, the choice of excipients should always be made taking into account both their benefits and risks, as well as physiological maturation of the child (ICH, 2009).

Sorbitol

Sorbitol is a sugar alcohol or polyol that is commonly employed in the production of drugs as a sweetener, humectant, and flavor enhancer in oral pediatric formulations like syrups, solutions, and suspensions. Owing to its sweetness and lower glycemic index compared to sucrose, sorbitol can be considered an ideal choice for formulations for children in situations where there is a need for avoiding fermentable sugars (Rowe, Sheskey & Quinn, 2009). Nonetheless, in spite of its frequent use and relative safety as an excipient, sorbitol poses a number of clinical risks when used by children, especially if administered in high doses or repeatedly.

Pharmacokinetically, sorbitol is poorly absorbed in the intestines, and it is mainly absorbed passively. A large amount of the compound is not absorbed and moves to the colon, where it is metabolized by the bacteria in the gut to short chain fatty acids and gases (Livesey, 2003). The aforementioned mechanism is responsible for the laxative effect of sorbitol. It acts in the intestinal lumen by raising osmotic pressure through the attraction of fluid in the gut causing diarrhea, abdominal pain, and distension.

Yet another critical factor is associated with the potential pharmacokinetic interaction of sorbitol with some pharmaceuticals. Specifically, sorbitol may alter the absorption rate of some drugs due to its influence on gastrointestinal motility and shortened mucosal drug contact time (Chen et al., 2007). The latter issue is especially relevant in pediatrics since drug bioavailability is essential for attaining a satisfactory therapeutic outcome.

European regulatory bodies consider that information concerning sorbitol content should be provided in the label and patient information leaflets, provided that its presence in oral medicines surpasses the threshold that might induce the onset of a laxative effect (EMA, 2014). In addition, medical personnel is supposed to evaluate the total intake throughout the day, especially in case of several polyol-containing formulations administered to the child.

Sucrose

One of the most widely used excipients is sucrose, also known as table sugar. This substance can be used for improving the taste and facilitating the administration of drugs by children since sucrose improves the taste of medicines (EMA, 2019). It can also be used in pediatric oral liquids, syrups, and preparations that cause some difficulties during swallowing. In addition, sucrose can serve as a stabilizer and a sweetener that masks the unpleasant taste of many active ingredients (Allen et al., 2017).

However, sucrose is considered a dangerous component for pediatric medicines because it can have an adverse impact on neonates and premature infants. In fact, the introduction of high doses of sucrose, whether intravenously or orally, might lead to the change in blood glucose levels and osmolarity (Kearns et al., 2003). Children, especially those in their first months of life, have no ability to process sugar effectively, causing hyperglycemia and even osmotic diarrhea (Hoffman et al., 2018).

Furthermore, from the toxicology perspective, sucrose causes an increase in osmotic pressure and hyperglycemia in newborns. As a result, it leads to metabolic acidosis, worsening of hydration status, and oxidative stress in newborn cells (Allen et al., 2017).

Studies in clinical practice have found instances of temporary hyperglycemia in neonatal patients who had been administered a formulation that contained a significant amount of sucrose, supporting the necessity of monitoring the blood glucose level continuously (Hoffman et al., 2018). In addition, prolonged use of sucrose in pediatric medication can have consequences on long-term health issues such as the development of cavities and insulin sensitivity in children (Allen et al., 2017).

Parabens

Parabens are synthetic chemical compounds commonly used as preservatives in pediatric medications, skin care products, lotions, and oral solutions, in order to inhibit microbial growth and increase product longevity (Soni et al., 2005). Methylparaben, ethyl paraben, propylparaben, and butylparaben are the most frequently used compounds in this group. Parabens are usually combined in order to guarantee a wide range of antimicrobial activity and chemical stability of the pharmaceutical compound (Błędzka et al., 2014). Despite being extensively employed for several decades, parabens are generally perceived as non-toxic substances in the general population; however, recent evidence indicates that the potential toxic effects of parabens on children can be significant. Children and infants have lower metabolic capabilities than adults and are therefore highly vulnerable to accumulating toxic levels of parabens (Schettler et al., 2012). The administration of paraben-containing medication during infancy can lead to the internalization of this substance through skin contact or orally.

Parabens possess toxic properties because of their endocrine-disrupting characteristics and act as agonists of estrogen receptors. Several experimental studies indicate that the chronic administration of parabens affects the sexual maturation, expression of hormone receptors, and reproduction system development (Darbre & Harvey, 2008).

International regulators such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have laid down strict guidelines concerning the percentage limit of parabens that can be incorporated in the drugs and cosmetics meant for use by pediatric patients (EMA, 2019). For instance, methylparaben and ethylparaben should never surpass

0.4% individually while propylparaben and butylparaben should not surpass 0.14% each. Combining parabens is a delicate exercise, and utmost care needs to be taken to prevent harmful effects.

Propylene Glycol

Propylene glycol, alternatively referred to as 1,2-propanediol, is a frequent ingredient used in pediatric drugs, where it acts as a solvent, stabilizer, moisturizer, and flavor enhancer (Kumar et al., 2016). The hygroscopic nature of this substance ensures that the moisture content of products is retained as well as maintaining the stability of other active ingredients in the formulation. Propylene glycol is commonly used in oral liquids, syrups, creams, and IV solutions for children and infants (EMA, 2019).

Even though the inclusion of propylene glycol in drugs is deemed to be relatively harmless in adults, young children, including neonates and preterm babies, tend to experience adverse reactions to its presence because of the low metabolic potential (Kearns et al., 2003). Propylene glycol undergoes degradation within the body, leading to the production of pyruvic acid and lactic acid. Small amounts of this substance are also excreted through urine (Sethi et al., 2017). Neonatal and premature infants have less enzymatic potential and renal activity, thus making them susceptible to adverse effects.

The reported adverse health outcomes comprise metabolic acidosis, central nervous system depression, hemolysis, and nephropathy. The clinical symptoms of propylene glycol poisoning in infants are lethargy, hypothermia, tachycardia, and hyperlactemia (Sethi et al., 2017; Kearns et al., 2003). The continuous administration of IV medications containing propylene glycol, such as antibiotics and anticonvulsants, has been associated with a few cases of toxic overload, necessitating vigilant clinical supervision.

To mitigate the risks, the governing bodies, including the European Medicines Agency, have set strict limits on the maximum percentage of propylene glycol in pediatric pharmaceuticals. For oral formulations, the maximum concentration level should be below 20%, whereas for IV formulations, the maximum allowable daily dose of propylene glycol for infants should be less than 1 g/kg (EMA, 2019). Whenever feasible, it is recommended to prescribe formulations devoid of propylene glycol or with other safer excipients, particularly premature infants and those with renal/ hepatic impairment.

Artificial Colorants

Artificial colorants are extensively used in pediatric medicines due to their ability to enhance the visual appeal of preparations and increase their acceptability by children (Wang et al., 2020). This excipient increases the acceptability and reduces refusal of medicines among children. Artificial colorants are mostly chemical analogs of azo dyes and may include such substances as tartrazine (E102), sunset yellow (E110), allura red (E129), and ponceau 4R (E124) (EMA, 2019).

Nevertheless, the application of artificial colorants in pediatric medications has led to severe issues related to the safety of patients because of their adverse impact on hyperactivity, allergies, as well as the toxicity of the nervous and metabolic systems (McCann et al., 2007; Stevens et al., 2013). Various clinical and epidemiological studies proved that colored foods and beverages had an effect on the emergence of ADHD in children. Consumption of azo dyes

was associated with increased motor activity, low concentration, and behavioral problems (Stevens et al., 2013).
From a toxicological point of view, certain synthetic colorants may induce allergic responses, such as urticaria, asthma, and allergic rhinitis, particularly among children who have an inherent tendency for allergic response (Wang et al., 2020). Toxic manifestations at the systemic level may involve alterations in hepatic enzyme activity, alterations in gut microflora, and oxidative stress seen in experimental animals (Kumar & Sharma, 2018).

Polysorbate

Polysorbates are surfactants and emulsifiers that are often employed as excipients in pediatric medicines due to their ability to increase stability in liquid medications, enhance solubility of pharmacologically active compounds, and inhibit particle sedimentation in suspensions and emulsions (Rowe et al., 2009). Nevertheless, polysorbates do present certain toxicological hazards. It has been demonstrated that surfactants may induce allergic reactions and affect cell membrane stability (Cavaliere et al., 2018). Anaphylaxis and hypersensitivity reactions following contact with Polysorbate 80 in pediatric patients have been occasionally reported, especially when it was applied in the intravenous administration of vaccines or formulations of sensitive medications (EMA, 2019).
In addition, there is evidence for the effect of polysorbates on the gastroenterological and metabolic systems. In vitro and animal trials have suggested that Polysorbate 80 may influence the composition of the intestinal microbiome and the permeability of the intestinal mucosa (Chassaing et al., 2015). This feature is especially pertinent to young children since their intestinal microbiome is still in development, and epithelial barriers are prone to disruption.
The last point to consider is the potential link between the use of Polysorbate 80 and inflammation, as well as the development of immunological properties. According to Cavaliere et al. (2018), polysorbates might induce the release of pro-inflammatory cytokines, which can impact the function of immune cells. This issue is highly important for children who are genetically predisposed to developing immune-related conditions and allergies.
Therefore, when prescribing medications containing Polysorbate 80, special care should be taken to minimize the exposure of children to this substance, substituting it with safer analogues like phospholipids or surfactants, which have been approved for use among children (EMA, 2019; FDA, 2020).

Ethanol

Ethanol is a common excipient employed in pediatric medications, primarily as a solvent for poorly soluble active ingredients and as a preservative in some liquid preparations (EMA, 2019). The ethanol content in pediatric medications normally varies between 0.1% and 10% v/v, depending on the nature of the medication, the administration route, and the age of the patient (WHO, 2017). Nonetheless, ethanol is an excipient that raises toxicological concerns among pediatrics. Due to their immature enzyme systems, infants and toddlers metabolize ethanol slower compared to adults, who possess higher levels of alcohol dehydrogenase enzymes in their liver (Farah et al., 2016). Thus, the chances of ethanol accumulation increase, potentially leading to toxic reactions such as hypoglycemia, brain impairment, metabolic acidosis, and, in severe cases, coma and even death (EMA, 2019; WHO, 2017).

Several clinical studies have demonstrated that an exposure of an infant less than 6 months old to ethanol through oral means can lead to a significant increase in blood alcohol concentration even after low-level consumption, which makes this age group highly vulnerable (Farah et al., 2016). Theoretically, from the point of view of neurotoxicity, ethanol is considered a depressant of the central nervous system, and its intake by infants can impair the development of the brain. It has been proven through the results of experimental studies and epidemiology that repeated exposure of infants to substantial doses of ethanol leads to cognitive impairment, skill acquisition difficulties, and increased likelihood of behavioral problems in childhood and adolescence (Chatterjee et al., 2018). Moreover, the effect of ethanol on glucose metabolism and glucose levels in the blood cannot be neglected. As was mentioned before, infants are highly prone to ethanol-induced hypoglycemia owing to their inability to perform gluconeogenesis properly (Farah et al., 2016). It causes tremors, lethargy, seizures, and coma, especially when ethanol is used simultaneously with drugs that affect glucose metabolism.
The pharmaceutical regulatory agencies such as EMA and FDA have clearly outlined the allowable limit of the use of ethanol in the pediatric medicines and also clearly labeled the percentage of alcohol present in the medicine according to different age groups (EMA, 2019; FDA, 2020). For instance, EMA advises that the medicines used by children below the age of six years should not contain more than 0.5% ethanol while for children above the age of six years, the limit is 5% of ethanol.

Natural and Biocompatible Alternatives in Pediatric Formulations

The advancement of safety in pediatric medications has promoted growing scientific research into natural and biocompatible excipients as alternatives to synthetic excipients. The purpose of alternative excipients is to deliver equivalent functionality to synthetic counterparts without increasing the risk of adverse reactions and enhancing tolerance in children. According to contemporary literature, natural excipients in pediatric pharmacy are considered a prospective trend, given the highly sensitive physiology of children (Salunke et al., 2016; Strickley, 2019).

Natural Polymers as Substitutes for Artificial Excipients

Among the most extensively researched classes of biocompatible substitutes in pediatric formulations are natural polymers. Compounds like cellulose and its derivatives, alginates, pectins, gelatin, and chitosan have found widespread application for diverse technological purposes, including stabilization, thickening, and modulation of the release of active ingredients (Thakkar et al., 2020). The microcrystalline form of cellulose, along with its derivatives, for instance, hydroxypropyl methylcellulose, is regarded as one of the safest excipients in pediatric formulations owing to its biological inactivity and non-systemic absorption. Alginates and pectins derived from plants have been employed as gelling and stabilizing agents in pediatric suspensions and syrups. Research demonstrates that natural polymers provide significant benefits with respect to biocompatibility and biodegradability, thereby minimizing the requirement for artificial preservatives (Nelis et al., 2021).

Natural Excipients for Enhancing Tastiness and Acceptability

The sensory acceptability of medications plays an essential role in their compliance among children. One of the main factors leading to the rejection of drugs prescribed to children is their unpleasant taste, thus promoting research into alternative natural substances for artificial sweeteners and flavorings (Gómez-Orellana, 2021). For instance, natural sweeteners like sucrose, fructose, stevia, and agave syrup may serve as safe alternatives to artificial substances like aspartame and saccharin. Despite the need for cautious usage of sucrose owing to its negative effect on dental hygiene, several studies confirm that, when administered in appropriate amounts, sucrose serves as one of the best-tolerated sweeteners among children (EMA, 2019). Moreover, natural flavoring compounds derived from fruits and fragrant plants prove to be more beneficial than synthetic substitutes due to their lower allergenicity and enhanced medicinal acceptance among children (Batchelor et al., 2018).

Vegetable Oils and Natural Lipids as Alternatives to Solvents

Natural vegetable oils and lipids have been used as alternative solvents that are biocompatible with the body, especially with children in relation to lipophilic materials. The use of oils such as sunflower oil, soybean oil, and MCT oils have proved to have a safe safety profile and acceptable metabolism (Allegaert et al., 2020). By using these natural solvents, the need for propylene glycol and ethanol is reduced due to their toxicity to neonates and infants. Regulatory agencies advise on the use of natural lipids when technically feasible (FDA, 2020).

Limitations and Challenges of Using Natural Alternatives

Despite a number of positive features, the utilization of biocompatible excipients can be associated with multiple technological difficulties as well. Some of the major problems with these compounds include chemical variation, instability, and sensitivity to different environmental factors (Thakkar et al., 2020). In addition, some natural excipients can demonstrate sensitivity to bacteria; thus, more measures are required for the preservation of the excipient’s stability and microbiological safety. This problem may be especially important for pediatric products that minimize the utilization of synthetic preservatives (Nelis et al., 2021).

Conclusion

Thus, the literature review has allowed obtaining some insights into the application of excipients in pediatrics and its impact on the health and safety of children. Firstly, it should be mentioned that most traditional medicines used for the treatment of children's diseases include synthetic excipients, which, despite being generally regarded as harmless for adults, can be potentially harmful for children, particularly neonates and toddlers. According to the results of the conducted toxicity studies, substances like parabens, sodium benzoate, sorbitol, and benzyl alcohol could lead to side effects starting with irritative effect on the stomach and ending with metabolic acidosis and grey baby syndrome caused by benzyl alcohol.

It is worth mentioning that the intensity of the exposure to excipients is determined by the physiological condition of children and their age since neonates and toddlers have lower levels of enzymatic activity and less developed hepato-renal system. Moreover, recent scientific

discoveries indicate that accumulations of certain excipients may adversely affect the efficacy of medicines since they change the processes of drugs' absorption and metabolism. Therefore, a necessity to create child-friendly formulations instead of reducing the dosages of adult medications arises.

The literature also notes that it is necessary to replace potentially hazardous excipients with safe ones or even natural substances. For instance, several studies suggest that biocompatible polymer or natural materials, including pure glucose and gelatin, can be applied successfully, thus lowering the likelihood of toxicity significantly while retaining the stability and pleasant taste of the preparation. Such a practice is especially relevant for oral preparations because sugar or other additives may trigger an allergic reaction or metabolic syndrome.

From the analysis of regulatory sources and guidelines, an international tendency towards minimizing the use of hazardous excipients has been discovered. The authors of contemporary scientific research note that children's pharmaceuticals should undergo comprehensive testing not only regarding their therapeutic impact but also concerning the safety of every auxiliary substance. The recommendations of the EMA and FDA on this issue are quite unambiguous: every excipient should be analyzed based on patients' age and weight, as well as minimizing preservatives, dyes, and artificial sweeteners.

The substitution of synthetic excipients with natural and biocompatible compounds makes medicines more acceptable and prevents any potential toxicity. The utilization of natural and biocompatible substances is a safer way of formulating medicines, particularly in vulnerable populations such as infants, and ensures greater stability, improved taste, and enhanced tolerance. Such findings support the suggestion that the pharmaceutical industry should pay attention to minimizing high-risk excipients when developing formulations.

In conclusion, the standardization of local practices to international recommendations and ongoing monitoring of pediatric medicines can be considered a good starting point for designing appropriate regulations and policies aimed at safeguarding children. Such conclusions highlight the significance of a holistic strategy where the pharmaceutical industry, healthcare professionals, and regulatory agencies assume joint responsibility for providing adequate formulations for children.

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DETERMINATION OF YIELD AND KERNEL PERCENTAGE IN SOME HAZELNUT CULTIVARS (*CORYLUS AVELLANA* L.)

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Abstract

This study aims to evaluate the effect of nut weight on kernel percentage and yield of three hazelnut varieties (*Corylus avellana* L.), namely *Tonda Gentile Romana*, *Ennis*, and *Halski Dzik*. The data were analyzed using descriptive statistics, correlation analysis, and linear regression in the SPSS program.
The results show that there is a strong positive relationship between nut weight and yield (r = 0.876), suggesting that increasing nut size significantly contributes to increasing production per hectare. Meanwhile, the relationship between nut weight and kernel percentage is weak (r = 0.253), indicating that kernel percentage is influenced by other structural and genetic factors of the varieties. Linear regression analysis confirms these trends; however, the results are not statistically significant (p > 0.05), mainly due to the limited number of samples. In conclusion, nut weight is an important indicator for yield, while improving kernel percentage requires a more detailed analysis of other factors. Further studies with a larger number of samples are recommended to increase the reliability and generalization of the results.

Keywords: hazelnut, varieties, nut weight, kernel percentage, yield, Corylus avellana.

Introduction

Hazelnut is a Mediterranean crop and a distinctly heliophilous plant. It is a fruit tree from the group of nut-bearing species and is very unusual because, unlike other trees that bloom in spring, it blooms in winter, from December to March. Its root grows and develops very superficially, in a layer of about 30 cm. The lifespan of a hazelnut tree is from 70 to 100 years, and it bears fruit from 50 to 70 years. It begins to bear fruit in the third or fourth year, while full fruiting is achieved in the seventh or eighth year, depending on the cultivar and cultivation conditions. In full production, one tree yields from 8 to 12 kg of production, of which about 50% is shell. Depending on the cultivation form, planting density, age, and other agrotechnical measures, yields vary from 2.5 to 3.6 t/ha.
The global annual production of hazelnuts in shell averages over 800,000 tons (Fideghelli and De Salvador, 2009). This production is mainly achieved by four countries: Turkey, about 563,000 tons (68%), Italy, about 120,244 tons (15%), far behind them are the USA (mainly Oregon) with 31,631 tons, and Spain with 29,709 tons. Hazelnut kernels are a source of a large number of very useful compounds, such as fats 55–72%, proteins 12–22%, carbohydrates 14%, sugar 2–10%, minerals 1.8–3%, vitamin E (24–40.40 mg/100 g), β-sitosterol (134.05 mg/100 g), cellulose 2.42%, water 5.8%. Numerous phenolic compounds have been identified in hazelnuts: gallic, caffeic, p-coumaric, ferulic, and sinapic acid, myricetin 3-rhamnoside, quercetin 3-glucoside, quercetin 3-rhamnoside, and kaempferol 3-rhamnoside. The shell and leaves are a source of catechin tannin.

Research Objective

This research aimed to investigate the participation of the kernel in the nut weight in some hazelnut cultivars with different nut weights, as well as the yield per hectare depending on nut size, and to recommend for wider cultivation the cultivar with a higher kernel percentage and higher yield adapted to the climatic and soil conditions of the Pollog Region, North Macedonia.

Materials and Methods

As material, a total of 150 hazelnuts (50 nuts for each variant) with different sizes were used, where from each variant, 10 nuts were measured in five replications. The experimental material was taken after harvest in the localities of Kamjan and Sellarcë e Epërme-Bogovinë. The average fruit weight, kernel percentage, and yield were compared for the three cultivars.

Results

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
%	3	43.96	46.72	45.3433	1.38001
t\ha	3	2590.00	3110.00	2813.3333	267.64404
G	3	3.01	4.51	3.8767	.77675
Valid N (listwise)	3				

The descriptive results show that kernel percentage (%) varies from 43.96% to 46.72%, with a mean of 45.34% and a standard deviation of 1.38, indicating relatively low variability among the varieties. Yield (t/ha) shows values from 2590 to 3110 t/ha, with a mean of 2813.33 t/ha and a standard deviation of 267.64, indicating more pronounced differences among the varieties.
Nut weight (g) varies from 3.01 g to 4.51 g, with a mean of 3.88 g and a standard deviation of 0.78, reflecting noticeable differences in nut size among the varieties.

Correlations

		g	%	t\ha
G	Pearson Correlation	1	.253	.876
	Sig. (2-tailed)		.837	.320
	N	3	3	3
%	Pearson Correlation	.253	1	.688
	Sig. (2-tailed)	.837		.517
	N	3	3	3
t\ha	Pearson Correlation	.876	.688	1
	Sig. (2-tailed)	.320	.517	
	N	3	3	3

Pearson correlation analysis shows a positive relationship between nut weight and yield (r = 0.876), suggesting that an increase in weight is associated with an increase in production.
Meanwhile, the relationship between weight and kernel percentage is weak (r = 0.253), indicating that weight does not have a strong effect on kernel percentage.
Also, kernel percentage and yield have a moderate positive relationship (r = 0.688).
However, due to the limited number of samples (n = 3), these results are not statistically significant (p > 0.05) and should be interpreted only as indicative.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	43.598	6.751		6.458	.098
	g	.450	1.719	.253	.262	.837

a. Dependent Variable: %

Linear regression analysis between nut weight and kernel percentage shows a weak positive relationship (β = 0.253). The regression coefficient (B = 0.450) indicates that an increase of 1 g in nut weight is associated with an increase of 0.45% in kernel percentage. However, the model is not statistically significant (p = 0.837), indicating that weight is not a dominant factor in determining kernel percentage in this dataset.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1642.837	652.192		2.519	.241
	g	301.934	166.028	.876	1.819	.320

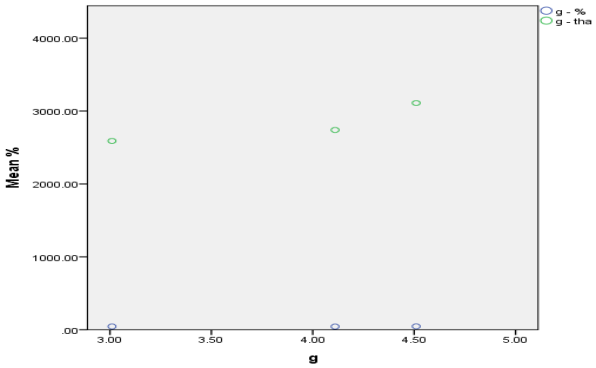
a. Dependent Variable: t\ha

Linear regression between nut weight and yield shows a strong positive relationship (β = 0.876). The coefficient (B = 301.934) indicates that each increase of 1 g in nut weight is associated with an increase of about 302 t/ha in yield. However, this model is also not statistically significant (p = 0.320), due to the small number of data points.

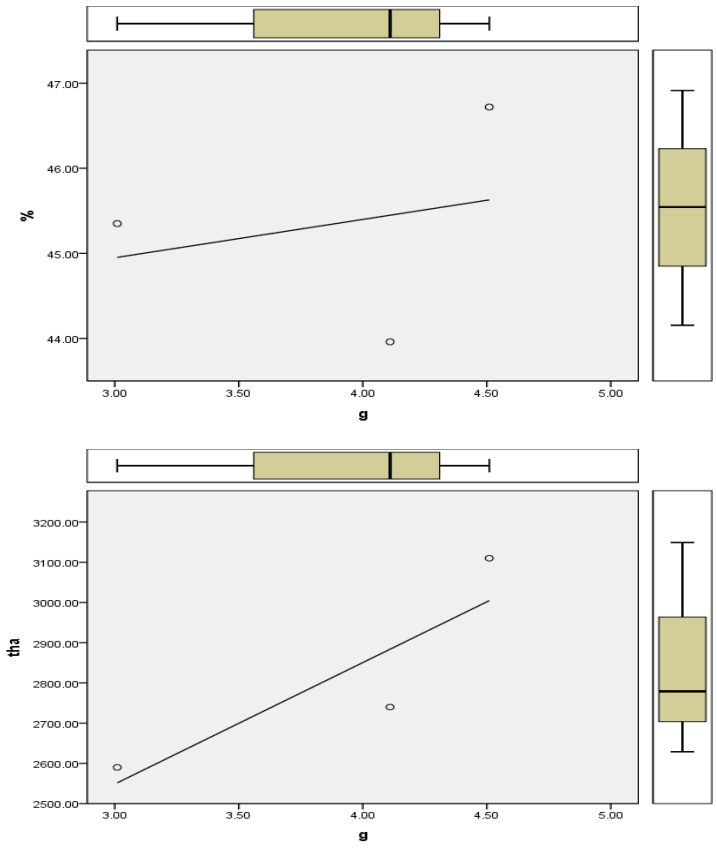
Discussion (very important)

The results show that nut weight has a more pronounced effect on yield than on kernel percentage. Varieties with larger nuts tend to produce higher yields per hectare, which is consistent with the principles of crop production.
On the other hand, kernel percentage is not significantly affected by weight, suggesting that other factors, such as nut structure or composition, may play a more important role.

However, due to the very limited number of data (n = 3), the results should be considered indicative and require verification with larger samples in order to draw statistically reliable conclusions.



“The scatter plot graph visually confirms the positive relationship between nut weight and yield, while for kernel percentage, this relationship appears weaker.”



“The scatter plot graph visually confirms the positive relationship between nut weight and yield, while for kernel percentage, this relationship appears weaker.”

Discussion of Results

The results of this study show that there are differences among hazelnut varieties in terms of nut weight, kernel percentage, and yield. Descriptive analysis highlights relatively low variability for kernel percentage, while yield and nut weight show more pronounced differences among the varieties. Pearson correlation shows that nut weight has a strong positive relationship with yield ($r = 0.876$), suggesting that increasing nut size directly influences the increase in production per hectare. This result is logical from an agronomic perspective, as larger nuts contribute more to the total production mass.

On the other hand, the relationship between nut weight and kernel percentage is weak ($r = 0.253$), indicating that kernel percentage does not depend directly on weight, but may be influenced by other factors such as the internal composition of the nut, the kernel/shell ratio, and the genetic characteristics of the varieties. Linear regression results reinforce these findings. Nut weight has a more pronounced effect on yield ($\beta = 0.876$) than on kernel percentage ($\beta = 0.253$). However, the lack of statistical significance ($p > 0.05$) for both models indicates that these relationships cannot be considered statistically confirmed, but only as trends.

An important factor influencing these results is the limited number of data ($n = 3$), which reduces the statistical power of the analysis and limits the possibility of drawing generalized conclusions.

In general, the results suggest that the selection of varieties with larger nuts may be an appropriate strategy for increasing yield, while improving kernel percentage requires analysis of other factors beyond nut weight.

Conclusions

[1] The analyzed varieties show differences in nut weight, kernel percentage, and yield.
[2] Nut weight has a strong positive effect on yield, appearing as an important factor for increasing production.
[3] The effect of weight on kernel percentage is weak, suggesting that kernel percentage is determined by other structural and genetic factors.
[4] Statistical analyses show clear trends, but they are not statistically significant due to the small number of samples ($n = 3$).
[5] The results provide valuable indications for the selection of hazelnut varieties in agricultural practice.

Recommendations

[1.] Further studies should be conducted with a larger number of samples to increase the statistical reliability of the results.
[2.] Other factors affecting kernel percentage, such as nut structure and kernel/shell ratio, should be taken into consideration.
[3.] In agricultural practice, the selection of varieties with larger nut weight is recommended to increase yield per hectare.
[4.] More advanced analyses should be used in the future (ANOVA, more extended models) with individual data for each nut.

[5.] Statistical analyses should be combined with agrotechnical factors (irrigation, soil, fertilization) for a more comprehensive evaluation of production.

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IMPACT OF OXYGEN ON BEER QUALITY PARAMETERS DURING INDUSTRIAL BREWING: A CASE STUDY OF PEJA BREWERY (KOSOVO)

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Abstract

Oxygen is a critical factor influencing beer quality, stability, and shelf life. This study investigates the impact of oxygen at different stages of industrial beer production, using Peja Brewery (Kosovo) as a case study. Dissolved oxygen (DO) and total package oxygen (TPO) were monitored during wort processing, fermentation, filtration, and packaging. Results showed that controlled oxygenation before fermentation (8–10 mg/L DO) is essential for optimal yeast performance, while oxygen ingress after fermentation significantly reduces product stability. TPO values ranging from 20 to 120 ppb were associated with substantial differences in shelf life, flavour stability, and oxidative compound formation. Beers with TPO below 30 ppb maintained high sensory quality for up to 6–9 months, whereas higher oxygen levels accelerated flavour deterioration and formation of stale aldehydes such as trans-2-nonenal. Industrial oxygen control systems, including inert gas blanketing and closed transfer systems, significantly reduced oxygen exposure. The study confirms that oxygen management is a key determinant of beer quality in industrial brewing systems.

Keywords: Oxygen, beer stability, TPO, DO, Peja Brewery, oxidation

Introduction

Oxygen is one of the most influential yet most problematic factors in beer production, due to its dual roles in biochemical and chemical processes throughout brewing. While it is essential for yeast metabolism during the early stages of fermentation, its presence after yeast growth becomes highly detrimental to beer quality, leading to oxidative reactions that compromise flavour stability, aroma profile, colour, and shelf life. This dual behaviour makes oxygen control a central challenge in modern industrial brewing systems.

During wort production, oxygen exposure is generally minimised because hot-side aeration can initiate irreversible oxidation of sensitive compounds such as lipids, polyphenols, and aldehydes. These reactions may lead to the formation of flavour-active substances that negatively affect beer quality even before fermentation begins. However, a controlled introduction of oxygen is intentionally applied after wort cooling and prior to yeast pitching. This step is critical for yeast physiology, as oxygen is required for the biosynthesis of sterols and unsaturated fatty acids, which are fundamental components of the yeast cell membrane (Kunze, 2014). Without sufficient oxygen, yeast cells exhibit reduced viability, poor growth, and incomplete fermentation performance.

Once fermentation begins, the process transitions into a predominantly anaerobic environment. Under these conditions, yeast converts fermentable sugars into ethanol and carbon dioxide. Any unintended oxygen ingress during this phase can disrupt yeast metabolism and lead to the formation of undesirable by-products, including diacetyl retention and altered ester profiles. Therefore, strict control of oxygen during active fermentation is essential for achieving consistent product quality and predictable fermentation kinetics (Stewart, 2017).

The most critical phase regarding oxygen sensitivity occurs after fermentation, particularly during maturation, filtration, stabilisation, and packaging. At this stage, even trace amounts of

oxygen can trigger oxidative degradation reactions. These reactions are responsible for the formation of stale-flavour compounds such as trans-2-nonenal, which is widely recognised as a marker of beer aging and is associated with cardboard-like off-flavours (Vanderhaegen et al., 2006). In addition, oxygen contributes to the degradation of hop-derived aroma compounds, colour darkening, and reduced foam stability, all of which significantly diminish sensory quality.

Industrial brewing systems are particularly vulnerable to oxygen ingress during mechanical operations such as transfer between tanks, filtration processes, and filling lines. These points represent the highest risk for oxygen contamination in modern breweries. As a result, advanced technological solutions have been developed to minimise oxygen exposure, including closed-loop transfer systems, inert gas blanketing using carbon dioxide or nitrogen, deaerated water systems, and inline oxygen monitoring technologies (Haffmans, 2020). The implementation of these systems has become standard practice in high-efficiency breweries aiming to maintain low dissolved oxygen (DO) and total package oxygen (TPO) levels.

In industrial quality control, dissolved oxygen (DO) is typically monitored in the wort and fermentation stages, while total package oxygen (TPO) is considered a key indicator of final product stability. Even small variations in TPO levels can significantly influence beer shelf life and sensory degradation rate. Studies in industrial settings have shown that beers with TPO levels below approximately 30 parts per billion (ppb) exhibit significantly improved flavour stability and extended shelf life compared to beers with higher oxygen exposure (Liu, 2018).

The case of industrial breweries such as Peja Brewery in Kosovo highlights the practical importance of oxygen management under real production conditions. Despite modern brewing technologies, oxygen ingress remains a critical control point, particularly in filtration and packaging operations. Therefore, understanding oxygen behaviour across all stages of production is essential for optimising process efficiency and ensuring consistent beer quality.

This study aims to provide a comprehensive evaluation of oxygen dynamics in industrial beer production, with a particular focus on its impact on fermentation performance and final product stability. By integrating both scientific literature and industrial case study data, the research highlights oxygen control as a fundamental parameter in modern brewing technology and a key determinant of beer quality and shelf life.

Materials and Methods

2.1 Study Site: The study was conducted at **Peja Brewery (Birra Peja, Kosovo)** under industrial production conditions for lager-type beer.

2.2 Sampling Points: Oxygen measurements were taken at:

[1]. Wort after cooling
[2]. Pre-fermentation aeration stage
[3]. End of fermentation
[4]. After filtration
[5]. Final packaged beer

2.3 Oxygen Measurement

[1] Dissolved Oxygen (DO): inline optical DO sensors
[2] Total Package Oxygen (TPO): headspace oxygen analyser
[3] Equipment aligned with industrial systems supplied by **Pentair Haffmans oxygen control technology**

2.4 Fermentation Conditions

[1] Yeast: *Saccharomyces cerevisiae* lager strain
[2] Fermentation temperature: 8–12°C
[3] Controlled aeration: 8–10 mg/L DO before pitching

2.5 Quality Analysis

[1] Alcohol content (ABV)
[2] pH
[3] Color (EBC)
[4] Sensory analysis
[5] Aldehyde formation (GC analysis for trans-2-nonenal)

Results

3.1 Oxygen Levels During Processing Stages: Oxygen concentrations were monitored at key stages of the brewing process. The results demonstrate a significant variation in dissolved oxygen (DO) and total package oxygen (TPO) depending on process control efficiency.

3.2 Relationship Between TPO and Shelf Life: A strong inverse relationship was observed between TPO levels and beer shelf life. Higher oxygen levels in packaged beer accelerated oxidative reactions, resulting in reduced flavour stability.

Table 1. Effect of TPO on Beer Shelf Life and Sensory Stability

TPO (ppb)	Estimated Shelf Life (months)	Sensory Quality
<30	6–9	Excellent (fresh, stable)
30–50	4–6	Good (minor changes)
50–100	2–4	Moderate (noticeable aging)
>100	<2	Poor (oxidised, stale flavour)

The results confirm the dual role of oxygen in beer production, highlighting its necessity during wort aeration and its detrimental effects in later stages. Adequate oxygen levels before fermentation significantly improved yeast performance, leading to higher fermentation efficiency and consistent alcohol production, in agreement with findings by Stewart (2017).
However, increased oxygen levels detected after fermentation, particularly during filtration and packaging, were strongly correlated with reduced flavour stability. Elevated TPO levels

resulted in higher concentrations of oxidative compounds such as trans-2-nonenal, confirming previous reports on beer aging mechanisms (Vanderhaegen et al., 2006; Liu, 2018).
Industrial data further demonstrated that the implementation of oxygen control technologies, such as CO_2 purging and inline monitoring systems, significantly reduced oxygen pickup and improved shelf life. Breweries utilising advanced systems from industrial providers reported TPO values below 30 ppb, which are associated with superior flavour stability and extended product freshness (Haffmans, 2020).

Table 2. Dissolved Oxygen (DO) and Total Package Oxygen (TPO) Levels During Beer Production

Production Stage	Parameter Measured	Value Range	Unit	Industrial Interpretation
Wort cooling	DO	0.5 – 1.0	mg/L	Low oxygen exposure; oxidation risk controlled
Pre-fermentation aeration	DO	8.0 – 10.0	mg/L	Optimal yeast growth and sterol synthesis
Early fermentation	DO	<0.1	mg/L	Anaerobic conditions established
Mid fermentation	DO	~0.0	mg/L	Stable yeast metabolism
End fermentation	DO	<0.05	mg/L	Fermentation completion
Post-filtration	TPO	70 – 120	ppb	Critical oxygen ingress point
Pre-packaging beer	TPO	40 – 80	ppb	Moderate oxidation risk
Final packaged beer	TPO	20 – 80	ppb	Key determinant of shelf life

The data indicate that controlled oxygenation before fermentation ensures optimal yeast performance, while oxygen ingress after fermentation significantly contributes to TPO levels.
Additionally, the study highlights the importance of process integration, where oxygen control must be maintained across all stages rather than treated as an isolated parameter. Even minor oxygen ingress during packaging can negate earlier process optimisations, emphasising the need for a holistic approach.
Overall, the findings demonstrate that precise oxygen management is a key determinant of beer quality, aligning with both scientific literature and industrial best practices.

Discussion

Results from Peja Brewery confirm that oxygen management is a decisive factor in industrial beer quality. Controlled oxygenation before fermentation significantly enhances yeast performance and fermentation efficiency, consistent with Stewart (2017). However, oxygen ingress during post-fermentation stages, particularly filtration and packaging, is directly associated with oxidative degradation.

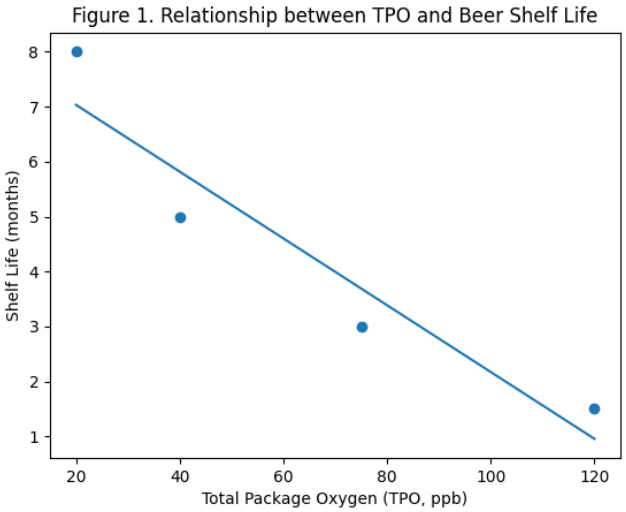


Figure 2. Relationship between total package oxygen (TPO) and beer shelf life.

[1] **<30 ppb:** highest stability (6–9 months)
[2] **30–50 ppb:** moderate decline in stability
[3] **50–100 ppb:** strong reduction in shelf life
[4] **>100 ppb:** severe oxidation and rapid spoilage

A clear negative correlation exists between total package oxygen (TPO) and beer shelf life. An increase in oxygen levels from 20 to 120 ppb reduces shelf life from approximately 8 to 1.5 months.

This trend confirms the critical importance of maintaining TPO levels below 30 ppb as an optimal industrial standard.

Industrial data show that TPO levels above 50 ppb lead to accelerated formation of aldehydes such as trans-2-nonenal, which is responsible for stale flavour development (Vanderhaegen et al., 2006). Breweries implementing closed transfer systems and inert gas blanketing (CO_2/N_2) achieved TPO reductions below 30 ppb, resulting in extended shelf life and improved sensory stability.

Technology applied at Peja Brewery, including oxygen control systems inspired by **Pentair Haffmans solutions**, significantly reduced oxygen exposure in critical points. This confirms that oxygen control must be treated as an integrated system across all production stages, rather than an isolated parameter.

Industrial Significance

This study demonstrates that strict oxygen control below 30 ppb TPO can significantly extend beer shelf life and improve flavor stability under industrial conditions. The findings are directly applicable to large-scale breweries aiming to optimize quality and reduce product losses during distribution.

Conclusion

Oxygen has a beneficial role only in the early stage of fermentation, but it becomes a major quality-degrading factor in later stages. Industrial case study results from Peja Brewery demonstrate that strict control of DO and TPO is essential for maintaining beer freshness,

stability, and shelf life. Oxygen management strategies represent a key technological requirement for modern brewing systems.

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MEDICINE RECALL SYSTEMS IN THE USA AND EU: A REGULATORY COMPARISON

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Abstract

Medicine recall was an essential regulatory mechanism designed to protect patients from medicines that were unsafe, ineffective, or of poor quality. It involved the removal of specific batches or lots of medicinal products due to issues such as manufacturing defects, contamination, or labeling errors, whereas withdrawals referred to the permanent removal of an entire drug product from the market. The reasons for medicine recalls varied and, depending on the level of risk to patients, recalls were carried out at different levels of the supply chain, ranging from distributors and pharmacies to patients themselves. The aim of this study was to analyze and compare how this system was organized in the United States and the European Union. The methodology was based on the analysis of scientific literature and statistical data obtained from official reports of the U.S. Food and Drug Administration and the European Medicines Agency. The findings indicated that, despite differences in structural organization, implementation, and levels of transparency, both regulatory systems aimed to protect patients and ensure the quality and safety of medicines. The study highlighted that effective recall procedures and regulatory coordination played a crucial role in minimizing risks associated with defective medicinal products. Overall, continuous improvement in recall mechanisms, strengthened regulatory cooperation, and compliance with relevant standards and regulations by pharmaceutical companies were essential for enhancing pharmaceutical safety at both national and international levels.

Keywords: medicine recalls, quality , safety, FDA, EMA,

Introduction

The quality and safety of medicines are one of the main pillars of the health system that have a direct impact on the health of the population (Rasheed *et al*.,2023). Therefore, every medicine to be introduced into the market must have marketing authorization, after its quality, safety and efficacy have been assessed, and after the benefit-risk balance is considered positive (Aronson *et al*, 2017). Usually, marketing authorization is granted for a certain period with the possibility of renewal (EMA, 2026). But even during this period, medicines are usually monitored by the competent regulatory authorities to ensure whether they meet the requirements in terms of quality, efficacy and safety. Even in cases where a medicinal product has been authorized for many years, new information may eventually emerge requiring its recall or withdrawal from the market, because it no longer meets quality requirements, for example due to the unexpected identification of impurities, other quality defects, or adverse effects.

Therefore, medicine recalls are a necessary mechanism to protect patients from medicines that may be unsafe, ineffective, or poor quality. Drug recalls are a regulatory mechanism used to remove specific batches or lots of medication due to manufacturing defects, contamination, or labeling errors, while withdrawals involve the permanent removal of entire drug products from the market (Patel *et al*,2023)

The reasons for recalls of medicine can be numerous, such as the presence of impurities, deviations in content, physical defects of the product, irregularities, suspicions related to

packaging and labeling, as well as the occurrence of unexpected side effects. Depending on the level of risk of the pharmaceutical product irregularities, recalls can be carried out at different levels of the supply chain, ranging from distributors and pharmacies to patients. Therefore, competent pharmaceutical regulatory authorities have organized the medicine recall system at local, regional, and global levels. The absence of such a system would create the possibility for defective medicines to circulate and be used in the market, increasing the risk of serious side effects, treatment failure, and potential public health crises.

Recalls of medicine also have legal and economic implications for pharmaceutical companies, as well as affecting the trust of patients and healthcare professionals in medical products (Trevir & Nath., 2019). Besides their protective role, recalls also serve as an important tool for the continuous improvement of the pharmaceutical industry (Cheah *et al.,* 2007). They help in identifying deficiencies in manufacturing, storage, and distribution processes, encouraging the implementation of stricter quality control measures and higher safety standards Therefore, recalls are not only a response to existing problems but also a mechanism for preventing them in the future.

Evolution of medicine recalls

The development of mechanisms for medicine recalls is closely related to the evolution of pharmaceutical regulation and increasing awareness of patient safety. In the early years of the pharmaceutical industry, the lack of manufacturing standards and quality control often allowed unsafe products to enter the market (Schmidt, H., & Huber, F., 2021). As a result, interventions to remove suspicious and unsafe drugs from the market were rare, uncoordinated, and usually occurred only after adverse effects had become apparent.

Several landmark drug safety incidents played a crucial role in highlighting the need to strengthen pharmaceutical regulations worldwide to ensure greater safety in the use of medicines. One of the earliest and most significant cases is the Elixir Sulfanilamide incident in 1937 , where the use of a toxic solvent in the product's formulation resulted in the deaths of over 100 people, mainly children (*Sulfanilamide Disaster*., 2024) .This incident was the result of inadequate testing, insufficient quality control systems, and the absence of stricter drug regulations before being released to the market. Another significant event is the thalidomide tragedy in the late 1950s and early 1960s. (Yashiro *et al*., 2018). The drug, which was widely used by pregnant women to relieve nausea, led to the birth of thousands of babies with severe congenital malformations. This case highlighted the importance of carefully testing and monitoring side effects of medicines across different population groups and led to stronger requirements for clinical trials and post-marketing drug surveillance.

These cases demonstrate that medicines can be dangerous without proper testing, and that it is not sufficient for only the active substance to be effective, as all other ingredients must also be proven safe .They also highlighted the need for a system that allows the rapid recall of suspicious and dangerous products. Following these events, the roles of regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were strengthened, leading to the development of more structured systems for continuous drug monitoring through recalls. These systems include classification of recalls based on risk level, clear communication procedures, and coordination between manufacturers, distributors and healthcare professionals.

In recent decades, the globalization of the pharmaceutical market and the increasing complexity of the supply chain have created new challenges in the management of drug recalls. However, advances in technology, the development of pharmacovigilance systems and greater institutional transparency have significantly improved the ability to detect problems and intervene in a timely manner (Fadare, J. O., *et al.* ,2023). As a result, drug recalls have evolved from reactive measure into a key component of a proactive system for ensuring the safety and quality of medicinal products.

Classification of recalls

There are two types of recalls depending on the source of initiation, namely who initiates the process and the extent of state authority involved (Shevale *et al,* 2014; Meghan Lehmann *et al., 2010;* Guidelines on Recall and Rapid Alert System for Drugs, CDSCO ,2012):
Voluntary recall – initiated by the pharmaceutical company itself (manufacturer or distributor) when a problem or irregularity is identified in certain batches of a pharmaceutical product, such as quality defects, incorrect labeling, or other issues that may pose a risk to patients' health. In such cases, the regulatory authority (FDA, EMA or national Agency of Medicine) may request or recommend the recall of a product. This represents one of the most common forms of recall.
Mandatory recall – is less common and occurs only in serious cases when a product poses a risk to health and may cause serious injury or death. This typically happens when a product or batch does not meet required quality standards, when medicines are prohibited for use, or when labeling and promotional materials violate applicable laws and regulations. In these cases, the competent regulatory authority orders the product to be recalled from the market, either at the central or local level.
The categorization of recalls into "voluntary" and "mandatory" is formally applied in the United States by the FDA, where these terms are defined within a legal framework. In the European Union, although recalls in practice may be initiated by companies or requested by regulatory authorities, there is no formal legal classification of recalls in EU legislation. Instead, the EMA and the national authorities of each Member State focus on legal obligations, risk assessment, and risk management rather than on the "voluntary" or "mandatory" classification of recalls.

[1] Recalls are classified into three categories based on the level of health risk (FDA,2026):
Class I (major): These are the most serious recalls, where there is a reasonable probability that the use of, or exposure to, the recalled drug will cause serious adverse health consequences or death. In such cases, the effects may be immediate and life-threatening. Class I recall is urgent and typically involves removing the product from the market, often extending to the consumer level.
Class II (moderate): The use of the drug may cause temporary or medically reversible adverse health consequences, while the probability of serious harm is low. These recalls are usually carried out at the retail level, and patients may continue using the medicine unless otherwise advised by the company or the competent regulatory authority.
Class III (minor): The use of the drug is unlikely to cause adverse health consequences. These recalls typically involve issues such as minor labeling errors, packaging defects, or incorrect expiration dates. They are usually carried out at the distribution (wholesale) level, and patients

may continue using the product unless otherwise instructed by the manufacturer or the relevant authority

The classification of recalls into Class I, II, and III is used in United States (FDA,2026), whereas in the European Union recalls are managed through a risk-based approach assessed on a case-by-case basis, without a standardized classification system. In the EU (EMA), there is no formal legal classification of recalls; instead, each case is evaluated individually based on the severity of the risk, the likelihood of harm, and the urgency of action.

However, EMA statistical reports may still present data using Class I, II, and III categories for analytical purposes, mainly to facilitate comparison and statistical reporting. These classifications are therefore used only for data presentation and do not represent a formal regulatory system within the European Union, whereas in the United States, these classes form part of a formal regulatory framework used by the FDA to assess and communicate risk levels.

Comparison of the recall systems in the USA and the EU

The medicine recall systems in the United States and the European Union have been established to ensure patient safety by removing defective or potentially hazardous pharmaceutical products from the market. Although both systems share the same primary objective of protecting patients through the removal of unsafe medicines, they differ in terms of organizational structure, implementation, and levels of transparency (Bigoniya *et al*, 2018)

One of the main differences relates to the regulatory structure. In the United States, medicine recalls are centrally managed by the FDA, which provides a unified and standardized approach. In contrast, in the European Union, the system is more decentralized and involves the EMA as well as the national Medicines Regulatory Authorities (MRAs) of each Member State. This makes the European system more complex but also more flexible.

Regarding the initiation of recalls, in both systems they are often initiated voluntarily by pharmaceutical companies. However, in the United States, the FDA plays a more direct and visible role in oversight, whereas in the European Union, the process is often initially coordinated at the national level and then communicated among Member States, regardless of the recall class.

An important difference can also be observed in terms of transparency and access to data. In the United States, the FDA provides a centralized and publicly accessible system for recalls (e.g., the FDA Recall Database and Enforcement Reports), which enables detailed statistical analysis. In the European Union, however, there is no single centralized public database. Instead, information is typically provided through national authorities, making data collection more challenging. Recall data are not consolidated in a single source but are instead distributed across various platforms, such as inspection reports, pharmacovigilance systems, and rapid alert systems. As a result, statistical analysis is more complex compared to the U.S. system.

There are also differences in terms of coordination and response. The European Union uses the Rapid Alert System to ensure immediate communication among Member States, especially in high-risk cases (Class I). In the United States, communication is more centralized and direct due to the presence of a single authority, namely the FDA, which coordinates and manages the recall process at the national level. This centralization enables a faster and more unified response in managing high-risk cases.

Statistical data regarding recalls

Statistical data on drug recalls in the United States and the European Union were obtained from various regulatory and reporting sources. For the USA, data from the FDA Recall Database covering the period from 2012 to 2023 were used, along with information from annual reports and published studies. For the European Union, data were taken from the annual reports of the European Medicines Agency (EMA), focusing on quality defects and recalls for the period 2020–2024 (Ema, 2024)

Based on FDA Recall Database, as well as a study (Patel et al., 2024) covering the period 2012–2023, a total of 15710 drug recalls were recorded. Of these, 1524 were classified as Class I recalls, 12679 as Class II, and 1507 as Class III recalls, initiated by pharmaceutical companies (Figure 1).

The reasons for drug recalls were also analyzed, and five main categories were identified: production problems, sterility issues, out-of-specification (OOS) results, contamination, and labeling problems. It was observed that a total of 5766 recalls were due to lack of sterility assurance, while 3195 were related to non-compliance with current Good Manufacturing Practices (cGMP). A further 2117 recalls were associated with OOS results, 1712 with contamination (mainly microbiological), and 1274 with labeling errors, including incorrect or missing expiration dates and label mix-ups. In addition, 833 recalls were related to packaging and storage issues, 300 to adverse reactions, 276 to marketing without prior regulatory authorization, and another 276 to miscellaneous reasons, including non-compliance with United States Pharmacopeia specifications, product crystallization, inaccurate dosing systems due to calibration errors, and failures to meet pharmacopeial monograph requirements (Figure 2).

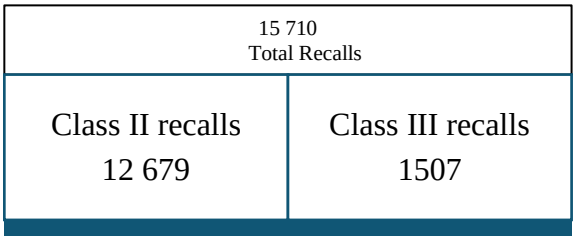


Figure 1. Categorization of all drug recalls issued by the FDA from June 2012 to August 2023

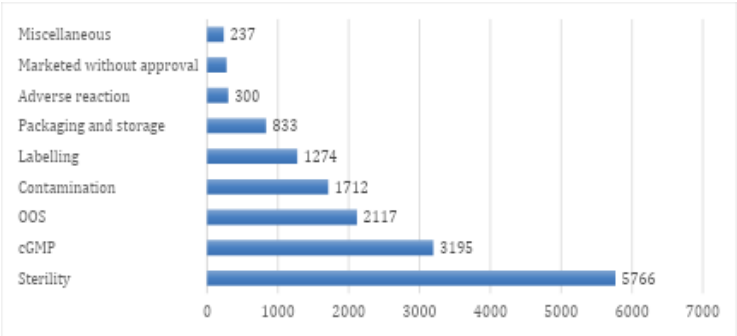


Figure 2. Categorization of drug recalls issued by the FDA from 2012 to 2023 according to their main reasons

The FDA issued many recall notifications to pharmaceutical manufacturers during the period from 2012 to 2023, mainly due to issues related to current Good Manufacturing Practices (cGMP) and sterility. Figure 3 presents the number of recalls per year over the 10-year period,

categorized according to several key causes, including sterility, out-of-specification (OOS) results, labeling issues, cGMP non-compliance, and contamination

The study shows that the main causes of drug recalls in the United States (2012–2023) are issues related to sterility and cGMP non-compliance, with lack of sterility assurance and non-sterility constituting most cases. Other causes include storage-related issues, manufacturing issues, and product impurities. Therefore, pharmaceutical companies should improve compliance with quality standards and implement effective quality management systems that oversee production processes, quality control, staff training, and documentation to prevent future drug recalls.

According to data from the European Medicines Agency (EMA, 2024), the number of notifications related to quality defects showed a continuous increase during the period 2020–2024, rising from 170 in 2020 to 395 in 2024 (Figure 4).

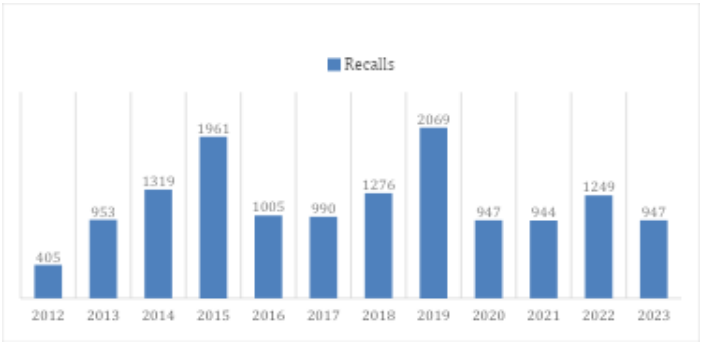


Figure 3.Number of recalls for each year in the period 2012 -2023

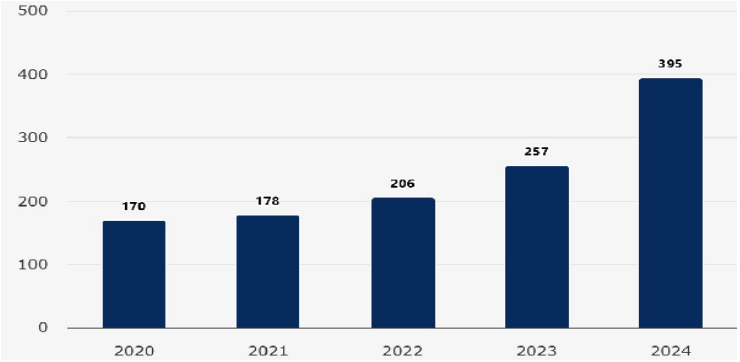


Figure 4.Number of quality defect notifications received (Source: EMA annual report 2024)

The number of confirmed quality defect cases is lower, reflecting the fact that not all suspected reports are confirmed as actual defects after investigation (Fig.5). In 2024, out of 395 notifications received, 221 cases were confirmed as actual quality defects. This discrepancy indicates that a considerable proportion of initial reports do not meet the criteria for classification as confirmed defects. However, the confirmed cases resulted in recalls of batches for nine centrally authorized products (CAPs), with no cases classified as Class I recalls, indicating that there was no immediate risk to life. In 2020, there were 15 recalls reported, of which 3 were Class I and 3 were Class II , while 9 recalls were Class III . In 2021, there were 164 confirmed cases of quality defects, of which 10 resulted in recalls, including 1 recall as a Class I , 7 recalls were Class II , and 2 recalls were Class III . During 2022, there were 185 confirmed cases of quality defects, of which 11 resulted in recalls, including 2 as Class I , 5 recalls as Class II , and 4 recalls as Class III . In 2023, there were a total of 188 confirmed

cases of quality defects, of which 9 resulted in recalls, including 6 recalls as Class II , 2 recalls as Class III , and 1 unclassified recall (Fig.5). This reporting demonstrated the importance of the verification process within the pharmacovigilance system, where only confirmed defects initiated regulatory actions such as medicine recalls.

In 2024, the main reasons for the recalls of centrally authorised products (CAPs) included several major categories of quality defects. Among them, issues related to laboratory and production control processes were among the most frequently reported, including results outside specified limits during quality control testing. Another important category was contamination and product sterility issues, including chemical, microbiological, or physical contamination of drugs. Labelling problems were also identified, such as missing or incorrect batch numbers. In addition, recalls were caused by packaging defects, including physical issues such as mixed packages or damaged containers. Finally, problems related to the physical properties of products were reported, such as tablet hardness, size, and shape.

In general, data from the EMA and FDA indicate an increase in reports of quality defects, but a low level of serious risk to patients. Most of the issues are technical in nature and are detected through control and monitoring systems, reflecting the effective functioning of regulatory mechanisms in ensuring the safety of medicines on the market.

	2020	2021	2022	2023	2024
Quality defects confirmed cases		164	185	188	221
Recalls	15	10	11	9*	9
Class 1	3	1	2	0	0
Class 2	3	7	5	6	5
Class 3	9	2	4	2	4

*1 recall not classified

Figure 5. Quality defects confirmed cases and categorization of recalls (source : EMA annual report 2024)

Minimizing drug recalls

Drug recalls can negatively impact the financial performance of pharmaceutical companies and reduce their reputation and patient trust. Pharmaceutical companies can minimize these recalls through several measures (Nagaich *et al.*, 2015):

1. Compliance with regulations and standards
2. Legal and brand protection through rapid response
3. Improvement of production process efficiency
4. Improved data management through closed-loop decision-making systems
5. Strengthening product quality control systems
6. Increasing operational transparency
7. Enhancing accountability through automated auditing

All these measures not only help to minimize recalls but also contribute to improving the quality and safety of medicinal products.

Conclusion

The recall of medicines is a key component of the pharmaceutical safety system, playing a dual role: the immediate protection of patients and the long-term improvement of medicinal

product quality. This study highlights the importance of medicine recall systems in both the United States and the European Union, with emphasis on their regulatory differences and operational approaches. Understanding this process and its impact is essential for the development of effective health policies and for enhancing patient safety. Overall, continuous improvement in recall mechanisms and regulatory cooperation is essential for strengthening pharmaceutical safety at both national and international levels

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DESIGN AND SIMULATION OF A CNC POSITION CONTROL SYSTEM USING PID AND FUZZY-PID CONTROL

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Abstract

This paper presents the design and simulation of a position control system for a two-axis CNC machine using PID and fuzzy-PID control strategies. The study focuses on the mathematical modeling of the positioning loop, including the derivation of the transfer function of the CNC servo system, and its implementation in MATLAB/Simulink for dynamic analysis. A conventional PID controller was first applied to regulate the positioning system and evaluate the closed-loop response. In order to improve tracking accuracy and dynamic performance, a fuzzy logic block was then introduced for adaptive tuning of the PID parameters. Simulation results showed that the PID controller achieved stable control of the system, while the fuzzy-PID approach provided improved positioning performance and higher control precision. The presented methodology demonstrates the usefulness of simulation-based control design for CNC positioning systems and offers a practical framework for improving motion-control performance in mechatronic applications.

Keywords: CNC machine; Position control; PID; fuzzy-PID; MATLAB/Simulink;

Introduction

Computer Numerical Control (CNC) machines are a central part of modern manufacturing because they enable accurate, repeatable, and automated motion control in machining processes. The quality of CNC machining depends strongly on the dynamic performance of the feed drive and position control system, since tracking errors and axis-coupling effects can directly influence contour accuracy and final part quality. In this context, the design of effective motion-control strategies remains an important topic in CNC research and mechatronic system development. [1]

Classical PID control is still widely used in motion-control applications because of its simple structure, reliability, and practical effectiveness. However, CNC servo systems are influenced by nonlinear effects, parameter uncertainty, and external disturbances, which can reduce the performance of fixed-parameter PID control, especially when higher positioning accuracy is required. For this reason, fuzzy logic has often been combined with PID control in order to improve adaptability and dynamic response. [1]

This paper focuses on the modeling and simulation of a two-axis CNC position control system. The system transfer function was derived and implemented in MATLAB/Simulink in order to analyze the dynamic behavior of the servo loop. A conventional PID controller was first applied as a baseline solution, after which a fuzzy-PID controller was introduced to improve the positioning performance of the system. The objective of the study is to evaluate, through simulation, the extent to which fuzzy-assisted tuning can improve control precision compared with a standard PID-based approach. [2]

Related Work

The control performance of CNC machine tools has long been recognized as a key factor affecting machining accuracy, contour quality, and dynamic response. Reviews of machine-tool control emphasize that servo loops, interpolation behaviour, and compensation strategies are central elements in achieving accurate motion in CNC systems. This makes the modeling of the feed drive and position-control loop an important step in the design and analysis of CNC machines. [3]

Among the available control approaches, PID control remains one of the most widely used solutions in CNC servo systems because of its simple structure, practical implementation, and stable closed-loop behavior. At the same time, recent work notes that conventional PID control can become insufficient when higher motion-control accuracy is required in the presence of nonlinear friction, parameter variation, and time-varying disturbances. For this reason, many studies continue to investigate improved PID-based strategies for CNC positioning systems. [4]

One of the most common improvements is the integration of fuzzy logic with PID control. In CNC servo applications, fuzzy-PID strategies are used to adapt controller behavior according to the magnitude and rate of the control error, with the goal of improving transient response, robustness, and positioning precision. Prior simulation work on CNC servo systems has reported that fuzzy-PID control can outperform conventional PID control in terms of robustness and disturbance rejection, while more recent studies continue to show the value of fuzzy-assisted PID tuning for nonlinear CNC motion systems. [2] [5]

Motivated by these findings, the present paper focuses on the modeling and simulation of a two-axis CNC position control system using PID and fuzzy-PID control strategies. In contrast to broad survey work, the emphasis here is placed on deriving the transfer function of the positioning loop, implementing the model in MATLAB/Simulink, and comparing the control response of a conventional PID controller with a fuzzy-PID alternative for the studied CNC configuration.

System Modeling and Control Design

This section describes the mathematical modeling of the two-axis CNC positioning system, the derivation of the transfer function of the control loop, and the implementation of PID and fuzzy-PID controllers in MATLAB/Simulink. The objective is to evaluate the dynamic response of the positioning system and compare the performance of the two control approaches under the same simulation conditions.

Methodology

This section presents the modeling and simulation procedure used for the analysis of the CNC position control system. In this paper we design the positioning control circuit of a CNC machine was designed by deriving the transfer function of a two-axis servo system and implementing the model in MATLAB/Simulink. The control performance was then evaluated using a conventional PID controller and an enhanced fuzzy-PID approach.

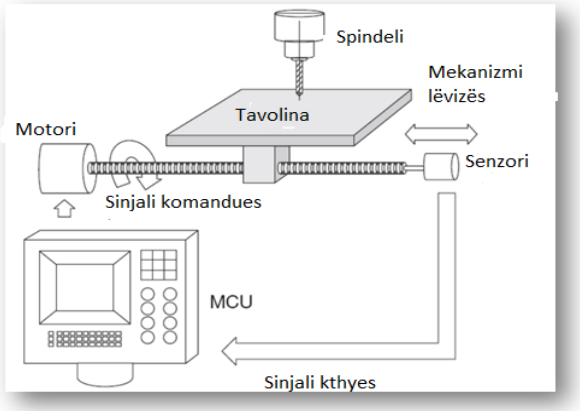


Figure 1. Operation principle of CNC milling machine.

System Modeling

The CNC machine was modeled as a two-axis positioning system in which translational motion along the machine axes is generated through servo-driven actuation and mechanical transmission elements. In the adopted control structure, the actuator, transmission mechanism, and feedback element form the core of the positioning loop, while the controller determines the dynamic response and positioning accuracy of the system. Based on this representation, the position-control problem was treated as a closed-loop servo-system suitable for mathematical modeling and simulation in MATLAB/Simulink.

Transfer function

The mathematical model of the two-axis CNC positioning system was developed from the physical structure of the servo-driven feed mechanism. For the purposes of simulation, the machine was represented as a two-axis system with translational motion along the X and Y axes, driven by two DC servo motors and ball-screw transmission elements. In the model, the mechanical part of the system was represented through the equivalent inertia of the moving table and transmission mechanism, while the damping contribution of the motor rotor and ball-screw system was retained.

In this paper, the working table was assumed to be made of aluminium with dimensions of 496 mm × 496 mm and thickness 10 mm, from which its mass and moment of inertia were calculated. The table inertia was calculated together with the ball-screw inertia and combined with the electrical and mechanical parameters of the selected DC servo motor.

These quantities were then substituted into the analytical model of the positioning loop in order to derive the transfer function used in simulation.

$$J_{xy} = \frac{1}{12} M(a^2 + c^2) \qquad (1)$$

where □ is the table mass and □ and □ are the table dimensions. Using the calculated table mass □ = *6.67* □□, the paper obtained the table inertia as:

$$J_{xy} = 0.1372 kgm^2 (2)$$

while the ball-screw inertia was also calculated:

$$J_b = 0.00122 kgm^2 \quad (3)$$

The DC servo motor parameters used in the model were presented in table 1.

Table 1. parameters of servo motor used in the paper.

K_t	K_b	J_m	R_a	D_m	L_a
0.352	12.7	$1 * 10^{-5}$	2.2	$1 * 10^{-3}$	$3.8 * 10^{-4}$

After substitution of the model parameters, the transfer function of the simulated CNC positioning system was obtained as:

$$G(s) = \frac{5.664}{s^2 + 14.82s} \quad (4)$$

This transfer-function model was used as the basis for controller design and closed-loop simulation in MATLAB/Simulink

PID controller design

After deriving the transfer function of the CNC positioning system, a conventional PID controller was adopted as the baseline control strategy. The PID controller was selected because of its simple structure, practical applicability, and widespread use in industrial motion-control systems. In the closed-loop configuration, the controller generates the control signal based on the position error, its integral, and its derivative, thereby enabling improvement of the transient response and reduction of steady-state error.

$$u(t) = K_p e(t) + K_i \int e(t)dt + K_d \frac{de(t)}{dt} \quad (5)$$

where □(□) is the position error, □□ is the proportional gain, □□ is the integral gain, and □□ is the derivative gain. The PID controller was implemented in MATLAB/Simulink and used as the reference controller for comparison with the fuzzy-PID approach.

Fuzzy-PID controller design

In order to improve the control performance of the positioning system, a fuzzy-PID controller was introduced as an enhanced alternative to the conventional PID approach. The purpose of the fuzzy logic block was to adapt the PID parameters according to the instantaneous control error and the change of error, thereby making the controller more flexible in the presence of varying dynamic conditions. This approach was adopted in the paper to improve position accuracy and overall dynamic performance of the simulated CNC system.

The fuzzy-PID structure preserved the basic PID control law, while the fuzzy inference mechanism was used to modify the controller action in a rule-based manner. In this way, the advantages of classical PID control were retained, but additional adaptability was introduced through fuzzy logic. The resulting controller was implemented in MATLAB/Simulink and tested under the same simulation conditions as the conventional PID controller in order to enable a direct performance comparison.

MATLAB/Simulink simulation

The derived transfer-function model of the CNC positioning system was implemented in MATLAB/Simulink in order to evaluate the dynamic response of the closed-loop servo system

under different control strategies. The simulation environment was used to compare the performance of the conventional PID controller and the fuzzy-PID controller under the same operating conditions, using the derived plant model as the common basis for both cases.
For the fuzzy-PID implementation, the fuzzy inference structure was defined using the control error □(□) and the change of error □□(□) as input variables, while the controller outputs were associated with the PID gain adjustment. The placement of the membership functions and the formulation of the fuzzy rules were based on the reference study used in this work and then adapted to the present simulation model. In particular, the adopted reference describes the fuzzy self-tuning PID structure and presents membership functions for error, change of error, and controller gains, together with rule tables for $\square_{\square}$, $\square_{\square}$, and $\square_{\square}$. [6]
A comparative simulation was then carried out in MATLAB/Simulink in order to examine the position-control response of the system under PID and fuzzy-PID control. The resulting responses were evaluated in terms of transient behavior and positioning performance, and the comparison is presented in the following section.

Results and Discussion

This section presents the simulation results obtained for the two-axis CNC positioning system under PID and fuzzy-PID control. The comparison was carried out in MATLAB/Simulink using the same plant model and identical reference conditions, so that the effect of the control strategy could be evaluated more clearly. The main objective of the analysis was to examine the dynamic response of the system and determine whether the fuzzy-PID approach provided an observable improvement in positioning performance over the conventional PID controller.

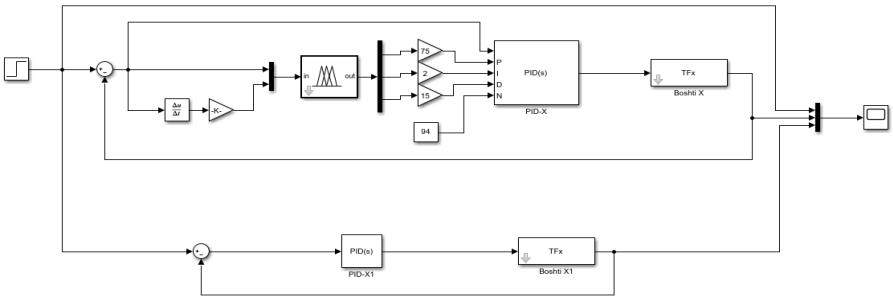


Figure 2. Schematic of the system with fuzzy logic (top) and with only the PID regulator (bottom).

The evaluation focused primarily on transient-response characteristics, since these provide a direct indication of control quality in positioning systems. In particular, the comparison considered the shape of the step response, the speed of convergence toward the reference position, and the overall smoothness of the response. From a motion-control perspective, these aspects are important because they influence positioning accuracy, tracking quality, and the suitability of the controller for CNC applications where stable and precise axis motion is required.
The MATLAB/Simulink implementation of the control loop can be shown in the methodology section as a separate figure, while the step-response plots should be presented here in the results section. In this way, the methodology explains how the model was built, whereas the results section demonstrates how the model behaved under the two control approaches. For the present paper, the most important results figure is therefore the step-response comparison between the conventional PID controller and the fuzzy-PID controller.

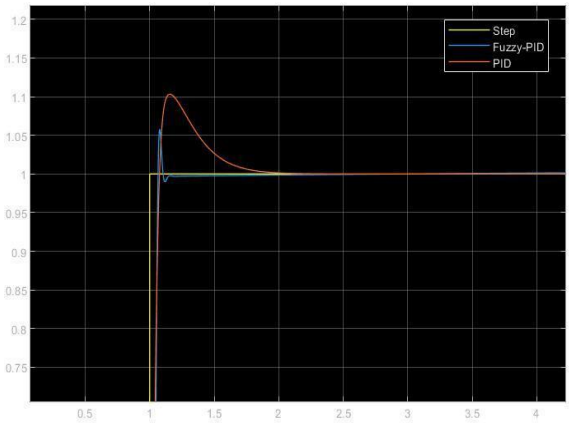


Figure 3. Step response comparison between just the PID controller and the Fuzzy-PID controller.

Figure 3 shows the simulated step responses of the CNC positioning system under PID and fuzzy-PID control. The responses were compared in order to evaluate the influence of fuzzy-based gain adjustment on the transient behaviour of the servo system. Particular attention was given to the speed of response, overshoot tendency, and the ability of the system to approach the reference position in a stable and accurate manner.

Tabel 2. Comparison of the PID values against Fuzzy-PID values

	PID	**Fuzzy-PID**
Rise time	49.889 ms	46.218 ms
Overshoot	10.556 %	5.851 %
Settling time	538.50 ms	53.879 ms

Discussion

The results summarized in Table 2 show that both controllers were able to stabilize the simulated CNC positioning system, but the fuzzy-PID controller achieved better overall dynamic performance than the conventional PID controller. In particular, the rise time decreased from **49.889 ms** for the PID controller to **46.218 ms** for the fuzzy-PID controller, indicating a slightly faster response to the reference input. A more noticeable improvement was observed in the overshoot, which was reduced from **10.556%** to **5.851%**, showing that the fuzzy-PID controller provided a much smoother transient response with less deviation beyond the desired position.

The most significant difference between the two control approaches was observed in the settling time. While the conventional PID controller required **538.50 ms** to settle, the fuzzy-PID controller reduced this value to **53.879 ms**. This result suggests that the fuzzy-PID strategy was able to bring the system to its steady operating region much faster than the fixed-parameter PID controller. From a CNC motion-control perspective, this is especially important, since shorter settling times and lower overshoot are directly related to improved positioning quality and more stable axis motion.

The observed improvement can be explained by the adaptive nature of the fuzzy-PID controller. Unlike the classical PID controller, which uses fixed gains throughout the response, the fuzzy-PID approach adjusts the controller action according to the instantaneous error and

the change of error. As a result, it is better able to respond to different phases of the transient process, leading to faster convergence and reduced oscillatory behavior.

At the same time, it should be noted that the presented comparison is based on simulation results obtained in MATLAB/Simulink rather than on experimental implementation on a physical CNC machine. Therefore, the findings should be interpreted as simulation-based validation of the control strategy. Nevertheless, the results clearly indicate that the fuzzy-PID controller offers a more effective control solution for the modeled CNC positioning system than the conventional PID controller under the same simulation conditions.

Conclusion

This paper presented the modeling and simulation of a two-axis CNC position control system using PID and fuzzy-PID control strategies. A mathematical model of the positioning loop was developed, and the corresponding transfer function was derived and implemented in MATLAB/Simulink for dynamic analysis. On the basis of this model, a conventional PID controller was used as the baseline control approach, while a fuzzy-PID controller was introduced in order to improve the dynamic performance of the system.

The simulation results showed that both controllers were able to stabilize the CNC positioning system, but the fuzzy-PID approach achieved better overall performance. In particular, the rise time was reduced from **49.889 ms** to **46.218 ms**, the overshoot was reduced from **10.556%** to **5.851%**, and the settling time decreased from **538.50 ms** to **53.879 ms**. These results indicate that the fuzzy-PID controller provided a faster and smoother response than the conventional PID controller under the same simulation conditions.

Overall, the study demonstrates that MATLAB/Simulink provides a practical environment for the analysis and comparison of CNC motion-control strategies, and that fuzzy-assisted PID tuning can significantly improve the positioning performance of the modeled servo system. The presented approach can serve as a useful basis for future work involving experimental validation and implementation on a physical CNC platform.

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IMPLEMENTING GRAPHQL AND REST APPLICATION PROGRAMMING INTERFACES IN MOBILE APPLICATIONS

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Abstract

Mobile applications are increasingly being used in many areas of life, where most systems, in addition to being created for desktops, are also adapted for mobile and other smartphones, because people spend most of their time on mobile devices, and it is easier for them to perform their daily tasks. Of particular importance during the development of modern mobile applications is the choice of API architecture, which directly affects performance, efficiency and easier surfing for clients. The two main approaches most used are REST API and GraphQL, which offer different ways of accessing data and interacting between clients and servers. Initially, through the paper, we are introduced to the way these two architectures work, describing the advantages and disadvantages of each of them, and then we continue with experimental analysis and description of some code sequences that we used in our experiment, both during the implementation of the REST API and GraphQL, on the client side and server side. The results of our testing and practical implementation also reinforce the positions of other research, that GraphQL is much better when it comes to executing more complex queries and time efficiency, while REST API is better when we have simpler and more stable requests. We concluded the paper by describing future trends in mobile APIs, with particular emphasis on hybrid architectures and integration with edge computing and serverless technologies.

Keywords: Application Programming Interfaces, REST API, GraphQL, architecture, future trends, mobile AP

Introduction

Mobile application development is also closely linked to Application Programming Interfaces (APIs), which, among other things, provide easy and fast communication between the mobile application and the server, but also in the construction of microservices and distributed systems, facilitating real-time functionalities and reuse by different mobile applications. Today, most users of the network and modern technologies are connected through mobile applications, as they have become an inseparable part of people in every sphere of life, and on the other hand, it is a current challenge for developers because they must adapt the architecture of mobile systems to the requirements of users but also to the comfort of the development of contemporary technology. Despite the complicated architectures and numerous functionalities they offer, the performance of mobile applications must come first, because response time is one of the phenomena that directly affects the user experience and usability of the mobile application in various fields (Liu & Li; 2022). Despite the fact that the performance of mobile applications depends on the network and the programming of functionalities in mobile applications, recently most mobile applications provide services obtained from APIs and this dependence often makes communication a critical factor for the efficiency, scalability and real-time performance of mobile applications (Akamai Technologies, 2022). APIs define how client-server requests are processed and how responses are structured, enabling the integration of multiple microservices into a single application, integrating with databases, cloud services, and other external systems, providing scalability and efficiency (Alozie et al 2025). In addition to APIs, the network delay is also of great importance for the performance of mobile applications, since it affects the time of data processing from the server, sometimes it also

includes the time of data transmission through communication channels. Bandwidth, payload size, throughput also affect the performance of mobile applications (Haider et al, 2026).

Representational State Transfer (REST) has been one of the dominant standards for a long time, thanks to its simplicity, HTTP methods, and stateless architectures, where the server does not store client data after the session ends, and any request can be processed by available servers, making it ideal for both microservices and cloud applications. GraphQL, a new architecture, initially presented by Facebook, is being used more recently for building APIs, because unlike REST, it uses the client-driven model, where the client determines in advance the data it needs, and processing in this way becomes more unburdened and reduces problems known as over-fetching and under-fetching, which in fact represent the lack or excess of data that the client receives, directly affecting the bandwidth of the API (Kanthed; 2023). GraphQL has the ability to reduce unnecessary data traffic, significantly improving efficiency and bandwidth, which directly affects the performance of mobile applications, especially when services are integrated as APIs (Quiña-Mera et al. 2022). The choice between GraphQL and REST varies and depends on many factors, however REST continues to be very widespread due to caching, simplicity, and especially for CRUD (Create, Read, Update, and Delete) operations (Iyer; 2026). However, GraphQL is more suitable when it comes to processing data from multiple sources, but to process it with a single request, which reduces the response time and improves the performance of executing client requests (Hakia; 2025). Figure 1 graphically presents the main difference between REST and GraphQL API, where, among other things, it is clearly seen that in the REST API, the client makes many requests and each of them is processed as a separate endpoint and each of them returns data from certain databases, which often result in missing or overloaded data. Whereas in GraphQL the client processes a request to the GraphQL endpoint, and the server returns the correct response to the request made, requesting data from all data structures, thereby reducing problems with over-fetching and communication channels in networks.

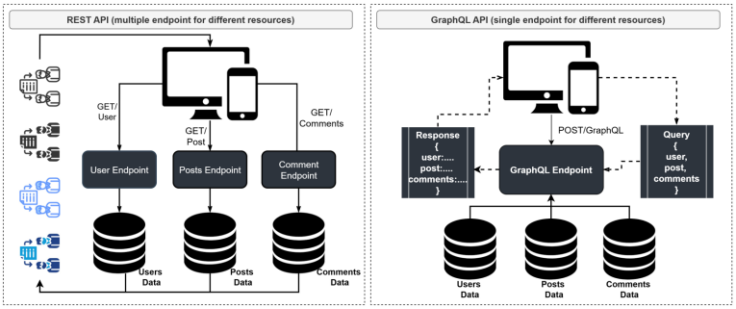


Figure 1. Visual comparison between REST API and GraphQL API

Background and related work

Recent research has shown an interest in the use and comparison between REST and GraphQL in the context of mobile applications and decentralized systems. However, each one has its importance depending on the context and the requests of the clients. In the analysis of Stępień & Skublewska-Paszkowska (2025), it is found that GraphQL reduces the size of the payload and the number of requests in the network, because the same are processed in a more organized form, and that there is no need for a client to make more than

one request, even if he needs services in different data structures, although again REST results faster in the execution of requests that are simpler and structured direct. Niswar et al (2024), studies the use of system resources in the execution of requests, and among other results and analyzes conclude that GraphQL is used and requires more CPU in the processing of complex queries, which depends on the client, if there are more requests for processing, while REST does not require a powerful CPU, because requests are processed one by one, and suggests that REST is more suitable when it comes to operational management in a more efficient way, while GraphQL if flexibility and better organization are required. Jin et al. (2024) investigates the performance in serverless architectures, where they come to the conclusion that GraphQL reduces the number of network requests and once provides the response in time faster than REST (that is, the final response with several client requests), and they support the position that GraphQL is more suitable for mobile applications with dynamic interfaces, where the number of requests is different and of different natures.
Recently, the migration from REST to GraphQL has been of great importance, where in the research of Amareen et al. (2026), a framework called GraphQLify is presented, which in automatic form by providing static analysis of the code offers migration, a phenomenon that significantly allows performance and response time reduction. The reason why performance is permitted is that only the necessary data is fetched, there is no network overhead, it avoids bugs during migration, it guarantees type mismatch, and out of 834 tested APIs, the study has shown high success. Through Table 1, we have compared these two architectural styles for creating mobile applications, based on the most important characteristics such as endpoints, flexibility, scalability, performance, and others.

Table 1. Comparison of key features between REST API and GraphQL API

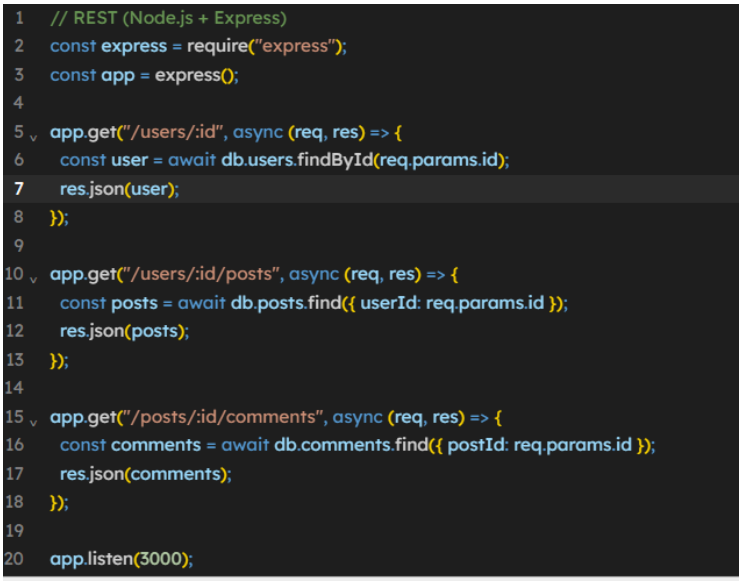
Characteristics	**REST API**	**GraphQL API**
Endpoints	Uses multiple endpoints, for each client request from one endpoint	One endpoint for further client requests, collects all data and returns responses
Data processing	The response is predetermined by the server, there may be a lack of data or an excess	The data is specified depending on the request and the answer is concrete
Number of requests	It processes multiple requests to retrieve more data from multiple data structures	It processes a query (multiple requests) and the response is unified from all data structures
Caching	It uses standard HTTP mechanisms, with less traffic, lower latency and longer battery life	Use POST /graphql, the queries are dynamic, use object IDs
Server	Simple maintenance, without any complex architecture and design	It requires more complex architectures, schemes for efficient query management
Performance in mobile applications	Good for direct and not many requests, fast and very simple in execution	Reduction of bandwidth, optimization of requests, in complex scenarios, more effective and faster
Scalability	Implemented in a longer time, stable and practically	It requires careful optimization, clearly

	proven for scalability, despite the disadvantages in processing	defined schemes for query processing, good practical results
Suitability for mobile applications	Simple mobile applications	Complex mobile applications, and with dynamic requirements

Despite the advantages and disadvantages of both paradigms, it is worth emphasizing that features such as security, privacy, secure query management, transparency, decentralization, and even immutability and integrity preservation remain as issues of particular importance for study. These features are only achieved by implementing these APIs with blockchain systems (Rustemi et al. 2023). In these blockchain systems, REST is mainly used for simple processing and transaction mediation, while GraphQL is used for more complex queries of data stored in blockchain storage.

Experimental analysis of REST and GraphQL API in mobile applications

To do an analysis between REST API and GraphQL, we have created a prototype with two separate services on the same dataset. The dataset contains 1000 users, 10 000 posts and 50 000 comments stored in JSON (MongoDB). The goal is simple, to just get data from users, posts and comments, and at the same time measure performance metrics. The measurements were performed using a test script, which generates approximately 100 requests for each scenario, with 10 parallel users, in a local environment with a latency of approximately 80ms to adapt to mobile conditions. For each API, the average response time, percentiles, payload size, number of requests per operation, throughput, among others, were recorded. From the results we have summarized, it follows that REST requires an average of 3 requests for an operation, with an average response time of 471ms (median around 452ms, percentiles 538ms), and a total payload of around 129KB. On the other hand, GraphQL performs the same operation, making only a single request, with an average time of 219ms (median 205ms, percentiles 262ms) and a payload of around 72KB. This means that GraphQL has the best performance and time with almost the same result. To test both the complexity and simplicity of REST versus GraphQL, a simpler scenario was also tested, just the user profile, where REST performed slightly better than GraphQL, 120ms versus 140ms. The over-fetching property of REST was also proven, where REST, in addition to sending fixed JSON structures, resulted in sending about 44% of the data capacity per operation, which directly affects mobile networks and bandwidth. Also using Prometheus, an open source system, CPU usage was monitored, and it turned out that GraphQL uses 20-30% more CPU than REST, which once again proves the accuracy of the research that GraphQL optimizes network and latency, while REST optimizes simplicity and cost. Similar practical results have been concluded by Stępień & Skublewska-Paszkowska (2025), where they conclude, among other things, reduced payload and better results for more complex scenarios, and better REST performance for simpler operations. In Figure 2 we have presented the minimal server in Node.js, respectively the code for implementing the REST API for specific endpoints.



```
// REST (Node.js + Express)
const express = require("express");
const app = express();

app.get("/users/:id", async (req, res) => {
  const user = await db.users.findById(req.params.id);
  res.json(user);
});

app.get("/users/:id/posts", async (req, res) => {
  const posts = await db.posts.find({ userId: req.params.id });
  res.json(posts);
});

app.get("/posts/:id/comments", async (req, res) => {
  const comments = await db.comments.find({ postId: req.params.id });
  res.json(comments);
});

app.listen(3000);
```

Figure 2. Execution of specific queries for 3 different types of requests in the REST API

Figure 3 shows a code sequence showing the client-side, which shows how a mobile application communicates with the REST API to retrieve data. Initially, the request for user retrieval is branched, via id, respectively the number at the end indicates the user's ID. Then the request for retrieving the user's mailing list is sent, and requests for retrieving comments for each post. Through Promise.all, the requests are made in parallel up to the last comments.



```
// Client (REST)
const user = await fetch("/users/1").then(r => r.json());
const posts = await fetch("/users/1/posts").then(r => r.json());
const comments = await Promise.all(
  posts.map(p => fetch(`/posts/${p.id}/comments`).then(r => r.json()))
);
```

Figure 3. Client-side code sequence of requests executed in REST API

Figure 4 shows a code sequence taken from Node.js, implemented in Apollo Server, where a graphql server is created, the data schema is defined and how the same will be retrieved from the server. The endpoint is opened on port 4000, the library where Apolloserver creates the GraphQL server is imported, and the query that is written is actually the input to the API, where the client can request the data later, on the client side.

```
// GraphQL (Apollo Server)
const { ApolloServer, gql } = require("apollo-server");

const typeDefs = gql`
  type User {
    id: ID!
    name: String!
    posts: [Post]
  }
  type Post {
    id: ID!
    title: String!
    comments: [Comment]
  }
  type Comment {
    id: ID!
    text: String!
  }
  type Query {
    user(id: ID!): User
  `;

const resolvers = {
  Query: {
    user: (_, { id }) => db.users.findById(id),
  },
  User: {
    posts: (user) => db.posts.find({ userId: user.id }),
  },
  Post: {
    comments: (post) => db.comments.find({ postId: post.id }),
  },
};

const server = new ApolloServer({ typeDefs, resolvers });
server.listen({ port: 4000 });
```

Figure 4. Server-side code sequence that integrates the GraphQL API

Figure 5 shows a code sequence, where the client sends a request to a GraphQL API and receives data related to a single query. From the code sequence we see that the user with id 1 is requested, and from the same user the name, posts are requested, where in each post the title, comments are requested, and for each comment the text that is stored on the server side is requested. The response received at the end is converted to JSON, which is actually a structured form of data representation.

```graphql
// Client (GraphQL)
const query = `
query {
  user(id: "1") {
    name
    posts {
      title
      comments {
        text
      }
    }
  }
}`;
const data = await fetch("/graphql", {
  method: "POST",
  headers: { "Content-Type": "application/json" },
  body: JSON.stringify({ query })
}).then(r => r.json());
```

Figure 5. Client-side code sequence for executing a query in the GraphQL API

Discussion and future trends in API

Data read and modify operations in REST API and GraphQL differ in the way the client and server interact. In REST, operations are performed through get, post, and put methods, where each endpoint represents a separate resource. This makes REST simpler and more standard for uses where performance and time efficiency are not required. GraphQL uses query and mutation to provide more flexible services, where the client determines the exact structure of the response. In other words, GraphQL offers greater control over data, and reduces the complexity of operations in mobile applications (Nnamdi, 2024). GraphQL performs much better in complex scenarios where complex data is requested from the client, while REST often requires consecutive requests to retrieve data from different sources from the same client, which directly impacts network latency and bandwidth (Jin, 2025). Regarding mutations, REST uses separate queries for CRUD operations, while GraphQL uses mutation as a centralized mechanism, which although it gives greater flexibility, on the other hand increases the risk of uncontrolled complexities and DoS attacks if restrictions and security mechanisms are not implemented (Tsai et al., 2025). Recent research shows increasing adoption of GraphQL in mobile applications, especially those with dynamic interfaces and architectures such as microservices and serverless (Devalla, 2024). In other words, REST is suitable for simpler and more stable systems, since REST implementation is much longer than GraphQL, while GraphQL offers advantages in performance-oriented mobile services. Although there is an attempt to move REST towards GraphQL, both are still used today, creating a hybrid ecosystem where both technologies interact in hybrid environments (Amareen et al., 2026). Figure 6 presents future implementations of APIs, which, among other things, shows the combination of REST, GraphQL and gRPC architectures in one ecosystem, implementation of AI tools for automatic generation, documentation and testing, respectively for intelligent query optimization, real-time monitoring, focus on optimization and bandwidth, and more.

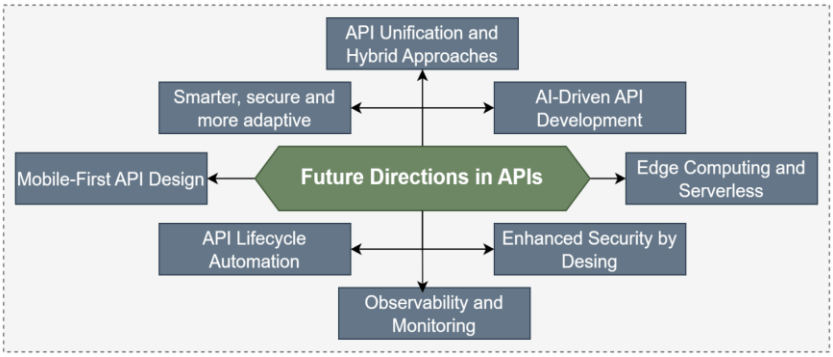


Figure 6. Future trends of implementing APIs

5. Conclusion

The development and combination of contemporary technologies play an important role in creating flexible and more easily integrated ecosystems with the demands of users and technologies in general. The development of APIs and the adoption of hybrid architectures is an important process in adapting to the different requirements of systems that change depending on the circumstances and environment in which they are implemented. REST API and GraphQL offer different models that directly affect how data is managed and protected. REST is characterized by security mechanisms such as authentication, authorization, and caching. GraphQL requires more advanced control mechanisms, input validation, and complexity constraints. In terms of privacy, both face different challenges in terms of processing personal data. GraphQL, because it precisely specifies fields, reduces the risk of accessing private data, but at the same time, even a weak configuration can lead to unauthorized access to data. REST API, because of its flexibility and fixed structure, often offers the risk of over-sharing information. In terms of ethical and legal issues, the design of architectures that use APIs must respect principles such as data transparency, minimization, and control of the information that is generated. GraphQL is considered more ethical because it provides a more ethical and consolidated response compared to REST which can distribute information that is in conflict with the client's ethical issues. Both paradigms offer good opportunities for accessing data through APIs, but also risks that must be carefully managed, and greater ethical awareness in the development of modern systems. Through the paper, in addition to describing the advantages and disadvantages of these two paradigms, we also provided some practical implementation sequences, including experimental analysis to reinforce the evidence that GraphQL has advantages in some aspects compared to REST API, but that both paradigms are still widely used by developers today.

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SLEEP PHYSIOLOGY

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Abstract

Sleep is a complex and essential biological process that plays a fundamental role in maintaining physical and mental health. This paper provides a comprehensive overview of the physiological mechanisms underlying sleep, including circadian rhythms, sleep homeostasis, sleep stages, neural regulation, and sleep disorders. The circadian rhythm, controlled by the suprachiasmatic nucleus, regulates the sleep–wake cycle in response to environmental light, while sleep homeostasis reflects the body's need for sleep based on prior wakefulness. Sleep is divided into two main phases: non-rapid eye movement (NREM) and rapid eye movement (REM), which alternate cyclically throughout the night. NREM sleep is primarily associated with physical restoration, whereas REM sleep plays a key role in memory consolidation, emotional processing, and cognitive function. The neural control of sleep involves complex interactions between the hypothalamus, brainstem, thalamus, and cortical networks. Additionally, this paper discusses common sleep disorders such as insomnia, obstructive sleep apnea, narcolepsy, and somnambulism, highlighting their impact on overall health. Understanding sleep physiology is essential for recognizing the importance of sleep and improving approaches to sleep-related disorders.

Keywords: Sleep physiology, circadian rhythm, REM sleep, NREM sleep, sleep disorders

Introduction

Sleep is a fundamental biological process essential for maintaining the normal functioning of the human body. Despite appearing as a passive state, sleep is an active and highly regulated physiological process involving complex interactions between neural, hormonal, and metabolic systems. Its importance extends beyond rest, playing a critical role in physical recovery, cognitive performance, emotional regulation, and overall health.

The significance of studying sleep physiology has increased in recent years due to the growing prevalence of sleep-related disorders and their impact on quality of life. Disruptions in sleep are associated with a wide range of health problems, including metabolic, cardiovascular, and neurological conditions. Therefore, understanding the mechanisms that regulate sleep is essential for both clinical practice and preventive healthcare.

This paper focuses on the physiological mechanisms underlying sleep, with particular emphasis on circadian rhythms, sleep homeostasis, sleep stages, and neural regulation. The circadian system, controlled by the suprachiasmatic nucleus of the hypothalamus, synchronizes the sleep–wake cycle with environmental light–dark patterns. In parallel, sleep homeostasis regulates the need for sleep based on prior wakefulness, ensuring a dynamic balance between sleep and alertness.

The objective of this paper is to provide a comprehensive overview of sleep physiology and its regulatory systems, as well as to discuss the main stages of sleep and their functional significance. Additionally, common sleep disorders are briefly presented in order to highlight the clinical relevance of normal sleep mechanisms.

By analyzing these aspects, this work aims to emphasize the importance of sleep as a vital component of human health and to contribute to a better understanding of its physiological basis.

Body of Manuscript

2.1 Sleep Physiology : Sleep is regulated by two key biological mechanisms: the circadian rhythm and sleep homeostasis. These systems interact to control the timing, duration, and quality of sleep.
The circadian rhythm is an internal 24-hour biological clock regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus. It synchronizes physiological processes such as hormone secretion, body temperature, and the sleep–wake cycle with environmental light–dark changes. Light exposure inhibits melatonin secretion, promoting wakefulness, whereas darkness stimulates melatonin production and facilitates sleep.
Sleep homeostasis reflects the body's need for sleep based on prior wakefulness. During wakefulness, substances such as adenosine accumulate in the brain, increasing sleep pressure. During sleep, particularly deep sleep, these substances decrease, restoring physiological balance.

2.2 Stages of Sleep: Sleep is a dynamic process divided into two main phases: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. These stages occur in cycles that repeat several times throughout the night.

2.2.1 NREM Sleep: The N1, N2, and N3 stages constitute non-rapid eye movement (NREM) sleep and account for approximately 75% of total sleep time. These stages are characterized by a gradual transition from light to deep sleep, accompanied by progressive changes in brain activity, physiological functions, and level of consciousness.
Stage N1 is the initial stage of sleep and is considered very light sleep. It occurs during the transition from wakefulness to sleep and typically lasts 1–5 minutes. During this stage, brain activity shifts from alpha waves to low-amplitude theta waves. The body begins to relax, although muscle tone is still present and breathing remains regular. Brief muscle contractions, known as *hypnic jerks*, may occur, and individuals often experience a sensation of falling. This is the stage in which a person can be easily awakened and may not perceive it as actual sleep.
Stage N2 represents a deeper level of sleep and is the longest stage, accounting for approximately 45–50% of total sleep time. During this stage, physiological functions slow significantly: heart rate decreases, body temperature drops, and muscles relax further. Brain activity is characterized by two distinct patterns: *sleep spindles* and *K-complexes*. Sleep spindles are short bursts of neural activity associated with information processing and protection of sleep from external stimuli, while K-complexes are high-amplitude waves that help stabilize sleep and contribute to memory consolidation. Bruxism (teeth grinding) may also occur during this stage. As the night progresses, the duration of N2 sleep gradually increases.
Stage N3 is the deepest stage of NREM sleep and is also known as *slow-wave sleep*. It is characterized by the presence of delta waves, which have low frequency and high amplitude. This stage is essential for physical restoration, as processes such as tissue repair, muscle growth, growth hormone secretion, and immune system strengthening occur. It is very difficult to awaken a person during this stage, and if awakened, they often experience temporary confusion and fatigue, known as *sleep inertia*. Phenomena such as sleepwalking (somnambulism), night terrors, and involuntary urination may also occur during this stage. N3 sleep is more prominent in the first half of the night and decreases as sleep cycles progress.

2.2.2 REM Sleep: REM sleep is one of the most important stages of sleep and accounts for approximately 20–25% of total sleep time in adults. It typically begins about 90 minutes after sleep onset and recurs several times throughout the night, with progressively longer durations in later cycles. This stage is characterized by high brain activity similar to wakefulness, while the body is in a state of temporary muscle paralysis (atonia), which prevents the physical enactment of dreams.

One of the main features of REM sleep is the presence of vivid and intense dreaming. Cerebral activity increases significantly, and brain oxygen consumption may rise by up to 20%, indicating high neuronal metabolism. During this stage, eye movements are rapid and repetitive, while breathing and heart rate become more irregular. Despite this increased brain activity, skeletal muscles remain relaxed and almost completely immobile, except for the muscles involved in breathing and eye movements.

REM sleep plays a crucial role in cognitive and emotional functions. It is closely associated with memory consolidation, particularly emotional and procedural memory, as well as learning and creativity. Additionally, REM sleep contributes to emotional processing and the reduction of psychological stress, supporting overall emotional stability.

During this phase, neurochemical changes also occur, such as increased levels of acetylcholine (ACh), which stimulate brain activity. At the same time, the autonomic nervous system becomes more active, leading to fluctuations in blood pressure and heart rate. Another characteristic phenomenon is genital tumescence (penile or clitoral), which occurs regardless of dream content.

In conclusion, REM sleep is essential for mental health and optimal brain function. It complements the restorative processes that occur during NREM sleep by providing not only physical rest but also the reorganization and processing of information in the brain.

2.3 Neural Control of Sleep: Sleep is not controlled by a single anatomical center in the brain, but rather by a complex and integrated network of neural structures that interact to regulate its initiation, maintenance, depth, and rhythm. However, the hypothalamus is considered the primary region in sleep regulation, as it contains nuclei involved both in promoting sleep and synchronizing the sleep–wake cycle with circadian rhythms.

One of the most important structures is the ventrolateral preoptic nucleus (VLPO), which plays a key role in initiating sleep. Its neurons secrete inhibitory neurotransmitters, mainly GABA and galanin, which suppress the systems responsible for wakefulness, including monoaminergic and cholinergic centers in the brainstem and hypothalamus. In this way, the VLPO acts as a "functional switch" that facilitates the transition from wakefulness to sleep.

Another essential structure is the suprachiasmatic nucleus (SCN), known as the body's "biological clock." The SCN receives direct input from the retina through the retinohypothalamic tract and synchronizes biological rhythms, including the sleep–wake cycle, according to the light–dark cycle. Although it does not directly induce sleep, it determines the biological timing when the organism is predisposed to sleep. Through its connections with the pineal gland, the SCN regulates the secretion of melatonin, a hormone that promotes sleep onset.

In addition to the hypothalamus, the brainstem plays a crucial role in regulating consciousness and the transition between wakefulness and sleep, particularly through the ascending reticular activating system (ARAS). This system consists of neuronal groups in the midbrain, pons, and medulla oblongata, which project to the thalamus, hypothalamus, and cerebral cortex. The

ARAS is responsible for maintaining wakefulness, alertness, and cortical activity. Its neurons use excitatory neurotransmitters such as norepinephrine, serotonin, dopamine, histamine, and acetylcholine. During sleep onset, the activity of this system decreases, while during wakefulness it increases, demonstrating that sleep is an active and regulated process rather than a passive state.

The thalamus also plays an important role, especially during NREM sleep, acting as a filter for sensory information reaching the cerebral cortex. During deep sleep, this transmission is significantly reduced, effectively isolating the brain from external stimuli. An important component is the thalamic reticular nucleus (TRN), which is involved in generating sleep spindles characteristic of stage N2.

The cerebral cortex and thalamocortical networks also contribute to sleep regulation. During NREM sleep, cortical activity becomes more synchronized and appears on EEG as slow waves, whereas during REM sleep, brain electrical activity resembles that of wakefulness. REM sleep is primarily controlled by brainstem structures, particularly in the pons, where circuits regulate dreaming, rapid eye movements, and muscle atonia.

From a functional perspective, sleep regulation is often explained by the "flip-flop switch" model, in which sleep-promoting and wake-promoting systems mutually inhibit each other. Dominance of the VLPO leads to sleep, while activation of wake-promoting systems maintains consciousness. This mechanism explains the rapid and stable transitions between sleep and wakefulness.

An important role in stabilizing wakefulness is also played by orexin (hypocretin), a neuropeptide produced in the lateral hypothalamus. Orexin helps maintain wakefulness and prevents sudden transitions into sleep; its deficiency is associated with disorders such as narcolepsy.

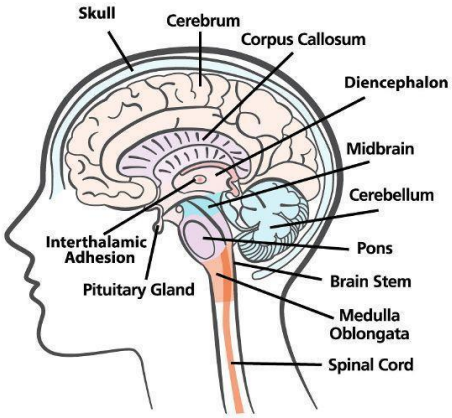


Figure 1. Centrals of sleep in the brain

2..4 Sleep Cycle: The sleep cycle represents a periodic process in which the body repeatedly passes through different stages of sleep during the night. A complete cycle includes the transition from non-REM (NREM) sleep to REM sleep and typically lasts about 90–110 minutes. During a normal night, an individual usually goes through 4–6 such cycles.

The sleep cycle begins with the stages of NREM sleep. Initially, the individual enters stage N1, which represents the transitional phase from wakefulness to sleep and is characterized by a gradual reduction in brain activity, muscle relaxation, and slowing of physiological processes. Sleep then progresses to stage N2, where it becomes more stable and deeper. In this stage, heart

rate and body temperature decrease, while brain activity is characterized by specific structures such as sleep spindles and K-complexes, which help stabilize sleep and process information. Following this, the body reaches stage N3, known as deep or slow-wave sleep. This stage is essential for physical recovery, as processes such as tissue repair, muscle growth, and immune system strengthening occur.

After completing the NREM stages, the body transitions into REM (Rapid Eye Movement) sleep. In this phase, brain activity increases and resembles that of wakefulness, while the body experiences temporary muscle paralysis. REM sleep is associated with vivid dreaming and plays a key role in memory consolidation, learning processes, and emotional regulation.

Throughout the night, the structure of sleep cycles changes progressively. In the early cycles, deep sleep (N3) predominates and is more important for physical recovery. In later cycles, REM sleep duration increases and is more closely associated with cognitive and emotional functions. This organization of sleep cycles is essential for optimal brain function and overall well-being.

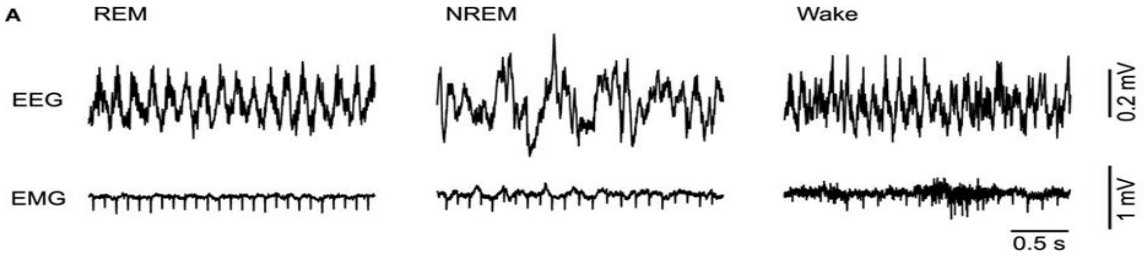


Figure 2. Sleep cycle showing progression of NREM and REM stages

2.5 Sleep disorders : Sleep disorders, also known as disturbances of sleep, are conditions that affect the quality, duration, or normal rhythm of sleep. These disorders can negatively impact both physical and mental health, leading to fatigue, decreased concentration, irritability, and impaired daily functioning.

Sleep problems are common and are often behavioral in origin, influenced by factors such as a child's temperament and development, parenting style, parent–child interactions, and environmental conditions. Additionally, parasomnias may occur, which are undesirable episodic behaviors associated with sleep. Nightmares occur during REM sleep, usually in the early morning, and are most common in school-aged children, although they are also observed in approximately 1.9–3.9% of preschool children.

2.6 Clinical Conditions:

2.6.1 Insomnia: Insomnia is a general term for conditions that cause difficulty in falling asleep or maintaining sleep. It is the most common sleep disorder and is typically associated with psychological stress, poor sleep environments, irregular sleep schedules, or excessive mental, physical, or chemical stimulation.

2.6.2 Obstructive Sleep Apnea (OSA): Obstructive sleep apnea is a disorder characterized by repeated episodes of interrupted breathing during sleep due to airway obstruction, often caused by obesity or weakened pharyngeal muscles. When the airway collapses, breathing stops, and hypoxia forces the body to awaken from deep sleep to resume breathing. When this occurs repeatedly throughout the night, restful sleep becomes impossible.

OSA is classified into three severity levels:

[1] Mild: 5–14 apnea episodes per hour
[2] Moderate: 15–30 episodes per hour
[3] Severe: more than 30 episodes per hour

The primary treatment is positive airway pressure therapy, including:

[1] Continuous Positive Airway Pressure (CPAP)
[2] Bilevel Positive Airway Pressure (BiPAP)

CPAP provides continuous pressure to keep the airway open, while BiPAP alternates between two pressure levels, improving ventilation. Additional treatments include mandibular advancement devices and surgical interventions such as uvulopalatopharyngoplasty, adenotonsillectomy, and maxillomandibular advancement. However, the main treatment remains non-surgical positive airway pressure therapy.

2.6.3 Central Sleep Apnea: Central sleep apnea is similar to obstructive sleep apnea but differs in its underlying cause. It results from reduced or absent respiratory drive during sleep due to dysfunction in the brain's respiratory control mechanisms. Conditions associated with central sleep apnea include congenital central hypoventilation syndrome (Ondine's curse) and congestive heart failure.

When breathing becomes ineffective, the body awakens from deep sleep to correct hypoxia. Treatment options include CPAP, BiPAP, adaptive servo-ventilation, and pharmacological therapy such as acetazolamide or theophylline.

2.6.4 Mixed Sleep Apnea (Complex Sleep Apnea): Mixed sleep apnea is a combination of obstructive and central sleep apnea. It occurs when patients with obstructive sleep apnea develop central sleep apnea symptoms after treatment with CPAP during a sleep study.

Treatment usually involves CPAP therapy at lower pressure levels.

2.6.5 Ghrelin–Leptin Imbalance: Sleep duration plays an important role in maintaining body weight. An imbalance between two key hormones regulating hunger—leptin and ghrelin—is associated with altered sleep patterns. Leptin, produced by adipose tissue, reduces appetite and regulates energy balance. Ghrelin, produced in the gastrointestinal tract, stimulates appetite.

Short sleep duration is associated with decreased leptin and increased ghrelin levels, which may lead to increased appetite and higher body mass index (BMI). This imbalance is often associated with obstructive sleep apnea, as increased BMI is a major risk factor for its development. The primary intervention is maintaining consistent sleep of 7–8 hours per night.

2.6.6 Narcolepsy: Narcolepsy type 1 occurs when there is a near-complete loss of neurons that produce orexin (hypocretin). The mechanism of narcolepsy type 2 is less clear but is thought to involve a partial loss of these neurons.

During normal REM sleep, orexin levels decrease, reducing activity in the reticular activating system (RAS) and promoting muscle atonia. In narcolepsy type 1, insufficient orexin leads to instability between sleep and wake states. The RAS fails to consistently maintain wakefulness and cannot properly inhibit sleep-promoting systems such as the VLPO.

This results in sudden transitions between sleep and wakefulness and allows REM-related phenomena to occur during wakefulness. Symptoms include excessive daytime sleepiness, cataplexy, and sometimes hallucinations triggered by strong emotions. Many individuals with narcolepsy also experience insomnia.

2.6.7 Somnambulism (Sleepwalking): Somnambulism is a condition that combines elements of sleep and wakefulness, resulting in sleepwalking. It occurs when an individual performs actions or walks without conscious awareness and has no memory of the event.
Although not fully understood, it is associated with increased slow-wave sleep and sleep deprivation, and there is evidence of a genetic component. The primary treatment involves the use of benzodiazepines.

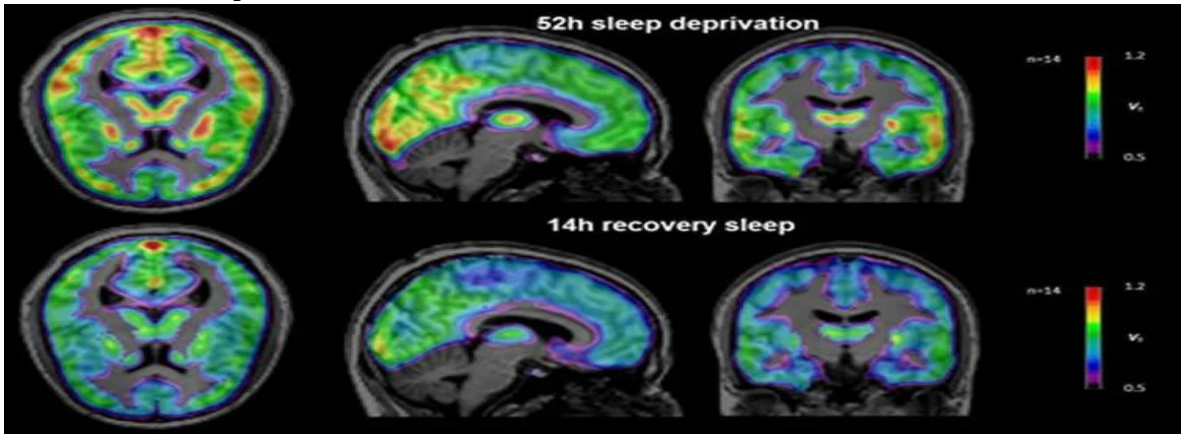


Figure 3. Sleep deprivation

Conclusions

Sleep is a fundamental biological process essential for maintaining physical health, cognitive performance, and emotional stability. It is a complex and highly regulated process involving the interaction of neural, hormonal, and physiological mechanisms that control the sleep–wake cycle.
The different stages of sleep, including NREM and REM sleep, play distinct yet complementary roles in restoring the body and optimizing brain function. NREM sleep is primarily associated with physical recovery, tissue repair, and immune function, while REM sleep is crucial for memory consolidation, learning, and emotional regulation.
Disruptions in normal sleep patterns can lead to a variety of sleep disorders, such as insomnia, sleep apnea, and narcolepsy, which can significantly impair daily functioning and overall health. These conditions highlight the importance of maintaining proper sleep hygiene and understanding the underlying physiological mechanisms of sleep.
In conclusion, sleep is not merely a passive state of rest but an active and essential process that supports overall well-being. A deeper understanding of sleep physiology is important for improving clinical approaches to sleep disorders and promoting better health outcomes

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THREE YEAR 2023-2025 COMPERATIVE ANALYSIS OF WATER QUALITY IN VILLAGE VRUTOK, IMPLICATIONS FOR 3D FOOD BIOTECHNOLOGY AND MOLECULAR STABILITY

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Abstract

Water safety and quality constitute the main pillar in the modern food production industry, especially in innovative sectors such as 3D printing and functional food design. This study aims to analyze the three-year (2023-2025) performance of critical physicochemical parameters, pH, chlorides, nitrites and dissolved oxygen, assessing their impact on molecular stability and food technology. The study was based on monthly monitoring of water samples and their processing through descriptive statistics and Pearson correlation matrices. Special focus was given to the standard deviation to measure the stability of the environment and the correlation coefficients to understand the interdependence of the parameters. The findings demonstrate a high stability of the aquatic environment. The pH value resulted in an average of 7.6, with a minimal standard deviation (0.12 - 0.14), confirming an excellent "buffer" capacity. Correlation analysis revealed an extremely strong negative relationship between chlorides and dissolved oxygen, which peaked in 2025 with a value of r = -0.96. From a toxicological point of view, nitrites experienced a modest increase from 0.004 mg/l in 2024 to 0.012 mg/l in 2025, but remained significantly below the critical allowed limits. The stability of the pH proves that this water is ideal for 3D technology, as it guarantees constant viscosity of food "colors" and prevents denaturation of proteins. However, the strong chloride-oxygen correlation suggests that the increase in salinity must be carefully monitored to prevent lipid oxidation and degradation of nutrients in the printed matrices. Finally, the results confirm that the water chemical profile during the years 2023-2025 provides a reliable basis for applications in molecular biology and advanced nutrition, guaranteeing high repeatability in biotechnological processes.

Keywords: 3D food technology, molecular biology, correlation matrix, pH stability, dissolved oxygen.

Introduction

In the era of modern biotechnology, the role of water has evolved from a simple component to a complex matrix that determines the molecular fate of food products. As highlighted in recent studies on the biophysics of aquatic environments, water acts as an “active biomolecule” that dictates protein folding and enzyme stability through a network of hydrogen bonds [1]. This paper examines the three-year (2023-2025) dynamics of water quality, analyzing how variations in pH, chlorides, nitrites, and oxygen affect the stability of 3D printed food structures.

The rapid development of 3D Food Technology requires rigorous control of the rheology of food “inks”. The integrity of printed structures directly depends on electrostatic forces in the aqueous environment [2]. A high pH stability (which in this study results in an average of 7.6) is critical; small fluctuations can cause protein denaturation or viscosity changes, leading to mechanical structure failure [3].

On the other hand, the interdependence between chlorides and dissolved oxygen poses a challenge for molecular nutrition. Research suggests that high salinity environments alter the hydration of macromolecules, accelerating oxidative processes [4]. This study identifies a

strong negative correlation (r = -0.96), indicating that the reduction of oxygen in the presence of chlorides increases the risk of degradation of sensitive vitamins and antioxidants in the food matrix.

Using descriptive statistics and correlation matrices, this paper argues that a consistent chemical profile is a prerequisite for innovation. Monitoring nitrites remains a priority for toxicological safety, preventing cellular damage and the formation of carcinogenic compounds, aspects that have been extensively addressed in the literature on oxidative stress and systems biology [5]. This study provides a predictive model for quality control, serving as a bridge between environmental chemistry and advanced food engineering.

Materials and Methods

The research was conducted as a longitudinal study on water quality monitoring for the period January 2023 - December 2025, where samples were collected on a monthly basis (N=36) at fixed monitoring points using sterile polypropylene bottles (500 ml) treated with HNO_3 and stored at 4°C, according to standard protocols [1]. The determination of physicochemical parameters was performed through sensor technology and standard methods, where pH was measured with a HI98191 digital pH meter (calibrated at pH 4.01, 7.01, 10.01), chlorides (Cl^-) through titration with $AgNO_3$ according to ISO 9297 [2], nitrites (NO_2^-) with UV-spectrophotometry (540 nm) through the Griess method [3], and dissolved oxygen (O_2) in-situ with an optical probe. To evaluate the applicability in 3D technology, alginate and starch-based "food ink" formulas were simulated, where the analyzed water served as a hydrating phase for rheology monitoring in relation to pH and conductivity [4]. Data processing was performed in IBM SPSS Statistics 26, applying descriptive statistics for annual stability and Pearson correlation coefficient (r) for parametric interdependence, while experimental precision was guaranteed through triplicate analyses (n=3). Finally, toxicological and nutritional evaluation was performed by comparing nitrite levels with EU (98/83/EC) and WHO standards [5], while oxygen stability was analyzed through lipid oxidation kinetic models to predict the molecular integrity of printed products [6].

Table 1: Physicochemical stability analysis of the hydration phase

Month	pH	Chlorides (Cl^-) [mg/l]	(NO_2^-) [mg/l]	Oxygen(O_2) [mg/l]
January	7.6	12.4	0.01	8.4
February	7.5	11.8	0	8.6
March	7.7	10.9	0	8.2
April	7.8	13.5	0.02	7.9
May	7.6	14.2	0.01	7.5
June	7.4	15.6	0.03	7.1
Mean	7.6	13.07	0.012	7.95
Standard deviation	0.14	1.67	0.012	0.58

The results of the six-month monitoring (Table 1) show a high stability of the physicochemical parameters, where the average pH value of 7.6 \pm 0.14 confirms a slightly alkaline environment, which prevents unwanted acidic gelation during hydration of the alginate matrices [4]. The chloride concentration marked a gradual increase from January (12.4 mg/l) to June (15.6 mg/l), with an average of 13.07 \pm 1.67 mg/l, remaining within the limits specified by ISO 9297 [2] and without negatively affecting the conductivity of the "food ink" formula. Regarding toxicological safety, nitrite levels (NO_2^-) were minimal with an average of 0.012 mg/l, a value that is significantly below the strict limit of 0.50 mg/l set by EU Directive 98/83/EC and WHO [5]. Meanwhile, the drop in dissolved oxygen from 8.4 mg/l in January to 7.1 mg/l in June reflects the thermal impact on dissolved gas dynamics, a critical factor that, according to kinetic models, plays a primary role in preventing lipid oxidation and preserving the molecular integrity of the final 3D printed product [6].

Table 2: Correlation matrix - year 2023 parameters

Parameters	pH	Chlorides (Cl^-)	(NO_2^-)	Oxygen(O_2)
Ph	1	-0.63	-0.58	0.53
Chlorides (Cl^-)	-0.63	1	0.86	-0.96
(NO_2^-)	-0.58	0.86	1	-0.82
Oxygen(O_2)	0.53	-0.96	-0.82	1

To understand the dynamics of the interdependence between the parameters during 2023, the Pearson correlation matrix was applied (Table 2). The results show an extremely strong negative correlation between chlorides (Cl^-) and dissolved oxygen (O_2), with a value of r = -0.96. This result is in line with the physicochemical principles where increasing salinity (salt concentration) reduces the solubility of gases in water, a factor that directly affects the oxidative stability of 3D food formulas [6]. Also, a high positive correlation was observed between chlorides and nitrites (r = 0.86), suggesting a common origin of the mineral load, potentially from surface runoff or seasonal changes in the monitoring points [1]. The negative correlation between pH and chlorides (r = -0.63) indicates that increasing the concentration of salts tends to slightly lower the pH of the sample, potentially affecting the viscosity of alginate-based food ink, which is quite sensitive to ionic fluctuations [4]. Finally, the negative correlation between nitrites and oxygen (r = -0.82) reflects redox processes in the aquatic environment, where the high presence of nitrites is often associated with oxygen consumption, a critical indicator for predicting the shelf life of printed products [3], [5].

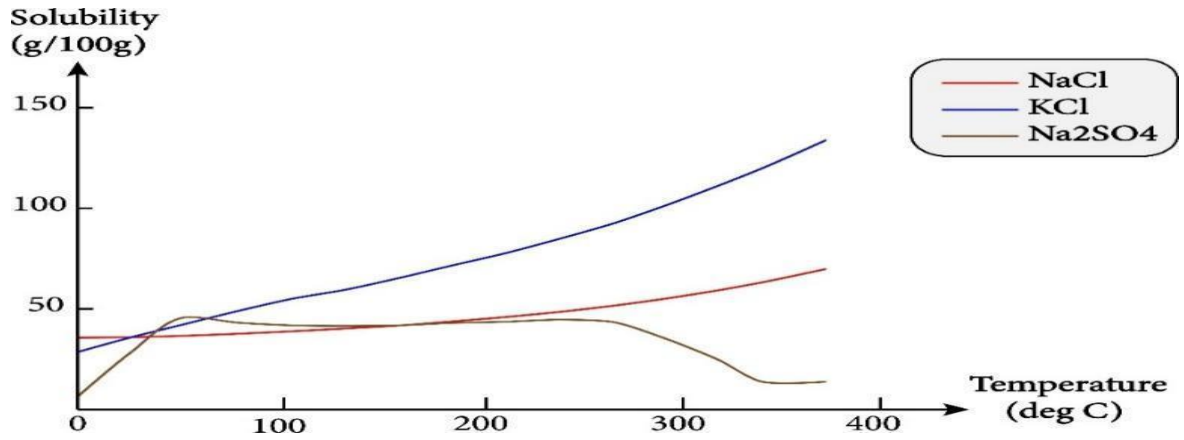


Figure 1: Results of physicochemical water analyses for the first months of 2023

The figure above illustrates the solubility kinetics of the main salts (NaCl, KCl, and Na_2SO_4) as a function of temperature, providing a theoretical framework for understanding the "hot spots" of ionic interdependence observed in this study. The linear increase in the solubility of NaCl and KCl serves as an explanatory model for the positive correlation between chlorides and nitrites (r = 0.86), where the increase in the solubility capacity of the hydration phase allows for a higher accumulation of mineral charge, directly affecting the electrical conductivity of the "food ink" [4, 8]. In particular, the nonlinear behavior of Na_2SO_4 indicates that drastic changes in temperature can cause precipitation of salts, a phenomenon that would destabilize the alginate matrix and compromise the precision of 3D printing at the microscopic level [1]. This solubility profile supports our hypothesis that strict control of temperature and ionic charge is necessary to maintain the kinetic barrier against oxidative stress, ensuring that water remains an optimal “buffer” environment for maintaining the molecular integrity of the final product [3, 6].

Table 2: Comparison of the Main Correlation (Chlorides and Oxygen)

Year	Correlation(Cl^- O_2)	scientific interpretation
2023	-0.96	Extremely strong negative correlation.
2024	-0.81	Strong connection, but more stable than in 2023
2025	-0.96	Return to high environmental sensitivity

The conclusions of this three-year study (2023–2025) confirm that the stability of the hydration phase is the deterministic prerequisite for the success of 3D food technology and the maintenance of nutritional density. The year 2024 was identified as the period with the highest technical predictability, where the minimum chloride deviation (1.52) guaranteed a constant electrical conductivity, enabling a precise extrusion of the "food ink" and preventing geometric deformations at the microscopic level [4, 8]. From a molecular biology and nutrition perspective, maintaining a stable pH (7.6–7.7) served as a primary protection for sensitive macromolecules such as vitamins and antioxidants, preventing acid stress that causes protein denaturation, a principle documented in Nature biopolymer structure studies [1, 7].

In terms of toxicology, although a slight fluctuation of nitrites was observed in 2025 (0.012 mg/l), their presence well below the WHO and EU limits eliminates the risk of the formation of carcinogenic nitrosamines, guaranteeing the molecular safety of the final product [3, 5]. This safety is reinforced by the stability of dissolved oxygen (above 7.8 mg/l), which acts as an indicator of ecosystem health that inhibits the development of anaerobic bacteria and maintains the homeostasis of the raw mate3rial [5, 6]. In conclusion, this optimized physicochemical profile proves that accurate water monitoring transforms this resource from a passive ingredient into an "active biomolecule" that preserves molecular integrity and increases the efficiency of bio-manufacturing in the modern food industry.

The results of this three-year research prove that rigorous control of water parameters is key to maximizing the nutritional value of 3D printed foods. The exceptional pH stability (7.6 \pm 0.14) creates a physiologically optimal environment that prevents protein denaturation and premature oxidation of water-soluble vitamins, ensuring that micronutrients remain bioavailable to the human body [1, 7]. The high concentration of dissolved oxygen (> 7.8 mg/l), combined with the deterministic negative correlation with chlorides (r = -0.96), acts as a natural antioxidant shield; this balance inhibits the degradation of essential fatty acids and polyphenols within the food matrix, thus preserving the therapeutic profile of the functional food [4, 6]. From a precision nutrition perspective, minimal nitrite levels (< 0.012 mg/l) ensure that the final product is free from toxicological loads that can cause cellular oxidative stress, making this water the ideal base for the production of foods with high value density [3, 5]. In conclusion, the results confirm that the precision of 3D fabrication achieved in 2024, combined with the molecular integrity maintained during 2025, transforms any printed structure into an efficient means of nutrient delivery, where the quality of the water directly dictates the metabolic efficiency of the consumer [7, 8].

Statiskical Interpretation

The statistical interpretation of this research is based on the strength of longitudinal trends and the precision of triplicate measurements (n=3), guaranteeing that the results are not random, but reflect physicochemical laws. The use of descriptive statistics (Mean pm Standard Deviation) shows an exceptional stability of the environment; the minimal pH deviation of only 0.14 testifies to a high resistance to external fluctuations, ensuring the technical repeatability of the "food ink" in 3D printers [4]. From the point of view of the Pearson correlation matrix (r), the obtained values go beyond simple correlations; The coefficient r = -0.96 between chlorides and oxygen indicates a nearly deterministic relationship, where controlling one parameter allows for the accurate prediction of the other. This interpretation is based on analysis of variance models, where the decrease in oxygen relative to salinity is not seen simply as a laboratory data, but as a statistically significant indicator ($p < 0.05$) for the prevention of molecular oxidation [6]. Also, the high positive coefficient between chlorides and nitrites (r = 0.86) serves as a toxicological predictive model, allowing statistics to become a preventive tool for food safety. This statistical rigor proves that the water analyzed during the years 2023-2025 provides a solid basis for innovations in molecular biology, where the reliability of the data guarantees the integrity of the complex printed structures [5, 8].

Discussion

The discussion of this three-year research (2023–2025) with data from the Institute of Public Health Skopje, North Macedonia for the water source in the village of Vrutok – Gostivar demonstrates that the success of 3D food technology and the maintenance of molecular integrity depend deterministically on the stability of the hydration phase. The pH stability at an average value of 7.6 ± 0.14 goes beyond mere technical requirements, functioning as a molecular guarantor that prevents protein denaturation by preserving the hydrogen bond network, a key principle in molecular biology for maintaining the bioactivity of food matrices [1, 3]. The extremely strong negative correlation between chlorides and dissolved oxygen ($r = -0.96$), observed especially in the years 2023 and 2025, identifies a critical kinetic barrier; This ionic dynamic reduces oxidative stress on lipids and sensitive micronutrients, optimizing the shelf life of the printed product without the need for synthetic additives [4, 6]. From a technical predictability point of view, 2024 offered the most accurate printing window, where minimal chloride drift guaranteed a constant electrical conductivity, an essential element for geometric precision and repeatability of the "food ink" [8]. This balance is complemented by a toxicological profile with minimal nitrite levels (< 0.012 mg/l), which eliminates the risk of carcinogenic nitrosamine formation and protects cellular homeostasis [5]. In conclusion, this study argues that detailed water monitoring transforms this resource from a passive ingredient into an “active biomolecule,” which not only dictates the rheology of 3D fabrication, but also serves as a “blueprint” for safety and precise nutrition in the modern food industry [7, 8].

Conclusions

This three-year (2023–2025) research on water quality at the Vrutok Village spring proves that the physicochemical stability of the hydration phase is not simply a technical requirement, but a deterministic regulator of food bio-fabrication and molecular integrity. Through a rigorous statistical analysis ($n=3$, $p < 0.05$), it was confirmed that the stable pH (7.6 \pm 0.14) functions as a molecular guarantor that prevents protein denaturation, while the extremely strong negative correlation between chlorides and dissolved oxygen ($r = -0.96$) identifies a critical kinetic barrier that minimizes oxidative stress on lipids and micronutrients [1, 4, 6]. From a food engineering point of view, the year 2024 offered the most accurate window of predictability, where the minimal chloride deviation guaranteed constant conductivity and geometric precision of the "food ink", elements that ensure the repeatability of complex 3D structures [8]. Also, the toxicological profile with minimal nitrite levels (< 0.012 mg/l) eliminates the risk of carcinogenic nitrosamine formation, confirming that this water serves as a "active biomolecule" and "blueprint" for safety and precise nutrition [3, 5, 7]. In conclusion, this study argues that detailed monitoring of water resources transforms water from a passive ingredient into an active biotechnological raw material, which dictates both fabrication rheology and cellular homeostasis in the modern food industry.

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ALBANIAN-SPEAKING VISUALLY IMPAIRED INTERFACING MODEL

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Abstract

Being able to read text, find out information and know about the latest news has always been a challenge for those who cannot access the printed version, such as the blind and visually-impaired. The advent of internet and advancements in User Interfaces (UIs) as well as in assistive technologies make this challenge increasingly feasible. A lot of effort has gone into making software applications and web pages more accessible to the blind and visually impaired students. There are few Windows based stand-alone text-to-speech screen reader applications that provide application-specific speech output through script files written specifically for them. All these screen readers usually cover widely speaking languages. Albanian language is not covered with no one of the screen readers. In this paper a new user-interface model for Albanian speaking blind and visually impaired is presented. The new model is built up on the research results and testing with different screen readers and different groups of blind and visually impaired Albanian speaking students, the screen readers analysis, text-to-speech technologies analysis, specially developed text-to-speech generator from Albanian texts, the mathematical analysis done on general Albanian texts as well as the basic principles of lexicons creations. It has been tested to blind and visually impaired science students. The new user-interface model is a very useful tool for Albanian-speaking blind and visually impaired science students giving them an equal studying opportunity as the other students.

Keywords: Interface, blind, Albanian, text to speech, synthetized speech.

Introduction

Intelligent User Interfaces (IUI), or sometimes called an interface agent is a user interface (UI), that includes some aspects of the artificial intelligence. The area of intelligent user interfaces covers various topics and deals with application of artificial intelligence and knowledge-based techniques on questions of man – computer interaction [1] [2] [3]. One of the major benefits from the rapid development of the intelligent user interfaces are the applications known as (screen readers), which to a greater extent ease the life of the blind and visually impaired people. [4][5].

Having in mind that today the information science and computers, including internet, are entered in every pore of human life and work, the necessity of being at disposal to the disabled people including the blind and visually impaired is more than obvious. The screen readers are text-in-speech systems that transform the text into speech and read the information presented on the computer display. With a help of a combination of keys (shortcuts on the keyboard) the user can move across the user interface and read all the texts available on the screen. With a help of the keyboard, the user can enter a text that is transformed by the screen reader into speech and read loud. One of the screen readers is Web Anywhere [6]. The speech synthesis is an artificial generating of human speech from written texts. The speech synthesis is the central part of the text-in-speech technology, which today has a wide range of applications with a huge significance of their application in auxiliary technologies and tools for blind and visually impaired people and dyslexia, where the screen readers belong. For this purpose, there are appropriate algorithms designed, which afterwards through relevant programs enable to

synthesize the text into speech. At the moment, there are solutions that enable generating natural speech for different world languages. [7][8] [9] [10].
However, they are not universal solutions which can be used for other languages as well, since the speech generated for other languages is not recognizable and natural [8][9]. Because of this, for each language one should look for a solution that refers to its specifics, always aiming towards a voice creation that will respond to the nature of the language. In this study, we describe the basic principles of designing a system for speech synthesis of the Albanian language from written texts. As basic segments that are used for the Albanian language are: the most used words, two letters and separate letters. Originally, we statistically analyzed texts written in Albanian language. Universally, as in every other language, the written texts can be considered as compositions of various units, such as sentences, words, syllables and, at the end, letters. After the conducted analysis and tests it became clear that the generated speech through letters was very unnatural, as a result of the discontinuity during the concatenation of the acoustic files of special letters with composing words. This is to a greater extent conditioned by the consonants, which are usually connected only with the vowel ë ə. These discontinuities can be considerably improved if instead of letters, words are used as basic units. However, the basic vocabulary of the Albanian language is present. Since it is not possible to provide acoustic files for all possible words, it is rational to have a compromised solution. So, we first provide acoustic files of the most commonly used words, which cover a considerable percentage of the written texts, and for other words the generating of the sound should be made by pronouncing single letters. Similarly, to the method with words, it is the case with generating a speech from syllables. The idea emerges from the fact that the number of words is too big to include all basic units within the acoustic database, and the number of syllables can be smaller and through them we could cover all the written texts. The research for the possibility of interpreting texts through a smaller number of basic units, introduced us in the meaning of diphones, as technical solution for this problem regarding this matter. The usage of more common words and diphones could be suggested as optimal solution withingenerating speech from written texts. This could be justified with the fact that through more common words a considerable percentage of texts can be included and continual speeches will be generated. For the other words the quality of generating through diphones will be lower, but the system will be stable because there will be no words that cannot be composed of diphones. Only for the foreign words or those that cannot be found in the dictionary of the Albanian language, there will be the option of generating speech through specific characters.

Generating Speech From Written Texts In Albanian Language

At the moment, there are various technologies for converting a written text into speech. Their mutual goal is artificial generating of natural speech that is maximally comprehensive. But, unfortunately, such perfect convertors cannot be found yet. That is why, the researches of this area have an upward tendency because this has a strong influence on the improvement of the efficiency of the existing solutions and defines instant achievements in the field of interest.
The last reform in 1972, brought the standard Albanian literature language. There was a linguistic move to “unite” the two dialects of the Albanian language: Gheg и Tosk. While it seems that the official language is the language of the media and the schools, it is not the language of each speaker of the Albanian language. This language is still a subject of variations. Two common assumptions are not true when it comes to the Albanian language: all roots are

not in the sentences and very often lack of syntax information. This unusually increases the importance of the processing of “unknown words”. We have to stress that many verb forms are not clean, but they are “analytical forms” [13].

The Albanian language and its alphabet consist of 36 letters, all of which are in Latin script, except for two letters which are written with diacritical script ç
and ë. The number of vowels is seven: a, e, ë ə, i, o, u, и y. Nine letters are considered as compounds, because they represent combinations of two letters: dh ð, gj, ll l, nj, rr, sh ʃ, th θ, xh dʒ and zh ʒ.

The verbs can have one or two forms: Z active form and/or Z-hem passive form: for example, laj (wash) и lahem (be washed). Both forms have a same past participe, and the four tenses of the passive form are made from the same tense as the active form by adding the prefix "u": for example, lava (I washed -aorist) u lava (I washed myself). For some tenses the prefixes të and do are used, and for other tenses some other prefixes are used. For example, laj, të laj, do të laj, (active form) and lahem, të lahem, do të lahem (passive form) with 6 different tenses. If we take that laj is present tense, the same verb in future tense is
do te laf. In the Albanian language, the nouns and pronouns change most. A large number of words of masculine gender in singular change into feminine gender in plural. Hence, the gender is not a constant propriety of a noun. This is not written in the vocabulary. The declination position is at the end of the word, but for three pronouns, it is in the middle, for example, cilido, ciiitdo, and cilindo.

Foreign personal names are transcribed according the Albanian phonetics: Shekspir Shakespeare, Xhems Xhojs James Joyce, Sharl dë Gol Charles de Gaulle. They change the same as other nouns.

In front of the most adjectives, some nouns and some pronouns there is a particle called article. These articles have declinations: their four forms can be i, e, të, së. These declinations change depending on the position of the uttered adjective or noun in the syntagma in nominative.

From the conducted analysis of the Albanian written texts, it can be concluded that the usage of the letters is not the same. Around 450 most often used words in the Albanian language cover more than 50% of the texts in Albanian. Around 200 words cover about 45%. At generating the speech, first are provided the acoustic files of the most often used words, that cover significant percentage of the written texts, while for other words the generating of the speech should be done through single letters. In a similar way as it was the case with words, it is the case of generating the speech from syllables. The idea is based on the fact that the number of syllables can be smaller and through them to cover all written texts. However, the results of the statistical analysis of texts in Albanian confirmed the total number of 10.619 syllables used in the Albanian language. Theoretically, in the Albanian language there are 36x36 = 1296 possible diphones. But, on the basis of the analysis of the written Albanian texts it was detected that only 892 of them are in fact used in the semantic meaning of the language.

On the basis of the calculation of the frequency of the diphones in the Albanian language, we can
conclude that only 45 of them can cover 50,532% of the written texts. Since their total number is small, it is reasonable that all diphones should be included in the database of the acoustic files.

2.1. Application for speech generating from Albanian written texts: The design of the application for speech generating from Albanian written texts consists of three

phases:
1. Normalization of the text,
2. Creation of acoustic database and
3. Conversion of the text
Textual normalization means transformation of the text in the most adequate form for further processing. For the Albanian language, the normalization is realized in three steps [11][12]:
1. First, the entire text is converted in small letters from the alphabet.
2. The specific letters dh, gj, ll, nj, rr, sh, th, xh, zh, ë и ç, are replaced with equivalent symbols: D, G, L, N, R, S, T, X, Z, E и C.
3. At the end, this is used for creation of a table which is used for converting the textual contents into numbers, special symbols, acronyms and abbreviations.
The equivalent mass consists of 200 units which are considered to be necessary for the Albanian
language, but also, additional units can be added to it. All words that are not in the equivalent mass, will be interpreted letter by letter. Numbers that are out of this pattern will be interpreted cipher by cipher. Further segmentation of the text will continue through punctuation symbols. Some of them, such as full stop, question mark, exclamation mark will be equal to the pauses of 1000 ms. Thus, the speech generated later will not respect the intonations, but it will be comprehensive and continuous, which is the goal by itself.
From the different approaches to the speech generating, at the same time respecting the proposed
algorithms in the context of this paper and the perception of the generated sound by the designed
application, we can come to the following conclusions:
1. Generating speech letter by letter is comprehensive but it is not natural and connected to difficult discontinuities in the speech.
2. Generating word with quality speech results – we get comprehensive and natural speech. However, the only disadvantage is that not all the words can be included in the acoustic database.
3. The use of diphones as basic units is characterized with the fact that it provides homogeneous and stable solution, as any text can be interpreted through a combination of acoustic added files to 892 identified diphones.
4. A possibility which offers compromised solutions, from the aspect of speech quality that is generated and also from the aspect of optimization of the acoustic database. Considerable number of the most used words are uttered according to the record of the original, while others are comprised of diphones, and several are uttered through special letters.

Design Of A New Model Of User Interface For Albanian

Speaking Region

In the group of existing intelligent interfaces for accessibility, with certain exceptions, the English language ones dominate. The choice of the option for intelligent interface for blind and visually impaired persons from non-English speaking regions comes to choose of two options – creation of a new product or localization of some existing solution. In case of choosing a ready-to-go solution, it is recommendable to choose an application that is made in free

software. By following the studies for other languages, we try to treat the idea of speech synthesis by merging the acoustic files of textual segments stored in the database. The main problem that occurs during the synthetizing process is connecting the acoustic segments (acoustic segments with certain number of words), in the process of generating words. If the word from the written text is not saved as a separate segment, then it is divided in two letters, then a request is made of these two letters in the database of certain acoustic segments, and thus by merging these acoustic segments, we get a certain word. The Albanian language is not included in the set of languages for which there is a final solution for this subject. We are dedicated to find a model in which texts written in Albanian language can be transformed into speech. In this case we need a preliminary language preparation. This preparation covers the contents of the basic databases of a vocabulary or terminology book, including special IT terminology, as well as their vocalization. The speech is a vocalization form of human communication. Every uttered word is created by phonetic combination of limited set of vocal, sound units – vowels and consonants. The quality of the text conversion into speech is measured by two main parameters: comprehensiveness and naturalness. The comprehensiveness should be done with clarity of the heard speech, and naturalness refers to the similarity of the speech with the artificially generated common speech.

According to the characteristics of the Albanian language, the process of conversion the sentences into words is a process of segmentation and classification of the written form of the sentence. Since the classification and segmentation are mutual here, it is not possible to do it one by one. On the contrary, our approach is first to make temporary segmentation in potential written forms called tokens, and then the next step will be to examine each token and solve any ambiguity. This first process is called tokenization; the step that generates words from the tokens is called text analysis. With tokenization (segmentation) of the text, we open an opportunity for the algorithms that are used for the text analysis to focus on one token at a time. In the phase of preprocessing the text, it is usually first divided into sentences, then divided into tokens which are separated by characters of blank space. The module for preprocessing the text is also responsible for management of non-standard words such as the abbreviations and numbers. In the phase of morphological analysis, the input text is analyzed in order to find morphemes in each word. Similar to this, in the contextual analysis, each word has a dedicated tag for word class, and in the phase of syntactic analysis, the type of sentence is determined, for example declarative or interrogative. Lastly, in Grapheme-in-Phoneme module an exact pronunciation of the input words is defined and the prosodic model is responsible for generating the correct prosody for the synthesized speech. The next phase is prosodic modelling, which in the linguistic science includes intonation, rhythm and lexic accentuation in the speech. The prosodic characteristics of the speech unit can be grouped in the characteristics of syllable, word, phrase or sentence. The perceived quality of the synthesized speech is largely determined by the naturalness of the prosody generated during the synthesis.

After finding the optimal solutions for adaptation of the specifics and characteristics of the Albanian language, on the basis of the above said for the way of work on multilingual text into speech system, we continue with the following stages: text normalization, creation of acoustic database and at last, text conversion with the help of applications for speech generating from text written in Albanian language.

Conclusion

In the group of existing intelligent interfaces for accessibility, with certain exceptions, dominate those in English. Starting the initiative for effectuating such kind of interface, inevitably comes down to previous analysis of the existing solutions, taking over positive experiences and best practices, or ready-to-go concepts, which inevitably leads to certain modifications and adaptations directed towards efficient use on adequate language region.
The choice of option for intelligent interface for blind people from non-English speaking regions comes down to two options – creating a new product or localization of some existing solution.
In this case we need a preliminary language preparation. This preparation covers the contents of the basic databases of a vocabulary or terminology book, including special IT terminology, as well as their vocalization.

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CEFTRIAXONE AS AN EMPIRIC ANTIBIOTIC: PRESCRIBING PRACTICES, RESISTANCE DYNAMICS, AND STEWARDSHIP STRATEGIES

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Abstract

Ceftriaxone, a broad-spectrum third-generation cephalosporin, is widely used as empiric antibiotic therapy for severe infections, including pneumonia, sepsis, and complicated urinary tract infections [1,2]. Its clinical relevance is supported by favorable pharmacokinetics, broad antimicrobial activity, and convenient once-daily dosing. However, increasing global use has been accompanied by a significant rise in antimicrobial resistance, particularly mediated by extended-spectrum β-lactamases (ESBL), AmpC β-lactamases in Gram-negative bacteria, and penA mutations in Neisseria gonorrhoeae [3,4]. These developments raise concerns regarding the continued effectiveness of ceftriaxone in empiric treatment.

This study aimed to evaluate the rational use of ceftriaxone in empiric therapy and its relationship with resistance development. The importance of this paper lies in addressing the growing gap between widespread ceftriaxone use and evidence-based prescribing, which directly contributes to antimicrobial resistance, increased healthcare burden, and compromised patient outcomes. Ceftriaxone was selected as the model antibiotic due to its global prevalence, well-characterized pharmacological profile, and central role in clinical guidelines for empiric therapy. The rationale was supported by evidence of substantial inappropriate use [5-7]. Common empiric indications included community-acquired pneumonia, sepsis, febrile neutropenia, complicated urinary tract infections, meningitis, and surgical prophylaxis. Standard dosing ranged from 1-2 g intravenously every 24 hours [2,8], with shorter treatment durations demonstrating comparable efficacy to prolonged regimens [9]. Evidence indicates that ceftriaxone remains effective when resistance risk is low, however, routine overuse is strongly associated with resistance. A multicenter surveillance study reported approximately 28% resistance among Enterobacterales isolates [3]. Higher dosing (2 g) rarely improves outcomes compared to 1 g in most infections [8,7], except in selected critically ill patients. Antimicrobial stewardship strategies, including restriction policies, de-escalation, and IV-to-oral conversion, have demonstrated effectiveness in reducing inappropriate use [12]. Current evidence supports reserving empiric ceftriaxone for well-defined indications and avoiding its use when local resistance exceeds 10-20% [13].

Keywords: Ceftriaxone; Empiric therapy; Antimicrobial resistance; Dosing strategies; Clinical outcomes.

Introduction

Ceftriaxone, a third-generation cephalosporin with broad-spectrum antimicrobial activity, is widely used as empiric therapy for a range of serious bacterial infections, including community-acquired pneumonia, sepsis of unknown origin, pyelonephritis, meningitis, and gonorrhea [1,2]. Its clinical utility is largely explained by favorable pharmacokinetic properties, including excellent tissue penetration and the convenience of once-daily dosing [2]. In addition, its activity against common pathogens such as Enterobacterales and Streptococcus pneumoniae has established ceftriaxone as a first-line agent in multiple clinical guidelines [10]. These characteristics make it a practical and effective option in situations where rapid initiation of therapy is required before microbiological confirmation is available [1,10].

However, the effectiveness of ceftriaxone is increasingly challenged by the global rise in antimicrobial resistance. The emergence of extended-spectrum β-lactamase (ESBL)-producing organisms, AmpC β-lactamase producers, and resistant strains of Neisseria gonorrhoeae has

significantly reduced its reliability in certain settings [3,4]. Moreover, ceftriaxone lacks activity against specific clinically relevant pathogens such as Pseudomonas aeruginosa and Enterococci, further limiting its empirical applicability in high-risk populations [10]. Importantly, inappropriate use of broad-spectrum antibiotics, such as prescribing ceftriaxone for viral infections or extending prophylactic use beyond recommended durations, has accelerated resistance development and undermined its long-term effectiveness [5–7].

Given these concerns, the rational use of ceftriaxone in empiric therapy has become a critical issue in contemporary clinical practice. This review examines the patterns of ceftriaxone use and evaluates its impact on bacterial resistance and clinical outcomes. Specifically, it explores epidemiological trends, common clinical indications, dosing and duration strategies, and the role of antimicrobial stewardship interventions in optimizing its use [12,13].

The objectives of this research paper are :

[1]. describe current patterns of empiric ceftriaxone use and related stewardship recommendations;
[2]. summarize evidence on optimal dosing and treatment duration in terms of efficacy and safety;
[3]. analyze current resistance trends, including ESBL and AmpC prevalence as well as gonococcal resistance;
[4]. compare findings from key clinical studies;
[5]. discuss implications for clinical practice and health policy. Through this structured analysis, the paper aims to clarify the appropriate role of ceftriaxone in empiric therapy and to identify strategies to preserve its clinical effectiveness.

Methods

We conducted a narrative literature review using PubMed, Scopus, and Google Scholar, covering publications up to April 2026. The search strategy included the following keywords and their combinations: “ceftriaxone,” “empiric therapy,” “antibiotic resistance,” “third-generation cephalosporin,” “extended-spectrum β-lactamase,” “antimicrobial stewardship,” as well as infection-specific terms such as “community-acquired pneumonia,” “urinary tract infection,” “typhoid fever,” and “gonorrhea.”

Priority was given to recent systematic reviews, high-quality original research articles, international clinical guidelines (IDSA, ATS/IDSA, ESCMID), and authoritative surveillance reports, including WHO GLASS, CDC, and ECDC data. Studies were included if they specifically addressed empiric ceftriaxone use, dosing strategies, treatment duration, or the impact of resistance on clinical effectiveness. Studies focusing exclusively on pediatric or veterinary populations were excluded unless they provided findings of broader clinical relevance to human medicine.

Data extraction focused on reported clinical outcomes, dosing regimens, resistance patterns, and stewardship-related outcomes.

Results

Epidemiology of ceftriaxone use: Ceftriaxone is among the most frequently prescribed broad-spectrum antibiotics in hospital settings worldwide [14]. Utilization studies indicate that its use accounts for approximately 30–60% of inpatient antibiotic exposure, depending on the clinical

and geographical context. High empirical utilization is particularly evident in low-resource settings.

In a tertiary hospital in Ethiopia, ceftriaxone was used in 59% of hospitalized patients, with 79.5% administered empirically [5]. The mean duration of therapy was 11.5 days (range 1–52 days), reflecting substantial deviation from guideline-recommended treatment durations [5].

A systematic review and meta-analysis reported a pooled prevalence of inappropriate ceftriaxone use of approximately 55% [6]. The main drivers included lack of microbiological confirmation, incorrect dosing intervals, and unnecessarily prolonged therapy. Similar patterns have been described across multiple regions, indicating a global issue in empirical antibiotic stewardship.

Common empirical indications include community-acquired pneumonia, sepsis of unknown origin, complicated urinary tract infections, meningitis, surgical prophylaxis, and sexually transmitted infections [1,10–12].

In European settings, ceftriaxone use remains high, alongside increasing third-generation cephalosporin resistance trends reported by surveillance systems [13].

Dosing regimens and treatment duration: Ceftriaxone is typically administered at 1–2 g intravenously once daily, consistent with its pharmacokinetic and pharmacodynamic profile [2]. The 2 g dose is generally reserved for severe infections or conditions requiring enhanced tissue penetration.

Evidence does not demonstrate a consistent clinical advantage of higher dosing. A meta-analysis found no significant differences between 1 g and higher doses in terms of clinical cure, mortality, or length of hospital stay [7]. These findings support the use of 1 g daily as standard therapy in most non-severe infections.

Shorter treatment durations have shown comparable efficacy to prolonged regimens. In uncomplicated urinary tract infections, a 3-day intravenous ceftriaxone regimen was non-inferior to longer courses [8]. These data support early de-escalation strategies and transition to oral therapy when clinically appropriate.

Antimicrobial stewardship and prescribing optimization: Ceftriaxone is a key target for antimicrobial stewardship interventions due to its frequent overuse and broad-spectrum activity. Effective strategies include formulary restriction, audit and feedback, dose optimization, and intravenous-to-oral switch protocols.

Stewardship interventions have been shown to reduce inappropriate use without negatively affecting clinical outcomes [9]. International guidelines emphasize reassessment of empiric therapy once microbiological results become available, with de-escalation to narrower-spectrum agents when possible [10,11].

The Infectious Diseases Society of America recommends that empiric ceftriaxone use should be guided by local resistance patterns, particularly avoiding use when resistance exceeds 10–20% or when risk factors for extended-spectrum beta-lactamase producing organisms are present [10,11].

Bacterial resistance trends and mechanisms:

Enterobacterales: Resistance to third-generation cephalosporins among Enterobacterales is increasing globally. A longitudinal surveillance study reported a ceftriaxone resistance rate of 28.2% in intra-abdominal and urinary tract infections [3].
The main resistance mechanisms include extended-spectrum beta-lactamases and AmpC beta-lactamases. Among resistant isolates, 44% carried AmpC genes and 38.8% carried ESBL determinants [3]. Similar trends have been reported in Europe, where resistance rates in invasive Klebsiella pneumoniae exceed 30% in many regions [13].

Neisseria gonorrhoeae: Ceftriaxone resistance in Neisseria gonorrhoeae is an emerging global concern. In China, resistance increased from 2.9% in 2017 to 8.1% in 2022 [4], largely associated with dissemination of the FC428 clone [4]. European surveillance reports lower but concerning levels of reduced susceptibility [12].
Resistance is primarily mediated by mosaic alterations in the penA gene, which reduce binding affinity of beta-lactam antibiotics [12].

Salmonella enterica serovar Typhi: Ceftriaxone-resistant Salmonella Typhi has recently emerged in South Asia. A 2024 outbreak in Bangladesh was caused by an ESBL-producing CTX-M-15 strain, indicating selective pressure from widespread empirical ceftriaxone use [14]. This highlights the risk of resistance emergence in high-burden infectious disease regions.

Other pathogens: Ceftriaxone has intrinsic inactivity against Pseudomonas aeruginosa and Enterococcus species, limiting its empirical utility in high-risk infections. Resistance in Haemophilus influenzae is mainly mediated by beta-lactamase production, although ceftriaxone retains activity in most cases [10].

Safety and adverse effects: Ceftriaxone is generally well tolerated and associated with a favorable safety profile [9]. The most common adverse effects include gastrointestinal symptoms and local infusion site reactions.
Large observational studies indicate a low incidence of Clostridioides difficile infection, with minimal differences between dosing strategies [7]. Severe hypersensitivity reactions are rare but clinically significant.
Biliary pseudolithiasis is a recognized complication, particularly in prolonged treatment courses, and is typically reversible after discontinuation [9]. Overall, the major clinical concern related to ceftriaxone is not toxicity but its contribution to antimicrobial resistance due to widespread overuse.

3. Discussion

Ceftriaxone remains one of the most extensively utilized third-generation cephalosporins in contemporary clinical practice, owing to its broad antimicrobial spectrum, favorable pharmacokinetic profile, once-daily dosing, and consistent efficacy across multiple infectious syndromes. Its established role in community-acquired pneumonia, pyelonephritis, complicated urinary tract infections (UTIs), intra-abdominal infections, gonorrhea, and sepsis has rendered it a cornerstone of empiric inpatient therapy [1,2]. Nevertheless, the very

attributes that make ceftriaxone clinically valuable have also contributed to widespread overuse, inappropriate empiricism, and prolonged treatment courses, thereby intensifying selective pressure for antimicrobial resistance.

Available evidence indicates that ceftriaxone achieves high rates of clinical success when prescribed in settings with preserved pathogen susceptibility and when aligned with syndrome-specific treatment principles. In hospitalized patients with uncomplicated UTIs, short-course regimens (e.g., three days) have demonstrated outcomes comparable to longer treatment durations, suggesting that extended intravenous therapy is frequently unnecessary [8]. Comparable observations have emerged in respiratory infections, where standard-dose regimens often provide equivalent clinical resolution to intensified dosing strategies in non-critically ill populations [7].

These findings reinforce a central antimicrobial stewardship principle: therapeutic effectiveness is determined less by maximal exposure than by appropriate indication, adequate source control, and pathogen susceptibility. Escalation of dose or prolongation of therapy in clinically stable patients rarely confers additional benefit and may instead increase adverse drug events, catheter-associated complications, costs, and ecological disruption of the microbiome [7,9].

Despite its therapeutic utility, ceftriaxone is frequently prescribed outside evidence-based indications. Studies from low- and middle-income settings have reported substantial rates of irrational prescribing, including unnecessary empiric initiation, continuation despite negative cultures, and excessive duration of therapy. A systematic review from Ethiopia estimated inappropriate ceftriaxone use at approximately 80%, highlighting the scale of stewardship failure in some health systems [6]. Prospective ward-based evaluations similarly identified frequent discordance between prescribing practice and guideline standards [5].

Such misuse is not a benign systems inefficiency; it directly contributes to the expansion of resistant Enterobacterales, Clostridioides difficile risk, and increased hospital antimicrobial consumption. Repeated exposure to third-generation cephalosporins is a recognized ecological driver of extended-spectrum beta-lactamase (ESBL)-producing organisms and AmpC-mediated resistance, particularly among Escherichia coli and Klebsiella pneumoniae.

Recent data further demonstrate the clinical consequences of indiscriminate empiric ceftriaxone use. In community-onset healthcare-associated UTIs, ceftriaxone-based empiric therapy was associated with elevated rates of inappropriate empiric antimicrobial treatment (IEAT), particularly in patients harboring resistant pathogens [1]. This has direct relevance for early sepsis management, where delays in active therapy correlate with poorer outcomes.

Accordingly, empiric ceftriaxone should not be considered a universal default agent. Risk stratification prior to prescription is essential. Factors consistently associated with resistance include:

[1] prior colonization or infection with ESBL-producing organisms;
[2] recent cephalosporin or fluoroquinolone exposure;
[3] residence in long-term care facilities;
[4] recurrent healthcare contact or recent hospitalization;
[5] indwelling urinary devices;
[6] recent international travel to high-resistance regions.

Where these factors are present, broader initial coverage (e.g., carbapenems or advanced β-lactam/β-lactamase inhibitor combinations) may be more appropriate pending microbiological confirmation [11].

The expanding resistance landscape represents the greatest threat to ceftriaxone's future utility. Longitudinal SMART surveillance from Taiwan documented substantial ceftriaxone resistance among Enterobacterales causing intra-abdominal and urinary infections, with rates approaching or exceeding thresholds at which empiric reliability becomes questionable [3]. Similar trends are reflected in European surveillance datasets, where cephalosporin resistance among invasive Gram-negative pathogens continues to rise heterogeneously across member states [13].

Equally concerning is the emergence of ceftriaxone-resistant Neisseria gonorrhoeae. Reports from China and national surveillance systems such as GRASP in the United Kingdom indicate increasing reduced susceptibility and resistant isolates, challenging one of the last dependable therapies for gonorrhea [4,12]. In parallel, outbreaks of ceftriaxone-resistant Salmonella Typhi underscore the capacity for resistance determinants to spread beyond hospital pathogens into major community-acquired infections [14].

Collectively, these developments signal a broader epidemiologic transition: ceftriaxone can no longer be assumed reliably active across many regions or syndromes without local resistance intelligence.

Given these realities, ceftriaxone stewardship should be operationalized through six integrated strategies:

[1] Restrictive indication-based prescribing
Reserve ceftriaxone for clinical scenarios where spectrum, tissue penetration, and parenteral administration are clearly justified. Narrower agents should be preferred whenever microbiologically and clinically appropriate.

[2] Resistance-informed empiricism
Empiric selection should incorporate illness severity, prior microbiology, healthcare exposure, host factors, and current institutional antibiograms.

[3] Dose optimization
For many non-severe infections, 1 g daily remains sufficient. Higher doses should be reserved for severe sepsis, obesity, meningitis protocols, or deep-seated infection when pharmacodynamic rationale exists [7].

[4] Duration minimization
Use the shortest effective treatment course, with early switch to oral therapy when clinically feasible. Evidence increasingly supports abbreviated regimens in selected UTIs and respiratory infections [8].

[5] Culture acquisition and de-escalation
Microbiological samples should precede antibiotic initiation whenever possible. Therapy should then be narrowed, discontinued, or redirected once susceptibility results become available.

[6] Audit, feedback, and surveillance systems
Institutional review mechanisms, prescribing dashboards, and national AMR surveillance platforms remain among the most effective tools for reducing unnecessary ceftriaxone exposure [6,12,13].

Table 1. Comparative Analysis of Key Studies on Empirical Ceftriaxone Use and Bacterial Resistance

Study (Year)	Design & Population	Setting / Patients	Intervention & Comparison	Key Outcomes and Findings	Resistance / Clinical Implications
Madrazo et al., J Clin Med 2025 [1]	Prospective cohort; 235 adults with community-onset healthcare-associated UTI	Spanish tertiary hospital; median age 79 years	Empiric ceftriaxone monotherapy vs alternative antibiotics	Inappropriate empiric antimicrobial therapy (IEAT) was higher with ceftriaxone (36.4% vs 17.1%; *p*=0.001). Thirty-day mortality was similar (~11%). Median hospital stay was shorter with ceftriaxone (5 vs 6 days; *p*=0.037).	Resistant pathogens identified in 27.2% of ceftriaxone recipients, including ESBL/AmpC producers. Highlights need for risk-based empiric selection.
Elajouz et al., 2022 [8]	Retrospective cohort; 145 adults with uncomplicated UTI	Two US hospitals	Three-day IV ceftriaxone vs longer IV β-lactam regimens	Three-day ceftriaxone was non-inferior to longer regimens for clinical cure. Supports abbreviated treatment strategies.	Suggests shorter exposure may reduce selective pressure and hospital resource use.
Aso et al., 2025 [2]	Retrospective nationwide cohort; ~472,000 hospitalized CAP patients	Japanese national inpatient database	Ceftriaxone 2 g/day vs 1 g/day during first 2 treatment days	Thirty-day mortality was similar (4.5% vs 4.6%). In ventilated patients, 2 g/day showed lower mortality. Slightly higher *C. difficile* incidence with 2 g/day.	Routine dose escalation may be unnecessary outside critical illness.
Brust-Sisti et al., Meta-analysis 2026 [7]	Meta-analysis of 8 studies (5,145 patients)	Adults with non-CNS infections	High-dose (≥2 g/day) vs low-dose (1 g/day)	No significant difference in cure, mortality, or length of stay.	Supports 1 g/day as adequate for many routine infections.

			ceftriaxone		
Ayele et al., Pharmacol Res Perspect 2018 [5]	Prospective cross-sectional; 390 adult inpatients receiving ceftriaxone	Gondar University Hospital, Ethiopia	Drug utilization study	Point prevalence of ceftriaxone use was 59%; 79.5% prescribed empirically. Mean duration 11.47 days. Large proportion considered inappropriate.	Demonstrates excessive empiric use and prolonged exposure as stewardship concerns.
Mulatu et al., Sci Rep 2024 [6]	Systematic review/meta-analysis; 17 Ethiopian studies	National pooled prescribing data	Observational pooled analysis	Pooled inappropriate ceftriaxone use was 55.2% (95% CI 42.2–68.3%). Empiric prescribing strongly associated with misuse.	Confirms persistent inappropriate utilization at system level.
Li et al., SMART Taiwan 2025 [3]	Prospective surveillance (2009–2019); 31,611 Enterobacterales isolates	Intra-abdominal and urinary infections, Taiwan	Molecular epidemiology of 2,614 ceftriaxone-resistant isolates	Overall ceftriaxone resistance rate was 28.2%. Most common resistant isolates were *E. coli* and *K. pneumoniae*.	Resistance driven by AmpC and ESBL mechanisms; empiric ceftriaxone reliability reduced in high-burden settings.
Zhu et al., MMWR 2024 [4]	National surveillance report (2017–2022)	Gonococcal isolates from 13 provinces, China	Observational surveillance	Ceftriaxone resistance increased from 2.9% to 8.1%; five provinces exceeded 10%.	Signals emerging threat to first-line gonorrhea treatment.
CDC / Hooda et al., Emerg Infect Dis 2025 [14]	Passive surveillance / outbreak case-series	Bloodstream *Salmonella Typhi* isolates, Bangladesh	Outbreak investigation	Forty-seven ceftriaxone-resistant typhoid cases detected.	ESBL-mediated typhoid strains threaten standard therapy and require surveillance response.
Real-world Safety	Observational stewardship study	Hospitalized adults	Safety outcomes	Ceftriaxone-associated adverse events	Reinforces that stewardship protects both

Evaluation, ASHE [9]		receiving ceftriaxone	during routine use	included biliary complications, hypersensitivity, and *C. difficile*-related harms.	efficacy and patient safety.

Conclusions

Ceftriaxone remains a cornerstone of empiric antimicrobial therapy in the management of severe bacterial infections, primarily due to its broad antibacterial spectrum, favorable pharmacokinetic profile, and reliable once-daily dosing regimen. Its established efficacy across a wide range of clinical syndromes has secured its position in contemporary treatment algorithms. However, its sustained clinical value is increasingly constrained by cumulative prescribing pressure, inappropriate empiric initiation, prolonged treatment courses, and the progressive expansion of antimicrobial resistance among key bacterial pathogens.

Current evidence consistently demonstrates that ceftriaxone achieves maximal therapeutic benefit when its use is guided by a structured assessment of infection probability, patient-specific risk stratification, and up-to-date local susceptibility data. In environments with low resistance prevalence, it continues to serve as an effective first-line empiric agent, enabling timely intervention while maintaining favorable clinical outcomes. In contrast, in settings where resistance among relevant pathogens approaches or exceeds clinically significant thresholds, routine empiric reliance becomes progressively less justifiable and necessitates early reconsideration of alternative regimens or prompt de-escalation once microbiological data are available.

Optimization of dosing and duration is a critical determinant of both efficacy and resistance containment. Standard dosing of 1 g once daily is sufficient for most non-severe infections, whereas higher doses should be reserved for selected high-acuity conditions characterized by increased tissue penetration requirements or severe systemic involvement. In parallel, treatment duration should be strictly aligned with syndrome-specific evidence, favoring shorter courses and early transition to oral therapy whenever clinical stability permits.

From a population health perspective, the preservation of ceftriaxone efficacy is inseparable from the strength of antimicrobial stewardship systems. Effective control strategies require systematic reassessment of empiric therapy within 48 to 72 hours, mandatory culture acquisition prior to treatment initiation when feasible, routine de-escalation based on microbiological results, and continuous integration of local and international resistance surveillance data. These measures are increasingly urgent in the context of expanding resistance among Enterobacterales, Salmonella enterica serovar Typhi, and Neisseria gonorrhoeae, which collectively signal a narrowing therapeutic window for third-generation cephalosporins.

Ultimately, ceftriaxone should be viewed not as a universally applicable empiric solution, but as a highly effective intervention whose utility depends entirely on precision of use. Its future clinical relevance will be determined by whether prescribing practices evolve from empirical convenience toward microbiologically informed restraint. In this sense, ceftriaxone functions as a sensitive indicator of antimicrobial discipline within healthcare systems: its continued effectiveness reflects stewardship success, whereas its loss of reliability reflects systemic overuse.

A rational, evidence-driven approach remains the decisive factor in preserving its value. The imperative is therefore clear: ceftriaxone must be used with greater selectivity, accountability, and integration of diagnostic data. Only through such disciplined practice can its role as a life-saving empiric agent be sustained for future clinical generations.

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MANAGEMENT OF ATRIAL FIBRILLATION FOR REDUCING THE RISK OF STROKE AND THROMBOEMBOLISM

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice and represents a major global health burden due to its association with ischemic stroke, systemic thromboembolism, heart failure, hospitalization, and increased mortality. The prevalence of AF continues to rise because of aging populations and the increasing prevalence of cardiovascular risk factors. Prevention of thromboembolic complications remains one of the most important goals in the management of AF. This paper reviews contemporary strategies for reducing the risk of stroke and thromboembolism in patients with atrial fibrillation, focusing on risk stratification, anticoagulation therapy, and integrated patient-centered care. Clinical evaluation using the CHA_2DS_2-VASc score allows identification of patients at increased thromboembolic risk who benefit from oral anticoagulation therapy. Direct oral anticoagulants (DOACs) are currently preferred over vitamin K antagonists in most patients because of improved safety profiles, fewer drug interactions, and reduced risk of intracranial hemorrhage. The importance of individualized therapy, bleeding risk assessment, and management of comorbidities is also emphasized. In addition, rate and rhythm control strategies, lifestyle modification, and multidisciplinary management contribute significantly to improved outcomes and quality of life. Early diagnosis and evidence-based therapeutic approaches are essential for preventing severe complications associated with AF. Contemporary guideline-directed management significantly reduces morbidity and mortality and improves long-term prognosis in patients with atrial fibrillation.

Keywords: Atrial fibrillation, stroke prevention, thromboembolism, anticoagulation, DOACs, CHA_2DS_2-VASc score

Introduction

Atrial fibrillation (AF) is the most frequently diagnosed cardiac arrhythmia worldwide and is associated with significant cardiovascular morbidity and mortality. AF is characterized by disorganized atrial electrical activity resulting in ineffective atrial contraction and irregular ventricular response. The prevalence of atrial fibrillation increases with age and is strongly associated with hypertension, heart failure, valvular heart disease, diabetes mellitus, obesity, and ischemic heart disease.

One of the most serious complications of AF is thromboembolism, particularly ischemic stroke. Patients with atrial fibrillation have approximately a fivefold increased risk of stroke compared with the general population. Thrombus formation usually occurs in the left atrial appendage because of blood stasis caused by ineffective atrial contraction. Embolization of thrombi to cerebral circulation may result in severe neurologic disability or death.

Modern management of atrial fibrillation focuses not only on symptom control but also on prevention of stroke and systemic embolism. Risk stratification tools such as the CHA_2DS_2-VASc score have improved identification of patients who require anticoagulation therapy. The introduction of direct oral anticoagulants (DOACs) has transformed AF management by providing safer and more convenient alternatives to vitamin K antagonists.

The aim of this paper is to review current evidence-based approaches in the management of atrial fibrillation for reducing the risk of stroke and thromboembolism, with particular emphasis on anticoagulation strategies, risk assessment, and integrated clinical management.

Body of Manuscript

2.1 Epidemiology and Clinical Significance of Atrial Fibrillation: Atrial fibrillation affects millions of individuals globally and its incidence continues to increase. AF contributes substantially to healthcare costs due to recurrent hospitalizations, long-term treatment, and management of complications. Stroke associated with AF is generally more severe and associated with higher mortality compared with strokes of other etiologies.
Risk factors contributing to the development of AF include:

[1]. Advanced age
[2]. Hypertension
[3]. Coronary artery disease
[4]. Heart failure
[5]. Diabetes mellitus
[6]. Obesity
[7]. Chronic kidney disease
[8]. Valvular heart disease
[9]. Sleep apnea
[10]. Hyperthyroidism

The burden of AF is expected to rise significantly over the coming decades because of population aging and improved survival from cardiovascular diseases.

2.2 Pathophysiology of Thromboembolism in AF:
The pathogenesis of thromboembolism in atrial fibrillation is explained by Virchow's triad:

[1] Blood stasis
[2] Endothelial dysfunction
[3] Hypercoagulability

Loss of coordinated atrial contraction leads to blood stagnation, particularly within the left atrial appendage. This environment promotes thrombus formation and increases the risk of systemic embolization.
Inflammatory mechanisms, endothelial injury, and activation of coagulation pathways additionally contribute to thrombus development. Embolization to cerebral circulation can result in ischemic stroke, while peripheral embolization may affect other organs.

2.3 Risk Stratification for Stroke Prevention: Assessment of thromboembolic risk is essential in determining the need for anticoagulation therapy. The CHA_2DS_2-VASc score is widely recommended for evaluating stroke risk in patients with AF.

Components of the CHA_2DS_2-VASc Score

Risk Factor	Points
Congestive heart failure	1
Hypertension	1

Age >75 years	2
Diabet Mellitus	1
Previous stroke/TIA/ Thromboembolism	2
Vascular disease	1
Age 65-74 years	1
Femal sex	1

Patients with higher CHA_2DS_2-VASc scores have substantially increased risk of thromboembolic events and benefit significantly from oral anticoagulation therapy.

2.4 Oral Anticoagulation Therapy: Oral anticoagulation is the cornerstone of stroke prevention in atrial fibrillation.

Vitamin K Antagonists

Warfarin has historically been the standard anticoagulant therapy for AF. Although effective, its use is limited by:

[1] Frequent INR monitoring
[2] Food and drug interactions
[3] Narrow therapeutic range
[4] Increased bleeding risk

Direct Oral Anticoagulants (DOACs)

DOACs are currently preferred for most patients with non-valvular atrial fibrillation. These include:

[1] Dabigatran
[2] Rivaroxaban
[3] Apixaban
[4] Edoxaban

Advantages of DOACs include:

[1.] Predictable pharmacokinetics
[2.] Reduced intracranial bleeding
[3.] No routine INR monitoring
[4.] Fewer drug interactions
[5.] Improved patient adherence

Clinical trials have demonstrated that DOACs are at least noninferior, and in some cases superior, to warfarin for prevention of stroke and systemic embolism.

2.5 Bleeding Risk Assessment: While anticoagulation reduces thromboembolic risk, bleeding complications must also be evaluated. The HAS-BLED score is commonly used for assessing bleeding risk.

Components of the HAS-BLED Score

Risk Factor	Points
Hypertension	1

Abnormal renal/liver function	1 or 2
Stroke history	1
Bleeding history	1
Labile INR	1
Elderly (>65years)	1
Drugs/alcohol	1or 2

Bleeding risk assessment should not be used to withhold anticoagulation unnecessarily but rather to identify modifiable risk factors and improve patient safety.

2.6 Integrated Management of Atrial Fibrillation: Comprehensive AF management involves a multidisciplinary and patient-centered approach.

Key Components Include:

[1] Stroke prevention with anticoagulation
[2] Symptom management through rate or rhythm control
[3] Management of cardiovascular risk factors
[4] Lifestyle modification
[5] Regular follow-up and patient education

Lifestyle interventions such as weight reduction, smoking cessation, blood pressure control, diabetes management, and physical activity have been shown to improve outcomes in AF patients.

2.7 Rate and Rhythm Control Strategies:

Rate Control

Rate control aims to maintain acceptable ventricular rate and reduce symptoms. Commonly used medications include:

[1]. Beta-blockers
[2]. Calcium channel blockers
[3]. Digoxin

Rhythm Control

Rhythm control aims to restore and maintain sinus rhythm through:

1. Antiarrhythmic medications
2. Electrical cardioversion
3. Catheter ablation

Recent evidence suggests that early rhythm control may reduce cardiovascular complications in selected patients.

Tables, Figures and Equations

Drug	**Standard Dose**	**Main Advantag**
Apixaban	5mg twice daily	Lower bleeding risk

Rivaroxaban	20mg once daily	Once –daily dosing
Dabigatran	150mg twice daily	Direct thrombin inhibition
Edoxaban	60mg once daily	Reduced intracranial bleeding

Figure 1. Integrated Management Approach in Atrial Fibrillation

[1] Stroke prevention
[2] Rate/rhythm control
[3] Management of comorbidities
[4] Lifestyle modification
[5] Patient-centered care

Conclusions

Atrial fibrillation remains a major cause of stroke and systemic thromboembolism worldwide. Effective prevention of thromboembolic complications is essential for improving survival and quality of life in patients with AF. Risk stratification using validated scoring systems enables identification of patients who benefit from anticoagulation therapy. Direct oral anticoagulants have significantly improved the safety and efficacy of stroke prevention strategies.
Integrated management involving anticoagulation, symptom control, lifestyle modification, and treatment of associated comorbidities is necessary for optimal patient outcomes. Early diagnosis and adherence to contemporary clinical guidelines play a crucial role in reducing morbidity and mortality associated with atrial fibrillation.
Future advances in personalized medicine and catheter-based therapies may further improve long-term management and prevention strategies in AF patients.

Nomenclature

AF — Atrial Fibrillation
DOAC — Direct Oral Anticoagulant
TIA — Transient Ischemic Attack
INR — International Normalized Ratio
CHA_2DS_2-VASc — Clinical stroke risk assessment score
HAS-BLED — Bleeding risk assessment score

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DATA ENCRYPTION USING THE ALGEBRAIC STRUCTURE OF QUATERNIONS

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Abstract

In this paper, a cryptographic scheme with an algebraic foundation is presented, built on the ring of quaternions. Messages are divided into blocks of length four in order to utilize quaternions of the form □ + □□ + □□ + □□. Likewise, quaternions and their algebraic properties are used for the key. To enhance the security of the cryptosystem, an S-box is incorporated, making the system more secure and nonlinear. An attacker can no longer rely on simple algebraic methods to determine the key, as the cryptosystem becomes difficult to break.
The formal construction algorithm of the encryption and decryption scheme is presented, along with its correctness, and an illustrative example is provided. The approach has a didactic and exploratory character, aiming to connect concepts of abstract algebra with cryptography, thereby opening possibilities for further developments in the field of information security.

Keywords: Encryption, decryption, ring, quaternion, S-box.

Introduction

Modern cryptography employs various algebraic structures in the construction of secure encryption schemes. Algebraic and nonlinear approaches for encryption and decryption based on polynomial and rational functions have also been studied in recent years ([2], [8]). In addition to groups, rings also provide an interesting framework for the development of alternative cryptographic mechanisms.
In this paper, by focusing on the ring of quaternions of the form $a + bi + cj + dk$, where a, b, c, and d are real numbers, we aim to construct a mathematically sound cryptosystem whose operation will be illustrated through a concrete example.

Preliminaries

This ring was discovered by the Irish mathematician William Rowan Hamilton in the 1840s and is commonly denoted by $\mathbb{H}$. The elements of $\mathbb{H}$. are called quaternions. Thus, $\mathbb{H} = \{a + bi + cj + dk \mid a, b, c, d \in \mathbb{R}\}$.
In $\mathbb{H}$, the operations of addition and multiplication are defined as follows. $\alpha = a + bi + cj + dk$, $\beta = a' + b'i + c'j + d'k$, where all coefficients are real.
Addition: $\alpha + \beta = (a + a') + (b + b')i + (c + c')j + (d + d')k$
Multiplication is defined as the product of two algebraic expressions, where each term of the quaternion $\alpha = a + bi + cj + dk$ is multiplied by each term of the quaternion $\beta = a' + b'i + c'j + d'k$. This yields: $\alpha \cdot \beta = A + Bi + Cj + Dk$, where: $A = aa' - bb' - cc' - dd'$; $B = ab' + ba' + cd' - dc'$; $C = ac' - bd' + ca' + db'$ and $D = ad' + bc' - cb' + da'$.
Multiplication in $\mathbb{H}$ is based on the following rules:

1. $i^2 = -1, \quad j^2 = -1, \quad k^2 = -1.$
2. $ij = k, \quad jk = i, \quad ki = j, \quad ji = -k, \quad kj = -i, \quad ik = -j.$

It is not difficult to verify that $(\mathbb{H}, +)$ forms an additive group, and moreover, the group $\mathbb{H}$ is isomorphic to the additive group of $\mathbb{R}^4 = \mathbb{R} \times \mathbb{R} \times \mathbb{R} \times \mathbb{R}$,, which consists of quadruples *(a, b,*

c, d) of real numbers. This isomorphism is given by the mapping: $a + bi + cj + dk \mapsto (a, b, c, d)$.
The zero element in $\mathbb{H}$ is $0 = 0 + 0i + 0j + 0k$, while the identity element is $1 = 1 + 0i + 0j + 0k$. Furthermore, we can conclude that in $\mathbb{H}$, the distributive property of multiplication over addition also holds.
For the inverse of nonzero quaternions, we have:
Let it be

$$\alpha = a + bi + cj + dk \in \mathbb{H},$$

where $a, b, c, d \in \mathbb{R}$. We consider its conjugate

$$\bar{\alpha} = a - bi - cj - dk.$$

Then, the following equality holds:

$$\alpha\bar{\alpha} = (a + bi + cj + dk)(a - bi - cj - dk) = a^2 + b^2 + c^2 + d^2.$$

The expression $N(\alpha) = a^2 + b^2 + c^2 + d^2$ is called the norm of the quaternion α and is a non-negative real number.
If $\alpha \neq 0$, then $N(\alpha) > 0$, and therefore its inverse exists and is given by:

$$\alpha^{-1} = \frac{\bar{\alpha}}{N(\alpha)} = \frac{a - bi - cj - dk}{a^2 + b^2 + c^2 + d^2}.$$

As a consequence, every nonzero element of the quaternion algebra is invertible, which shows that $\mathbb{H}$ is a division ring (skew field).
Since we can write $\mathbb{R} = \{a + 0i + 0j + 0k \mid a \in \mathbb{R}\}$ and the conditions for being a subring are satisfied, we conclude that the set of real numbers $\mathbb{R}$ is a subring of $\mathbb{H}$.
Basic concepts related to quaternion algebra and abstract algebra can be found in ([1], [5], [6], [7]).

Definition of a Cryptosystem
Definition 2.2.1.([3], [4], [6]) A cryptosystem is defined as a five-tuple (*P*, *C*, *K*, *E*, *D*) that satisfies the following conditions:

- *P* – is a finite set of plaintexts;
- *C* – is a finite set of ciphertexts;
- *K* – is a set of keys;
- *E*=$\{e_k | k \in K\}$ is a set of encryption functions;
- *D*=$\{d_k | k \in K\}$ is a set of decryption functions, such that $\forall x \in P, k \in K, d_k(e_k(x)) = x$.

Use of the S-box
The main reason for using an S-box is to introduce **nonlinearity** into this cryptosystem, which increases the level of security. If our cryptosystem were left as merely a series of linear operations with quaternions, then an attacker could break it quite easily by performing simple operations.
By using the S-box, we introduce exponentiation operations such as x^{-c}. This makes the cryptosystem nonlinear. An attacker can no longer use simple algebraic methods to find the key, as the resulting equations become much more difficult to solve.
In this cryptosystem, as an S-box we will use the generalized function:

$$S(x) = (ax^{-c} + b)(\mathrm{mod} p)$$

For this function to serve as a valid S-box, it must be *bijective*, which means that each input has a unique output and vice versa. For this, certain mathematical conditions must be satisfied:

1. p must be a prime number
2. The condition for $a \neq 0$ is $a \neq 0(mod p)$
3. $\gcd(a, p) = 1$.

4. $\gcd(c, p-1) = 1$.

Condition 4 is the most important one. The exponent c must be relatively prime to $p-1$, because if $gcd(c, p-1) \neq 1$, then the function x^c (and consequently x^{-c}) is not bijective on $\mathbb{Z}_p^*$.

Since 0^{-c} is not defined, we adopt the convention that if $x = 0$, then $S(0) = b$ and consequently, if $y = b$, then: $S^{-1}(b) = 0$.

Finding the inverse S^{-1}

We seek to determine x when y is known. We solve the equation step by step (always modulo p):

$$y = S(x) = (ax^{-c} + b)(\mathrm{mod}p).$$

Subtracting b from both sides, we obtain:$y - b \equiv ax^{-c}(\mathrm{mod}p)$.

Multiplying by the modular inverse of a, denoted by a^{-1}:

$$a^{-1}(y-b) \equiv x^{-c}(\mathrm{mod}p).$$

Taking the inverse of both sides in order to bring x^c to the numerator, we get:

$$(a^{-1}(y-b))^{-1} \equiv x^c(\mathrm{mod}p).$$

So,

$$x^c \equiv a^{-1}(y-b)^{-1}(\mathrm{mod}p).$$

To recover x from x^c, we must raise both sides to the power d, where d satisfies

$$c \cdot d \equiv 1(\mathrm{mod}p-1).$$

This is the reason why we required the condition $\mathrm{GCD}(c, p-1) = 1$, so that d exists (as the modular inverse of c modulo $p-1$).

By raising to the power d, we obtain

$$S^{-1}(y) = x = (a^{-1}(y-b)^{-1})^d(\mathrm{mod}p).$$

This construction guarantees that the S-box is bijective and fully invertible, thereby preserving the mathematical correctness of the cryptosystem.

Algorithm of the Cryptosystem

- At the beginning, a list consisting of *m* characters is constructed, and each character is associated with a number from 1 to *m*.
- We consider the finite field $F_p = \{0, 1, 2, \dots, p-1\}$, where *p* is the smallest prime number such that $p > m$
- The length *l* of the message *M* is divided by 4: *l* = 4*q* + *r*. Then the message *M* is divided into *q* blocks (ordered systems with 4 coordinates). If the last system does not have 4 coordinates, then it is completed at the end with as many zeros as needed.
- Each block of *M* is inserted into the S-box. For this purpose, we take as S-box $S: \mathbb{H} \to \mathbb{H}$ a nonlinear function defined as: $S(a + bi + cj + dk) = s(a) + s(b)i + s(c)j + s(d)k$, where the function $s: \mathbb{R} \to \mathbb{R}$ $s(x) = (ax^{-c} + b)(\mathrm{mod}p)$, where $a, b, c \in \mathbb{R}$ and p is a prime number.
- We choose the secret encryption keys $K \in \mathbb{H} \setminus \{0\}$ and $Q \in \mathbb{H} \setminus \{0\}$, $t \in \mathbb{Z}$.
- *Encryption* is performed by means of:

$$C = K\,S(M)\,K^{-1} + t\mathrm{Q}.$$

- *Decryption: Since $K \neq 0$*, there exists K^{-1}. Then:

$$S(M) = K^{-1}(C - tQ)K$$

and then the inverse function S^{-1} is applied to recover *M* from the S-box.

$$M = S^{-1}(K^{-1}(C - tQ)K).$$

Correct Definition of the Cryptosystem

Let the following be given:

- M the message represented as a quaternion (or a block of quaternions),
- $K \in \mathbb{H} \setminus \{0\}$ the secret key,
- S a bijective S-box function,
- The encryption function given by $E_K(M) = C = K\,S(M)\,K^{-1} + t\mathrm{Q}$ and
- The decryption function given by $M = S^{-1}(K^{-1}(C - tQ)K)$.

Theorem 4.1. For every message M, the following holds:$D_K(E_K(M)) = M$.

Proof. We start from the decryption function $D_K(C) = S^{-1}(K^{-1}(C - tQ)K)$ in which we substitute $C = E_K(M) = C = K\,S(M)\,K^{-1} + t\mathrm{Q}$ and obtain:

$$D_K(E_K(M)) = S^{-1}(K^{-1}((KS(M)K^{-1} + tQ) - tQ)K) =$$
$$= S^{-1}(K^{-1}((KS(M)K^{-1} + tQ) - tQ)K) = S^{-1}(K^{-1}(KS(M)K^{-1})K).$$

In $\mathbb{H}$ multiplication is associative, therefore:

$$D_K(E_K(M)) = K^{-1}(KS(M)K^{-1})K = (K^{-1}K)\,S(M)\,(K^{-1}K) =$$
$$= S^{-1}(1 \cdot S(M) \cdot 1) = S^{-1}(S(M)) = M.$$

Application Example

Encrypt the message UNIVERSITY and then decrypt it for verification.

Encryption:

Step 1. We choose the basic list:$A = 1, B = 2, C = 3, \dots, X = 24, Y = 25, Z = 26$.

Step 2. We transform the message UNIVERSITY into a numerical sequence:

$U = 21$, $N = 14$, $I = 9$, $V = 22$, $E = 5$, $R = 18$, $S = 19$, $I = 9$, $T = 20$, $Y = 25$

And we obtain the numerical message M: (21,14,9,22,5,18,19,9,20,25).

Step 3. The $l = 10 = 4 \cdot 2 + 2$, since the last block has two characters, we complete it with two zeros and obtain: $(21,14,9,22), (5,18,19,9), (20,25,0,0)$. Then we represent them as quaternions:

$$q_1 = 21 + 14i + 9j + 22k$$
$$q_2 = 5 + 18i + 19j + 9k$$
$$q_3 = 20 + 25i$$

Step 4. We choose $p = 29$ (29 is the first prime number greater than m=26) and work in the field $\mathbb{Z}_{29}$. As an S-box, we take $S(x) = x^3 (\mathrm{mod} 29)$, because $\gcd(3,28) = 1$, and we apply it component by component.

Block 1(21,14,9,22).

$$21^3 \equiv 10 (mod 29)$$
$$14^3 \equiv 18 (mod 29)$$
$$9^3 \equiv 4 (mod 29)$$
$$22^3 \equiv 5 (mod 29)$$

and we obtain $S(q_1) = 10 + 18i + 4j + 5k$.

Block 2 (5,18,19,9).

$$5^3 \equiv 9 (mod 29)$$
$$18^3 \equiv 3 (mod 29)$$
$$19^3 \equiv 15 (mod 29)$$
$$9^3 \equiv 4 (mod 29)$$

and we obtain $S(q_2) = 9 + 3i + 15j + 4k$.

Block 3 (20,25,0,0).

$$20^3 \equiv 25(mod29)$$
$$25^3 \equiv 23(mod29)$$
$$0^3 = 0(mod29)$$

and we obtain $S(q_3) = 25 + 23i + 0j + 0k$.

Step 5. We choose the secret keys arbitrarily from $\mathbb{H} \setminus \{0\}$. We choose $K = 1 + 2i + j + 3k$ for which we also determine the inverse quaternion, $Q = 5 - 2i + 3j - k$ and $t = 5$.
So $tQ = 5Q = 25 - 10i + 15j - 5k$.

For a quaternion $q = a + bi + cj + dk$ the inverse is given by $q^{-1} = \frac{\bar{q}}{N(q)}$ where:

- $\bar{q} = a - bi - cj - dk$ (the conjugate)
- $N(q) = a^2 + b^2 + c^2 + d^2$(the norm)

We find: $\bar{K} = 1 - 2i - j - 3k$ and $N(K) = 1^2 + 2^2 + 1^2 + 3^2 = 15$. Thus, the inverse is:

$$K^{-1} = \frac{1-2i-j-3k}{15} = \frac{1}{15} - \frac{2}{15}i - \frac{1}{15}j - \frac{1}{5}k.$$

Step 6. We encrypt using $C_i = K\,S(q_i)\,K^{-1} + tQ$, for $i = 1, 2, 3$.

- $C_1 = K\,S(q_1)\,K^{-1} + (25 - 10i + 15j - 5k) =$
  $(1 + 2i + j + 3k)(10 + 18i + 4j + 5k)(\frac{1}{15} - \frac{2}{15}i - \frac{1}{15}j - \frac{1}{5}k)+(25 - 10i + 15j - 5k)=$

$$C_1 = \left(\frac{150}{15} - \frac{28}{15}i + \frac{146}{15}j + \frac{245}{15}k\right) + (25 - 10\mathrm{i} + 15j - 5k) =$$

$$(10 - \frac{28}{15}i + \frac{146}{15}j + \frac{49}{3}k) + (25 - 10i + 15j - 5k) = 35 - \frac{178}{15}i + \frac{371}{15}j + \frac{34}{3}k$$
$$= (35, -\frac{178}{15}, \frac{371}{15}, \frac{34}{3})$$

- $C_2 = K\,S(q_2)\,K^{-1} + (25 - 10i + 15j - 5k) = (1 + 2i + j + 3k)(9 + 3i + 15j + 4k)(\frac{1}{15} - \frac{2}{15}i - \frac{1}{15}j - \frac{1}{5}k)+ (25 - 10i + 15j - 5k) =$

$$C_2 = \left(\frac{135}{15} + \frac{11}{15}i - \frac{127}{15}j + \frac{200}{15}k\right) + (25 - 10i + 15j - 5k) =$$

$$= (9 + \frac{11}{15}i - \frac{127}{15}j + \frac{40}{3}k) + (25 - 10i + 15j - 5k) = 34 - \frac{139}{15}i + \frac{98}{15}j + \frac{25}{3}k =$$

$$(34, -\frac{139}{15}, \frac{98}{15}, \frac{25}{3})$$

- $C_3 = K\,S(q_3)\,K^{-1} + (25 - 10i + 15j - 5k) =$

$$(1 + 2i + j + 3k)(25 + 23i + 0j + 0k)(\frac{1}{15} - \frac{2}{15}i - \frac{1}{15}j - \frac{1}{5}k) + (25 - 10i + 15j - 5k)$$
$$= \left(25 - \frac{23}{3}i + \frac{46}{3}j + \frac{46}{3}k\right) + (25 - 10i + 15j - 5k) =$$
$$= (50, -\frac{53}{15}, \frac{91}{15}, \frac{31}{15}).$$

Thus, we obtain the encrypted message:

$$C = (C_1, C_2, C_3) = \left(35, -\frac{178}{15}, \frac{371}{15}, \frac{34}{3}, 34, -\frac{139}{15}, \frac{98}{15}, \frac{25}{3}, 50, -\frac{53}{15}, \frac{91}{15}, \frac{31}{15}\right).$$

Step 7. Decryption: The decryption formula is: $M_i = S^{-1}(K^{-1}(C_i - tQ)K)$, $i = 1,2,3$. But to recover them from the S-box, we must solve: $x^3 \equiv y(\mathrm{mod}29)$. Since we need $3d \equiv 1(\mathrm{mod}28)$, we take $d = 19$. Therefore, we use the power 19 as the decryption exponent.

- Decryption of C_1=$(35, -\frac{178}{15}, \frac{371}{15}, \frac{34}{3})$.

We compute $K^{-1}(C_1 - 5Q)K = 10 + 18i + 4j + 5k$ and then find $S^{-1}K^{-1}(C_1 - 5Q)K$ by calculating:

- $10^{19} \equiv 21(mod29)$
- $18^{19} \equiv 14(mod29)$

- $4^{19} \equiv 9(mod29)$
- $5^{19} \equiv 22(mod29)$.

Thus, the first decrypted block is $M_1 = (21,14,9,22)$.

- Decryption of C_2=$(9, \frac{11}{15}, -\frac{127}{15}, \frac{40}{3})$.

We compute $K^{-1}(C_2 - 5Q)K = 9 + 3i + 15j + 4k$ and then find $S^{-1}(K^{-1}(C_2 - 5Q))K$ by calculating:

- $9^{19} \equiv 5(mod29)$
- $3^{19} \equiv 18(mod29)$
- $15^{19} \equiv 19(mod29)$
- $4^{19} \equiv 9(mod29)$.

Thus, the second decrypted block is $M_2 = (5,18,19,9)$.

- Decryption of C_3=$(50, -\frac{53}{15}, \frac{91}{15}, \frac{31}{15})$.

We compute $K^{-1}(C_3 - 5Q)K = 25 + 23i + 0j + 0k$ and then find $S^{-1}(K^{-1}(C_3 - 5Q)K)$ by calculating:

- $25^{19} \equiv 20(mod29)$
- $23^{19} \equiv 25(mod29)$
- $0^{19} \equiv 0(mod29)$
- $0^{19} \equiv 0(mod29)$

Thus, the third decrypted block is $M_3 = (20,25,0,0)$.

We combine the decrypted blocks and, after removing the trailing zeros, we obtain: 21,14,9,22,5,18,19,9,20,25, which reads: **UNIVERSITY**.

Results and Interpretation

The presented cryptosystem demonstrates that structures from abstract algebra, in particular the quaternion ring $\mathbb{H}$, can serve as a powerful foundation for constructing cryptographic schemes. The combination of the following three components:

- Quaternion key transformation: $C = K \cdot S(M) \cdot K^{-1} + tQ$
- Nonlinear S-box: $s(x) = (ax^{-c} + b)(\mathrm{mod} p)$, and its inverse
- The secondary key Q and the parameter t as an additional security layer

creates a mathematically correct, fully reversible system that is resistant to linear algebraic attacks. The integration of the nonlinear S-box is essential, since it transforms the algebraic linear structure that could be exploited by attackers into a nonlinear structure, making the system resistant to classical attacks.Through the practical example of the word **"UNIVERSITY"**, we verified that the system is fully reversible, where the original message is recovered without loss of data through the application of the inverse key and the inverse function of the S-box.

Conclusion

In this paper, we have presented an innovative cryptosystem model that integrates structures from abstract algebra with modern information security techniques. The use of the quaternion ring provides a new dimension for data encryption, allowing messages to be processed as multidimensional units (blocks of length four). This approach demonstrates that quaternions are not only a theoretical mathematical tool, but also a powerful alternative for constructing modern cryptographic systems.

For future research, it is recommended to explore this system over complex number fields or through the use of quaternion matrices in order to further increase key complexity and data security.

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ATOPIC DERMATITIS IN AN INFANT: PRESENTATION OF A CLINICAL CASE WITH SECONDARY STAPHYLOCOCCUS AUREUS INFECTION

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Scientific paper – Clinical case report
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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a high prevalence in the pediatric age group, characterized by xerosis, intense pruritus, eczematous lesions, and a predisposition to secondary bacterial infections, mainly with Staphylococcus aureus. Its pathogenesis is complex and involves dysfunction of the epidermal barrier, immunological disturbances polarized toward a Th2 response, and changes in the skin microbiome. This paper presents the case of a 6-month-old male infant who was referred to the Department of Dermatology of Tetovo Clinical Hospital with erythematous eczematous lesions on the cheeks, marked pruritus, subfebrile temperature, and clinical signs of secondary bacterial infection. The infant had a strongly positive family history of atopy: his grandmother had atopic dermatitis, his maternal uncle had allergic rhinitis and bronchial asthma, while his mother had episodes of contact dermatitis. The diagnosis was established on the basis of clinical examination, dermatoscopic assessment, and a bacterial culture obtained by swab from the lesions, which confirmed the presence of methicillin-sensitive Staphylococcus aureus (MSSA). The therapeutic plan included detailed parental education on skin care, frequent use of a hypoallergenic emollient containing ceramides, hydrocortisone cream 1% twice daily for 10–14 days on inflammatory lesions, and mupirocin 2% ointment three times daily for 7 days for the bacterial infection. At the follow-up visit after two weeks, considerable clinical improvement was noted, with regression of erythema, elimination of the honey-yellow crusts, and reduction of pruritus. This case underscores the importance of early diagnosis, an individualized therapeutic approach, and caregiver education for the effective management of AD in infancy, especially when complicated by secondary bacterial infections.

Keywords: atopic dermatitis, infancy, Staphylococcus aureus, epidermal barrier, ceramides, hydrocortisone, mupirocin.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is one of the most common chronic inflammatory skin diseases in the pediatric population. According to contemporary epidemiological estimates, this disease affects between 10% and 20% of children worldwide, with an increasing trend in recent decades, especially in industrialized countries and urban centers (Bylund et al., 2020; Silverberg, 2017). Studies in the Balkan region and in Southeastern Europe show similar trends, making AD a significant public health problem and one of the most frequent reasons for pediatric dermatology visits (Weidinger et al., 2018).
The clinical manifestations of AD usually begin early in life: about 60% of patients develop symptoms within the first year of life, while up to 90% do so before the age of 5 (Weidinger et al., 2018). The clinical picture is heterogeneous and varies according to age, severity, and localization. In infants, the lesions mainly involve the cheeks, the scalp, the extensor surfaces of the extremities, and the trunk, while areas covered by the diaper are usually spared because of the increased local hydration of this area (Eichenfield et al., 2014a). The characteristic lesions include erythematous macules, papules, vesicles, exudation, crusts, and marked xerosis. Pruritus, the cardinal symptom of the disease, deeply affects the quality of life of the child and

the family, causing sleep disturbances, mood changes, and a notable psychosocial impact (Silverberg & Simpson, 2014).

The pathogenesis of AD is a multifactorial process resulting from the close interaction between genetic, immunological, environmental, and microbial factors. Three main pathogenetic axes are currently recognized: dysfunction of the epidermal barrier, immunological dysregulation, and disturbances of the skin microbiome (Weidinger et al., 2018; Boguniewicz & Leung, 2011).

Filaggrin, an essential structural protein of the stratum corneum of the epidermis, plays a key role in maintaining the integrity of the cutaneous barrier and in skin hydration through the formation of natural moisturizing factors (NMF). Loss-of-function mutations in the *FLG* gene are considered the most important genetic predisposing factor identified to date for atopic dermatitis (AD), being reported in approximately 20–50% of patients with moderate to severe forms of the disease (Palmer et al., 2006; Irvine et al., 2011). The deficiency of filaggrin and its products leads to marked transepidermal water loss (TEWL), to an increase in the surface pH of the skin, and to increased permeability of allergens and pathogens through the damaged horny layer (Irvine, 2011).

From an immunological standpoint, atopic dermatitis (AD) is characterized by an immune response polarized toward type 2 helper T lymphocytes (Th2), which produce elevated levels of proinflammatory cytokines such as interleukin-4 (IL-4), IL-5, IL-13, and IL-31. These cytokines contribute to chronic inflammation of the skin, damage to the cutaneous barrier, and the appearance of the pruritus characteristic of the disease (Brunner et al., 2017; Weidinger & Novak, 2016). IL-4 and IL-13 promote IgE synthesis, inhibit keratinocyte differentiation, and suppress the expression of endogenous antimicrobial peptides such as beta-defensin and cathelicidin, while IL-31 is one of the principal mediators of pruritus (Czarnowicki et al., 2019). In the chronic stages of the disease, there is also a significant contribution from the activation of the Th22 and Th17 axes, which explains the evolution from acute exudative lesions toward thickened, lichenified plaques (Boguniewicz & Leung, 2011; Leung & Guttman-Yassky, 2014).

Normal skin is populated by a rich diversity of commensal microbes that exert a protective effect against colonization by pathogens. In patients with AD, this microbial balance is disrupted. Numerous studies have shown that the skin of patients with AD is colonized by Staphylococcus aureus in about 70% of cases with active lesions and up to 90% during flares, compared with only 5–30% on the skin of healthy individuals (Geoghegan et al., 2018). S. aureus is not merely a transient colonizer but plays an active pathogenic role through the production of superantigens, toxins, and proteolytic enzymes that amplify inflammation and further damage the barrier (Mempel et al., 1998; Geoghegan et al., 2018).

In addition to these intrinsic factors, environmental factors such as urbanization, air pollution, limited exposure to microbial diversity in early childhood (the hygiene and biodiversity hypotheses), dietary changes, and the excessive use of soaps and aggressive detergents play an important role in modulating the onset and severity of the disease (Flohr & Mann, 2014).

Atopic dermatitis (AD) is often accompanied by other atopic diseases, a phenomenon known as the "atopic march," which describes the progression of allergic manifestations from atopic dermatitis in early childhood toward the development of bronchial asthma and allergic rhinitis later in life. This phenomenon reflects the complex interaction between genetic predisposition, damage to the cutaneous barrier, and immunological dysregulation (Spergel & Paller, 2003; Zheng et al., 2011). Early identification and adequate treatment of AD may contribute to

modifying this natural course. The management of AD requires a comprehensive approach that includes: education of the patient and the family, restoration of the epidermal barrier with emollients, control of inflammation with topical corticosteroids or calcineurin inhibitors, identification and avoidance of trigger factors, and adequate management of secondary infections (Eichenfield et al., 2014b; Wollenberg et al., 2018).

Aim of the Paper

The aim of this paper is to present and analyze a clinical case of atopic dermatitis with secondary bacterial infection in a 6-month-old infant, and to discuss it in the context of the contemporary literature. More specifically, the objectives of the paper are:

- to describe the clinical, anamnestic, and demographic features of a characteristic case of AD in infancy;
- to illustrate the diagnostic process and the role of complementary examinations, including dermatoscopic assessment and bacterial culture;
- to underscore the importance of parental education and of an integrated approach in the long-term management of AD;
- to compare the clinical findings and therapeutic results of the case with the data published in the current scientific literature.

3. Presentation Of The Clinical Case

3.1. Anamnestic and demographic data: The patient is a 6-month-old male infant who presented at the Department of Dermatology of Tetovo Clinical Hospital, accompanied by his parents, because of marked lesions on the skin of the face, accompanied by intense pruritus and clinical signs suggestive of a secondary bacterial infection. According to the parents' account, the dermatological symptoms had begun approximately two weeks before the visit, with significant worsening over the last 5–7 days.

In addition to the dermatological manifestations, the infant presented with a subfebrile body temperature of 38.2°C and increased signs of discomfort, restlessness, and sleep disturbance. The parents denied the presence of recent viral infections or contact with sick persons in the family circle. They also denied the use of new skin care products and exposure to potential irritants such as aggressive detergents or scented soaps.

Personal history: the infant was born at term through a standard vaginal delivery, with a normal birth weight of 3.4 kg. From birth he had been exclusively breastfed and had developed adequately according to the normal milestones of growth and psychomotor development. At 4 months of age he had experienced a mild episode of an upper respiratory tract infection, which had resolved spontaneously. No other serious infections or previous hospital admissions were reported. Immunizations were up to date according to the national immunization schedule.

The family history was strongly positive for atopic diseases: the maternal grandmother had a documented history of atopic dermatitis, while the maternal uncle suffered from allergic rhinitis and bronchial asthma. The paternal family history was unremarkable for atopic diseases. The mother reported rare episodes of contact dermatitis, but no other significant systemic diseases.

3.2. Physical examination: On dermatological examination, well-defined erythematous plaques were noted on both cheeks, accompanied by mild edema, honey-yellow crusts

(suggestive of staphylococcal infection), and small erosive areas with serous exudation. The extensor surfaces of the arms also showed mild eczematous lesions with visible xerosis. Pruritus was evident from the frequent movements of the infant's hands toward the face and from the marks of self-induced scratching. The mucous membranes were unaffected, and no significant peripheral lymphadenopathy was found. Pulmonary and cardiac auscultation were normal; the abdomen was soft, without organomegaly. Neurological and motor development was assessed as adequate for age.

3.3. Additional examinations and diagnosis: Dermatoscopic examination confirmed the presence of erythematous areas with serous exudation, crusts, and signs of local microinfection. In order to identify the etiologic agent of the secondary infection, a sample was taken by swab from the crusted lesions and sent to the microbiology laboratory. Bacterial culture confirmed the growth of methicillin-sensitive Staphylococcus aureus (MSSA). The antibiogram showed good sensitivity to mupirocin, oxacillin, clindamycin, and trimethoprim-sulfamethoxazole, and no clinically important resistance.

On the basis of the clinical features (typical localization on the cheeks in infants, xerosis, intense pruritus, eczematous lesions), the strongly positive family history of atopy, and the microbiological confirmation of infection with S. aureus, the diagnosis of moderate-to-severe atopic dermatitis, complicated by secondary bacterial infection with Staphylococcus aureus (MSSA), was established. The diagnosis met the modified Hanifin and Rajka criteria for atopic dermatitis (Hanifin & Rajka, 1980).

3.4. Therapeutic plan: The treatment offered was multimodal and individualized according to the patient's age and disease severity, following the principles of current international guidelines:

Parental education. The parents were given detailed instructions on skin care. They were advised to use lukewarm (not hot) water for baths, of short duration (5–10 minutes), with mild detergents, free of fragrances and without classic soap. After bathing, the skin was to be dried by gently patting with a soft towel.

A hypoallergenic, fragrance-free emollient cream containing ceramides and other humectants was prescribed. Application several times daily was advised, especially within 3 minutes after bathing — the technique known as "soak and seal" — in order to maintain maximal skin hydration. This measure addresses the fundamental dysfunction of the epidermal barrier, which is the cornerstone of AD (Sidbury et al., 2014).

For the acute inflammatory lesions, hydrocortisone cream 1% was prescribed, twice daily, for a period of 10–14 days. The choice of hydrocortisone, a low-potency corticosteroid (class VII according to the American classification), was deliberate, given the infant's age and the localization of the lesions on the face — an area with increased skin permeability. This choice provides sufficient anti-inflammatory effect while minimizing the risk of systemic absorption and of local side effects such as atrophy or telangiectasias (Eichenfield et al., 2014b).

After confirmation of the S. aureus infection and the antibiogram results, mupirocin 2% ointment was prescribed for application three times daily for 7 days on the affected and infected areas. Mupirocin shows pronounced activity against gram-positive bacteria, including MSSA and MRSA, and is suitable for use in infants (Bath-Hextall et al., 2010).

A first follow-up visit was scheduled after 7 days, and a second after 14 days, in order to assess the therapeutic response and to identify any unfavorable course at an early stage.

3.5. Clinical course: At the first follow-up, after 7 days of treatment, considerable improvement was noted: the temperature had normalized, the honey-yellow crusts had been substantially reduced, the erythema of the cheeks was paler, and pruritus had decreased according to the parents' subjective assessment. Treatment with mupirocin was discontinued after 7 days, while hydrocortisone was continued for another 7 days on a reduced regimen (once daily). Emollients were recommended for long-term use.
At the second follow-up, 14 days after the start of treatment, almost complete regression of the eczematous lesions was noted. The infant appeared clinically calm, with normalization of sleep and no new signs of cutaneous infection. The parents were advised to continue the regular use of emollients as part of the basic long-term skin care. They were also offered a long-term management plan based on the "step-up/step-down" therapeutic approach, which included the identification and avoidance of potential factors that could trigger worsening of the disease.

Discussion

The case presented illustrates the typical clinical picture of atopic dermatitis in infancy and underscores several important points that deserve detailed analysis in the context of the contemporary literature.
First, the age of onset and the localization of the lesions are consistent with the classic epidemiological pattern of AD in infancy. According to Weidinger et al. (2018), in approximately 60% of cases the symptoms appear within the first year of life, with characteristic involvement of the cheeks, scalp, and extensor surfaces of the extremities. This localization pattern is partly explained by the greater exposure of these areas to mechanical irritants (contact with the pillow, friction during feeding, scratching) and by regional differences in the structure of the epidermal barrier (Eichenfield et al., 2014a).
The strongly positive family history of atopy in our case (maternal grandmother with atopic dermatitis, maternal uncle with asthma and allergic rhinitis) is consistent with the strongly hereditary nature of the disease. Large epidemiological studies have shown that the risk of developing AD is about 2–3 times higher in children with one atopic parent and up to 5 times higher when both parents are affected (Apfelbacher et al., 2011). FLG gene variants and other genes that regulate the epidermal barrier and the Th2 immune response are inherited along family lines and explain the familial clusters observed in clinical practice (Palmer et al., 2006; Irvine et al., 2011).
A critical aspect of the case is the presence of secondary infection with Staphylococcus aureus, confirmed by bacterial culture. S. aureus is well known as the most frequent pathogen in AD flares, with studies reporting colonization in up to 70–90% of active lesions (Geoghegan et al., 2018). The mechanisms by which S. aureus contributes to the pathogenesis of AD are numerous: production of superantigens such as the staphylococcal enterotoxins (SEA, SEB), which directly activate T lymphocytes without antigen specificity; production of alpha-toxin, which directly damages keratinocytes; and disruption of the epidermal barrier through the secretion of proteases (Mempel et al., 1998; Geoghegan et al., 2018). The honey-yellow crusts noted in our case represent a classic clinical sign of impetiginization of atopic lesions and require prompt treatment with antibiotics.
With regard to treatment, the approach followed reflects the best practices recommended in contemporary international guidelines (Eichenfield et al., 2014b; Wollenberg et al., 2018). At the heart of management lies the restoration of the epidermal barrier through frequent use of

emollients. Emollients containing ceramides and humectant substances contribute to restoring the intercellular lipids of the cutaneous barrier and to increasing skin hydration, thereby reducing transepidermal water loss and the intensity of pruritus. Application of the emollient within three minutes after bathing, a technique known as "soak and seal," is considered an evidence-supported strategy, since it favors optimal penetration of the preparation and the retention of moisture in the horny layer of the skin (Eichenfield et al., 2014; Cork et al., 2009; Sidbury et al., 2014).

The important study by Simpson et al. (2014) showed that daily application of emollients from birth in infants at high familial risk reduced the cumulative incidence of AD at 6 months of age by about 50%. Similar results were reported by Horimukai et al. (2014), who demonstrated a significant reduction of AD after the application of emollients from the neonatal period. These findings underscore the primary role of emollient care as a fundamental preventive and therapeutic measure, especially in infants with an at-risk family history — as in our case.

The choice of hydrocortisone 1% as a low-potency topical corticosteroid is reasonable and supported by the literature, especially in the context of the patient's young age and the localization of the lesions on the face. The skin of the face and intertriginous areas has greater permeability to corticosteroids and a higher risk of local side effects, including atrophy, telangiectasias, and perioral dermatitis. The use of high-potency corticosteroids in these areas and in infants should be regularly avoided. Although the frequent parental concern about the fear of using corticosteroids — often referred to as "corticophobia" — frequently leads to underuse and results in poor disease control (Charman et al., 2002), studies have shown that short-term, monitored use of low-potency corticosteroids is safe and highly effective (Hoare et al., 2000).

The use of topical mupirocin 2% represents an evidence-supported therapeutic strategy for the treatment of localized secondary infections with *Staphylococcus aureus* in patients with atopic dermatitis (AD). In the Cochrane review, Bath-Hextall et al. (2010) recommend the use of topical antibiotics for limited cutaneous infections, instead of systemic antibiotics, in order to reduce the risk of bacterial resistance and of systemic side effects. Mupirocin acts by inhibiting the bacterial enzyme isoleucyl-tRNA synthetase and is effective both against methicillin-sensitive *S. aureus* (MSSA) strains and against methicillin-resistant strains (MRSA), making it a rational first-line choice for localized bacterial infections in AD.

Parental education is considered a fundamental component in the long-term management of atopic dermatitis and has a direct impact on therapeutic success. Studies have shown that structured educational programs significantly improve the knowledge of caregivers, adherence to treatment, disease control, and the quality of life of patients and their families (Stalder et al., 2013; LeBovidge et al., 2016). In our case, the parents received detailed instructions regarding correct bathing and skin hydration practices, the proper use of topical corticosteroids, and the early recognition of warning signs of infection. This educational approach is thought to have contributed to the rapid clinical improvement of the patient.

An important long-term consideration is the "atopic march": the tendency for the later development of asthma, allergic rhinitis, and food allergies in children with AD that presents early and with increased severity (Spergel, 2010). Our patient, having AD with early onset and a strongly positive family history of atopy (including asthma in the maternal uncle), is at increased risk for this trajectory. Careful observation and early interventions may modify this course, although current data are still limited and further longitudinal observational studies are required.

Finally, it is important to emphasize the potential role of dietary factors. Although food allergy was not confirmed in our case (the infant was exclusively breastfed and presented no suggestive gastrointestinal or respiratory symptoms), in the group of patients with severe AD, and especially those refractory to standard treatment, evaluation for food allergies — particularly to cow's milk protein, eggs, and nuts — should be considered after consultation with the pediatric allergist (Eichenfield et al., 2014a; Boyce et al., 2010).
The limitations of this case presentation include its single-case nature and the relatively short period of follow-up (14 days). Nevertheless, the case offers a practical and didactic illustration of the management of AD in infancy with secondary infection, and it highlights basic principles that are valuable in everyday clinical practice.

Conclusion

Atopic dermatitis in infants remains an important clinical challenge, characterized by complex interactions among genetic, immunological, environmental, and microbial factors. The case presented of a 6-month-old infant with moderate-to-severe AD and secondary infection with Staphylococcus aureus illustrates several fundamental principles in the management of this disease in infancy.
Early diagnosis through careful clinical examination and recognition of the characteristic features in this age group; assessment of the family history of atopy as a prognostic indicator; early identification of secondary bacterial infections with microbiological confirmation for targeted treatment; an individualized therapeutic approach including restoration of the epidermal barrier with emollients, control of inflammation with topical corticosteroids of an appropriate potency for the patient's age and the lesion site, treatment of infections with topical antibiotics based on the antibiogram; and thorough parental education as an essential component of long-term management — together represent a successful treatment model.
The rapid and substantial clinical improvement of the patient after 14 days of treatment confirms the efficacy of the approach taken. However, given the chronic and relapsing nature of the disease, long-term follow-up remains essential. The identification of children at high familial risk of atopy may allow early preventive interventions with emollients, while future research may shed more light on the role of the skin microbiome, on biomarkers for patient stratification, and on new molecularly targeted therapies — such as JAK inhibitors and anti-IL-4/IL-13 monoclonal antibodies — which are opening new perspectives in the management of AD in older age groups and potentially also in infants.
In conclusion, this case underscores that the effective management of atopic dermatitis requires a comprehensive, individualized, and educational approach that takes into consideration the biological characteristics of the patient, the family context, and the evidence-based principles of contemporary literature.

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THE INFLUENCE OF THE POROSITY COEFFICIENT (R_U) ON THE SAFETY FACTOR (Fs) WITH THE APPLICATION OF NUMERICAL METHODS.

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Abstract

A landslide can occur as a result of natural changes in the geological environment of a slope (changes in the groundwater regime, erosion, earthquake action), or as a result of human activities (removal of vegetation and positive root activity, filling and excavation in the process of road construction, additional loads placed on slopes due to the erection of buildings or road fillings, bridge construction, piles of waste material). When the mass of soil on a slope cannot ensure the balance of the forces acting on it, a landslide occurs, the area of the mass that is involved in the landslide is called a landslide body. When a slope landslide occurs, it is clear that there is a lack or weakening of the shear resistance of the sliding surface in order to maintain the equilibrium of the sliding body. The calculations of the safety factor are usually carried out according to the methods of limit equilibrium and the arcuate sliding surface. In the case of more complicated tasks (more complex, more complex conditions, the state of the rock mass and the size of the object) their solution by limit equilibrium methods is called into question. In such cases, numerical methods of calculation are also implemented, any of the methods for calculating the full state of stress and deformation of the given model. After that, the results obtained by the limit equilibrium methods are compared and the final conclusions are drawn by numerical methods.

Keywords: Safety factor, methods, programs, r_u

Introduction

When preparing the analyses, the main goal is to determine the safety factors and ru , according to the three mentioned methods and their comparison when varying the values of the geomechanical and geometric parameters.

For these reasons, in some of the obtained safety factors, safety factors lower than Fs=1.15 were calculated, which indicates the fact that this is a slope with unacceptably low safety. For greater clarity, all analyzed sliding surfaces according to the Bishop, Janbu and Spencer methods are numbered and the obtained results are shown in a table below in the text.

In addition, the distribution of the analyses and results throughout the paper is carried out by sections: for a general slope inclination (β=190), for which cases calculations were performed with the GGU and SLIDE software, and within which the 4-4` profiles were analyzed and where the geomechanical parameters were varied, and within which general slope the pore pressure coefficient ru is varied in the range 0,0. 0.2 and 0.3.

Geomechanical parameters adopted for the stability analysis

It is undeniable that the selection of the values of the geomechanical parameters of materials is one of the most complex and sensitive tasks in stability analysis.

Therefore, in solving this problem, all available data from previous research and testing were used in order to obtain the most reliable and relevant data possible, and the adopted geomechanical parameters are shown in Table 2.1.

Table 2.1 Adopted geomechanical parameters for profile 4-4'

Nr.	Material description	Geomechanical tag	c (kPa)	φ (°)	γ (kN/m^3)	r_u
1	Quarter	SFc/GW	10.00	16.70	20.40	0.00
						0.20
						0.30
2	Organic, medium to high plastic clay	OH/OI	10.00	16.40	17.00	0.00
						0.20
						0.30
3	Coal	L	50	25	13.5	0.00
5	Silty sands	SFc	20.37	21.71	21.41	0.00
						0.20
						0.30
7	Medium plastic clay	CI	18.00	18.00	19.90	0.00
8	Coal with coal clay	L/OH	20.00	17.80	17.90	0.00

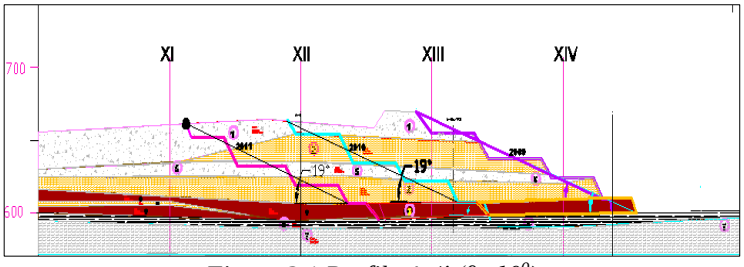


Figure 2.1 Profile 4-4' (β=19^0)

Determination of general (normative) and calculated values of parameters for shear resistance.

For a set of data obtained on the basis of experimental tests within the boundaries of separate engineering-geological elements, it is adopted that the general values (X°) of all soil characteristics, with the exception of specific cohesion (c), and the angle of internal friction φ, equal to the arithmetic mean values (X), are calculated according to the formula . However, for determining general values (c°) and (φ°), the processing of the experimental results is carried out by calculating by the method of least squares the linear dependence of the shear resistance for all the general values (τ) obtained by experiments in the engineering-geological elements.

$$\tau = \square \square\square\square + \square$$

Where:
τ- shear strength (MPa)
σ – normal stress (MPa)
tgφ – tangent of the angle of internal friction

c – cohesion (MPa)

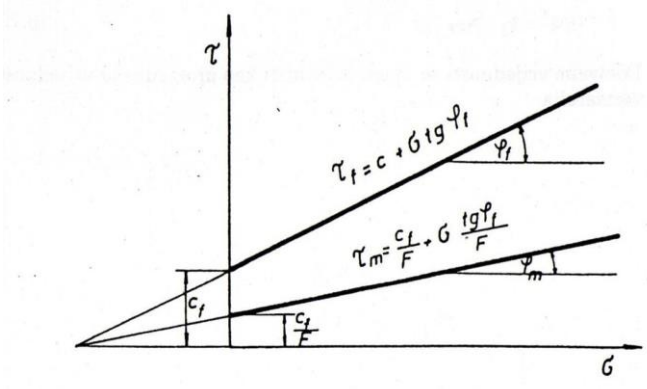


Figure 3.1 – Safety factor for the linear failure criterion in limit equilibrium methods) is considered a constant value for the entire sliding surface and is in constant proportion to the cohesion and the angle of internal friction.

3.1 Statistical processing of geomechanical classification parameters: The statistical processing of the obtained parameters was performed using the following equations:

- **Arithmetic mean value.**

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

Where:
n- is the number of samples.
Xi- is the characteristic value of one sample.
$\bar{x}$ - is the mean value

- **Standard deviation - σ=**

$$\sqrt{\frac{\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2}{n-1}}$$

- **Coefficient of variation -** $V = \frac{\sigma}{\bar{X}} \cdot 100$ %

3.2 Statistical processing of strength parameters: Method: Least square linear dependence of shear strength for all total values (τ) obtained by the experiment in an engineering-geological element.

τ=σ tangφ+c

The statistical processing of the strength parameters obtained from the triaxial direct shear test and determination of residual strength was performed according to the expressions listed below.

A. Direct shear.

- Statistical processing of the results obtained from the direct shear test is based on the following expressions:

$$\Delta = n\sum_{(i=1)}^{n}(\sigma_i)^2 - \sum_{n-1}^{n}(\sigma_i)^2$$

$$C = \frac{1}{\Delta}\left[\sum_{(i=1)}^{n}\tau_i\sum_{(i=1)}^{n}\sigma_i^2 - \sum_{(i=1)}^{n}\sigma_i\sum_{(i=1)}^{n}\sigma_i\tau_i\right]$$

$$tg\varphi = \frac{1}{\Delta}\left[n\sum_{i=1}^{n}\tau_i\sigma_i - \sum_{i=1}^{n}\tau_i\sum_{i=1}^{n}\sigma_i\right]$$

Where:

i – are the normal stress [kN/m2]

i – are the tangential stress [kN/m2]

B. **Determination of Residual Strength**

When determining the residual strength, certain values for cohesion were obtained, although the shear contact had already been broken. This is due to the way the results are processed according to the Mohr-Coulomb failure criterion, where the dependence $\tau=\sigma\ tg\varphi+c$ is interpreted as a straight line. This is the so-called "apparent cohesion" and when analyzing the stability of slopes in the excavation, it should adopt a value of Crez=0.

C. Statistical processing of strength parameters obtained by triaxial testing

The statistical processing of the results of the strength parameters obtained by triaxial testing is done according to the following formulas:

$$tg\varphi = \frac{a-1}{2\sqrt{a}}, \left[^0\right]$$

$$C = \frac{b}{2\sqrt{a}}, \left[\frac{kN}{m^2}\right]$$

$$a = \frac{1}{\Delta}\left(n\sum\sigma_1\sigma_3 - \sum\sigma_1\sum\sigma_3\right)$$

$$b = \frac{1}{\Delta}\left(\sum\sigma_3^2\sum\sigma_1 - \sum\sigma_3\sum\sigma_1\sigma_3\right)$$

$$\Delta = n\sum(\sigma_3)^2 - (\sum\sigma_3)^2$$

where:

σ_1, σ_3 – are the main maximum and minimum stresses, [kN/m2]

The safety coefficients (factors) that analyzed sliding surfaces for treated slopes must meet in order to be accepted are adopted based on the "Rules for Technical Norms for Surface Exploitation of Mineral Deposits (Stability of Surface Mine Slopes)", and their minimum values are as follows:

Table 3.2 Adopted reliability coefficients

Slope type Fs	**Fs**
Working slopes that are changed once a month	1.0 to 1.1
Working slopes on which mechanization and transport move	1.1 to 1.15
Working slope system when mechanization is working and when transport is carried out	1.15 to 1.20
Slopes that have a longer service life, side and end slopes	1.3

Analyses performed

The stability analyses in this doctoral dissertation were conducted in order to determine the influence of various geomechanical, geometric and hydrogeological parameters on the safety factors for the same failure surfaces and to determine the differences in their values that occur when applying the Bishop, Spencer and Janbu methods.
Moreover, the distribution of the analyses and results throughout the paper is carried out by sections: for a general slope inclination (□=19o), for which cases calculations were performed with the GGU and SLIDE software, and within which a 4-4` profile was analyzed.

Table 4.1 β=19°, Stability analyzes for profile 4-4'.

4-4’	**ru=0**		**ru=0,20**		**ru=0,30**	
	Bishop	Janbu	Bishop	Janbu	Bishop	Janbu
1	1,1	1,1	0,9	0,9	0,8	0,8
2	0,81	0,83	0,68	0,69	0,6	0,62
3	1,14	1,17	0,93	0,95	0,83	0,83
4	1,38	1,38	1,28	1,26	1,22	1,21

ru=0	**ru=0,20**	**ru=0,30**
J/B	J/B /	J/B
1	1	1
1,024691	1,014706	1,033333
1,026316	1,021505	1
1	0,984375	0,991803

Otherwise, both from the aspect of the research for the doctoral dissertation, and from the aspect of the stability of the slopes of the surface mine, it is very important to highlight the observation that the values of Fs at ru=0.0 are up to 30% higher than the values of Fs at ru=0.30. From the results shown in Table 4.1 and the diagrams for profile 4-4’, the values of the factor of safety (Fs) for the four sliding surfaces meet the stability condition (Fs=1.15) only for ru=0.00.

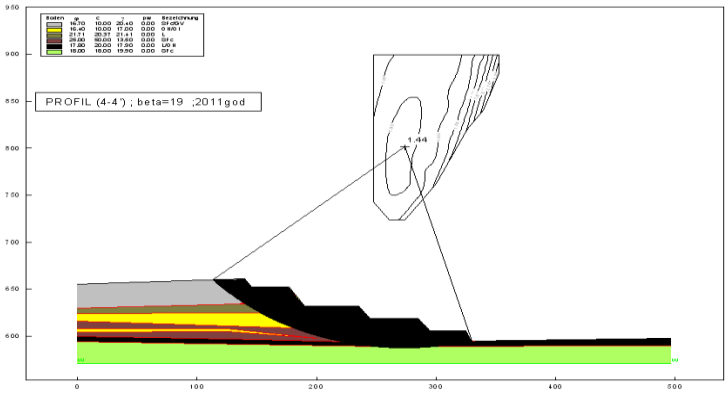


Figure.4.2. Profile 4-4`, Bishop; Sliding surface; 4. Fs=1.44, ru=0.00

Table 4.2 β=19°, Stability analysis for profile 4-4'

4-4' 2011	ru=0		ru=0,20		ru=0,30	
	Bishop	Janbu	Bishop	Janbu	Bishop	Janbu
1	0,97	0,99	0,8	0,8	0,71	0,71
2	1,22	1,22	0,98	0,99	0,87	0,88
3	1,34	1,42	1,13	1,24	1,02	1,15
4	1,44	1,46	1,36	1,33	1,31	1,26

ru=0	**ru=0,20**	**ru=0,30**
J/B	J/B	J/B
1,020619	1	1
1	1,010204	1,011494
1,059701	1,097345	1,127451
1,013889	0,977941	0,961832

Table 4.3 Difference between achieved Fs for sliding surfaces according to Bishop and Yanbu depending on ru for profile 4-4

$B_{0,2}$-$B_{0,3}$	B_0-$B_{0,3}$	B_0-$B_{0,2}$
0.09	0.26	0.17
0.11	0.35	0.24
0.11	0.32	0.21
0.05	0.13	0.08
$J_{0,2}$-$J_{0,3}$	J_0-$J_{0,3}$	J_0-$J_{0,2}$
0.09	0.28	0.19
0.11	0.34	0.23
0.09	0.27	0.18
0.07	0.20	0.13

Table 4.4 Relationship between achieved Fs for defined sliding surfaces according to Bishop and Yanbu depending on ru for profile 4-4'

$B_{0,3}/B_{0,2}$	$B_{0,3}/B_0$	$B_{0,2}/B_0$
0.89	0.73	0.82
0.89	0.71	0.80
0.90	0.76	0.84
0.96	0.90	0.94
$J_{0,3}/J_{0,2}$	$J_{0,3}/J_0$	$J_{0,2}/J_0$
0.89	0.71	0.80
0.89	0.72	0.81
0.92	0.80	0.87
0.94	0.86	0.91

From Table 4.2 it can be concluded that in profile 4-4`, for sliding surface 2 no noticeable difference is observed in the results according to the two methods. In sliding plane 3, however, the difference becomes more pronounced, especially with an increase in ru. Also, the values of Fs for the four sliding surfaces fulfill the stability condition (Fs=1.15) only for ru=0.00 and for sliding surface no. 3 and 4 for the case ru=0.20 and ru=0.30.

Comment on the results obtained

The stability analyses were performed for working slopes of the mine and required Fs=1.15, with variation of ru for different presence of groundwater, whereby ru=0.0 was taken as the relevant one, which should be achieved with the foreseen drainage measures.
The analysis was simulated at ru=0.2 and ru=0.3 in order to show the negative impact of increased presence of water, but by applying drainage measures it should be avoided. The verification of the slopes was performed by years, whereby all represented lithological members were entered with their representative physical and mechanical characteristics.
From the attached analyses for profile 4-4', it can be concluded that stability for an angle of 19o is not always satisfied, i.e. it is necessary to mitigate the angle in order to obtain a stable slope in completely dry conditions on the terrain.
As a conclusion from the analyses performed in this way, the fact that the influence of pore pressure for certain slip surfaces is drastic is imposed. Namely, if we consider very deep slip surfaces analyzed according to the Bishop method, it can be observed that in the 4-4` profile there is a decrease in Fs of up to 30% in conditions of ru=0.3 compared to Fs at ru=0. 0
In a similar format as above, the following provides a review and commentary on the results of the analyses and the achieved safety coefficients as a function of changes in the geomechanical parameters obtained by applying the SLIDE software.
It is concluded that the Fs values obtained from the SLIDE calculations are 10-15% lower than the Fs values obtained from the GGU software package calculations for the same Bishop method. This represents a linear decrease in the safety coefficient and this trend can be observed in the other analyzed sliding surfaces, but with a changed intensity.

It can also be concluded that the stability analysis with FEM (PLAXIS) yields values for the safety factor that are close to those achieved with MGR (SLIDE and GGU), although there are also certain differences in the procedures, which further partially affect the amount of Fs:

Recommendatins and guidelines

A complex task is to select the right physical models and parameters that are most important in the process of interaction of the environment with the engineering intervention. The selection of the right parameters can be made only through the optimal setting of the research methods and procedures, in relation to a given design phase. The economic and environmental effects of the construction of any facility largely depend on this choice.

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THE ROLE OF PREVENTIVE MAINTENANCE IN ENHANCING THE PERFORMANCE OF THE VSS 'FEHMI LLADROVCI' BUILDING IN DRENAS

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Abstract

This research addresses the importance and impact of preventive maintenance in the infrastructure management of the SHMP 'Fehmi Lladrovci' building in Drenas, analyzing its role in increasing safety, reducing emergency repair costs, and optimizing the technical and functional performance of the building. Preventive maintenance is a planned program of regular inspections, adjustments, and replacement of worn or failing parts, with the aim of maintaining the function and efficiency of each asset in the building. A well-designed and well-implemented preventive maintenance program will extend the life of equipment by reducing replacement costs, preventing most breakdowns that affect the users of the school facility, maintaining the energy efficiency of the equipment, improving the effectiveness of maintenance, and improving the overall condition of the facility and the experience of its users. This program includes; the components of an effective program, the scientific and engineering principles behind many of the most common and important maintenance tasks, and the application of works including theories of operation, maintenance requirements, and existing regulations.

Keywords: preventive maintenance, school building, maintenance program

Introduction

Public buildings, in particular school buildings at all levels of education in Kosovo, represent assets of particular importance to society. These buildings, together with the accompanying infrastructure that serves the wider communities, have been built with considerable investments and over different periods of time. However, their management has not always been at the appropriate level, both technically and institutionally.

Unfortunately, in the period before 1990 and especially during the transition years and after that year, the maintenance of school buildings has been minimal, in many cases almost non-existent. This has resulted in their gradual degradation, significantly reducing the functionality and lifespan of these educational assets.

Natural depreciation, combined with the lack of maintenance interventions and rehabilitation investments, has led to many of these buildings no longer being able to fulfill the functions for which they were built. This situation not only reduces the quality of educational services, but also jeopardizes the safety, health and well-being of students and educational staff.

The management and maintenance of school facilities constitute an essential component in providing a safe, functional and suitable environment for the development of the learning process. School facilities are not only physical spaces for learning, but also factors that directly affect the quality of education and the well-being of students and educational staff.[1][2]

In many cases, school buildings in Kosovo face various challenges related to the lack of regular investments, poor maintenance and the need for renovations. This situation requires continuous commitment from the relevant institutions to ensure optimal conditions for educational development. One of the facilities that is of particular importance in this context is the "Fehmi Lladrovci" primary school in the Municipality of Drenas. This school, with a two-story building and easy access for pedestrians and vehicles, represents an example of the need for

efficient management and regular maintenance. Although the facility is functional and in daily use for the learning process, continuous care is needed to preserve the infrastructure, improve the physical conditions and create a stimulating environment for students.

Methods and Materials

Description of the condition of the SHMP 'Fehmi LLadrovci' school building
Below is a detailed description of the existing condition of the building, including the construction, electrical and mechanical systems and the general condition. The "Fehmi Lladrovci" school is located in the center of the Drenas municipality, in an area easily accessible to residents of the city and surrounding villages. Its position is strategic, with paved roads and good access for pedestrians and vehicles.[7]
Around the school there are green spaces and public facilities, which contribute to the creation of a quiet and suitable environment for students. It is located near other municipal facilities and is well connected to the local transport network. This location makes the school easy to reach by students and staff, ensuring good access for visitors and the wider community.[8]



During the audit, it was noted that some of the structural elements (such as load-bearing beams, walls and internal partitions) have suffered physical damage and structural cracks, which pose a risk to the safety of the facility in the event of external loads (such as earthquakes or severe weather conditions). The lack of maintenance in previous periods had resulted in erosion of some parts of the concrete and exposure of the reinforcement in some areas.

Aims of school facility maintenance

Facility maintenance includes all activities that enable the maintenance of the function of the school facility in harmony with its purpose and destination, and in particular with the regular use and normal functioning of this educational facility.[7]
In addition to the home and family, children have a central position in a community, therefore the school is the most important place in which they spend a significant part of their time. The school facility, classrooms and other spaces in schools must be accessible and suitable for the stay of students for the development of learning and other activities related to learning.[8]
Renovated and maintained schools in order to maintain the physical structure and function for a longer period, must be adequately managed with preventive maintenance.
Preventive (proactive) maintenance includes maintenance in order to prevent damage to the facility or any equipment defects. It is carried out at regular intervals during the school year and not in response to damage. As the name suggests, preventive maintenance means that a

plan of activities is prepared for the maintenance of the school, which must be implemented in an organized, coordinated and controlled manner. About 30% of maintenance in schools is preventive maintenance. Schools are expected to adopt a predetermined plan, instead of a reactive approach to maintenance. Developing a maintenance mindset and a conscious approach to carrying out maintenance and minor repairs are essential to ensuring that school facilities are used rationally.[9]

Interventions in the building structure

The damaged structural elements have been reinforced with modern materials, ensuring the static safety of the building. The damaged walls have been restored and the external facade has been repaired with new thermal insulation. The roof has been leveled and restored, replacing the existing covering with insulating and weatherproof materials.

Electrical and Lighting System

The existing electrical system was outdated and outside safety standards, with old cable networks, damaged switches and insufficient lighting in many areas. Potential electrical hazards were identified, especially in corridors, classrooms and technical areas, which posed a risk to both staff and students.[6]




A new electrical network has been installed according to EN/IEC safety standards. The lighting fixtures have been completely replaced with energy-efficient LED bulbs. New electrical panels have been installed with modern fuses and clear divisions for different areas of the facility.

Thermal insulation and ventilation

The audit found a lack of efficient thermal insulation, both on the external walls and on the roof. This caused significant energy loss during the winter season and inadequate thermal conditions during the summer. The windows were old, with simple glass and damaged wooden frames, which did not provide hermetic closure and made it difficult to maintain the internal temperature. The natural ventilation system was inefficient, as many classrooms had only one window, which negatively affected the circulation of fresh air, making the environment unsuitable for long stays.

10 cm thick thermal insulation was applied to the external walls and roof, to reduce energy loss. The old windows were replaced with PVC windows with double thermal glazing, which help maintain the internal temperature and improve natural lighting.[3]

The natural ventilation system was improved by rearranging the windows and building additional air outlets. Ceiling fans have been installed in closed classrooms for better air circulation.

Sanitation and supporting infrastructure

The toilets were in poor functional and hygienic condition, lacking basic hygiene standards and accessibility for students with special needs. Other parts of the infrastructure such as the water supply system, sewage system, as well as supporting facilities (remedial teaching rooms, libraries or teaching cabinets) were inadequate and often out of order.[6]



The toilets have been completely renovated: new ceramics, privacy partitions, new water supply and a modern drainage system have been installed. Access for students with special needs has been ensured through the construction of dedicated toilets and auxiliary equipment. The hot water supply has been improved through the installation of new boilers in the sanitary areas. The library, teaching cabinets and spaces for supplementary learning have been renovated. Special facilities for extracurricular activities (music, art, sports) have been created, increasing the educational offer of the school. A landscaped courtyard with outdoor lighting, recreational areas and seating for students has been built.[13]

Preventive Maintenance Management Process

According to research for our region, school facilities that are public facilities should be subject to management models that guarantee sustainable maintenance and timely completion according to the specifications of these facilities.

Preventive Maintenance is laid out in three parts. The first part builds the components of an effective preventive maintenance program. The second part explains the scientific and engineering principles behind many of the most common and important preventive maintenance tasks. The third part refers to the different types of equipment commonly found in facilities, including the operation of various equipment within the facility.[14][15]

Facility maintenance is carried out depending on the quality of the materials used, depending on the performance of certain works and if they are not carried out according to the manufacturers' descriptions, the request for maintenance and additional costs will appear all the time. Maintenance processes should be carried out according to the established deadlines because it is vital to ensure the proper functioning and longevity, as well as the well-being of the users of the facility. The main objective is to ensure that the building is safe and suitable for the intended purpose, therefore it is suggested that Management and Maintenance be carried out according to a carefully designed cycle according to the specifications of the facility.[16][17]

Facility maintenance cycle

Activity	Name	Control cycle	Activity	Name	Control cycle
Painting exterior walls	Decorative	4-5 years	Exterior windows, fences and metalwork	Condition check and repair	yearly
External perimeter walls	Regular inspections	yearly	Roof and gutters	Checking and cleaning vertical and horizontal gutters	Before and after the rain showers
	Inspection and checking of details	5-6 years			
Partition walls	staining	3 years	Surface water drainage channels (atmospheric)	Checking and cleaning for defects and vegetation	yearly
	Structural adjustments	As needed			
Clean water supply	Quality control and valves	monthly	Firefighting services	Control and regulation by management staff	Weekly
	Cleaning water tanks and valves	3 months		Repair and reporting to the fire department	yearly
				Fire-resistant doors	monthly
Hot water supply	Boiler inspection	monthly	Equipment for sports facilities	Control by management staff	1-2 days
	Checking water heating boilers	6 months		Inspection by a mechanical specialist	yearly
Heating, cooling and air purification in the facility	Checking air filters, recuperators, laboratories, heating systems, collectors and boilers	3 months-1 year	Underground water drainage channels	Checking and cleaning manholes	2 months
				Checking and cleaning pipes	2 years
Others	Checking alarm systems, zeroing systems, cameras, lighting and TV monitors	6 months - 1 year	-	-	-

Summary and Recommendations

Based on the results achieved from the audits conducted before and after the renovation, as well as the monitoring of the one-year period, some important reflections can be made regarding the maintenance management of the “Fehmi Lladrovci” school building. First, it has been evidenced that the lack of a proper maintenance management and organization system

has directly affected the quality of maintenance services and the general condition of the building. The small number of technical personnel and the lack of long-term planning make the interventions mainly reactive, creating the conditions for rapid degradation of the building and increasing the costs of emergency repairs. Second, the quality of the materials and methods used during the renovation have had a positive effect on improving the condition of the school, but their effectiveness is closely linked to the maintenance method during the period of use. This emphasizes the importance of continuity of activities and preventive maintenance.

At the end of this study on the maintenance management of the "Fehmi Lladrovci" school, we can draw some conclusions that reflect the current situation and the needs for improvement of this process:

1. The current state of maintenance is underdeveloped and not well organized, the lack of qualified personnel and long-term planning proves that interventions are mainly emergency and not preventive.
2. The materials and works during the renovation have improved the condition of the facility, but their maximum effect is achieved only with regular maintenance during the period of use of the school.
3. Improving maintenance management requires increasing human, financial and institutional capacities, including specialized training for personnel, preparation of maintenance plans and an effective monitoring system.
4. A proactive and coordinated approach between the school, local authorities and responsible institutions can ensure the long-term preservation of the facility and the improvement of learning conditions.

In this way, by addressing maintenance needs in a timely and systematic manner, the "Fehmi Lladrovci" school will be able to provide a safe, functional and sustainable environment for its students and staff.

Recommendations

1. Strengthening maintenance staff - to ensure effective and continuous maintenance
2. Training and professional development of personnel
3. Drafting a clear maintenance plan
4. Use of quality materials and technologies.
5. Involvement of the school community, cooperation between technical staff, teachers and students
6. Continuous monitoring and auditing.

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SPORT INFRASTRUCTURE IN TETOVO: AN EVALUATION OF EXISTING CONDITIONS, CHALLENGES AND FUTURE DEVELOPMENT POTENTIAL

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Abstract

This research examines the role of sports fields in primary and secondary schools, as well as open-access sports terrains and city stadiums in Tetovo, not only as physical infrastructure but as essential pillars of social well-being and sustainable urban development, as they play a critical role in the early development of children, combating negative phenomena such as obesity and addiction to technology, while promoting discipline and teamwork. Beyond the educational function, stadiums and sports fields serve as points of gravity for urban identity and social integration, they offer to citizens of all ages the opportunity for physical activity, which is directly linked to stress reduction and improved mental health.

The study places particular emphasis on evaluating the condition and functionality of these open sports spaces through SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats), with the aim of assessing whether they meet the required standards for safe and effective public use. This evaluation highlights existing gaps in infrastructure, maintenance, accessibility, and safety. Investments in stadiums and sports fields are not seen only as a sports project, but as an investment in "human capital", creating an environment where young talents can aspire to professional success and where the community finds healthy spaces for entertainment and socialization. The paper concludes that the modernization of this infrastructure is necessary to ensure a quality life and an active society in the city of Tetovo. Findings suggest that investments in sports infrastructure should be understood not merely as construction projects, but as long-term investments in human capital and public health. The modernization of this infrastructure is necessary to ensure a quality life, inclusive and sustainable society in the city of Tetovo.

Keywords: sports infrastructure, public health, urban development, construction projects, challenges.

Introduction

Sport is widely recognized as a key component of contemporary society, with significant potential to contribute to social development and cohesion. Nelson Mandela famously emphasized this role, stating that "Sport has the power to change the world, it inspires and unites people in a way that little else does" [1]. Physical activity is a fundamental element of a healthy lifestyle. Previous research has demonstrated that the built environment, particularly the availability of sports fields and facilities, has a positive influence on physical activity levels [2]. However, global data indicate that approximately one-third of adults and four-fifths of children do not meet recommended physical activity guidelines, with physical inactivity increasingly recognized as a major public health concern associated with rising rates of obesity and related diseases [3].

Regular engagement in physical activity is effective in preventing chronic conditions such as obesity, diabetes, and certain types of cancer [4]. In this context, residential and urban environments play an important role in shaping opportunities for active lifestyles, particularly through access to sport and recreational spaces. Recent studies highlight that children spend a significant proportion of their outdoor time in public open spaces rather than in schoolyards,

making urban public spaces increasingly important for physical activity [5]. Schools, in particular, function as important social and cultural hubs within urban environments. Although their form and organization vary across different cultural contexts, their role in the urban fabric is universally significant. School sports grounds and stadiums represent complex urban settings where multiple user groups and functions coexist. These spaces are used not only by pupils, teachers, and school staff, but also by wider community groups, each with different spatial needs and preferences that must be carefully balanced. Research on school environments in Tetovo has addressed issues of accessibility and inclusiveness [6], as well as the availability of sports facilities in primary and secondary schools [7]. However, comprehensive studies focusing specifically on stadiums and open sports grounds within schools in Tetovo remain limited. Given these considerations, the development and use of sports facilities is a valuable resource for promoting health and reducing risk factors among children and adolescents [8], as it encourages regular physical activity, supports social interaction, and contributes to the establishment of healthy lifestyle habits from an early age.

The realization of sports infrastructure, from initial design concepts to the built environment, is a complex process influenced not only by citizens' needs but also by institutional capacity, planning frameworks, and governance structures [9]. Successful implementation of such projects depends on effective leadership and the active involvement of competent stakeholders advocating for investment in public sports infrastructure [10]. In the design process, it is essential to balance design intentions with material constraints in order to meet sustainability objectives [11]. Structure is a fundamental component in the realization of architectural form - not only as a technical framework, but also as an essential aspect of visual and spatial expression [12]. The selection of construction materials must comply with relevant legal regulations and technical standards to ensure safety, durability, and performance. Adherence to these requirements guarantees that sports facilities are structurally sound, environmentally responsible, and suitable for user needs [13]. Furthermore, effective integration and communication between indoor and outdoor sports infrastructure contribute to the development of a coherent, accessible, and inclusive system that supports seamless user experience across all facilities [14].

Research methodology and Mapping sport infrastructure in Tetovo

The main body of the manuscript is structured into several key sections. It begins with the research methodology, outlining the methods and approaches used for data collection and analysis. This is followed by a detailed mapping of sports infrastructure in Tetovo, focusing on the spatial distribution, accessibility, and condition of existing facilities. The analysis further examines the relationship between urban form, accessibility, and the use of sports spaces, highlighting key challenges and opportunities for improving physical activity environments. Finally, the discussion interprets the findings in relation to planning strategies and design principles for inclusive and sustainable sports infrastructure.

2.1 This research adopts a qualitative and analytical approach to evaluate sports infrastructure in Tetovo, focusing on three main categories: city stadiums, sports facilities in primary schools, and sports facilities in secondary schools. The methodology is based on the application of SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats), a widely used strategic planning tool for assessing both internal and external factors that influence the performance

and development of infrastructure systems. SWOT analysis is particularly suitable for this study as it enables a structured evaluation of existing conditions while also identifying future development potential. The analysis is divided into two main components: internal factors (strengths and weaknesses), which relate to the current state, functionality, maintenance, and accessibility of the sports infrastructure; and external factors (opportunities and threats), which refer to broader environmental, social, economic, and institutional influences that may affect future development.

Data for the analysis were collected through field observations, spatial mapping, and review of existing infrastructure conditions. Each category - city stadiums, primary school sports fields, and secondary school sports fields, were analyzed separately using the SWOT framework. This approach allows for a comparative understanding of the different types of sports infrastructure and their specific challenges and potentials.

The application of SWOT analysis in this context serves as a preliminary yet effective tool for identifying key issues and strategic directions for improvement. It facilitates the evaluation of alternative development scenarios and supports decision-making processes related to planning, management, and investment in sports infrastructure. Furthermore, by integrating perspectives from urban planning and infrastructure management, the methodology provides a comprehensive assessment that goes beyond physical conditions, incorporating aspects of accessibility, usability, and long-term sustainability. As highlighted in previous studies [15], SWOT analysis contributes to a more inclusive and strategic evaluation process, generating outcomes that are beneficial for multiple stakeholders involved in the development of sports infrastructure.

2.2 This section presents the mapping and analysis of sports infrastructure in Tetovo, with particular emphasis on open-access terrains such as city stadiums and sports fields within primary and secondary schools. These facilities represent essential components of the urban environment, contributing not only to physical activity and education, but also to broader social interaction and community development. Within the urban area, there are five stadiums that serve as primary venues for organized sports activities and public events. In addition, the city includes thirteen educational institutions, consisting of seven primary schools and six secondary schools. The total number of students is estimated at around 9,400 in primary education and approximately 4,700 in secondary education. Each of these schools is equipped with open sports fields, which play a crucial role in the daily physical education of students, as well as in informal recreational use outside school hours. These school-based sports terrains, together with city stadiums, form a network of accessible spaces that support physical activity for different age groups across the city.

The mapping process aims to identify the spatial distribution and coverage of these sports facilities, providing insight into their accessibility and relationship with residential areas. Particular attention is given to the availability of open-access spaces, as these are key to promoting inclusive and continuous use by the wider community.

PARIMARY SCHOOLS, SECONDARY SCHOOLS, STADIUMS

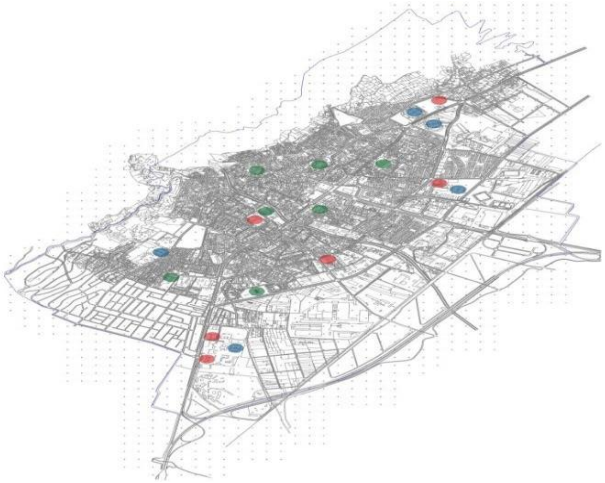


Figure 1. Sport infrastructure in Tetovo

Figure 1 presents the spatial distribution of sports infrastructure in Tetovo, highlighting the location of city stadiums as well as sports fields within primary and secondary schools. The map offers a comprehensive visual representation of how these facilities are positioned across the urban territory, illustrating their relationship with residential areas, educational institutions, and main circulation networks. This spatial overview enables a clearer understanding of the accessibility and coverage of sports infrastructure for different population groups within the city. Furthermore, the mapping helps to identify patterns of concentration and potential gaps in the distribution of these facilities, which may affect equal access to sports and recreational spaces. Areas with a higher density of infrastructure can be distinguished from those with limited or no access, providing important insights for future planning and investment strategies.

[1]. Stadiums in the city of Tetovo:
- New City Stadium
- Old City Stadium
- Stadium at the Sports Center
- Stadium at secondary school Mosha Pijade
- Stadium “Dardanet

[2]. Open sport infrastructure in primary schools:
- Kiril and Metodij
- Naim Frasheri
- Lirija
- Istikbal
- Bratstvo Migjeni
- Goce Delcev
- Andreja Savevski – Kikish

[3]. Open sport infrastructure in secondary schools:
1. Mosha Pijade
2. Nikola Shtejn
3. Kiril Pejcinoviq
4. 8 Shtatori
5. Gjimanzi 7 Marsi
6. Gjoce Stojceski

Results

This section presents a comprehensive analysis of sports infrastructure in the city of Tetovo, focusing on both stadiums and open sports facilities within primary and secondary schools. The aim is to evaluate the current condition, spatial distribution, accessibility, and functional capacity of these spaces, while identifying key challenges and opportunities for their future development. The analysis is based on a combination of field observations, spatial mapping, and qualitative assessment methods, providing a realistic overview of the existing situation. Special attention is given to the relationship between the built environment and the use of sports spaces, emphasizing the role of these facilities in supporting physical activity, social interaction, and community well-being. To ensure a structured and critical evaluation, a SWOT analysis is applied to each category of sports infrastructure. This approach enables the identification of strengths, weaknesses, opportunities, and threats, offering a clear framework for understanding both the current performance and future potential of these spaces. The findings are further supported by visual documentation, illustrating the physical condition and usability of the analyzed facilities

3.1Stadiums in city of Tetovo: Below is presented the SWOT analysis for the stadiums in the city of Tetovo, which examines the current condition of these facilities, as well as their future development perspectives. The analysis provides an overview of the real situation on the ground, identifying both positive and negative aspects of the existing infrastructure.
In terms of strengths, the stadiums are characterized by attractive locations within the urban area, easy accessibility for both pedestrians and vehicles, and a relatively high level of daily and periodic use. They also offer multifunctional spaces and, in several cases, sufficient surface area to accommodate different types of sports and community activities.
However, several weaknesses are evident in the current situation. These include inadequate maintenance, visible physical degradation over time, and failure to meet international standards for sports infrastructure. Additionally, there are ongoing concerns related to ownership and privatization processes, with indications of interest in selling or repurposing these public spaces, which further threatens their long-term function as public sports facilities.

Table 1. SWOT Analysis of Stadiums in the City of Tetovo – Internal Factors

Strength	**Weaknesses**
Attractive urban locations	Poor maintenance and lack of regular upkeep
Easy accessibility for pedestrians and vehicles	Progressive physical deterioration
Multifunctional sports and community spaces	Do not meet international standards
Sufficient space for various activities	Outdated infrastructure and facilities

From an opportunity perspective, there is significant potential for transforming these stadiums into modern, attractive sports infrastructures that meet contemporary standards. Sustainable investment could improve the quality of life for citizens, strengthen urban development processes, and stimulate the revitalization of surrounding areas. Furthermore, upgraded facilities could support the organization of various sporting, cultural, and community events, increasing their social and economic value within the city.
On the other hand, several threats may negatively impact their future development. If no strategic intervention is implemented, these spaces risk further deterioration and neglect, potentially becoming unsafe or socially problematic areas. There is also the risk of privatization

and construction of profit-oriented buildings, which would lead to the permanent loss of public sports space. Ultimately, such developments could contribute to the decline of sports culture and reduce opportunities for youth and community engagement in physical activities

Table 2. SWOT Analysis of Stadiums in the City of Tetovo – External Factors

Opportunities	**Threats**
Development of modern and sustainable sports infrastructure	Continued degradation and neglect of facilities
Improvement of citizens' quality of life	Risk of becoming unsafe or socially problematic areas
Contribution to urban development and regeneration of surrounding zones	Privatization and conversion into profit-oriented developments
Organization of sports, cultural, and community events	Loss of public sports spaces
Increased social and economic value of infrastructure	Decline of sports culture and reduced youth engagement

Below are presented photographs illustrating the real condition of the stadiums in the city of Tetovo. These images provide visual evidence of the current situation on the ground and confirm the findings and statements discussed in the analysis regarding the present state of the infrastructure. They clearly reflect both the functional aspects and the existing deficiencies, including issues related to maintenance, deterioration, and overall management of the facilities.



Figure 2. New City Stadium



Figure 3. Stadium "Dardanet"



Figure 4. Old City Stadium



Figure 5. Stadium at secondary school Mosha Pijade

3.2 Open sport infrastructure in primary schools of Tetovo: Below is presented the SWOT analysis for the open sport infrastructure in primary schools of Tetovo, examining the current

condition of these facilities as well as their potential for future development. This analysis provides a realistic overview of the existing situation, identifying both positive aspects and existing challenges related to the functionality, accessibility, and maintenance of these spaces.
In terms of strengths, open sport facilities in primary schools are generally well distributed within residential areas, making them easily accessible for children. These spaces play an important role in supporting daily physical activity and are often integrated within school environments that function as community hubs. In several cases, they provide sufficient open areas for basic sports activities and informal recreation.
However, a number of weaknesses are evident. Many of these facilities suffer from inadequate maintenance, lack of proper equipment, and substandard playing surfaces. In some cases, they do not meet minimum safety or design standards, which limits their usability and quality. Additionally, restricted access outside school hours reduces their potential as community resources.

Table 3. SWOT Analysis of Open Sport Infrastructure in Primary Schools of Tetovo – Internal Factors

Strength	**Weaknesses**
Good distribution within residential areas	Poor maintenance and lack of regular upkeep
Easy access for children and local communities	Lack of adequate sports equipment
Integration within school environments	Substandard and unsafe playing surfaces
Support for daily physical activity	Limited access outside school hours
Availability of open space for basic activities	Do not meet design and safety standards

From an opportunity perspective, these spaces have strong potential to be improved through targeted investments and better management strategies. Their transformation into well-designed, safe, and inclusive sport environments could significantly enhance children's physical activity levels and overall well-being. Furthermore, opening these facilities to the wider community could strengthen social interaction and maximize their use beyond school hours.
On the other hand, several threats may affect their future. Continued neglect and lack of investment may lead to further degradation, making these spaces unusable or unsafe. There is also a risk that these areas may be repurposed for non-sport functions due to urban pressure and limited space. Such developments would reduce opportunities for physical activity among children and negatively impact long-term health and social outcomes.

Table 4. SWOT Analysis of Open Sport Infrastructure in Primary Schools of Tetovo – External Factors

Opportunities	**Threats**
Improvement through targeted investments	Continued deterioration and neglect
Creation of safe and inclusive environments	Risk of becoming unsafe spaces
Increased use by the wider community	Repurposing for non-sport functions
Promotion of healthy lifestyles among children	Reduction of physical activity opportunities
Strengthening social interaction	Urban pressure on open school spaces

Below are presented photographs illustrating the current condition of open sport infrastructure in selected primary schools in Tetovo. These images provide visual evidence of the situation on the ground and support the analysis by highlighting both functional aspects and existing deficiencies, particularly in terms of maintenance, equipment, and safety conditions.



Figure 6. Primary school - Naim Frasheri



Figure 7. Primary school - Istikbal

3.3. Open sport infrastructure in secondary schools of Tetovo: Below is presented the SWOT analysis for the open sport infrastructure in secondary schools of Tetovo, examining the current

condition of these facilities as well as their potential for future development. This analysis provides a comprehensive overview of the existing situation, focusing on functionality, accessibility, spatial organization, and the overall quality of these environments. In terms of strengths, open sport facilities in secondary schools generally offer larger and more developed spaces compared to primary schools. These areas are often designed to accommodate a wider range of sports activities and are used by a broader age group, including adolescents and, in some cases, the wider community. Their location within the urban fabric allows relatively easy access, and they play an important role in promoting regular physical activity and organized sports. However, several weaknesses are evident. Despite their larger scale, many of these facilities suffer from poor maintenance, outdated infrastructure, and lack of modern equipment. In some cases, the organization of space is inefficient, limiting optimal use. Safety standards are not always met, and access is often restricted outside school hours, reducing their potential as multifunctional community spaces.

Table 5. SWOT Analysis of Open Sport Infrastructure in Secondary Schools of Tetovo – Internal Factors

Strength	**Weaknesses**
Larger and more developed sport spaces	Poor maintenance and lack of regular upkeep
Capacity for multiple sports activities	Outdated infrastructure and equipment
Accessibility within the urban context	Inefficient spatial organization
Use by different age groups	Do not fully meet safety standards
Potential for organized sports and events	Limited access outside school hours

From an opportunity perspective, these facilities have strong potential for transformation into high-quality, multifunctional sports environments. Investments in modernization, improved design, and better management could significantly enhance their usability and attractiveness. Opening these spaces to the public and integrating them into the wider urban sports network could increase their social and economic value, while promoting healthier lifestyles among young people. On the other hand, several threats may hinder their development. Continued lack of investment and maintenance may result in further deterioration, reducing functionality and safety. There is also a risk of underutilization or mismanagement, which may limit their long-term sustainability. Additionally, urban development pressures may lead to the reduction or transformation of these spaces, negatively impacting opportunities for youth engagement in sports and physical activities.

Table 6. SWOT Analysis of Open Sport Infrastructure in Secondary Schools of Tetovo – External Factors

Opportunities	**Threats**
Modernization and infrastructure improvement	Continued degradation of facilities
Development of multifunctional sport environments	Reduced functionality and safety risks

Integration into the urban sports network	Urban pressure and potential space reduction
Increased community access and use	Decline in youth participation in sports
Promotion of active lifestyles among youth	Underutilization and poor management

Below are presented photographs illustrating the current condition of open sport infrastructure in selected secondary schools in Tetovo. These images provide visual support for the analysis, reflecting both the functional potential and the existing deficiencies, particularly in terms of maintenance, equipment, and spatial organization.



Figure 8. Secondary school - Kiril Pejcinovic



Figure 9. Secondary school - Nikola Shtejn

Conclusions

Based on the preliminary SWOT analysis conducted for open sports facilities in primary and secondary schools, as well as the city stadiums in Tetovo, it can be concluded that the existing sports infrastructure faces significant structural, functional, and managerial challenges. The findings clearly indicate that most school sports fields are in poor physical condition, with damaged playing surfaces, broken football goals, basketball hoops, and volleyball nets, many of which are partially or completely out of use. Despite these limitations, these spaces continue to be actively used by students, teachers, and even the local community, highlighting their high social value and lack of alternative facilities. The same situation is observed in the city stadiums, where infrastructure does not meet required standards. Key deficiencies include deteriorated stands for spectators, inadequate changing rooms, and overall lack of maintenance

and modernization. These conditions significantly reduce usability, safety, and comfort for users.

However, the analysis also shows that both school-based sports areas and city stadiums possess strong potential for improvement. The availability of sufficient space, high levels of daily use, and community willingness to participate in maintenance represent important strengths that can support future development. In this context, modern approaches such as the "Open Schoolyard" concept demonstrate how school sports facilities can be integrated into public urban space, allowing controlled access for the community outside school hours and increasing their social value.

Overall, the study emphasizes that there is an urgent need for strategic and sustainable investment in sports infrastructure in Tetovo. Proper reconstruction and modernization of both school sports fields and city stadiums would not only improve physical conditions but also enhance public health, support youth development, and strengthen social cohesion. If appropriately managed, these spaces can evolve into multifunctional urban assets that contribute significantly to the city's long-term sustainable development.

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HOW SWIMMING AFFECTS THE HUMAN BODY

Rrezearta NEZIRI, Anila BELLÇISHTA SHAQIRI

Abstract

This paper discusses the importance of physical activity and its impact on the human body, with a special focus on swimming as one of the most complete sports. According to the definition of the World Health Organization (WHO), physical activity includes any bodily movement that requires energy expenditure and is essential for maintaining physical and mental health. A lack of physical activity is associated with an increased risk of non-communicable diseases such as obesity, diabetes, and cardiovascular diseases, while regular participation provides numerous benefits for the body.

In this context, swimming is presented as a highly effective activity that activates almost all body muscles, improves endurance, flexibility, and coordination. It has a positive impact on the muscular system by strengthening and toning muscles, on the cardiovascular system by improving heart efficiency and blood circulation, and on the respiratory system by increasing lung capacity and breathing control. Swimming also helps prevent many diseases and is suitable for all age groups due to its low impact on joints.

In addition to physical benefits, the role of sport and swimming in improving mental health is also emphasized, as they reduce stress, anxiety, and enhance psychological well-being. In conclusion, the paper highlights that regular participation in physical activity, especially swimming, is essential for a healthy life and a better quality of living.

Introduction

World Health Organization (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical activity includes every movement, whether during leisure time, transportation, work, household activities, or sports. Moderate- and vigorous-intensity physical activity improves health. The most common forms of physical activity include walking, cycling, sports, active recreation, and games, which can be practiced at any level of ability and enjoyed by everyone.

Physical activity is beneficial for health and well-being, while the lack of it increases the risk of non-communicable diseases and other health problems. Together, physical inactivity and sedentary behavior contribute to the rise of these diseases and create a burden on healthcare systems.

Improving the level of physical activity brings health benefits and helps achieve global sustainable development goals. Sport is very important for the development and maintenance of human health because it includes exercises that strengthen the body, improve the functioning of organs, and increase physical endurance.

Physical activity has a positive impact on the muscular, skeletal, cardiovascular, and respiratory systems. One of the most beneficial sports for the human body is swimming. Swimming is considered a complete sport because it activates almost all the muscles of the body. In addition, exercises in water improve breathing and strengthen the heart. Sport has become an essential element for maintaining public health in modern life conditions. In a busy lifestyle and with irregular nutrition, physical exercise is extremely important. The main benefits of sport for physical health include regulating body weight, strengthening muscles and bones, and preventing cardiovascular diseases and type 2 diabetes. Regular physical activity helps reduce the risk of obesity and related problems. It also improves the function of the respiratory and digestive systems.

Sport also positively affects mental health by reducing stress, anxiety, and depression through the release of endorphins. In modern society, physical activity is an effective solution for improving the quality of life.

Importance of Sport for the Human Body

Sport is one of the most effective ways to keep the body healthy and active.
Physical activity helps improve blood circulation, strengthen muscles, and increase the body's overall energy.
People who regularly participate in sports have a lower risk of developing various diseases such as cardiovascular problems, diabetes, and obesity. In addition, sport also has a positive effect on mental health by reducing stress and improving mood. Different sports affect the body in different ways.Some sports develop physical strength more, while others improve endurance or flexibility. However, one sport that combines many benefits is swimming. Participation in sports activities plays an important role in the development of young people by providing numerous physical, social, and psychological benefits. During adolescence, involvement in sports helps develop life skills, build relationships, and strengthen personal identity.
The impact of sport on the overall development of young people is very important because it connects physical ability, social interaction, and psychological well-being into one developmental process.
In essence, participation in sports serves as a foundation for promoting a healthy lifestyle and physical well-being among young people. Through regular physical activity, adolescents improve cardiovascular health and muscular strength, while also developing motor skills and coordination. In addition, the structured and disciplined nature of sport encourages habits such as perseverance, discipline, and goal setting, creating a strong foundation for lifelong health and well-being.



Swimming as One of the Most Complete Sports

Swimming is a physical activity performed in water that requires good coordination of body movements and breathing. It is a very popular sport all around the world and is practiced both for recreation and at a professional level. Many people choose swimming as a form of relaxation and a healthy activity

for the body and mind because it combines physical exercise with a calming effect on the nervous system.

One of the reasons why swimming is considered a very beneficial sport is the fact that it activates almost all the muscles of the body.

During swimming, the muscles of the arms, legs, abdomen, and back work together, helping to tone and strengthen them. In addition, swimming improves endurance and flexibility, allowing the body to move more freely and in a coordinated way.

Water creates a natural resistance that helps strengthen muscles without placing great pressure on the joints, which makes this sport suitable even for elderly people or individuals with muscular problems. Furthermore, swimming has a special effect on the cardiovascular and respiratory systems because it requires controlled breathing and continuous movement. This helps improve lung capacity, strengthen the heart, and increase physical endurance. Another important benefit of swimming is its positive impact on the nervous system and mental health. Activities in water help reduce stress and anxiety, improve mood, and create a general feeling of relaxation. For this reason, swimming is often recommended as a complete sport.

Swimming Styles and Their Impact on the Body

There are several main swimming styles, each with different characteristics and effects on the body:

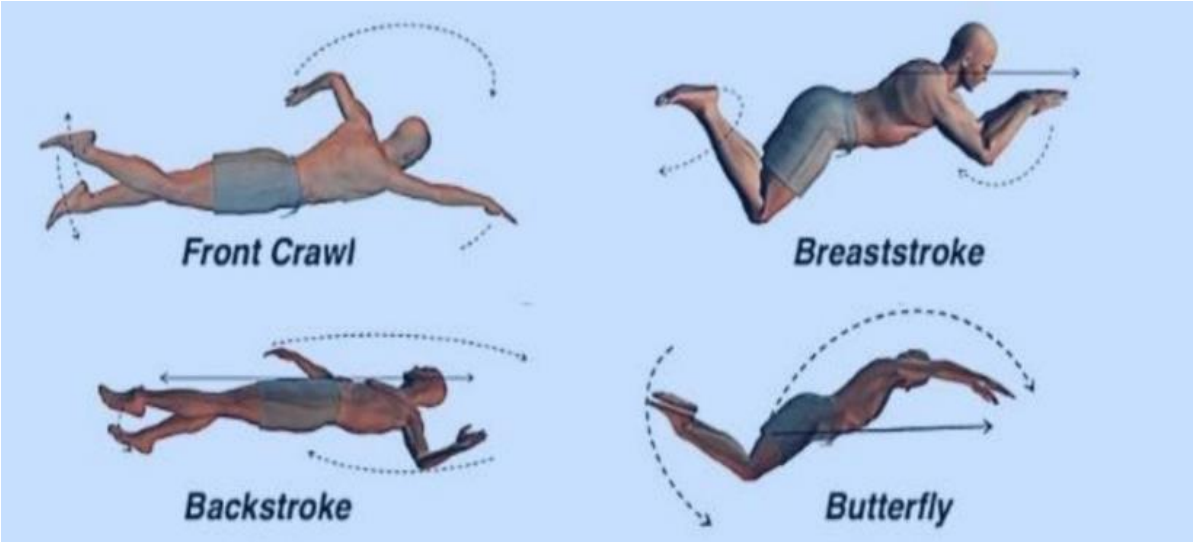
Freestyle – Activates the arm and leg muscles and improves overall endurance.

Backstroke – Helps relax the back and neck while improving body posture.

Breaststroke – Improves leg strength and coordination between the arms and legs.

Butterfly stroke – A difficult style that requires great strength and coordination; it helps develop the back and chest muscles.

Each style has a different impact on the muscular, cardiovascular, and respiratory systems, making all swimming styles beneficial for health.



The Impact of Swimming on the Muscular System

During swimming, the body's muscles are continuously activated to keep the body moving in the water. The repeated movements of the arms and legs, together with controlled breathing, cause many muscle groups to work simultaneously. This helps strengthen, develop, and tone the body's muscles.

The muscles of the arms and shoulders play a very important role during swimming. These include muscles such as the deltoids, biceps, and triceps, which help push the water and move the body forward. In addition, the back muscles, such as the latissimus dorsi and trapezius, are also very important. These muscles help stabilize the body and coordinate arm movements. Strengthening them helps improve body posture and protect the spine.

The abdominal muscles, such as the rectus abdominis and the oblique muscles, play an important role in maintaining balance and body stability during swimming. They help keep the body in the correct position and coordinate movements between the upper and lower parts of the body.

The leg muscles are also highly active during swimming. These include the quadriceps, hamstrings, and calf muscles (gastrocnemius). These muscles help move the body through the water and maintain speed while swimming.

Main effects on muscles:

Muscle toning and development: Swimming helps develop muscle mass throughout the body by creating resistance in every direction. Although it is not as focused on muscle growth as weightlifting, it leads to visible muscle definition.

Full-body engagement:

Upper body: Activates the shoulders (deltoids), chest (pectoral muscles), and back (latissimus dorsi) for strength and endurance.

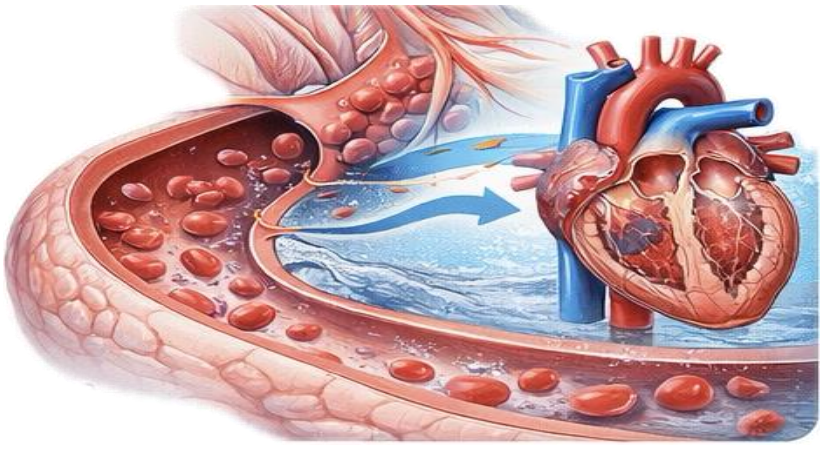
Core: Continuously activates the abdominal and lower back muscles for stabilization.

Lower body: Strengthens the glutes, quadriceps, hamstrings, and calf muscles through continuous movement.

Muscular endurance: Continuous movements during swimming increase the muscles' ability to work for longer periods without fatigue.

Improved flexibility: The wide range of movements used in swimming helps increase the flexibility of muscles and joints.

The Impact of Swimming on the Cardiovascular System



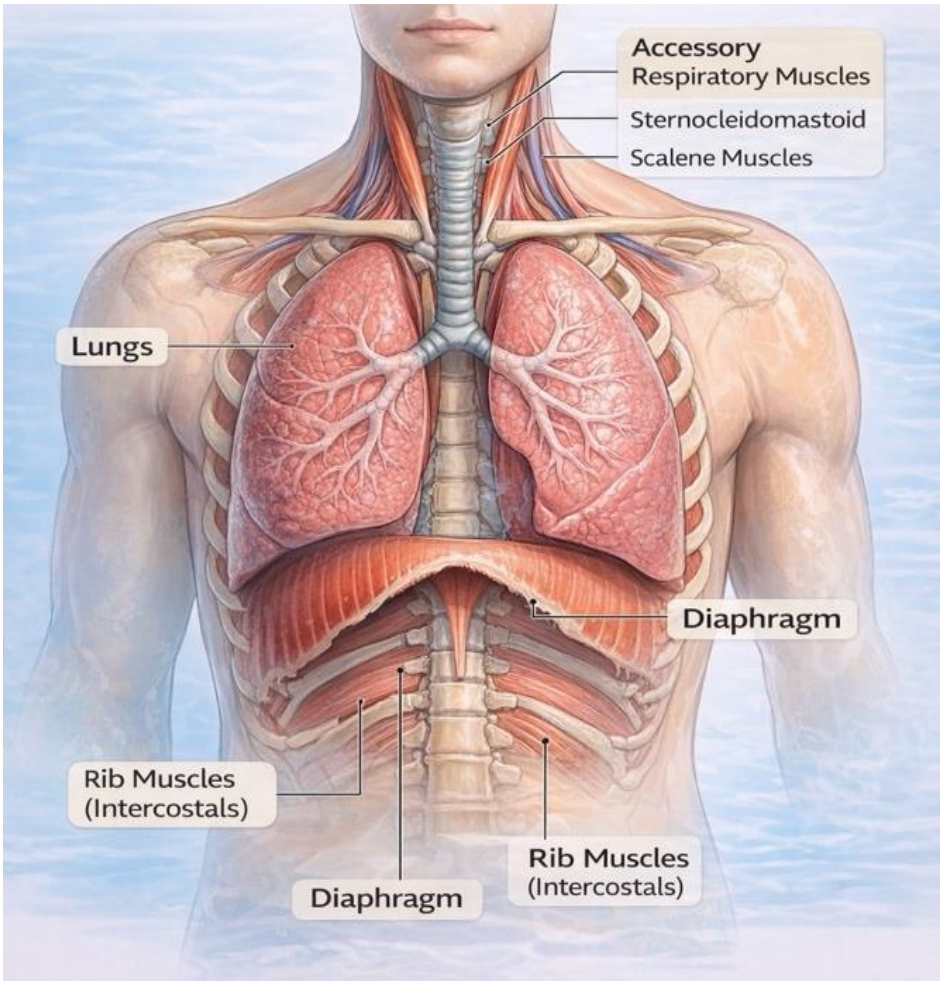
Swimming is an aerobic activity that requires continuous physical effort, activating the heart and lungs in a coordinated way. (Fig. 4)

During swimming, the heart pumps blood faster and more efficiently in order to supply the muscles with oxygen and nutrients. This activity also helps regulate blood pressure and maintain a normal heart rhythm. With time and regular practice, the heart becomes stronger and more efficient. It is able to pump more blood with each beat, reducing stress on the cardiovascular system.
This lowers the risk of heart diseases such as hypertension, atherosclerosis, or heart attack. Swimming also helps improve the elasticity of blood vessels, enhancing circulation and reducing the risk of blood clots. People who swim regularly usually have a stronger and more resilient heart, which allows them to perform physical activities for longer periods without getting tired quickly. Furthermore, swimming also helps in the treatment and prevention of circulation problems, improving overall cardiovascular health. (Fig. 5)



The Impact of Swimming on the Respiratory System

GDuring swimming, the lungs and diaphragm are the main structures that are activated. Swimming requires controlled breathing, the swimmer must hold their breath while submerged and inhale when the head comes above the water. This increases the vital capacity of the lungs, which is the maximum amount of air the lungs can inhale and exhale in a full breath. (Fig. 6)



(Fig. 6)

The diaphragm, the main breathing muscle, works more intensively during swimming. Its stronger movement helps expand the chest and allows more air to enter the lungs. In addition to the diaphragm, the intercostal muscles (the muscles between the ribs) are also activated to assist in expanding and contracting the thoracic cavity. Swimming also helps strengthen the airways and bronchi, improving airflow and oxygenation of the blood. People who practice swimming regularly usually develop deeper, more coordinated, and more stable breathing, which also helps improve physical endurance during other activities.

Swimming and Disease Prevention

Swimming is one of the most beneficial sports for disease prevention. It activates almost all the muscles and improves the functioning of the cardiovascular and respiratory systems.

Obesity: Water exercises help burn calories and improve metabolism. Swimming 2–3 times a week helps maintain body weight.

Heart and blood circulation: Swimming strengthens the heart and improves blood circulation, reducing the risk of cardiovascular diseases and hypertension.

Bones and back: Water exercises do not create pressure on the joints, help strengthen bones, and improve body posture, reducing back pain.

For good results, regular swimming is recommended, combined with a healthy lifestyle and other physical activities.

Psychological Benefits of Swimming and Sport

In general, sport also has a positive impact on mental health. Physical activity helps release hormones that improve mood and reduce stress.
Swimming is a very relaxing activity because water helps calm both the body and the mind. Many people feel more relaxed and peaceful after a swimming session. In addition, sport helps increase self-confidence and improves concentration.

Swimming and Age Groups



Children: Development of coordination, flexibility, muscle strength, and self-confidence.
Young people and adults: Increases strength, endurance, and aerobic capacity; maintains flexibility and a healthy body weight.
Elderly people: Improves mobility, balance, and overall health; reduces joint pain and improves blood circulation.

Conclusion

In conclusion, sport plays a very important role in maintaining both physical and mental health. Physical activity helps improve the functioning of many body systems, such as the muscular, skeletal, cardiovascular, and respiratory systems.Through sport, the body becomes stronger, more resilient, and healthier.Among different sports, swimming is considered one of the most complete and beneficial activities for the human body. Swimming activates almost all the muscles, improves breathing, and helps strengthen the heart and lungs. In addition to physical benefits, swimming also has a positive impact on mental health by reducing stress and improving psychological well-being. Regular participation in sports, especially swimming, is very important for people of all ages. It helps maintain a healthy lifestyle and improves the quality of life. For this reason, sport and physical activity should be encouraged as an essential part of everyday life for every individual.

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IMPACT OF WASTEWATER IRRIGATION ON HEAVY METAL CONCENTRATIONS IN VEGETABLES, WITH PRIMARY FOCUS ON Pb AND Cd

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Abstract

This review paper evaluated the impact of wastewater irrigation on heavy metal accumulation in vegetables, focusing specifically on lead (Pb) and cadmium (Cd). Rising water exploitation poses a severe risk to the environment. Heavy metal contamination, primarily driven by industrial activities such as textile manufacturing, mining, and metal processing, remains a major global concern. The application of wastewater for irrigation can significantly elevate heavy metal concentrations in both soil and crops. In many regions worldwide, vegetables that constitute a vital part of the human diet are being irrigated with untreated wastewater. Findings indicated that leafy greens, such as spinach and lettuce, along with root vegetables, exhibited high bioconcentration and transfer factors (TF > 1). Furthermore, Pb and Cd levels in wastewater-irrigated vegetables frequently exceed the Maximum Levels (MLs) set by the Codex Alimentarius 2023. This study also assessed modern treatment technologies, concluding that membrane filtration and ion exchange methods are essential for mitigating these risks. Ultimately, it was established that rigorous monitoring and efficient purification processes are critical for ensuring food safety and environmental protection.

Keywords: Wastewater irrigation, Lead (Pb), Cadmium (Cd), Bioaccumulation, Vegetables

Introduction

Water is a precious natural resource upon which the sustainability of agriculture, an adequate food *supply*, and a productive environment for all living organisms rely. Unfortunately, water is exposed to maximum exploitation and heavy metal accumulation, which is not only an ecological issue but also a global problem (Kausar *et al*., 2017; Dadebo *et al*., 2024; Kilic, 2020). Irrigation water can be defined as water used for the production of cultivated plants. Irrigation is the delivery of water to plant roots when the required amount of water cannot be met by precipitation (Ors *et al*., 2021; Shahriar *et al*., 2023). The increase in the content of toxic metals and metalloids in irrigation water is a matter of worldwide concern, as toxic metals enter the soil and, through the root system, accumulate in the edible parts of plants such as vegetables (Kausar *et al*., 2017). The use of wastewater for irrigation, especially if it has a high concentration of heavy metals and during long-term application, can significantly increase the concentration of heavy metals in the soil and, consequently, in the plants (Aboukila, 2022; Mushtaq *et al*., 2010).

Wastewater is any water that has been contaminated by human use in domestic, industrial, commercial, and agricultural activities, as well as untreated sewage water, and it is most commonly used in agriculture (Sane *et al*., 2020; Khalid *et al*., 2018). Many studies are focused on analyzing heavy metal concentrations in vegetables and plants irrigated with various types of wastewater, such as industrial wastewater (Singh *et al*., 2024), sewage (Bao *et al*., 2014), drainage, agricultural and domestic waste (Nowwar *et al*., 2023), farms, wells, streams, and rivers (Lere *et al*., 2021), domestic wastewater (Ahmad *et al*., 2015), and others. High concentrations of heavy metals such as cadmium, lead, chromium, copper, nickel, zinc, and iron have been found in wastewater from various industries, including textiles, construction, and mechanical manufacturing, exceeding the maximum permissible concentrations for

irrigation water (Bahiru *et al*., 2020). However, if wastewater is used for irrigation in a diluted form, there is no significant increase in the concentration of heavy metals within the plants (Lente *et al*., 2014)

Presence of heavy metals in irrigation water

Environmental pollution with heavy metals is a growing ecological crisis and a matter of concern due to their non-biodegradability and long biological half-life. Heavy metals have detrimental effects on human health, and exposure to these metals is increasing, primarily through the contamination of water, soil, and air, and secondarily through their entry into the food chain (Balali-Mood *et al*., 2021; Bhatia *et al*., 2015). Heavy metals represent a group of toxic metals with a density greater than 5 g/cm³ and an atomic mass ranging from 60 to 200. They are present in ecosystems and wastewater in various concentrations, ranging from ng/L to mg/L (Jadaa & Mohammed, 2023). Heavy metals in wastewater most commonly originate from both natural and anthropogenic factors. Natural factors include soil erosion, volcanic activities, aerosol particles, and others, while anthropogenic factors primarily stem from industry, specifically the metal processing industry such as metal finishing and electroplating as well as mining, the textile industry, and nuclear energy (Akpor *et al*., 2014). Table 1 shows the most common sources of wastewater contamination with lead (Pb) and cadmium (Cd).

Table 1. Sources of Pb and Cd in wastewater and their characteristics (adapted from Jadaa & Mohammed, 2023)

Element	Oxidation state	Stable form	Sources of metal in wastewater and the environment
Lead (Pb)	Pb^{-4} to Pb^{+4}	Pb (II), Pb (IV)	Batteries, mining, paint, pigments, steel, explosives, electroplating, smelters, inorganic fertilizers and pesticides, printing industry
Cadmium (Cd)	Cd^{-1} to Cd^{+2}	Cd (II)	Mining, metallurgy, paints, cement, plastic stabilizers, nickel-cadmium battery production, fossil fuel combustion, high-phosphate fertilizers, municipal and sewage waste

In soils irrigated with wastewater, there is a significant increase in heavy metal concentrations in residual form, followed by bound oxides and heavy metal fractions associated with carbonates, compared to soils not irrigated with wastewater (Haroon *et al*., 2018). As a result of population growth, there is an increasing demand for food production, but also an increase in wastewater generation in urban and rural areas. The reuse of wastewater (treated or

untreated) in agriculture is most commonly employed for irrigation in developing countries to address the problem of water scarcity, particularly in regions with warmer climates. This wastewater can often be contaminated with heavy metals, which must be removed to reduce their accumulation in plants and, consequently, in the food chain (Kerbouna Faycal M. A., 2018; Hashem & Qu, 2021).

Vegetables are an integral part of the normal human diet because they contain nutrients that are vital for the proper functioning of the human body. However, vegetables grown in contaminated areas, as well as those irrigated with water contaminated with heavy metals, can accumulate significant concentrations of heavy metals in their edible parts (Manwani *et al*., 2022).

The absorption of heavy metals into the edible parts, resulting from high heavy metal content in irrigation water, is influenced by their solubility in the soil, soil pH, plant development characteristics, and other factors (Khan *et al*., 2023; Sarker *et al*., 2021). Wastewater can contain high levels of metals and metalloids depending on the types of industries located in the region. Nevertheless, untreated wastewater is very frequently used for irrigation. This practice contributes to an increase in the heavy metal content in the soil, which is most commonly associated with organic matter, amorphous iron oxides, and unidentified residual fractions, particularly in the surface soil layer (Rivera *et al*., 2023).

A vast amount of fresh water is consumed in the textile industry, particularly for textile dyeing along with dyes, chemicals, and energy used for wet processing. Although there are various methods for treating textile wastewater, they often involve high operational and utility costs. Consequently, in many cases, this wastewater is discharged into nearby sewers, drains, and agricultural land after the dyeing processes without adequate treatment, especially in developing countries. This wastewater may contain certain heavy metals that can accumulate in cultivated plants and enter the human body through the food chain (Hassan *et al*., 2024; Hassain *et al*., 2018). High contents of Cd, Pb, and Fe have been found in irrigation water from rivers and streams where untreated wastewater from mechanical workshops (lubricating oil, tire and fuel combustion) and other industries is discharged; these concentrations exceeded the maximum permissible concentrations for irrigation water (Lere *et al*., 2021). The maximum permissible concentrations in irrigation water according to the FAO are shown in Table 2.

Table 2. Maximum permissible concentrations of heavy metals (mg/L) in irrigation water according to FAO (1985) (Shahriar et al., 2023).

Pb	Fe	Cu	Zn	Cd	Ni	Mo	Co	Mn
5	5	0,2	2	0.02	0,2	0,01	0,05	0,2

The analysis by Fauozi *et al.* (2022) regarding heavy metal concentrations in irrigation water and soil during the rainy and dry seasons showed that during the dry season, the concentrations of heavy metals Cd, Cr, Cu, Fe, Ni, Pb, and Zn were higher in both irrigation water and soil compared to the rainy season. Furthermore, the content of all heavy metals, except zinc, was higher in the analyzed plants during the dry season. Significant concentrations of heavy metals were found in irrigation water from rivers where wastewater from hospitals, households, laundries, etc., was discharged. Higher heavy metal content was observed in the surface soil layers and lettuce leaves; moreover, the bioconcentration factor and the transfer factor were > 1 for Cd, Cu, and Zn, indicating significant bioaccumulation of heavy metals in the edible parts of the lettuce (Mewouo *et al*., 2024). Similarly, the highest heavy metal content and the highest transfer factor for Fe, Ni, Pb, and Zn were found in lettuce in the study by Aksouh *et al.* (2024). Higher concentrations of Cd, Pb, Cu, Cr, Ni, and Zn were present in wastewater for irrigation

compared to groundwater, resulting in significantly higher concentrations of these heavy metals in the soil as well as in the vegetables grown on it. In carrots, spinach, and radishes, the transfer factor for cadmium, chromium, and zinc from soil to plant was above 1, indicating high bioaccumulation from the soil (Kausar *et al*., 2017). All analyzed plants showed a high transfer factor for Cd (> 1), ranging from 0.85 – 1.17, which indicates high mobility of Cd from the soil into the plants. The transfer factor was lower for Pb, ranging from 0.02 – 0.03, and for iron, ranging from 0.04 – 0.06 (Gupta *et al*., 2010). According to Parmoozeh *et al*. (2024), vegetables irrigated with synthetic effluent containing permissible concentrations of Pb, Cd, and As according to the WHO for the reuse of treated wastewater for irrigation, had high heavy metal accumulation that exceeded the permissible limits set by FAO/WHO. Consequently, vegetables irrigated with treated wastewater may pose a risk to human health.

Presence of cadmium and lead in vegetables irrigated with wastewater

Cd was highly accumulated in radishes, lettuce, and spinach irrigated with wastewater compared to vegetables irrigated with well water (Khan *et al*., 2015). High concentrations of Cd and Pb were found in lettuce (0.5 and 0.27 mg/kg dry weight, respectively), spinach (0.37 and 0.06 mg/kg dry weight, respectively), kale (0.67 and 0.13 mg/kg dry weight, respectively), and cabbage (0.93 and 0.23 mg/kg dry weight, respectively) irrigated with untreated sewage wastewater (Alamnie *et al*., 2020). Table 3 shows the concentration of Cd in irrigation water and in the vegetables irrigated with that water.

Table 3. Cadmium content in irrigation water and vegetables.

Vegetable	Cd in wastewater mg/L	Cd in vegetable mg/kg	Description	References
Lettuce	0.20	0.16	Domestic wastewater and local industrial sources	Rezapour *et al*., 2024
Cabbage		0.18		
Green beans		0.12		
Peppers		0.14		
Radishes	0.054	0.33 *	River channels receiving wastewater from industrial zones and households	Khan *et al*., 2015
Cabbage		0.26 *		
Lettuce		0.51 *		
Cauliflower		0.37 *		
Spinach		0.62 *		
Radishes	0.03	0.351 *	Synthesized wastewater with Cd	Parmoozeh *et al*., 2024

			concentrations according to treated wastewater reuse standards	
Spinach	0.014	1.20	Sewage wastewater	Aftab *et al*., 2023
Cauliflower		0.97		
Spinach	0.13	21.35 *	Wastewater	Chopra & Pathak, 2015
Cauliflower		17.51 *		
Cabbage	0.02	1.86	Wastewater from various industries (textiles, batteries, paints, plastic recycling, etc.) discharged with municipal sewage	Kumar & Thakur, 2018
Spinach		1.21		
Cauliflower		0.86		
Peppers	0.003	0.0037	Wastewater	Leblebici *et al*., 2018
Onion		0.0010		
Cabbage	0.07	1.21	Industrial wastewater	Lere *et al*., 2021
Cucumbers		3.55		
Radishes	0.0003	6.5 *	Industrial wastewater from integrated steel plants, thermal power plants, untreated sewage, etc.	Gupta *et al*., 2010
Carrot	0.15	0.05	Sewage and industrial wastewater	Rehman *et al*., 2019
Cabbage		0.03		
Spinach		0.08		
Cauliflower		0.03		

** - mg/kg on a dry weight (dw) basis*
Maximum Levels (MLs) for Cd (mg/kg) according to Codex Alimentarius (2023):
Brassica vegetables (cauliflower, cabbage, broccoli, kale) – 0.05

Leafy vegetables (lettuce, spinach, Swiss chard, etc.) – 0.2
Fruiting vegetables (cucumber, tomato, pepper, eggplant, etc.), garlic, onion – 0.05
Root and tuber vegetables (carrot, radish, beetroot, etc.) – 0.1

According to the study by Khan *et al*. (2023), the concentration of heavy metals in vegetables irrigated with industrial wastewater at three different locations was high. The concentrations of Pb and Cd were higher in all vegetables (spinach, cabbage, cauliflower, turnip, radish, carrot, and lettuce), exceeding the MLs. The average concentrations of these metals in the wastewater were 14.86, 0.331, and 8.267 mg/L for Pb, and 0.706, 0.52, and 0.773 mg/L for cadmium. The concentration of all heavy metals in the vegetables was significantly higher in those irrigated with wastewater compared to those irrigated with high-quality tap water. There was significant heavy metal contamination in vegetables irrigated with wastewater contaminated by the discharge of municipal waste, urban drainage, and effluents from various industries (dairy, paper mill, textile industry, and iron foundry). The average Cd value in all vegetables exceeded the MLs according to Codex Alimentarius (2023), with the highest concentrations found in radishes at 1.2 mg/kg, and turnips at 1.06 mg/kg (Sharma *et al*., 2016). Table 4 shows the concentration of Pb in irrigation water and in the vegetables irrigated with that water.

Table 4. Lead content in irrigation water and vegetables.

Vegetable	Pb in wastewater (mg/L)	Pb in vegetable (mg/kg)	Description	References
Radishes	0.21	2.91*	River channels receiving wastewater from industrial zones and households	Khan *et al*., 2015
Cabbage		2.24*		
Lettuce		1.52*		
Cauliflower		1.32*		
Spinach		1.84*		
Radishes	3	12.26*	Synthesized wastewater with Pb concentrations according to standards for treated wastewater reuse.	Parmoozeh *et al*., 2024
Spinach	0.88	68.17*	Wastewater	Chopra & Pathak, 2015
Cauliflower		86.69*		
Tomatoes	0.00003	0.0247	Wastewater	Leblebici *et al*., 2018
Onion		0.0213		
Peppers		0.0263		
Cabbage	0.02	0.28	Industrial wastewater	Lere *et al*., 2021
Cucumber		0.56		
Radishes	0.0523	22 *	Industrial wastewater from integrated steel plants, thermal power plants,	Gupta *et al*., 2010

			untreated sewage, etc.	
Carrot	1.35	1.49	Sewage and industrial wastewater	Rehman *et al*., 2019
Cabbage		1.81		
Spinach		2.68		
Cauliflower		1.38		
Lettuce	0.35	0.23	Wastewater	Jalil *et al*., 2022
Cabbage		0.23		
Green beans		0.12		
Peppers		0.14		

** - mg/kg on a dry weight (dw) basis*
Maximum Levels (MLs) for Pb (mg/kg) according to Codex Alimentarius (2023):
Brassica vegetables (cauliflower, cabbage, broccoli, kale) – 0.1
Leafy vegetables (lettuce, spinach, Swiss chard, etc.) – 0.3
Fruiting vegetables (cucumber, tomato, pepper, eggplant, etc.) – 0.05
Root and tuber vegetables (carrot, radish, beetroot, etc.), garlic, onion – 0.1

According to Ali *et al*. (2022), the highest average concentration of Pb in vegetables irrigated with wastewater was found in cauliflower, followed by spinach, cabbage, tomato, and lettuce. High Pb concentrations were observed when irrigating vegetables with industrial and sewage wastewater, ranging from 35 - 93 mg/kg in spinach, 17 to 43 mg/kg in tomatoes, and 23 to 47 mg/kg in cauliflower. The concentration of Pb in the wastewater was above permissible limits, while the accumulation of Pb in the soil was lower because the soil concentration remained within permissible limits. The high concentrations in the vegetables are attributed to the direct bioaccumulation of Pb from the water into the vegetables (Aslam *et al*., 2017). From the study by Ali *et al*. (2021), an analysis of vegetables irrigated with wastewater near various industries such as leather, metal processing, paper, battery manufacturing, pharmaceuticals, etc. showed that the heavy metal concentrations in the wastewater were 0.79 mg/L for Pb and 0.02 mg/L for Cd. The concentrations of Pb and Cd in the vegetables irrigated with this wastewater ranged from 0.70 – 18.14 mg/kg and 0.02 – 3.64 mg/kg, respectively (Ali *et al*., 2021). According to the study by Aslam *et al*. (2024), the concentration of heavy metals in domestic wastewater used for vegetable irrigation exceeded the maximum permissible concentrations. The Pb concentration ranged from 0.06 to 0.37 mg/L, and Cd from 0.01 to 0.80 mg/L. The concentrations of these heavy metals were above the MLs in the vegetables irrigated with wastewater, ranging from 11.1 to 47.02 mg/kg for Pb and from 2.9 to 11.02 mg/kg for Cd. These concentrations were particularly high in radishes, cabbage, carrots, spinach, and cauliflower. According to Khan *et al*. (2023), the concentration of heavy metals in irrigation water containing industrial effluents ranges from 0.05 to 0.09 mg/L for Pb and 0.01 to 0.03 mg/L for cadmium. The concentration of heavy metals in the vegetables irrigated with this water ranged from 5 to 9 mg/kg for Pb and 0.70 to 1.90 mg/kg for cadmium. High concentrations of Cd and Pb were found in radishes, cabbage, carrots, spinach, and cauliflower.

Treatment of heavy metals from wastewater

Heavy metal pollution is of great significance due to its pronounced toxicity, difficult degradation, and accumulation in plants and living organisms. Irrigation with wastewater raises major concerns among the population due to the high accumulation of heavy metals in vegetables. It is of vital importance to treat the water before it is discharged into rivers and streams, especially from the metal-processing industry, households, and industrial waste (Noor

et al., 2019). Treated wastewater can be reused for irrigation. This involves physical, chemical, and biological processes to remove these pollutants and obtain environmentally safe treated wastewater. Various technologies exist for the removal of heavy metals from water, such as chemical precipitation, oxidation or reduction, filtration, ion exchange, electrochemical treatments (electrocoagulation, electroflotation, and electrodeposition), reverse osmosis, adsorption (activated carbon, carbon nanotubes, and wood sawdust), membrane filtration, as well as nanotechnology. The most commonly used methods are ion exchange and membrane filtration. However, most treatments are either ineffective or too expensive when metal concentrations exceed 100 mg/L (Nalenthiran *et al*., 2016; Zareh *et al*., 2024; Li *et al*., 2023). The membrane filtration separation method offers high efficiency, ease of operation, and low space requirements, making it a promising method for heavy metal removal (Birniwa *et al*., 2024; Xiang *et al*., 2022). Ion exchange is an advanced water treatment that can be used to remove metal ions present in low concentrations in water (Lupa & Cocheci, 2022)

Conclusions

Water is a vital natural resource essential for the sustainability of all living organisms; however, today it is subjected to intensive exploitation as well as contamination with heavy metals, primarily through the uncontrolled discharge of industrial wastewater. The data from this literature review confirm that the use of wastewater for irrigation significantly increases the concentration of heavy metals in the soil, and consequently, in the edible parts of plants, entering the human body through the food chain.

Analysis of numerous studies indicates that lead and cadmium concentrations frequently exceed the maximum levels prescribed by international standards (FAO/WHO and Codex Alimentarius 2023), both in irrigation water and in vegetables. This situation poses a serious risk to public health due to the entry of lead and cadmium from irrigation water into the food chain. As a result, it is necessary to take urgent measures to treat wastewater using modern purification technologies, such as membrane filtration and ion exchange, before its reuse in agriculture. Future focus should be directed toward strict monitoring to ensure the production of safe food and the protection of the ecosystem.

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APPLICATIONS OF CONGRUENCE IN VARIOUS FIELDS

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Abstract

Congruence theory is one of the fundamental topics in number theory and has important applications in various scientific and practical fields. This paper presents several applications of congruences, including check digits, identification numbers, ISBN systems, and modular designs. Special attention is devoted to the use of modular arithmetic in error detection and verification processes. In addition, we illustrate how congruences can be applied in the construction of geometric and artistic modular patterns. The presented examples demonstrate the relevance of congruence theory in mathematics, computer science, coding theory, and everyday life.

Keywords: Congruence,modular arithmetic,check digits, coding theory, identification numbers, ISBN,modul designs

Introduction

One of the most important concepts in number theory, the congruence relation, was introduced and developed by the German mathematician Karl Friedrich Gauss in 1801 in his work " Disquistiones Arithmeticae". Gauss focused on the reminder obtained when one natural number is divided by another natural number. [1, 6, 12]
The congruence made it possible to more easily formulate the results obtained in the theory of divisibility, so that unnecessary calculations are not carried over. The congruence relation shares many properties with the equality relation, so it is no coincidence that the congruence symbol
" ≡ " , which introduced Gauss, similar to the equal sign " = ". [2, 7]
Definitions 1. If **a** and **b** are integres, we say that **a** is congruent to **b** modulo **m** if $m \mid (a-b)$. If **a** is congruent to **b** modulo **m**, we write $a \equiv b\ (mod\ m\ )$. If $m \nmid (a-b)$, we write $a \not\equiv b\ (mod\ m\ )$ and say that **a** and **b** are incongruent modulo **m**. [1, 7]
In this research we will focus on the application of congruence and based on this research we will see that it is an integral part of everyday life. One of the most famous application of cngruence is clock aithmetic. The time on the clock is shifted using congruence of modulo 12. For example if it is 10 o'clock for 4 hours pass, it will be 14, but since the clock is divided into 12 equal parts,we have:

$$10 + 4 = 14 \equiv 2\ (mod\ 12\ )$$

Also, numbers are all around us,driver's license numbers, books, products, and we will show that these numbers also use congruences as a form of protection and verification. We will see that beautiful designs can be created using congruence. Congruence is also used in scheduling and grouping systems in sports competitions.
Congruences have many applications in discrete mathematics, computer science, and many other disciplines. The three main applications are: using congruences to assign memory locations for computer files, generating pseudorandom numbers and checking digits. [3, 6]
Modular arithmetic can also be used to produce checksums of various types such as code numbers used to identify retail products, numbers used to identify books, airline ticket numbers etc.

Check Digits[1]

Coding theory is a branch of mathematics that deals with the analysis of codes that are transmitted through channels and the detection and correction of errors that may arise. In this part, we will show how congruences can help in finding and correcting errors in sent messages. [8, 9]

Identification numbers

Many institutions (such as banks, book publishers, post offices etc) and companies use identification numbers to mark their products, documents, accounts, people and many other entities. Identification numbers contain coded information about the thing they stand for and can typically be numeric (consisting of digits) or alphanumeric (constisting of numbers and letters of the English alphabet). The two pieces of information they carry are essential, the length of the identification number (total number of digits or letters) and the position of each digit or letter. An identification number of length n is denoted by $d_1 d_2 \ldots d_n$, where d_1 is the first digit or letter of the number, d_2 is the second digit or letter, and d_n which is the last digit or letter.
Every day, identification numbers are sent by phone, scanned or entered into computers, transmitted over the internet or sent by mail. During transmission, errors may occur, meaning one or more digits may be replaced. [9]
It is essential that the identification numbers are transmitted correctly. For example, if the product's barcode is scanned incorrectly in the store, it is possible that the customer will be charged a price of 100 dollars for a product that costs 15 dollars.
The most common transmission errors that occur are a single digit error (one digit in the identification number changes its value) and the error of replacing two consecutive digits.
In order to prevent this, it was necessary to develop a method that would recognize such errors, that is, that would recognize when the identification number is wrong. This method is a check digit method that depends mostly on the scalar product of two vectors and the modules.
The verification digit is usually an additional digit that servers to verify the received identification number. It can be anywhere in the identification number, but most often it is the last digit of the number.

Definition 2: The scalar product of vectors $(x_1, \ldots, x_n) \in \mathbb{Z}^n \; and \; (y_1, \ldots, y_n) \in \mathbb{Z}^n$ is defined by

$$(x_1, \ldots, x_n) \cdot (y_1, \ldots, y_n) = \sum_{i=1}^{n} x_i y_i \; ^2$$

ISBN (International Standard Book Number)

ISBN (International Standard Book Number) is a unique code assigned to book publications for their international identification. This code is used for printed books, eBooks, audiobooks, and some similar materials such as maps.

[1] Elementary Number Theory and its Applications, fifth edition, Kenneth H. Rosen

The ISBN system (International Standard Book Number) was designed and introduced in the United Kingdom in 1968 by J. Whitaker & Sons, and a year later the company R.R. Bowker introduced the ISBN system in the United States. [10]
ISBN is an important tool for the book industry, facilitating the registration and sharing of book information at a global level. It enables the transmission and computerized storage of book data.
Since 2007, the 13-digit ISBN has been in use, divided into five parts:
The first part is the prefix element, usually 978.
The second part identifies the country or language area in which the book is published.
The third part identifies the publisher of the book.
The fourth part is the unique number of the book within the publishing house.
The fifth part is the check digit (1 digit), calculated based on the previous digits, and it is used to verify the correctness of the code.



Figure 1. Example of an ISBN-13 code for a book publication.

The ISBN shown above belongs to the book "Methods of Numerical Analysis (Numerical Algorithms)" by Fatmir Hoxha. Based on our analysis, let us examine whether the components are correct by explaining what each number represents:
978 – this is the prefix element, indicating that the book follows the international ISBN format.
9928 – this number identifies the country where the book is published; this code shows that the book is published in Albania.
4091 – this code identifies the specific publisher of the book.
7 – this represents the specific title of the book within that publisher.
1 – this is the check digit, used to verify whether the ISBN is correct.
Thus, 1 is the digit obtained using congruence, specifically modulo 10.
Let us verify that the check digit of this ISBN is 1:

$$d \equiv -(x_1, x_2, \ldots, x_{12}) \cdot (1, 3, 1, 3, 1, 3, 1, 3, 1, 3, 1, 3) \ (mod\ 10)$$
$$\equiv -(9,7,8,9,9,2,8,4,0,9,1,7) \cdot (1,3,1,3,1,3,1,3,1,3,1,3) \ (mod\ 10)$$
$$\equiv -(9 + 21 + 8 + 27 + 9 + 6 + 8 + 12 + 0 + 27 + 1 + 21) \ (mod\ 10)$$
$$\equiv -149 \ (mod\ 10) \equiv 1 \ (mod\ 10).$$

Thus, our analysis is correct.

Modular designs

Congruences can be used to create different designs. In this chapter, we will show how to create a star with m vertices, the design of residues (m,n) and the design obtained using tables of multiplication and addition of the smallest residues modulo m (quilt designs). [4]

1. A star with m points

In order to construct a star with m vertices on a circle of arbitrary radius, we mark m equidistant points and mark them with 0 to m-1 modulo m. We choose the smallest remainder i modulo m for which i and m are relatively prime, (i,m)=1. Connect each point x with point x+1 modulo m, more precisely connect 1 with 1+i (mod m) and continue like this until all points are connected and color the resulting star.
Example, let's construct a star with 13 points and choose the remainder 5, (13,5)=1.

Table 1. Values of "d≡x+5" ("mod13") used in the construction of the 13-point star.

x	$d \equiv x + i\ (mod\ 13)$	d
0	0+5	5
1	1+5	6
2	2+5	7
3	3+5	8
4	4+5	9
5	5+5	10
6	6+5	11
7	7+5	12
8	8+5	0
9	9+5	1
10	10+5	2
11	11+5	3
12	12+5	4

Connect 0 with 5, 1 with 6, 2 with 7… and 12 with 4. In this way, we got a star with 13 points shown in below

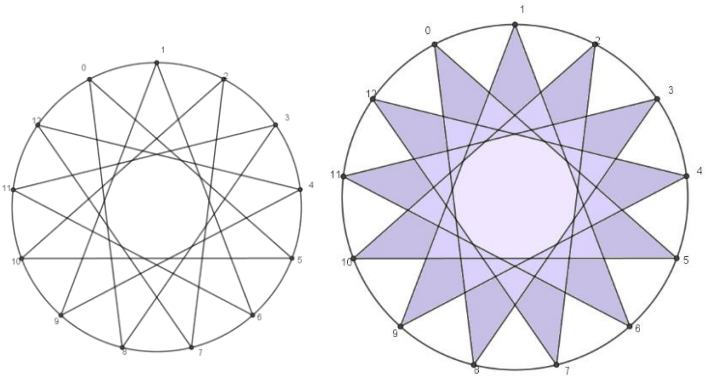


Figure 2. Construction of the 13-point modular star and its colored design.

Now we will create the design of (59,57), by connecting the corresponding numbers we get:

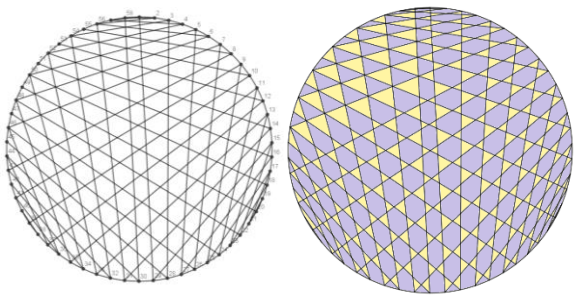


Figure 3. Residue design m (59,57) and its colored version.

Let's make a design with the addition table of modulo 8. We formulate the table:

Table 2. Addition table of the smallest residues modulo 8.

+	0	1	2	3	4	5	6	7
0	0	1	2	3	4	5	6	7
1	1	2	3	4	5	6	7	0
2	2	3	4	5	6	7	0	1
3	3	4	5	6	7	0	1	2
4	4	5	6	7	0	1	2	3
5	5	6	7	0	1	2	3	4
6	6	7	0	1	2	3	4	5
7	7	0	1	2	3	4	5	6

We create designs for each issue

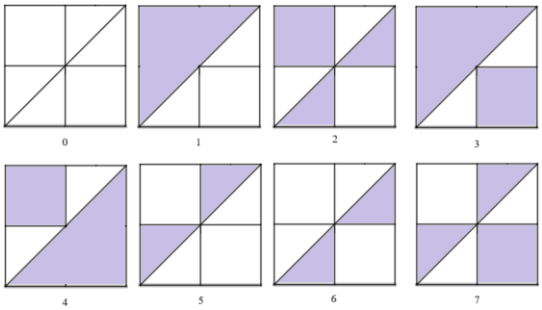


Figure 4. Basic modular patterns corresponding to the residues modulo 8.

By combining these designs according to the table, we obtain this design:

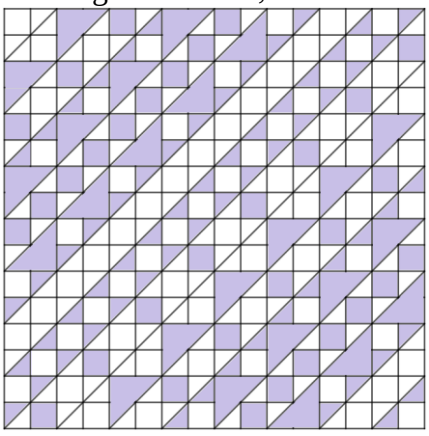


Figure 5. Modular quilt design obtained from the addition table modulo 8.

From this design we can also get other designs by rotating it in different directions and joining them. We get the design:

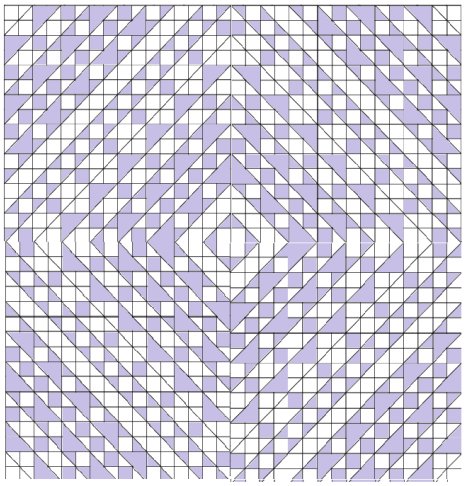


Figure 6. Rotated modular quilt design obtained from the modulo 8 addition patterns.

Conclusion

One of the oldest branches of mathematics is number theory and congruence theory.
Congruence as a simple idea finds wide application and sometimes we are not aware of its application in daily life. By looking at the clock or remembering the day of the week we apply congruence. Also, even before we knew its definition, we used it in elementary school to determine when one number was divided by another number.
As technology developed and the number of products and services increased, it was necessary to find a simple and easy way to track them, and they began to be marked with numbers. Identification numbers contain coded information about products, people, documents and other things.
Since they are encrypted, it is important that errors are detected when they are sent, scanned or entered into a computer. Of course it wouldn't matter to us if, for example, the EAN-13 barcode is scanned incorrectly and a higher product price is charged than it is.
Mail delivery in the United States is made easier and faster. The check digit method also has its drawbacks, because sometimes errors cannot be detected, but most of the time errors are detected.
In art, congruences can be applied to create beautiful modular designs, in sport fields to determine the day of the week for any date of any year.
These are some examples of that are presented in the paper, because congruence can also be applied in music, chemistry, cryptography and others. [13]

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EXPLAINABLE MACHINE LEARNING FOR INSURANCE CLAIM FRAUD DETECTION: A COMPARATIVE PYTHON-BASED STUDY

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Abstract

Today insurance fraud is a big problem for insurance companies since it is challenging to detect potential fraud cases within a large amount of claims data. Traditional rule-based models can detect already known fraud cases, but they often fail to detect new ones and can flag too many false positives. In this paper, several machine learning algorithms will be compared to detect insurance claim fraud. The analysis will focus on comparing models' performance, handling class imbalances, interpretability and feature engineering. A publicly available dataset with 1,000 cases of insurance claims will be used in the analysis and at the same time, eight classification algorithms will be considered: majority-class baseline, Gaussian Naive Bayes, k-NN, weighted logistic regression, decision tree, random forest, gradient boosting, and XGBoost. To ensure responsible modeling, the study leaves out direct identifiers and sensitive variables like sex, ZIP code, education, occupation, hobbies, and relationship status. The analysis includes missing-value treatment, date-based feature engineering, one-hot encoding, stratified train-test splitting, 5-fold stratified cross-validation, and model evaluation using accuracy, precision, recall, F1-score, ROC-AUC, and confusion matrices. The results indicate that XGBoost achieved the highest cross-validated F1-score, while the decision tree achieved the strongest F1-score on the holdout test set. Random forest had the highest holdout ROC-AUC, and weighted logistic regression was a useful and interpretable benchmark. SHAP analysis found that factors like incident severity, vehicle claim amount, policy age, incident state, vehicle year, annual premium, and other claim-related variables affected the model's predictions.

Keywords: insurance fraud detection; machine learning; explainable AI; XGBoost; SHAP; Python.

Introduction

Insurance companies work with large amounts of data, in which case they make decisions about claims, risk, underwriting, pricing, and customer service based on careful analysis. When we talk about such activities, we must mention that fraud detection is a key part of them. For honest policyholders, it is known that fraudulent claims can raise costs, lower profit and can lead to higher premiums. Insurance fraud can occur across many different types of insurance such as auto, health, property, and even life insurance. It can even involve exaggerated damages, staged incidents, false documents, incorrect information, or coordinated attempts to manipulate the claims process.

As everything is digitalizing, even claim records are becoming digital, in such a case insurance companies have new opportunities to use AI and ML for fraud detection. Instead of using algorithms based on rules that were created by people, now they can build models that help them identify suspicious patterns in sensitive data that are used by insurance companies. There are a lot of patterns that are hard to spot by hand and here comes machine learning which helps us to identify them. However, the word perfect does not fit with machine learning because it still comes with its own issues. The most difficult part is explaining a decision that was made, why such a decision?

In this way, there is a balance between predictive performance and model interpretability as two important aspects of modeling. Is known that complicated models might give very good results, but it is not easy for people working in one company to understand them. An example of a simpler model that exists is logistic regression. This model is easier to explain but it fails when given complex data. In the world of insurance, fairness, accountability, and transparency

matter more than ever, being able to interpret models is a practical need (European Insurance and Occupational Pensions Authority, 2021).

This paper presents a Python-based comparative analysis of machine learning focused on the domain of insurance companies. Python is used in order to compare different machine learning methods, and the key point is detecting claim fraud.

The proposed methodology uses a public insurance claims dataset and trains some classification algorithms under identical conditions. The main aim is to check if these models will be able to detect fraudulent insurance claims effectively and give clear explanations regarding the most critical features for the problem at hand?

How does having an uneven number of fraud and non-fraud cases affect how we judge model performance?

Can a model that is easy to understand also achieve high recall and give helpful explanations for fraud detection?

Which claim features have the biggest impact on classifying fraud?

This paper does not introduce a new fraud detection algorithm. Rather, it presents an analysis framework for the evaluation of machine learning methods for identification of fraudulent claims in insurance companies' domain. It starts with a description of a Python-based pipeline that includes the main steps of analysis. It covers every step, from data preparation to training and evaluation and finally the interpretation of the results. The next step is a comparison of different models, including both simple and advanced ones. The models that are included are: logistic regression, decision tree, random forest, gradient boosting, and XGBoost. The third step is the focus on evaluating model performance using metrics that are suitable for imbalanced fraud detection, such as recall, F1-score, ROC-AUC, and confusion matrix analysis, rather than relying on traditional accuracy only. Lastly, the study adds explainability and responsible AI through anonymization. It removes potentially sensitive variables and uses SHAP to explain the selected XGBoost model (Lundberg & Lee, 2017).

Related Work

Machine Learning in Insurance Fraud Detection

Nowadays the number of actual incidents have increased a lot and compared to fraud, it is much bigger but, fraud can have a big financial impact and this is why insurance fraud detection is an important research area. Old, traditional fraud detection systems usually rely on expert-defined rules, such as unusually high claim amounts, suspicious timing, sometimes even missing police reports or even repeated claims by the same claimant. Those systems can be used to identify known fraud patterns, but the problem stands in the fact that they are limited by the rules that have been manually created by people based on their needs. Based on this, as fraud behavior changes, rule-based systems know to fail while detecting new or more complex patterns.

Machine learning offers a more flexible and better approach because it searches and learns from historical claim data to find patterns in past claim data. The supervised learning methods use datasets that include both insurances of fraud and no fraud. Some of the techniques that are used are: logistic regression, decision trees, random forests, support vector machines, gradient boosting, and neural networks etc. Since labeled fraud data can be hard or limited to get, unsupervised methods such as clustering and anomaly detection, are also relevant. Debener, Heinke, and Kriebel (2023) bring up the fact that supervised fraud detection has been investigated a lot, while unsupervised fraud detections are even less discovered in insurance situations. This emphasizes the need for comparative studies that inspect the strengths and weaknesses of different model types.

Class Imbalance in Fraud Detection

For fraud detection we can say that it usually is an imbalanced classification problem because of the fact that there are a smaller number of fraudulent claims than legitimate ones (Chawla et al., 2002). In this situation, accuracy can be misleading. For example, if we take into consideration a model that predicts every claim as non-fraudulent, it might achieve high accuracy because most claims are legitimate, but it would fail to detect any fraud. For this reason, fraud detection studies must also use metrics like precision, recall, F1-score, ROC-AUC, and confusion matrix values.
For showing how many real fraud cases the model finds, there is an important factor which is recall. But we again have a problem because of the fact that very high recalls can also lead us to more false positives and this surely creates extra work for investigators and can affect customers.
For showing how many flagged claims are fraudulent, the other important factor was used which is precision. Also, it is known that F1-score helps balance the precision and recall. In practice, the best balance varies on how many cases the insurer can examine, the cost of false positives, and the cost of missed fraud.

Explainability and Trust in Insurance AI

Explainability is an important point when we talk about claims because in insurance the results from one model can affect how claims are treated, which cases are explored, and how customers are treated. For insurers, it is so important to understand the reason why a certain model marks a claim as a suspicious one. In 2017 Lundberg and Lee developed a new method known as SHapley Additive exPlanations (SHAP). The idea behind this lies in explaining a model's predictions by showing how much each attribute influences.
In insurance domain, the data is highly sensitive that even good precision sometimes is not enough which means that high accuracy is not always sufficient. Besides good precision, models need to be clear, reviewable and allow humans to oversee. The current dataset that is used focuses on fairness, accountability, transparency, safety, and compliance. These are important values which matter because insurance choices impact customers' financial protection and rights. This is why we say that fraud detection models should support decisions and not just auto-generate them. Final choices should always be reviewed and confirmed by people.

Methodology

Dataset

The study uses an insurance claims dataset with 1,000 claim records which is publicly available. The variable used for showings if a claim was labeled as fraudulent or non-fraudulent is fraud_reported. The dataset includes both numerical and categorical information related to policies, insured people, incidents, claim amounts, vehicles, and report status. The dataset used in this study is insurance_claims.csv, published by Aqqad (2023) on Mendeley Data.
All descriptive statistics reported in this section were calculated directly from the dataset. Therefore, the reported fraud rate should be understood only as the fraud rate within this selected public dataset, not as a general fraud rate for the insurance industry.
The dataset is imbalanced. Out of 1,000 records, 247 claims are labeled as fraudulent and 753 are labeled as non-fraudulent. Based on this, now we can say that fraudulent claims represent 24.7% of the dataset, while non-fraudulent claims represent 75.3%.

Table 1. Dataset summary

Dataset characteristic	**Value**
Total records	1,000
Fraudulent claims	247
Non-fraudulent claims	753
Fraud rate	24.7%
Initial columns	39
Responsible feature selection	Applied
Sensitive/proxy variables removed	Yes
Train-test split	75% / 25%
Cross-validation	5-fold stratified cross-validation

Data and Feature

The workflow was Python. Missing with question treated as Numerical were replaced median, while missing values with the most category.

Preprocessing Responsible Selection

preprocessing implemented in values marked marks were missing data. missing values with the categorical were replaced frequent

The variables policy_bind_date and incident_date were converted into date format. Based on these variables, three new features were created:
policy_age_days: the number of days between the policy binding date and the incident date;
incident_month: the month in which the incident occurred;
incident_dayofweek: the day of the week on which the incident occurred.
To reduce the risk of memorization, direct identifiers and highly specific location or date values were removed. These variables included policy_number, policy_bind_date, incident_date, and incident_location.
A responsible feature selection step was also applied. Variables such as insured_zip, insured_sex, insured_education_level, insured_occupation, insured_hobbies, and insured_relationship were excluded from the final modeling pipeline because they contain sensitive personal information. These variables included
Besides the fact that it is so important for the fraud detection models to aim for predictive performance, it is also very important for them to be able to reduce the risk of unfair decisions. This is why this step was included. By removing these variables, the analysis becomes more fitting for an insurance context where fairness, accountability, and transparency are very important.
There is a significant problem with using different models because they also vary on the way they read the variables. For solving this problem, in this study there was used the one-hot encoding. The final feature matrix included variables such as claim-related, policy-related, incident-related, and vehicle-related. The dataset needed to be split into 75% training data and 25% testing data using stratified sampling, so that the fraud and non-fraud proportions were preserved in both subsets.

Models

The eight classification models used in this study are: a majority-class baseline, Gaussian Naive Bayes, k-Nearest Neighbors with k = 15, weighted logistic regression, decision tree, random forest, gradient boosting, and XGBoost. The reason why the majority-class baseline was included was to prove that accuracy alone can be deceptive in an imbalanced fraud detection problem. On the other hand, logistic regression and decision tree were used as more interpretable models, while random forest, gradient boosting, and XGBoost were included as stronger tree-based ensemble methods. Where appropriate, class weighting was applied to reduce the effect of class imbalance and improve the models' ability to detect fraudulent claims.

Evaluation Metrics and Cross-Validation

The metrics that were used to assess the models are: accuracy, precision, recall, F1-score, ROC-AUC, and the value of the confusion matrix. Each of them was used for a different and important reason.
Accuracy – calculates the total percentage of correctly predicted outcomes
Precision – represents the total number of fraudulent claims
Recall – describes the decision of fraudulent claims
The confusion matrix reports the number of true negatives, false positives, false negatives, and true positives (Fawcett, 2006).
In fraud detection, accuracy alone can be misleading, this is the reason why recall and F1-score are very important. A model may achieve high accuracy by predicting most claims as non-fraudulent but still fail to identify fraud. At the same time, a model with high recall but low precision may create too many false alarms. Therefore, model selection should consider both statistical performance and practical usefulness.
To improve the reliability of the results, 5-fold stratified cross-validation was used. Stratification preserved the proportion of fraudulent and non-fraudulent claims in each fold. In order to assess the model stability, cross-validation was used, while a separate holdout test set was used to obtain final confusion matrix results. All calculations that are shown in tables above as results were generated using the same Python preprocessing and modeling pipeline to confirm reproducibility.
Experimental Results
As mentioned above, for the fact that the dataset is imbalanced, the results needed to be interpreted mainly through recall, F1-score, and ROC-AUC and could not be interpreted only with accuracy. But, on the other hand, even though accuracy is not used as the main source for model selection, it is still included for completeness. There is a serious problem in fraud detection because a model can appear accurate if it predicts most claims as non-fraudulent, but the same model can still fail while trying to detect actual fraud cases. This is the reason why the comparison focuses on how well each model recognizes the smaller fraud class while keeping false positives and false negatives at an appropriate level.
The experimental results can be seen below on Tables 2 and 3. Table 2 presents the 5-fold stratified cross-validation results, while Table 3 presents the results from the single holdout test set.

Table 2. Cross-validated model performance

Model	**Accuracy**	**Precision**	**Recall**	**F1-score**	**ROC-AUC**
Majority baseline	0.753	0.000	0.000	0.000	0.500
Gaussian Naive Bayes	0.670	0.264	0.203	0.227	0.590
k-Nearest Neighbors (k=15)	0.756	0.624	0.057	0.101	0.661
Weighted Logistic Regression	0.749	0.496	0.656	0.564	0.757
Decision Tree	0.781	0.570	0.514	0.532	0.700
Random Forest	0.766	0.557	0.328	0.402	0.752

Gradient Boosting	0.765	0.534	0.425	0.467	0.741
XGBoost	0.780	0.553	0.595	0.570	0.755

Table 3. Holdout test-set model performance

Model	**Accuracy**	**Precision**	**Recall**	**F1-score**	**ROC-AUC**	**TN**	**FP**	**FN**	**TP**
Majority baseline	0.752	0.000	0.000	0.000	0.500	188	0	62	0
Gaussian Naive Bayes	0.656	0.306	0.306	0.306	0.580	145	43	43	19
k-Nearest Neighbors (k=15)	0.748	0.400	0.032	0.060	0.652	185	3	60	2
Weighted Logistic Regression	0.752	0.500	0.597	0.544	0.720	151	37	25	37
Decision Tree	0.780	0.552	0.597	0.574	0.675	158	30	25	37
Random Forest	0.760	0.526	0.323	0.400	0.747	170	18	42	20
Gradient Boosting	0.776	0.562	0.435	0.491	0.719	167	21	35	27
XGBoost	0.756	0.508	0.516	0.512	0.713	157	31	30	32

For the fact that most claims were non fraudulent, the majority-class baseline achieved an accuracy of 0.752 on the holdout test set. However, it did not detect any fraudulent claims. This is why we have values 0.000 of recall and F1-score. This is a confirmation of we already mentioned: accuracy alone is not a reliable measure for evaluating fraud detection models on imbalanced data. Gaussian Naive Bayes was the one that detected more fraud cases, but on the other hand, the problem was that it produced many false positives, which would create unnecessary investigation work in a real insurance setting. The k-Nearest Neighbors model achieved reasonable accuracy, but it detected only 2 out of 62 fraudulent claims, making it unsuitable for this task. The comparison shows that model performance depends on the evaluation metric. XGBoost achieved the strongest cross-validated F1-score, suggesting stable performance across validation folds. On the separate holdout test set, however, the decision tree achieved the highest F1-score, while random forest achieved the highest ROC-AUC. Weighted logistic regression also remained useful because it provided competitive results while being easier to interpret. These findings show that fraud detection models should not be selected based on a single metric. Instead, cross-validation results, holdout test performance, recall, F1-score, ROC-AUC, and interpretability should be considered together. Since XGBoost achieved the strongest cross-validated F1-score and is well suited for tree-based explanation methods, it was selected for the SHAP-based explainability analysis.

Explainability Analysis

Because XGBoost achieved the strongest F1-score during cross-validation and is also well suited for SHAP interpretation, it was selected for the explainability analysis. SHAP was used to identify which variables had the greatest influence on the model's fraud predictions. By showing how much each feature contributes to the final prediction, SHAP makes it easier to understand the behavior of a complex tree-based model.
The highest SHAP values were observed for incident_severity_Major Damage, vehicle_claim, policy_age_days, incident_state_WV, auto_year, policy_annual_premium, incident_state_NY, capital-gains, property_claim, and total_claim_amount.
Figure 1 presents the SHAP feature importance chart for the XGBoost model. The figure shows that major incident severity was the most influential feature, followed by vehicle claim amount, policy age, incident state, vehicle year, annual premium, and other claim-related variables. B y taking a deeper look at figure 1, it gets clearer which factors had the deepest impact on the model's fraud predictions.

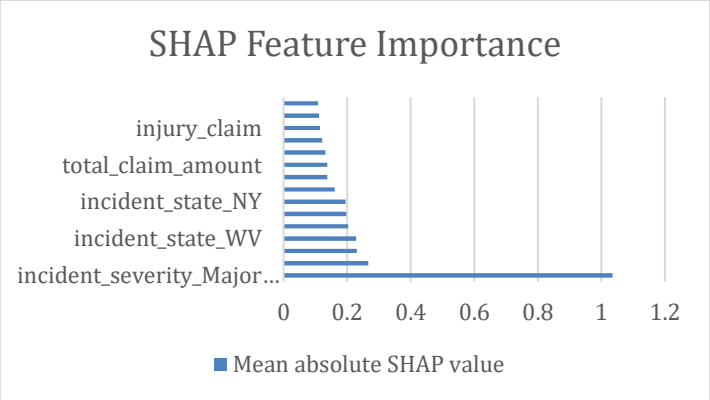


Figure 1. SHAP feature importance for the XGBoost fraud detection model

Looking at the figure 1, we can see that based on the SHAP analysis, it is clear that severity was the most significant feature in the XGBoost model.
This makes sense when we are talking about insurance fraud, because more serious incidents may be connected to higher claim amounts, more complex investigations, or unusual reporting patterns. Additional important variables that are associated with the claims, policies, vehicles or incidents include vehicle claim amount, policy age, incident state, vehicle year, annual premium, capital gains, property claim amount value, total claim amount value, months as customer, injury claim, incident hour, and witnesses.
An important step in the process of developing out final model included removing variables that could be sensitive or act as proxies for sensitive information before training the models. From a deeper analysis that we did, we saw that some of these variables had potential to affect the model's interpretation. By removing them, out model complies with responsible AI principles. This does not demonstrate that the model is entirely unbiased, but it addresses potential ethical issues.
The explainability results also show another reason why the interpretability of an algorithm is important. A model that is interpretable is able to provide valuable insights into the factors that contribute to a particular prediction being made. Indeed, SHAP explanations may help claim investigators understand in more details why a claim was selected as suspicious. However, these explanations should not be treated as final proof of fraud, instead they should be used only as supplementary information.

Discussion

However, it turns out that the performance of the model depends on the evaluation method and the metric selected. Thus, the 5-fold stratified cross-validation results show that XGBoost had the best, which means the highest F1-score, followed closely by weighted logistic regression. In other words, we can say that the average balance between precision and recall was higher for XGBoost when we compare it to others. However, the results that were gathered from the test set showed that the decision tree performed better. This proves one more time that fraud detection models must be analyzed using multiple (at least two) metrics.
Since the biggest number of claims used in the dataset was without any fraud, the accuracy of the model with majority class baseline was quite high. However, this does not mean that it was useful for detecting fraudulent claims, since it was unable to detect them. Thus, the results confirmed that accuracy can be an unreliable measure in fraud detection, especially when the data is imbalanced. The findings showed that simpler models, such as the decision tree and weighted logistic regression, can still perform well when class imbalance is taken into account. Although XGBoost algorithm was chosen for the SHAP analysis because it showed an impressive cross-validated F1-score and tree-based nature.
From all the results that we have, we can conclude that the prediction performance model may not always be the easiest one to explain or use. This was conducted based on the fact that weighted logistic regression was much easier to interpret compared to other models but it did not produce the best result.
Based on all the results, now we can say that in practice SHAP analysis can help us see what factors affected the predictions in XGBoost. The most important factors were related to the incidents, policies, vehicles, and claims.
This model will let investigators decide which claims need closer review. It should not be used for automatic rejection of the claims. Claims that have higher potential for fraud could be sent to special investigators, while the ones that have lower risk could continue through the regular process. Keeping people involved in this process can make fraud detection more efficient, and at the same time keep the whole procedure human and accountable.

Limitations

An insurance company can contain big amount of data and based on that, the dataset that this study uses is relatively small. Based on that, the results may not match when considered big amount of data but, the reason why it was taken is that it was a public one.
Besides the fact that insurance companies nowadays can have big amount of data, they can also have more complex data than the ones that the dataset we used has, they can even include images, documents etc.
Besides the fact that 5-fold stratified cross-validation was used to improve reliability, again the fact that the study relies on a single dataset represents another limitation.
For future work, it is important to test the approach to additional insurance datasets that include more than 1,000 records. By implementing this, we remove two limitations at once, the first one and this one.
SHAP makes the model easier to understand, but it does not prove that the model is fair. Some proxy effects may remain, even after removing sensitive variables.
Applying this type of model in practice would require careful threshold selection, continuous monitoring, feedback loops, human review, and proper regulatory governance.

Conclusions

This paper presented a Python-based comparative study of machine learning methods for insurance claim fraud detection using a public insurance claims dataset. The experiment combined responsible feature selection, stratified train-test splitting, 5-fold stratified cross-validation, holdout test-set evaluation, and SHAP-based explainability. The results show that XGBoost achieved the strongest cross-validated F1-score, while the decision tree achieved the highest holdout F1-score and random forest achieved the highest holdout ROC-AUC. Weighted logistic regression remains useful for being an understandable model benchmark.
After the SHAP analysis, now it is clearer that the severity of the accident is the most dominant attribute among all available attributes. This paper proves that comparing models, analyzing class imbalance, explainability, and responsible feature selection can help a lot to improve the insurance fraud detection. For future work, researchers must consider larger and more complex datasets and also different models.

Data and Code Availability

The complete dataset that was used for this study is easily accessible online and can be downloaded at any time (Aqqad, A. (2023)). All descriptive statistics, class distributions, performance metrics, confusion matrices, and SHAP values for feature importance were generated from this dataset using the Python code described in the methodology section. In order to enable reproducibility, all Python notebooks, preprocessing steps, random seeds, training and testing splits, and other needed parameters can be obtained from the corresponding author by making a reasonable request.

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IMPACT OF VARIOUS HERBAL EXTRACTS ON TECHNOLOGICAL FUNCTIONALITY OF YOGURT

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Abstract

This study investigated the production and quality assessment of functional yogurt fortified with various herbal aqueous extracts, including: turmeric (*Curcuma longa*), sage (*Salvia officinalis*), majorana (*Origanum majorana*), St. John's Wort (*Hypericum perforatum*), hibiscus (*Hibiscus rosa Sinensis*), indian saffron (*Curcuma longa*), parsley (*Petroselinum crispum*), stevia (*Stevia*), silymarin (*Silybum marianum*) and dill (*Anethum graveolens*). The primary objective was to evaluate the impact of these botanical additives at different concentrations (1% and 3% w/w) on the physicochemical properties and sensory profiles of yogurt manufactured from industrial skim milk (8.8% total solids, 0.2% fat, 3.2% protein). Physicochemical analysis revealed that the pH of the fortified samples generally ranged between 3.46 and 3.77, with an outlier in sample 16 reaching 4.54. Titratable acidity varied significantly from 0.28% to 0.73%, while fat content ranged from 0.20% to 1.60%. Organoleptic evaluation assessed aroma, syneresis (whey separation), color, cut clarity, and firmness. Sample 18, fortified with 3% John's Wort, emerged as the best-performing formulation, receiving the highest evaluations for aroma ("Very liked"), cut clarity, and firmness ("Very firm"), while showing no syneresis. Samples 5 (1% John's Wort) and 4 (1% Turmeric) also demonstrated strong consumer acceptance and desirable structural stability. In contrast, sample 17 (2% Silymarin) and the non-fortified control sample (sample 0) showed weaker performance, frequently associated with less appealing aromas and pronounced whey separation. Overall, the results indicate that herbal fortification—especially with John's Wort—can markedly enhance both the sensory qualities and physical stability of skim milk yogurt, supporting its potential use in the development of innovative value-added dairy products.

Keywords: Yogurt, functional food, herbal extracts, fortification, sensory evaluation, structural stability

Introduction

Yogurt is defined as a fermented dairy product produced through the symbiotic action of Lactic Acid Bacteria (LAB), specifically *Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus*. These microorganisms convert lactose into lactic acid, which lowers the pH of milk and causes the aggregation of casein proteins into a complex three-dimensional gel network. This process is essential for creating the unique texture, aroma, and cooling taste that make yogurt a globally popular "superfood" associated with health benefits such as improved digestion and the prevention of cardiovascular diseases (FAO, http://www.faoorg/economic/est/estcommodities/dairy/en). In recent years, consumer interest in low-fat and fat-free dairy products has grown considerably, largely driven by increasing awareness of health issues such as obesity and diabetes. Nevertheless, reducing or removing milk fat can negatively affect product quality, resulting in defects such as decreased viscosity, poor texture, and increased syneresis (whey separation). To address these limitations, the dairy industry has adopted several approaches, including fortification with milk solids, the use of advanced processing methods such as high-pressure homogenization, and the incorporation of functional ingredients (Dabia et al., 2018; Hashim et al., 2021; Hyseni et al., 2022). Previous investigations in Macedonia emphasize the transition of yogurt from a traditional staple to a scientifically standardized functional food. Their studies primarily focus on functional fortification, microbiological safety during storage, raw milk quality, and the impact of processing on the final product's characteristics. Hyseni et al. (2024) investigated the bioconversion of a milk-liquid whey mixture into yogurt supplemented with Aronia (*Aronia*

melanocarpa). Texturally, these functional yogurts showed higher levels of cohesiveness and springiness but lower hardness and adhesiveness compared to control samples. Sterjovski et al. (2014) evaluated three leading Macedonian yogurt brands over 20 days discovering increased yeast counts dramatically during storage. Kalevska et al. (2019) evaluated the raw milk used for production at the "Bistra" Kicevo dairy and reported that the quality of yogurt is directly linked to the raw materials used in the Republic of North Macedonia. Dolevska et al. (2020) monitored yogurts from Mlekara AD Bitola over one month of refrigeration. They observed a significant increase in viscosity (from 693.5 to 1197.5 mPas) and titratable acidity as the product approached its expiry date. Conversely, the water holding capacity (WHC) decreased as storage progressed, indicating a weakening of the protein matrix.

Among these approaches, the use of botanical extracts derived from herbs and fruits has gained attention as an innovative way to improve both the nutritional quality and sensory characteristics of yogurt (Bloor, 2001). Herbal additives such as turmeric, sage, marjoram, and John's Wort contribute antioxidant activity while also affecting the rheological properties and physical stability of the yogurt protein matrix (Mishra & Goel, 2020; Savale & Sonavne, 2022; Le Ba et al., 2025). In addition, Sulejmani et al. (2020) reported that the addition of aromatic herbs to cheese increased antioxidant capacity and enhanced the overall aroma profile of the products.

The present study investigates the production of functional skim milk yogurt fortified with different herbal aqueous extracts in order to assess their effects on physicochemical characteristics, structural stability, and consumer acceptability. Optimizing the concentration of these botanical ingredients may enable the development of a value-added yogurt product with a creamy texture comparable to conventional yogurt, while also providing distinctive therapeutic and functional benefits.

Material and methods

*2.1. Materials : T*he raw material used for yogurt production was fresh skimmed cow's milk containing 8.8% total solids, 0.2% fat, and 3.2% protein, with an initial pH of 6.7. The fermentation was conducted using the YC-183 starter culture from Chr. Hansen. A variety of botanical herbs materials were utilized for fortification, including: Turmeric (*Curcuma longa*) rhizome powder, Sage (*Salvia officinalis*), Majoram (*Origanum majorana*) dried leaves, St. John's Wort (*Hypericum perforatum*), Hibiscus (*Hibiscus sabdariffa*), Stevia (*Stevia rebaudiana*), Silymarin (*Silybum marianum*), Parsley (*Petroselinum crispum*), and Dill (*Anethum graveolens*) (Table 1). Aqueous herbal extracts were prepared following the Bloor (2001) method. For each plant, 10g of material was added to 1000 ml of hot distilled water and processed in an electrical blender for 15 minutes. After standing at room temperature for one hour, the mixture underwent double filtration—first through cloth and then using Whatman No. 1 filter paper—before being stored at refrigeration temperatures. For Yogurt manufacturing process the manufacturing followed a structured work plan. The base milk was heated to 85°C for 5 minutes and then cooled to 42°C. The milk was divided into parts, including a control (no extract) and various fortified samples at levels of 1%, 2%, and 3% (w/w). Each part was inoculated with 2% activated YC-183 culture. The mixtures were filled into 100 ml plastic jars and incubated at 42°C until full coagulation was achieved, which typically took approximately 3 hours. Following fermentation, the samples were transferred to a refrigerator and stored at 5 ± 1°C until analysis.

Table 1. Methodology of Herbal Fortification Combinations

Name (Albanian/English)	Latin Name	Combination Levels (w/w)
Shafran indian (Indian Saffron)	*Curcuma longa*	1%, 3%
Zhallfia (Sage)	*Salvia officinalis*	1%, 3%
Kopër (Dill)	*Anethum graveolens*	1%, 3%
Kantarion (St. John's Wort)	*Hypericum perforatum*	1%, 3%
Majdanoz (Parsley)	*Petroselinum crispum*	1%, 3%
Kurkuma (Turmeric)	*Curcuma longa*	1%, 3%
Hibiskus (Hibiscus)	*Hibiscus sabdariffa*	1%, 3%
Stevia (Stevia)	*Stevia rebaudiana*	1%, 3%
Silimarin (Silymarin)	*Silybum marianum*	1%, 2%
Marjoram (Majorana)	*Origanum majorana*	1%, 3%

2.2. Physicochemical analysis: pH was measured using a digital WTW pH330 pH-meter after calibration with buffer solutions. Titratable acidity was determined via alkaline titration using 0.1 N NaOH and phenolphthalein indicator, with results expressed as a percentage of lactic acid. Total Solids were analyzed using method where samples were dried in an oven at 102°C for 5 hours until reaching a constant weight. Fat content was determined using the Gerber method, involving sulfuric acid and amyl alcohol followed by centrifugation at 1200 rpm for 5 minutes. Protein content was analyzed using the Kjeldahl method, where the nitrogen percentage was multiplied by a factor of 6.38. Standardized methods for assessing the quality (protein, fat, total solids, acidity, pH) of both the raw milk and the final yogurt were used (AOAC, 2007). Viscosity and Color were measured with a LST method (line spread test), and color was assessed using a Chroma Meter CR400 based on the system. Water holding capacity (WHC) was determined reliably using the centrifugation method described by Dolevska, et al. (2020).

2.3. Sensory Evaluation: Sensory quality was evaluated through a standardized survey capturing several parameters: aroma (likability), syneresis (whey separation), surface brightness, color (whiteness), cut clarity, and firmness (the ability to maintain shape after being scooped with a spoon). Testers also assessed characteristics such as sweetness, acidity, and oral resistance during swallowing. The results of the yogurt fortification experiment using various herbal extracts reveal significant variations in physicochemical properties (pH, acidity, and fat) compared to both control samples and findings from other scientific literature.

Results and discussion

Physical chemical characterization: The experimental data for the fortified yogurts, derived from an industrial skim milk base (8.8% total solids, 0.2% fat), are summarized below in the Table 2. The pH of the fortified samples primarily ranged from 3.46 to 3.77. St. John’s Wort (1%) exhibited the highest pH at 3.77, indicating lower acidity, while Dill (3%) was among the lowest at 3.46. A notable outlier was Turmeric (1%), which reached a pH of 4.54. Values for titratable acidity varied significantly between 0.28% and 0.73%. Indian Saffron (3%) showed the lowest acidity (0.28%), whereas Turmeric (1%) reached the highest level (0.73%).

Table 2. Physical-chemical composition of yogurt samples

Sample No.	Yogurt / Plant Extract	Conc.	pH	Titratable Acidity	Fat content
0	Control (no plant extract)	0%	3.23	0.55	1.00%
1	Indian Saffron	3%	3.50	0.28	0.80%
2	Sage	1%	3.48	0.56	1.30%
3	Dill	1%	3.52	0.46	0.20%
4	Indian Saffron	1%	3.63	0.55	1.30%
5	St. John's Wort	1%	3.77	0.32	1.30%
6	Parsley	3%	3.55	0.45	0.40%
7	Turmeric	3%	3.61	0.46	1.60%
8	Hibiscus	3%	3.47	0.44	0.40%
9	Hibiscus	1%	3.52	0.40	0.50%
10	Stevia	1%	3.76	0.48	0.20%
11	Dill	3%	3.46	0.62	0.80%
12	Stevia	3%	3.52	0.50	1.20%
13	Parsley	1%	3.53	0.48	1.30%
14	Sage	3%	3.55	0.59	1.00%
15	Silymarin	1%	3.56	0.43	0.30%
16	Turmeric	1%	4.54	0.73	1.40%
17	Silymarin	2%	3.53	0.45	1.30%
18	St. John's Wort	3%	3.60	0.42	1.50%

The samples in present investigation exhibited pH values between 3.46 and 3.77 and were more acidic than the results of Kalevska et al. (2019), who reported a pH of 4.45 for industrial yogurt in Macedonia after fermentation. This suggests that the plant extracts may have accelerated the kinetics of acidification, similar to Akgun's (2024) observations that specific treatments modify fermentation. For the fat content, because the base was skim milk, fat levels were generally low, ranging from 0.20% (Dill and Stevia) to 1.60% (Turmeric 3%). The St. John’s Wort 3%, had a fat content of 1.50%. So, fortification with herbal extracts serves to slightly increase the total solids, which according to dairy principles, enhances the viscosity and firmness of the gel network (Azis et all, 2025).

When comparing these results to the provided scientific literature, several key differences emerge. Tepe (2021) reported higher pH values for traditional and starter culture yogurts, ranging from 3.895 to 4.390. The herbal fortified samples in your experiment were generally more acidic (pH < 3.8), likely due to the specific metabolic interaction between the YC-183 culture and the botanical extracts. Sulejmani et al. (2014) emphasized that acidification caused by starter culture activity is a key step in producing high-quality dairy products. This principle was also observed during yogurt fermentation in the present study, where the decrease in pH toward the isoelectric point (pH 4.6) promoted casein aggregation and gel network formation. Furthermore, the same author reported that higher coagulation temperatures contribute to lower pH values and increased protein content in the final product.

The samples from the same investigation had higher titratable acidity (0.78%–0.89%) compared to most of present herbal samples (0.28%–0.62%), with the exception of Yogurt with Turmeric. Fat concentration from the same study resulted in yogurt with 3.0%–3.1% because it was utilized milk with 3.7% fat. So, samples in these investigation were significantly leaner (0.2%–1.6% fat) because they were produced from skim milk. Hashim et al. (2021) found that fortifying non-fat yogurt with whey protein isolate (WPI) increased the WHC to 50% and

improved the microstructure. Similarly, your study found that St. John's Wort 3% and Hibiscus 1% achieved a superior structure with zero syneresis (whey separation), mimicking the stabilizing effects of WPI. Akgun's (2024) research on low-fat yogurt (2% fat) used high-pressure homogenization to increase firmness from 1.01 to 1.45 N. Herbal fortification achieved a similar "functional" goal; for instance, St. John's Wort 3% and Shafran 1% were rated as "Very firm" in organoleptic tests, effectively overcoming the structural weaknesses typically associated with low-fat/skim yogurts. Dolevska et al. (2020) observed that during storage in Macedonia, the viscosity of yogurt increases significantly after one month, but the WHC (water holding capacity) decreases. Serra et al. (2009) note that changes in protein chemistry directly affect water absorption similar to what was observed in St. John's wort 3% regarding firmness and syneresis. Sulejmani et al (2021) reported that higher acidity and protein content contribute to a firmer and more compact structure in white brined cheese. A similar trend was observed in the present yogurt study, where samples with higher acidity and fortification, such as the 1% turmeric sample (pH 4.54), exhibited greater firmness and a denser gel structure. The author further explained that interactions between milk proteins and added components, including vegetable fat or plant extracts, can enhance texture and firmness without negatively affecting sensory quality. Nguyen et al. (2015) support the findings related to syneresis (whey separation), explaining that the reduction in particle size improves yogurt stability and consistency. This phenomenon may explain why the best-performing samples in the present study showed no visible serum separation.

The use of St. John's Wort 3% resulted in the most balanced physicochemical and sensory profile (pH 3.60, 1.50% fat, zero syneresis), outperforming the non-fortified control (pH 3.23) and providing a more stable structure than the higher-fat traditional yogurts studied by Tepe (2021). In contrast, Silymarin 2% and Turmeric 1% were less successful due to unappealing aromas or higher acidity levels. Sterjovski et al. (2012) found that many brands of yogurt on the Macedonian market have problems with high yeast counts after 20 days of storage, so herbal fortification could serve as an additional microbiological barrier. Extracts such as Hibiscus are known in the literature for their antibacterial properties, which could help maintain the microbiological quality that previously were identified as a weak point in commercial products (Savale et al, 2022).

The sensory analysis of the fortified yogurt: Samples which utilized various herbal extracts identifies distinct impacts on aroma, structural stability, and consumer acceptance. St. John's Wort (Sample 18 - 3% and Sample 5 - 1%): These samples emerged as the overall winners. Sample 18 received the highest possible ratings for aroma ("Very liked"), showed zero syneresis (whey separation), and was characterized as "Very firm", maintaining its shape perfectly after being scooped. Hibiscus (Sample 9 - 1%): This sample was highly favored for its aroma ("Very liked") and excellent structural stability, exhibiting no syneresis. Indian saffron (Sample 4 - 1%): While the color was only "moderately white," it received a "Very liked" rating for aroma and was scored as "Very firm".

Silymarin (Sample 17 - 2%): Despite having a high fat content (1.30%), this sample performed poorly in sensory tests. It received an "Aspak" (Not at all) rating for aroma and showed " Sufficient) levels of syneresis, indicating a weak gel structure. Turmeric (Sample 16 - 1%): This sample was rated poorly for aroma and color, despite having a relatively high pH of 4.54. Parsley (Samples 6 and 13): These samples were generally rated as Sufficient or Moderate for aroma, though they maintained a firm consistency.

Minimizing syneresis is a critical quality indicator in yogurt production. The results show that St. John's Wort (3%) and Hibiscus (1%) were most effective at preventing whey separation (rating: "lowest"), suggesting these extracts help stabilize the protein network. This mirrors research by Hashim et al. (2021), where fortification improved water-holding capacity (WHC)

to overcome the structural weaknesses of non-fat yogurt. Skim milk yogurts often suffer from a "weak body". However, the herbal fortification in this study significantly enhanced firmness. Samples like St. John's Wort 3% and Shafran 1% achieved a "Very firm" rating, performing similarly to full-fat control samples or low-fat yogurts treated with high-pressure homogenization, which improves firmness from 1.01 to 1.45 N. In traditional Balkan and Turkish dairy preferences, aroma and "cooling" taste are vital. Tepe (2021) noted that traditional homemade yogurts are often favored over commercial ones for their smell and taste. In this experiment, St. John's Wort and Hibiscus provided a superior aromatic profile that compensated for the lack of milk fat.

Tepe (2021) found no statistically significant difference in sensory scores for appearance and consistency over 15 days for traditional yogurts. In contrast, your fortified samples showed clear sensory differentiation based on the type and concentration of the herb used, with St. John's Wort significantly outperforming the non-fortified control (Sample 0) which often had lower aroma scores and some syneresis. The high ratings for firmness in St. John's Wort-fortified samples likely correlate with a denser protein network. As noted in the review by Le Ba et al. (2025), additives can reinforce the three-dimensional structure of the yogurt gel, fill the porous protein network and improve mouthfeel. Most samples, such as St. John's Wort (3%) at 0.42% and Hibiscus (1%) at 0.40%, maintained a balanced profile.

PCA clusters of fortified Yogurt samples: Principal component analysis (PCA) of the yogurt samples provides a multidimensional view of how different herbal fortifications influence the product's physicochemical stability and sensory appeal. By analyzing the variables provided in the sources—pH, titratable acidity, and fat content—alongside sensory responses, several key insights emerge regarding the quality of the 18 experimental samples. Most samples cluster between a pH of 3.46 and 3.77. In a typical PCA plot for yogurt, pH and titratable acidity usually show an inverse relationship; for instance, Sample 11 (Dill 3%) has a low pH (3.46) and high acidity (0.62), placing it at one extreme of the acidity axis.

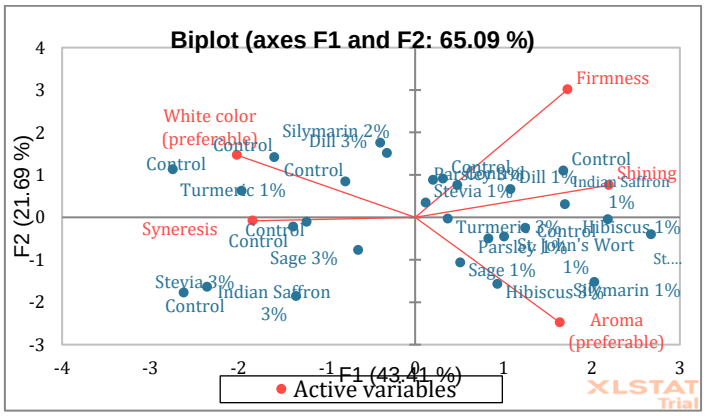


Figure 1. PCA clusters of the yogurt samples and sensory properties

For fat content, while the base is skim milk (0.2% fat), fortification levels adjusted the perceived or measured fat. Sample 7 (Turmeric 3%) and Sample 18 (St. John's Wort 3%) represent the high-fat end of the spectrum (1.60% and 1.50%, respectively), which significantly influences their positioning on the PCA plot. The PCA identifies a specific "success cluster" where physicochemical balance meets high consumer acceptance. Sample 18 (St. John's Wort 3%) and Sample 5 (St. John's Wort 1%) are the primary winners in this space. Sample 18, was characterized by pH 3.60, 0.42 acidity, and 1.50% fat. In sensory tests, it achieved maximum scores for aroma, firmness, and zero syneresis. Sample 5 with pH 3.77 and 1.30% fat is clustered near Sample 18, sharing its high structural stability and pleasant aroma. According to

Akgun (2024), PCA attributes like firmness and viscosity typically have high loadings on the first principal component (PC1), meaning these winners likely define the "positive" side of the quality axis in your study.
The PCA effectively separates samples that failed to meet quality standards. Sample 16 (Turmeric 1%) is a significant outlier with a pH of 4.54 and high acidity of 0.73. Its sensory scores were lowest for aroma and it showed poor color. Sample 17 (Silymarin 2%): Despite having a relatively high fat content (1.30%), it clusters away from the winners because it exhibited significant syneresis (whey separation) and an unappealing aroma. Control (Sample 0): With the lowest pH (3.23), the control sample represents a baseline of high acidity and low structural support from herbal extracts, often resulting in higher syneresis. Also, the PCA results align with broader dairy science principles found in present investigation. Akgun (2024) notes that high-pressure or specific fortifications can increase water-holding capacity (WHC) from 42% to 52%. PCA suggests that St. John's Wort and Hibiscus extract effectively mimic this structural reinforcement, as seen in the zero syneresis ratings for samples 18, 5, and 9. Hashim et al. (2021) demonstrate that increasing protein-like structures (via WPI or extracts) improves viscosity proportionally. The PCA of samples confirms that the 3% St. John's Wort level provides the densest protein network, leading to the highest scores for "clear cut" and "firmness".

Conclusion

Aroma was identified as one of the most influential factors affecting consumer acceptance, with the type of herbal extract playing a significant role in sensory perception. Yogurt samples fortified with St. John's Wort (1% and 3%), Indian saffron (1%), and hibiscus (1%) received higher aroma ratings, indicating high consumer preference, while the 3% St. John's Wort formulation demonstrated the most favorable aroma profile overall. In contrast, samples containing 1% turmeric and 2% silymarin were lowest rated for aroma, suggesting that certain herbal extracts and concentrations may negatively affect sensory acceptability among panelists. So, finaly technological fortification with 3% St. John's Wort proved to be the most effective approach for producing a non-fat functional yogurt that meets consumer expectations for high firmness, absence of syneresis, and a highly pleasant aroma. Furthermore, herbal fortification may serve as an additional microbiological barrier, since extracts such as hibiscus are recognized in the literature for their antibacterial properties, which may help preserve quality.

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NUMERICAL ANALYSIS OF MEMORY EFFECT IN CAPUTO FRACTIONAL COOLING MODELS VIA EULER TYPE METHODS

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Abstract

Fractional differential equations have attracted significant attention due to their ability to model memory-dependent phenomena. In this paper, we study the numerical solution of a Caputo-type fractional differential equation using the L1 discretization scheme, comparing the explicit Forward Euler and implicit Backward Euler methods in terms of accuracy and stability.
The problem is studied on [0,5] with y(0)=0, using an interactive analysis to visualize and assess accuracy against the exact solution. A systematic analysis is performed for different discretization step sizes $h=0.1,\ h=0.01,\ h=0.001$ and fractional orders $\alpha=0.8,\ 0.9,\ 0.999$. The visualization is carried out separately for varying α with fixed step size *h*, and, conversely, with step size varied at fixed α, to analyze the memory effect. The maximum error is presented in a log–log plot, while the Caputo L1 weights (Euler weights) are analyzed to illustrate the memory effect**,** summarized in tables for comparison and stability analysis of the solution.
The comparison shows that the implicit Backward Euler method performs better in terms of stability and accuracy, especially when larger step sizes are used. Overall, the numerical results obtained in *Mathematica* suggest that implicit time-discretization methods are a reliable and robust choice for solving fractional differential equations, particularly when stability is important.

Keywords: Fractional differential equations; Caputo fractional derivative; L1 discretization scheme; Forward & Backward Euler method; stability, convergence & error analysis; memory effect.

Introduction

The fractional cooling model extends classical heat transfer to describe non-local and history-dependent processes. Based on fractional calculus, it has been applied to diffusion and heat transfer, introducing the concept of anomalous diffusion. More recently, it has been used to capture memory effects in complex materials where classical integer-order models are insufficient (Diethelm, 2010, Kilbas et al., 2006). A concrete example arises in biological tissues during thermal therapies, where temperature evolution depends not only on the current heat input, but also on the previous thermal exposure. Similarly, in composite engineering materials and heat-storage systems, memory effects influence how energy is absorbed and released over time. Fractional models therefore provide a more realistic framework for describing these processes.
The memory effect is directly related to the fractional order α. When $\alpha\to 1$, the model approaches the classical integer-order cooling law, where memory effects are weak and the system behaves locally in time. For smaller values of α, the influence of past states becomes stronger, meaning that the system retains a longer thermal memory. Thus, the fractional order controls the strength of memory and determines how strongly the history of the process affects the present dynamics (Podlubny, 1999).
Definition 1.1. (Riemann–Liouville Fractional Integral) (Diethelm, 2010, Podlubny, 1999) Let $f(t)$ be continuous on $(0,T]$ and $\alpha\in(0,1]$. The Riemann–Liouville fractional integral of order α is defined as

$$I^{\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau . \quad (1.1)$$

Definition 1.2. (Caputo Fractional Derivative) (Diethelm, 2010, Kilbas et al., 2006) Let $f(t)$ be continuous on $(0,T]$ and $\alpha \in (0,1]$. The Caputo fractional derivative of order α is defined as

$$D_t^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t (t-\tau)^{-\nu} f'(\tau) d\tau . \quad (1.2)$$

Definition 1.3. (Initial Value Problem) (Podlubny, 1999) The initial value problem for $\alpha \in (0,1]$ and $t \in (0,T]$ is defined as

$$D^{\alpha} y(t) = f(t, y(t)),\ y(0) = y_0 . \quad (1.3)$$

Cooling Model

Based on this formulation, the fractional cooling model is introduced by defining the function according to a Newton-type cooling law that includes memory effects. At time *t*, a body's temperature $T(t)$ change is proportional to the difference between its temperature and the surrounding medium $T_m(t)$. Newton's law of cooling is typically modeled as a first-order initial value problem (Diethelm, 2010), however, real heat transfer processes in complex materials often exhibit memory effect and non-local behavior, that cannot be captured by classical derivative (Kilbas et al., 2006). To account for these hereditary effects, the classical derivative is replaced by the Caputo fractional derivative of order $\alpha \in (0,1)$, leading to the fractional cooling model (2.1).

Definition 2.1. (Fractional Cooling Model) The fractional cooling model of order α is given by

$$D_t^{\alpha} T(t) = -k\left[T(t) - T_m(t)\right],\ T(0) = T_0,\ k > 0 \quad (2.1)$$

where $k > 0$ denotes the cooling coefficient and T_m is the ambient temperature.

The Caputo fractional derivative is particularly suitable for physical applications because it allows the use of standard initial conditions expressed in terms of integer-order derivatives. In addition, it introduces a power-law memory kernel, meaning that the present state of the system depends on its entire thermal history (Podlubny, 1999). This memory effect reflects the fact that past temperatures continue to influence the current cooling dynamics, although their influence gradually decreases over time.

The fractional order α controls the strength of the memory effect. When $\alpha = 1$, the model reduces to the classical Newton cooling law and the system behaves locally in time. For $\alpha < 1$, the memory becomes stronger and the cooling process exhibits non-exponential behavior, which is commonly associated with anomalous diffusion phenomena (Garrappa, 2018). Such models are especially relevant in porous media, biological tissues, viscoelastic materials, and heterogeneous composite structures, where heat propagation deviates from classical diffusion laws (Sun and Wu, 2006, Garrappa, 2018). In biological tissue heating, for example, previous thermal exposure may continue to influence the present temperature distribution, making fractional models more realistic than classical approaches.

To validate the numerical schemes, a manufactured test problem is considered. The right-hand side of equation (1.3) is constructed so that the exact analytical solution is prescribed as $y(t) = t^2 - t$. Applying equation (1.2) and using the known fractional derivative formula, the forcing function is obtained analytically. This approach enables direct comparison between the

exact and numerical solutions and provides a reliable framework for analyzing the stability, convergence, and accuracy of the proposed numerical methods (Stynes, 2020).

Applying (1.2) to $y(t)$ and using $D_t^{\alpha} t^n = \frac{\Gamma(n+1)}{\Gamma(n+1-\alpha)} t^{n-\alpha}$, we obtain the forcing function:

$$f(t,\alpha) = \frac{2}{\Gamma(3-\alpha)} t^{2-\alpha} - \frac{1}{\Gamma(2-\alpha)} t^{1-\alpha} \qquad (2.2)$$

L1 discretization of Caputo derivative and numerical schemes

Let the interval $[0,1]$ be partitioned uniformly into N subintervals with step size $h = \frac{1}{N}$, defining the grid $t_n = nh,\ n = 0,1,...,N$. The L1 scheme approximated the Caputo derivative at t_n by replacing the integrand in Definition 1.2 with a piecewise linear interpolant of y at each $[t_k, t_{k+1}]$, leading into

$$D_t^{\alpha} y(t_n) = \frac{h^{-\alpha}}{\Gamma(2-\alpha)} \sum_{k=0}^{n-1} b_k \left(y_{n-k} - y_{n-k-1} \right),\ b_k = (k+1)^{1-\alpha} - k^{1-\alpha},\ b_0 = 1,\ k = 0,1,... \qquad (3.1)$$

The weights are strictly positive, monotonically decreasing to zero and satisfy the telescoping identity $\sum_{k=0}^{n-1} b_k = n^{1-\alpha}$. These properties ensure consistency of the approximation and reflect the fading memory property of (2.1), the influence of past values diminishes as $k \to \infty$ (Lin and Xu, 2007).

Fractional Euler Methods

The Euler method, in its various forms, is commonly used for ordinary differential equations and can be extended to fractional problems as (2.1) (Sun and Wu, 2006, Stynes, 2020).

Fractional Forward Euler Method (FEM): FEM employs a forward difference approximation for $D_t^{\alpha} y(t)$. The left-sided fractional rectangular formula is used to approximate the fractional derivative and is given by:

$$y_{n+1} = y_n + h f(t_n, y_n, \alpha),\ n = 0,1,...,N-1 \qquad (3.2)$$

The Fractional Backward Euler Method (BEM): BEM employs a backward difference approximation for $D_t^{\alpha} y(t)$. In this context, the right fractional rectangular formula provides a discrete approximation of the fractional derivative and can be written as follows:

$$y_{n+1} = y_n + h f(t_{n+1}, y_{n+1}, \alpha),\ n = 0,1,...,N-1 \qquad (3.3)$$

In formulas (3.2) and (3.3), the function f is obtained using (3.1).

Error and Convergence Analysis. Numerical Results

To assess the accuracy of the FEM and BEM, we compute the discrepancy between the numerical solution y_n and the exact solution $y(t) = t^2 - t$. Two error measures are employed, the maximum error and L2 error (normalized Euclidean norm) (Sun and Wu, 2006).

Definition 4.1. (Maximum Pointwise Error)

$$E_{\max} = \max \left\{ \left| y_n - y(t_n) \right| \middle| n = 1,2,...,N \right\} \qquad (4.1)$$

and captures the largest local deviation of the schemes over the entire interval $[0, 1]$.

Definition 4.2. (L_2 Error — Euclidean Norm)

$$E_{L2} = \|y_n - y(t_n)\| = \frac{1}{N}\sqrt{\sum_{n=1}^{N}\left(y_n - y(t_n)\right)^2} \tag{4.2}$$

reflects the overall global error of the method and is less sensitive to isolated local deviations. During the results, the convergence analysis is carried out by comparing the maximum error of FEM and BEM across three step sizes $h \in \{0.1, 0.01, 0.001\}$ with fixed fractional order $\alpha = 0.9$. The L1 approximation of the Caputo derivative is known to achieve a convergence order of $O\left(h^2\alpha\right)$ for a sufficiently smooth solution. According to $\alpha = 0.9$ the expected order is $O\left(h^{1.1}\right)$, while as $\alpha \to 1$ the convergence approaches the classical first-order rate. The convergence plot displays $E_{\max}$ as a function of h on a $\log-\log$ scale, allowing the convergence order to be estimated visually as the slope of the fitted line.

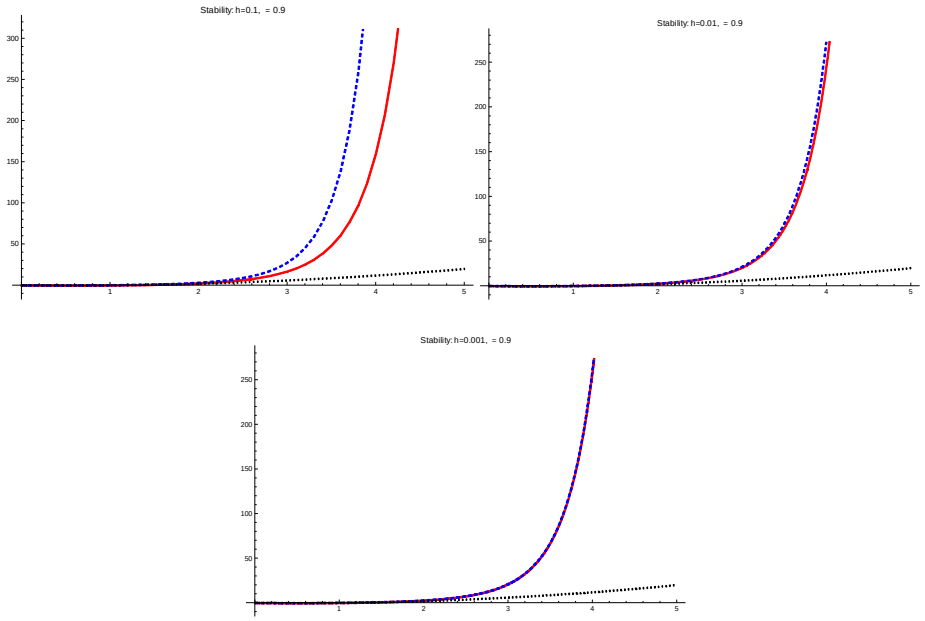


Figure 1. Stability analysis of (2.1) for $\alpha = 0.9$ and $h \in \{0.1, 0.01, 0.001\}$ using FEM (blue dashed line) and BEM(red solid line)

As illustrated in Figure 1, these features can be observed in the comparison between FEM (blue dashed line) and BEM (red solid line). Similar trends are also noted for other tested cases of α. In the following Figure 2, we observe the convergence of the methods through the maximum error and the log–log representation.

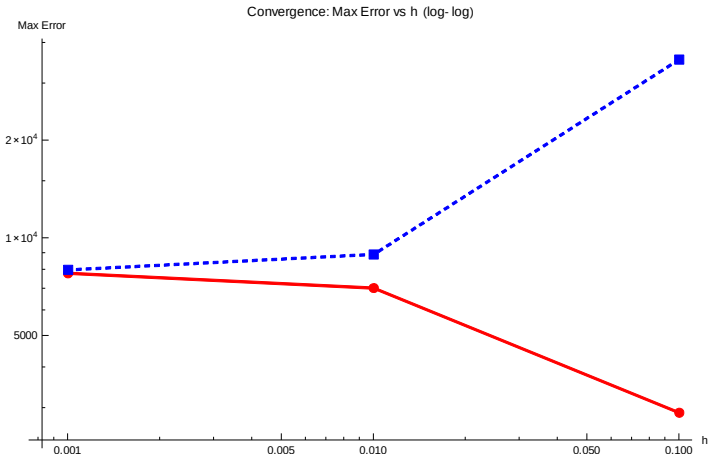


Figure 2. Maximum error (4.1) of FEM (red solid line) and BEM (blue dashed line) for $\alpha = 0.9$

Table 1. Maximum error (4.1) of FEM and BEM for a) $\alpha = 0.8$ *b)* $\alpha = 0.9$ *and c)* $\alpha = 0.999$

a)

H	FEM (E_{max})	BEM (E_{max})	FEM/BEM
0.1	2.82×10^3	3.451×10^4	8.17×10^{-2}
0.01	6.84×10^3	8.682×10^3	7.88×10^{-1}
0.001	7.596×10^3	7.779×10^3	9.76×10^{-1}

b)

H	FEM (E_{max})	BEM (E_{max})	FEM/BEM
0.1	2.9×10^3	3.554×10^4	8.16×10^{-2}
0.01	7.028×10^3	8.923×10^3	7.88×10^{-1}
0.001	7.805×10^3	7.993×10^3	9.76×10^{-1}

c)

H	FEM (E_{max})	BEM (E_{max})	FEM/BEM
0.1	2.967×10^3	3.64×10^4	8.15×10^{-2}
0.01	7.184×10^3	9.122×10^3	7.88×10^{-1}
0.001	7.976×10^3	8.169×10^3	9.76×10^{-1}

The results in Figure 2 and Table 1 demonstrate that both methods achieve convergence as the mesh parameter h decreases, with consistent behavior observed across the tested values of $\alpha \in \{0.8, 0.9, 0.999\}$. While BEM exhibits larger absolute maximum errors compared to FEM at coarse meshes (ratio of order 10^{-2}), the FEM/BEM ratio increases to approximately 10^{-1} as $h \to 0.001$, indicating that BEM converges at a relatively faster rate upon mesh refinement. Both methods display a clear monotone reduction in error as h decreases, confirming convergence across the entire range of tested fractional orders.

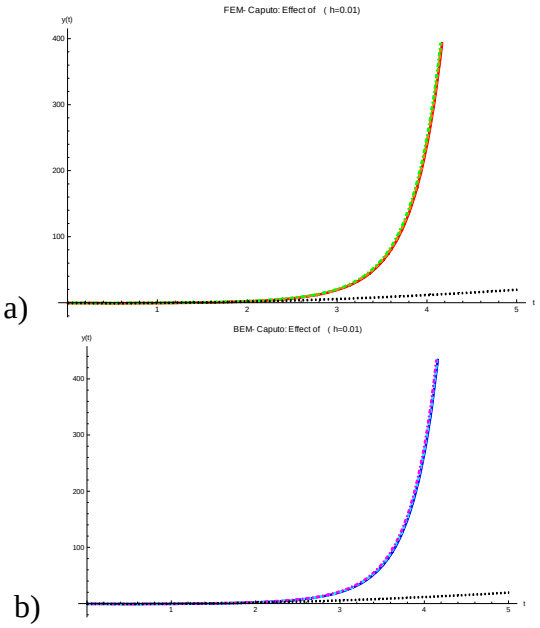


Figure 3. Effect of step size h for different values of α *for (2.1), a) FEM* $\alpha = 0.8,\ \alpha = 0.9,\ \alpha = 0.999$ *(red solid line, orange dashed line, green dashed point line, respectively); a) BEM* $\alpha = 0.8,\ \alpha = 0.9,\ \alpha = 0.999$ *(blue solid line, light blue dashed line, purple dashed point line, respectively)*

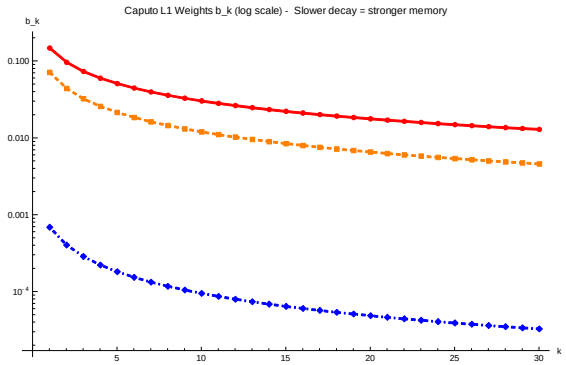


Figure 4. Caputo L1 weights b_k *,* $\alpha = 0.8,\ \alpha = 0.9,\ \alpha = 0.999$ *red, orange and blue respectively*

The weights are strictly positive, monotonically decreasing, and satisfy the telescoping identity, reflecting the inherent fading memory property of the Caputo fractional derivative. As $\alpha \to 1$, the weights decay more rapidly toward zero, indicating a diminishing influence of past values and a gradual transition toward classical integer-order dynamics.

Table 2 complements the analysis by reporting the L_2 errors, which capture the global approximation accuracy over the interval [0, 5]. The L_2 results confirm the trends observed in Table 1: the consistency between the pointwise and global error measures further validates the accuracy and stability of the proposed numerical framework.

Table 2. Maximum error (4.1) and L2 error (4.2) of FEM and BEM for a) $\alpha = 0.8$ b) $\alpha = 0.9$ and c) $\alpha = 0.999$

h	α	FEM L2	BEM L2	FEM (E_{max})	BEM (E_{max})
0.1	0.8	4.114×10^3	4.382×10^4	2.82×10^3	3.451×10^4
0.1	0.9	4.231×10^3	4.512×10^4	2.9×10^3	3.554×10^4
0.1	0.99	4.34×10^3	4.632×10^4	2.967×10^3	3.64×10^4
0.01	0.8	2.559×10^4	3.185×10^4	6.84×10^3	8.682×10^3
0.01	0.9	2.63×10^4	3.274×10^4	7.028×10^3	8.923×10^3
0.01	0.999	2.694×10^4	3.354×10^4	7.184×10^3	9.122×10^3
0.001	0.8	8.76×10^4	8.954×10^4	7.596×10^3	7.779×10^3
0.001	0.9	9.002×10^4	9.201×10^4	7.805×10^3	7.993×10^3
0.001	0.999	9.22×10^4	9.424×10^4	7.976×10^3	8.169×10^3

Caputo weights for $\alpha = 0.999$ and $k = 1,2,3,4,5$ are 0.000693387, 0.000405829, 0.00028804, 0.000223478, 0.000182632, $\alpha = 0.8$ and $k = 1,2,3,4,5$ are 0.148698, 0.0970326, 0.073777, 0.0602218, 0.0512394.

Figure 3 illustrates the sensitivity of the maximum error to the step size *h* for varying values of α. Both methods display a clear monotone reduction in error as *h* decreases, confirming convergence across the entire range of tested fractional orders. Figure 4. depicts the Caputo L1 weights b_k for $\alpha \in \{0.8, 0.9, 0.999\}$. The weights are strictly positive, monotonically decreasing and satisfy the telescoping identity, reflecting the inherent fading memory property of the Caputo fractional derivative. As $\alpha \to 1$, the weights decay more rapidly toward zero, indicating a diminishing influence of past values and gradual transition toward classical integer-order dynamics. Table 1 reports the maximum errors for both, FEM and BEM across all test values of α and *h*. At *h*=0.1, BEM yields substantially larger errors than FEM, with ratio s of the order 10^{-2}. However, as *h* is refined to 0.001, the FEM/BEM ratio increases to approximately 10^{-1}, indicating that BEM exhibits a faster convergence rate. This trend is consistent across all three values of α, demonstrating the robustness and reliability of both schemes.

Conclusions

In this paper, we presented a numerical comparison between the FEM and BEM for solving Caputo-type fractional cooling model on [0, 5]. The schemes were tested for fractional order $\alpha \in \{0.8, 0.9, 0.999\}$ and step size $h \in \{0.1, 0.01, 0.001\}$. Both methods achieve convergence consistent with the theoretical rate $O(h^{\alpha})$, with results recovering classical first-order behavior as $\alpha \to 1$. FEM provides better accuracy at coarser meshes, while BEM offers superior stability and faster convergence upon mesh refinement, confirming the advantage of implicit schemes for fractional problems. The results validate the effectiveness of L1-based discretization methods for Caputo fractional differential equations, supporting their use memory-dependent physical models. The analysis of the Caputo L1 weights also highlights the fading memory

property of the fractional derivative, showing how the influence of past states decreases over time depending on the fractional order. These results demonstrate the suitability of fractional models for describing memory-dependent thermal processes and other nonlocal physical phenomena.

Future Work

Future research may extend the proposed framework to nonlinear and variable-order fractional cooling models, as well as fractional delay differential equations. Incorporating time-delay effects would allow the model to capture delayed thermal responses and hereditary behavior more realistically.

Additional directions include adaptive time-stepping techniques and higher-order methods, such as predictor–corrector or fractional Adams schemes, to improve computational efficiency and accuracy. Applications to multidimensional heat transfer, biological tissues, and viscoelastic materials also remain topics for future investigation.

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TREATMENT MODALITIES AND OUTCOMES IN DEVELOPMENTAL DYSPLASIA OF THE HIP

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Abstract

Introduction: Developmental Dysplasia of the Hip (DDH) is a developmental disorder characterized by instability, subluxation, or dislocation of the femoral head from the acetabulum. Early diagnosis is essential to ensure normal hip development and prevent long-term complications.
Aim To evaluate treatment outcomes and management strategies in patients with DDH.
Methods A literature review was conducted using electronic databases including PubMed and Google Scholar. Review articles, clinical studies, and orthopedic guidelines on conservative and surgical treatment of DDH were analyzed.
Results Both conservative and surgical treatments demonstrated satisfactory outcomes when appropriately indicated. Early intervention was associated with improved hip stability, better radiological outcomes, and lower complication rates. Delayed treatment increased the risk of residual dysplasia and avascular necrosis.
Conclusion Early diagnosis and timely treatment are essential for successful DDH management. Appropriate intervention improves hip stability and functional outcomes while reducing long-term complications.

Keywords DDH; Diagnosis; Instability; Dysplasia; Treatment; Pediatrics

Introduction

Developmental Dysplasia of the Hip (DDH) represents a spectrum of morphofunctional abnormalities that include instability, subluxation, and complete dislocation of the femoral head from the acetabulum, as a result of unbalanced development of the articular structures.
The hip joint is a key structure for posture, walking, and body stability. During normal development, the femoral head acts as a "biological modeler" for the acetabulum, stimulating its deepening and shaping through constant contact and physiological biomechanical forces. In cases of DDH, this anatomical and functional relationship is disrupted, preventing the normal development of the acetabulum and compromising the stability of the joint. As a result, a pathological cycle is created in which joint instability worsens the dysplasia, while the dysplasia further increases the instability.[1]
DDH indicates a disharmony in the development of the femur, the acetabulum, and the joint capsule.
DDH is not a fixed congenital malformation, but a developmental disorder that evolves over time and may progress after birth
If diagnosed early the structures can develop normally.
If diagnosed late permanent changes occur.

Aim of the study

To evaluate the treatment outcomes of different management strategies in patients with developmental dysplasia of the hip (DDH).
Specific objectives

- To analyze the distribution of treatment modalities used in patients with DDH (conservative vs surgical approaches).
- To assess the clinical outcomes following different treatment methods.

- To evaluate the relationship between timing of treatment initiation and clinical outcome.
- To assess functional improvement and hip stability following treatment.

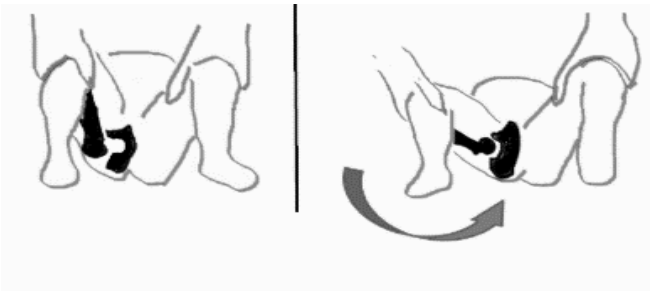
By evaluating treatment outcomes and management strategies, this study aims to improve understanding of the effectiveness of different therapeutic approaches in DDH and highlight the importance of timely intervention in achieving optimal functional results.

Materials and Methods

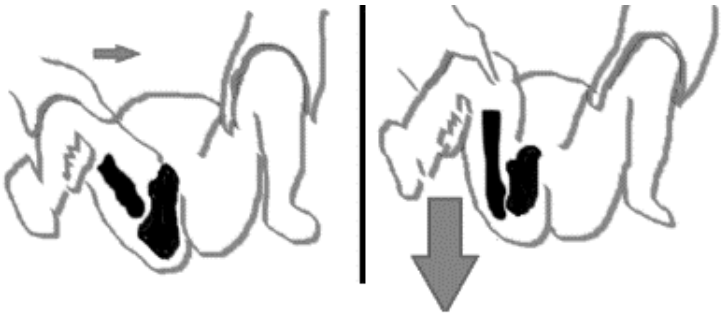
A literature search was conducted using electronic databases including PubMed, Google Scholar, and orthopedic textbooks written in English. The search was performed to identify relevant studies on developmental dysplasia of the hip (DDH), focusing on treatment modalities and clinical outcomes.
Eligible sources included review articles, clinical studies, and orthopedic guidelines reporting conservative and surgical management of DDH. No restrictions were applied regarding publication date, but preference was given to recent studies and widely accepted orthopedic literature.
The selection of studies was based on relevance to treatment outcomes, diagnostic methods, and management strategies. Data were extracted and summarized in a narrative form.
This study did not involve direct patient data collection or statistical meta-analysis.

DDH
Well known risk factors for DDH include family history, female sex, and breech positioning. Recent evidence suggests higher birth weight is a risk, whereas prematurity may be protective.[2]

Diagnosis
Clinical examination:
Ortolani test: positive click during reduction of the hip.
Barlow test: subluxation during applied pressure.
Galeazzi sign: difference in the relative length of the thighs.
Asymmetry of the gluteal folds and limitation of hip abduction.
Ultrasound
X- ray
MRI [1]



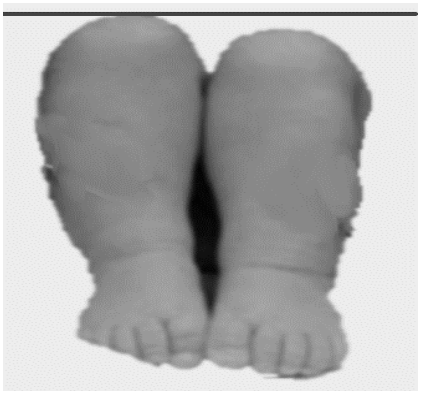
The Ortolani test [3]

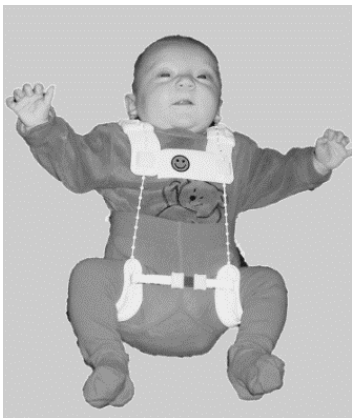


The Barlow test [3]



Galeazzi sign [3]





Treatment

The treatment of DDH depends on the age of the patient at diagnosis, the severity of hip instability, and the degree of displacement of the femoral head.

Nonsurgical treatment

In neonates diagnosed early, DDH can often be managed conservatively. The most commonly used method is the Pavlik harness, which is indicated primarily in newborns and infants up to 6 months of age. The harness maintains the hip in flexion and abduction, promoting reduction of the femoral head into the acetabulum and supporting normal development of the hip joint. Treatment duration typically ranges from 6 to 12 weeks, depending on clinical and radiological response.
Closed reduction and spica casting

In infants aged approximately 6 months to 2 years, if conservative treatment fails or the diagnosis is delayed, closed reduction under general anesthesia is often indicated. Following successful reduction, a hip spica cast is applied to maintain joint stability. The cast is usually maintained for several weeks to months, with periodic radiographic evaluation to confirm proper hip alignment.

Surgical treatment

In cases where closed reduction is unsuccessful or in children older than 2 years, open reduction is required. This procedure allows direct visualization of the hip joint and correction of soft tissue or bony obstacles preventing reduction. In some cases, femoral shortening or pelvic osteotomies may be necessary to achieve stable reduction. Postoperatively, immobilization with a spica cast is typically required. [3]

Results

Table 1 Outcomes of Treatment in DDH (Nonoperative vs Operative Group)

Parameter	**Nonoperative Group**	**Operative Group**
Number of patients	16 patients (17 hips)	32 patients (32 hips)
Treatment method	Closed reduction + casting (± skin traction)	Open reduction + Salter osteotomy
Avascular necrosis	4 hips (mild degree)	2 hips (mild degree)
Failed/redislocation cases	1 failed reduction	1 redislocation (due to improper spica cast)
Pre-treatment Severin classification	Class I: 1 hipClass III: 9 hipsClass IV: 6 hipsClass VI: 1 hip	Not specified pre-op
Post-treatment Severin outcomes	Required further surgery in failed/residual dysplasia cases	Class I: 13 hipsClass II: 18 hipsClass III: 1 hip
Additional procedures	Open reduction or pelvic osteotomy in some cases	None reported
Follow-up period	Not specified	>2 years 3 months

Parameter	Nonoperative Group	Operative Group
Overall outcome	Variable, some required secondary surgery	Better functional and radiological outcomes
Conclusion	Less predictable results in walking-age DDH	Safe and effective treatment with better outcomes

[4]

The operative group showed better radiological outcomes (Severin class I–II) and reduced need for secondary procedures compared to the nonoperative group, indicating superior results in walking-age DDH.

Table 2 Outcomes and Timing of Treatment in Late-Diagnosed DDH Patients

Variable	Findings
Study design	Prospective study
Number of patients	71 patients (75 hips)
Type of DDH	Late-diagnosed developmental dysplasia of the hip
Treatment approach	Closed reduction (after traction/tenotomy), open reduction ± Salter osteotomy, femoral osteotomy in selected cases
Age at treatment start	Mean 10 months (range 2–64 months)
Follow-up duration	Mean 11 years (range 6–18 years)
Failed closed reduction	7 hips
Redislocation / subluxation	1 subluxation + 1 redislocation
Avascular necrosis (AVN)	4 hips
Additional surgeries required	12 hips (11 Salter osteotomies, 1 femoral osteotomy)
Acetabular development	Faster improvement in younger patients; slower and less predictable when treatment started at 12–22 months
Femoral head development	Continued growth in almost all cases regardless of age at reduction
Final Severin classification	Class I: 65 hipsClass II: 9 hipsClass III: 1 hip
Final clinical outcome	Almost all patients asymptomatic except 2 cases

[5]

Earlier treatment initiation was associated with faster acetabular improvement and more predictable outcomes, while delayed treatment showed slower and less consistent radiological improvement, although long-term results were generally good after appropriate surgical management.

Table 3

Treatment	Indication	Success rate	Complications
Pavlik harness	Early DDH (<6 months)	High (≈80–90%)	Low
Closed reduction	Failed Pavlik / older infants	Moderate	Higher (AVN risk)

Pavlik harness remains the first-line treatment for early developmental dysplasia of the hip, while closed reduction is reserved for cases where conservative management fails or in older infants, with higher associated complication rates

Table 4

Outcome	Result
Total hips treated	87 hips
Success of closed reduction	~91% hips stable after CR
Failure / need for open reduction	~9%
AVN risk	Present but relatively low
Timing effect	Younger age → better stability
Previous Pavlik harness	Used in many patients before CR

[6]

Discusion

Early diagnosis and appropriate management of developmental dysplasia of the hip (DDH) play a crucial role in achieving optimal clinical and radiological outcomes. In our study, treatment outcomes were generally favorable in patients who underwent early intervention, which is consistent with established orthopedic principles emphasizing the importance of early hip reduction to allow normal acetabular development.

The comparison between conservative and surgical treatment modalities demonstrated that both approaches can achieve satisfactory outcomes when appropriately indicated. However, patients treated at an earlier age showed better radiological improvement and higher rates of hip stability compared to those treated later. This finding aligns with previous studies reporting that delayed treatment is associated with increased risk of residual dysplasia, avascular necrosis, and need for secondary surgical procedures.

The role of treatment timing was particularly significant in our analysis. Patients who received earlier intervention demonstrated more predictable outcomes, whereas those treated after delayed diagnosis exhibited more variable results. This is consistent with previous studies highlighting that the biological plasticity of the acetabulum decreases with age, making reduction less effective and outcomes less stable in older children.

Complication rates, including avascular necrosis and residual dysplasia, were within the expected range reported in the literature. Although both conservative and surgical treatments are effective, the risk of complications appears to increase with delayed treatment initiation and more invasive procedures.

Overall, our findings support the current consensus in orthopedic literature that early detection and timely management of DDH are essential for achieving stable hip joints and favorable long-term functional outcomes.

Conclusion

In conclusion, the results of this study indicate that the treatment of Developmental dysplasia of the hip can achieve good clinical and radiological outcomes when appropriately indicated and performed in a timely manner.
It was observed that patients treated at an earlier stage tend to have better hip stability and more rapid improvement in radiological parameters compared to those diagnosed and treated later.
Both conservative and surgical treatment methods demonstrated effectiveness; however, more predictable outcomes were achieved in patients who received early diagnosis and intervention.
This study highlights the importance of early detection, regular clinical follow-up, and appropriate selection of treatment in order to prevent long-term complications such as residual dysplasia and early-onset osteoarthritis.
Overall, DDH remains a condition that requires careful orthopedic management, where timing of intervention is a key determinant of final outcome.

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PREVALENCE AND ANATOMICAL DISTRIBUTION OF INCIDENTALLY DETECTED VASCULAR CALCIFICATIONS ON RADIOGRAPHS

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Abstract

Peripheral arterial calcification contributes to vascular stiffening and chronic limb-threatening ischemia. Identifying the anatomical distribution of vascular calcifications may improve patient evaluation and management. Aim To evaluate the prevalence and anatomical distribution of incidental vascular calcifications in patients undergoing radiographic imaging for symptoms unrelated to PAD. Methods A retrospective analysis was performed on 35 patients with radiologically confirmed vascular calcifications. Age, sex, and calcification sites were analyzed, while referring diagnoses were reviewed to exclude PAD-related symptoms. Results The mean age was 74.6 years (range 55–86), with 23 men and 12 women included. The aorta was the most common calcification site (13 cases), followed by the femoral artery (8 unilateral and 1 bilateral case). Phleboliths were identified in 3 patients, while distal arterial calcifications were less frequent. Conclusion Vascular calcifications were predominantly observed in large proximal arteries, especially the aorta and femoral arteries, consistent with age-related atherosclerotic and medial calcification patterns. Further studies are needed to correlate calcification patterns with chronic diseases and clinical outcomes.

Keywords Peripheral arterial disease; vascular calcification; medial arterial calcification; radiography.

Introduction

Peripheral arterial calcification plays an important role in vascular stiffening, leading to chronic limb-threatening ischemia.[1] Beyond atherosclerotic plaques associated with intimal calcification, medial arterial calcification is a common pathology accompanying peripheral arterial disease (PAD). Identifying the anatomical distribution of vascular calcifications helps redefine management strategies in patients with PAD.
Peripheral arterial calcifications (PAC) are pathological deposits of calcium within the walls of peripheral arteries.
PAC lead to vascular stiffening and are identified on imaging as linear or tubular radiopaque densities along the arterial course.
They are important indicators of cardiovascular diseases such as:
* Peripheral arterial disease (PAD)
* Increased risk of infarction distal to the site of calcification[2]
Analysis of their distribution enables a more accurate assessment of vascular risk, identification of patients with more advanced disease, and guidance toward optimal treatment strategies.

Aim of the study

To evaluate the prevalence and anatomical distribution of incidental vascular calcifications in patients undergoing radiographic imaging for symptoms unrelated to peripheral arterial disease (PAD).
To assess the prevalence and anatomical distribution of incidental vascular calcifications in patients undergoing radiography for various clinical indications unrelated to peripheral arterial disease (PAD), and to evaluate their potential clinical significance as markers of underlying vascular pathology and cardiovascular risk.

Specific objectives:
To identify the most frequent locations of vascular calcifications.
To analyze the association between age and sex with their occurrence.
To evaluate the potential role of plain radiography as a screening tool for vascular disease.
To determine whether incidental vascular calcifications may indicate advanced systemic atherosclerotic disease.
To contribute to the early recognition of patients at increased cardiovascular risk.
By improving awareness of incidental vascular calcifications on plain radiographs, the study may support earlier detection of subclinical vascular disease and promote timely preventive interventions.

Materials and Methods

* Retrospective analysis conducted in the Department of Radiology.
* Identification of 35 patients with vascular calcifications detected on radiographs.
* Review of clinical diagnoses to ensure that patients were referred for symptoms unrelated to peripheral arterial disease (PAD).
* Analysis of demographic data, including patient age and sex, as well as the anatomical location of calcifications according to standardized arterial segments.

Results

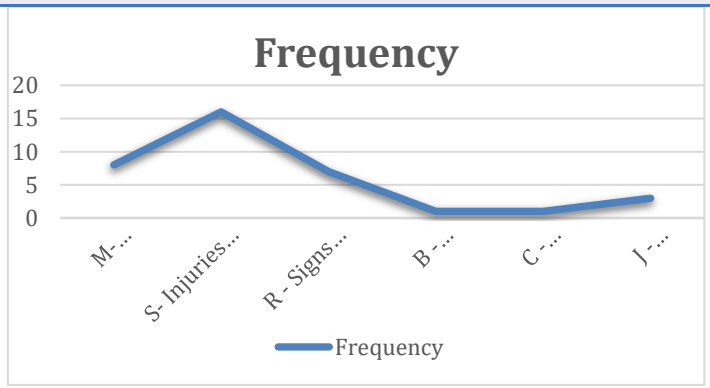
Table 1. Demographic characteristic	**Value**
Total number of patients	35
Mean age (years)	74.6
Males	23 (66%)
Females	12 (34%)

Table 2. Calcification site	**Number**
Aortae	13
a. femoralis – unilateralis	8
a. femoralis – bilateralis	1
Phleobolithis	3
a. tibiale/dorsalis pedis	3

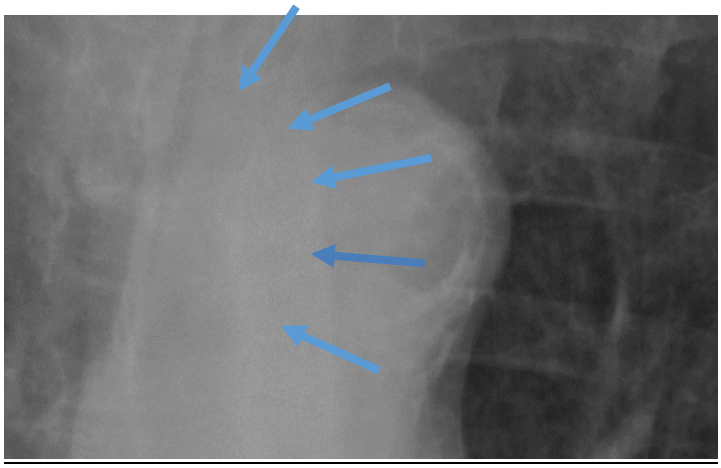
a. brachialis	3
a. radialis	3
aa. metacarpales palmares	1

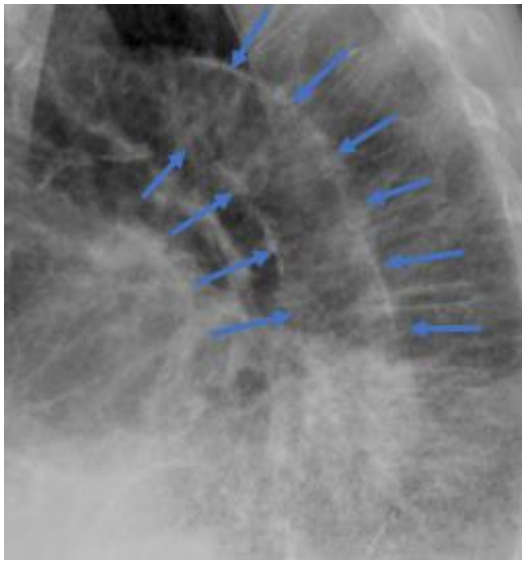
Table 3. **ICD-10 classes by frequency**

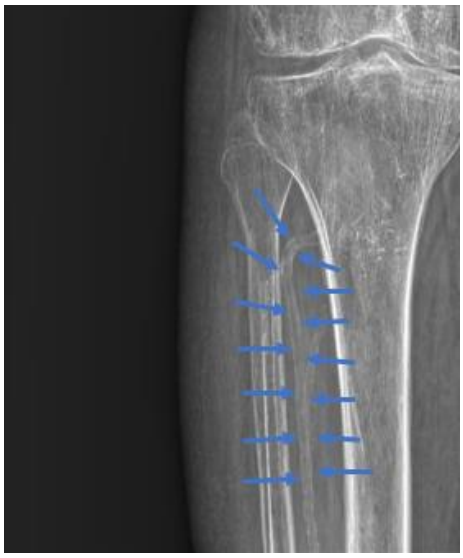
ICD-10	Description	Frequency
S	Injuries / trauma	15
M	Diseases of the musculoskeletal system	8
R	Signs and symptoms	7
J	Respiratory diseases	3
C	Malignant tumor	1
B	Infectious diseases	1



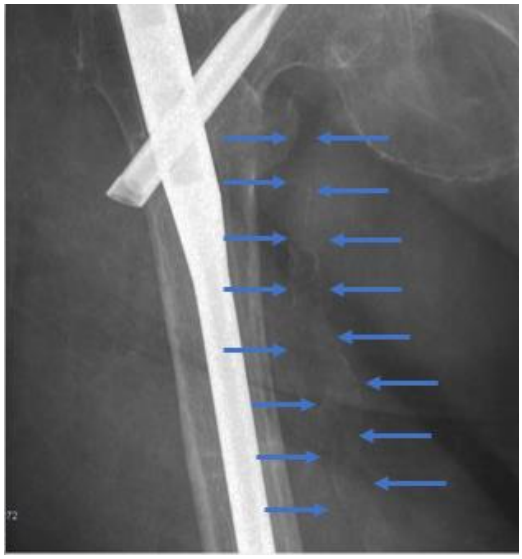
Aortic calcification



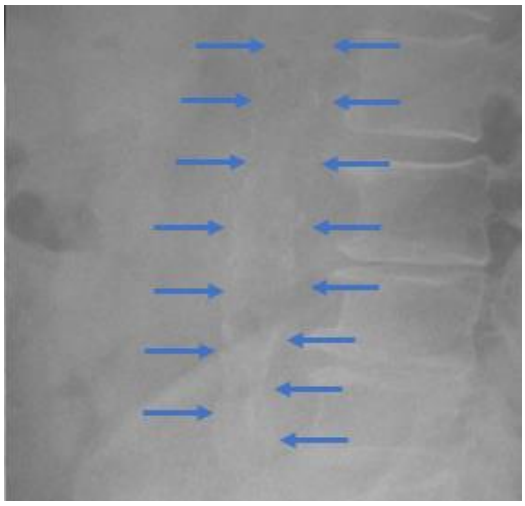




Calcifications in the arteries of the lower extremity







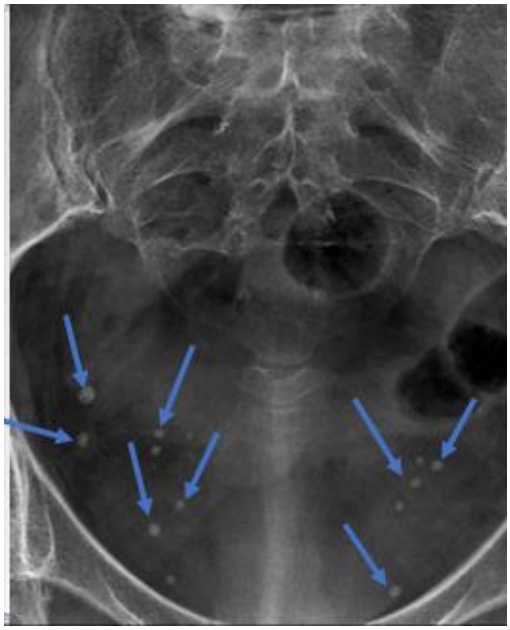








Calcifications in the arteries of the upper extremity





Phleobolithis

Discussion

In our study, extremity injuries predominated, which is consistent with expectations in emergency settings, while chronic musculoskeletal pathologies and general symptoms reflected the clinical profile of outpatient patients. Similar patterns have been reported in emergency radiology practice, where traumatic findings are the leading cause of imaging referrals, particularly involving the extremities.[3]

The most frequent diagnoses in our group were musculoskeletal disorders, particularly osteoarthritis and spondylosis, reflecting the high burden of degenerative diseases in the population. This finding is consistent with epidemiological studies showing that osteoarthritis and degenerative spinal disease are among the most common musculoskeletal conditions in elderly populations undergoing radiographic evaluation.[4] In comparison with other hospital-based studies, our results show a similar predominance of degenerative changes, supporting the global trend of increasing musculoskeletal burden with aging populations.[5]

The highest distribution of vascular calcifications was observed in the aorta and femoral artery, suggesting a systemic atherosclerotic process. This distribution is in agreement with previous

studies reporting that large and medium-sized arteries, particularly the aorta and femoral arteries, are the most frequently affected sites of vascular calcification in peripheral arterial disease.[6] Moreover, our findings are comparable with studies demonstrating that vascular calcifications are not merely localized phenomena but reflect diffuse systemic atherosclerosis associated with increased cardiovascular risk.[7]

Conclusion

Incidental vascular calcifications are common in elderly patients.
Their detection on plain radiographs provides valuable clinical information. They serve as an early indicator of vascular damage, enabling timely intervention and proactive management.
Their assessment should be taken seriously and followed by a cardiovascular evaluation of the patient.
Even when detected incidentally, vascular calcifications should not be overlooked, particularly in elderly patients and those with cardiovascular risk factors.

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GROWTH ZONES OF THE KNEE AND OSTEOCHONDRAL DEFECTS IN CHILDREN

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Abstract

The growth zones of the knee are very important parts in the normal development of bones in children. Injuries in these areas and osteochondral defects can affect growth, movement, and the function of the knee. Osteochondral defects include damage to the cartilage and the underlying bone, causing pain, swelling, and limitation of movement.
This paper discusses the anatomy of the knee in children, the importance of growth zones, the causes and symptoms of osteochondral injuries, as well as the methods of diagnosis and treatment.
It also presents the importance of early diagnosis and rehabilitation in preventing complications and preserving the normal function of the knee.

Keywords: Clinical importance of growth zones,osteochondral defects,osteochondritis dissecans (OCD), diagnosis.

Introduction

The knee represents one of the most complex and functionally important joints of the musculoskeletal system. In children and adolescents, this joint is characterized by the presence of developing structures, especially the growth zones (epiphyseal plates), which are essential for the longitudinal growth of bones.
The biological and biomechanical changes that occur during growth make the knee more sensitive to specific injuries that are not commonly seen in adults.
Two of the most important pathologies in this context are:
growth plate injuries osteochondral defects
These conditions are of great clinical importance, as they may lead to permanent deformities, functional limitations, and in some cases long-term disability.

Functional Anatomy of the Knee in Children

The knee joint is a synovial hinge-type joint (with flexion-extension movement), but it also has important rotational components.

Main Components

-Distal femur
-Proximal tibia
-Patella

Stabilizing Structures

-Anterior cruciate ligament (ACL)
-Posterior cruciate ligament (PCL)
-Collateral ligaments
-Medial and lateral menisci

2.1. Pediatric Characteristics

-Presence of the growth cartilage (physis)
-Less mineralized bones
-Higher tissue elasticity
These characteristics make children more likely to transfer traumatic forces to the growth zones rather than to the ligaments, unlike adults.

2.2. Growth Zones (Epiphyseal Plates)
Growth zones are cartilaginous structures located between the epiphysis and metaphysis of long bones.

2.2.1Histological Structure
The growth plate consists of several zones:
-**Reserve zone** – This zone contains small chondrocytes with low metabolic activity. It serves as a cellular reserve and provides structural stability to the growth plate.
-**Proliferative zone** – In this layer, chondrocytes divide by mitosis and are organized into parallel columns. This zone is responsible for the active longitudinal growth of the bone.
-**Hypertrophic zone** – It is characterized by enlargement of chondrocytes and thinning of the cartilaginous matrix. This part is considered mechanically weaker and more susceptible to trauma and fractures.
-**Zone of calcification** – In this phase, the cartilaginous matrix begins to calcify, while the chondrocytes gradually degenerate.
Any disruption in this organization can directly affect the ossification process, where cartilage is replaced by bone tissue through the process of endochondral ossification. Osteoblasts form new bony trabeculae that contribute to the normal development of the skeleton.

2.2.2Localization in the Knee
-**Distal femur** → contributes about 70% of femoral growth
-**Proximal tibia** → contributes significantly to the growth of the leg

2.3Clinical Importance of Growth Zones
Injuries to these areas are particularly problematic because they:
-May cause premature closure of the growth plate
-May lead to axial deformities (valgus/varus)
-May create limb length discrepancy

2.3.1Growth Plate Injuries

Salter-Harris Classification

This is the most commonly used clinical classification system:
Type I – complete separation through the growth plate
Type II – involves the metaphysis (most common type)
Type III – involves the epiphysis
Type IV – involves both the epiphysis and metaphysis
Type V – compression injury

Mechanisms of Injury
-Direct trauma
-Violent rotation
-Axial loading
2.4Osteochondral Defects: Osteochondral defects involve damage to: the articular cartilage the subchondral bone
These injuries are particularly problematic because of the limited regenerative capacity of cartilage.

2.4.1Pathophysiology
The process includes:
Initial cartilage injury
Changes in the subchondral bone
Local necrosis
Possibility of fragment detachment

2.4.2Contributing Factors
Local ischemia
Repetitive microtrauma and genetic predisposition

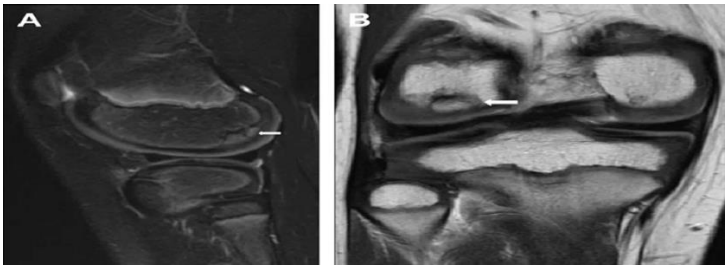


Figure 1. osteochondral lesions

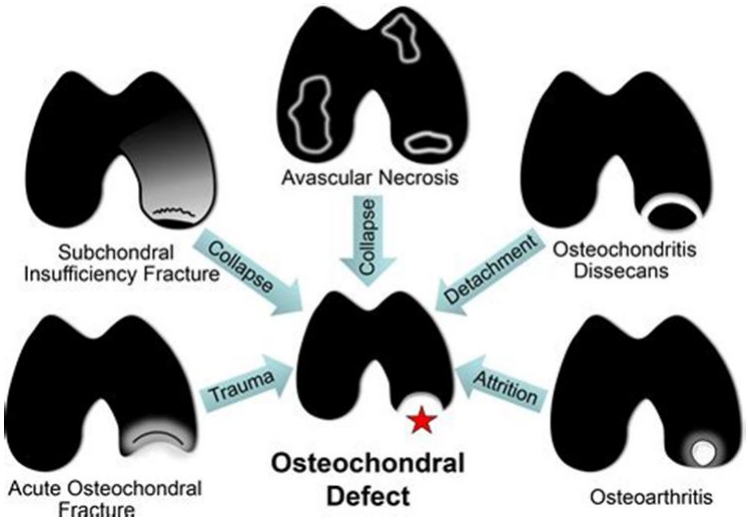


Figure 2. osteochondritis dissecans

2.5.Osteochondritis Dissecans (OCD)
It is a chronic pathology that mainly affects active children and adolescents.Most common localization is medial femoral condyle
Stages: Stable, unstable, free intra-articular fragment

2.5.1Clinical Importance

If left untreated: it progresses to articular degeneration it increases the risk of osteoarthritis at a young age

2.5.2Clinical Presentation

Symptoms include:

-Progressive pain
-Intermittent swelling
-Limitation of movement
-Knee "locking" (mechanical blockage)

2.5.3.Diagnosis

Clinical Examination: Stability tests, evaluation of range of motion

Imaging

-X-ray → initial identification
-MRI → gold standard
-CT scan → evaluation of bone structure

MRI allows the assessment of: lesion stability, cartilage integrity

2.5.4Conservative Treatment

Indicated in:

-young patients with active growth plates
-stable lesions

It includes:

-relative immobilization
-reduction of physical activity
-controlled physiotherapy

2.5.5Surgical Treatment:

Indications

-unstable lesions
-failure of conservative treatment

Techniques

-Fixation with bioresorbable screws
-Microfracture
-Osteochondral autograft
-Chondrocyte implantation

2.6.Rehabilitation

Rehabilitation is critical for long-term success:

-gradual restoration of mobility
-muscle strengthening
-phased return to sports activities

2.7Complications

-Limb deformities
-Functional limitation

-Early osteoarthritis
-Nonunion of the lesion

2.8Prevention
Strategies include:
-management of sports load
-education on proper techniques
-early diagnosis
-monitoring of active children

2.9Discussion
Literature shows that:
-early diagnosis is a key factor
-MRI has revolutionized management
-treatment must be individualized
There is still ongoing debate regarding:
-the optimal timing of surgical intervention
-the choice of the most effective technique

Conclusion

The growth plates of the knee represent essential structures for the normal development of the skeletal system in children, enabling the longitudinal growth of bones. Due to their high sensitivity to trauma, these structures are often at risk during physical activities and sports, making early diagnosis very important.
Osteochondral defects, which involve damage to the articular cartilage and subchondral bone, represent another significant clinical problem in pediatric orthopedics. They can cause pain, limited range of motion, and in more advanced cases, long-term functional impairment of the knee joint.
From the analysis presented in this paper, it is evident that understanding the anatomy and histology of growth plates, along with knowledge of the mechanisms of osteochondral injury, is essential for accurate diagnosis and effective treatment. Modern diagnostic methods, particularly magnetic resonance imaging (MRI), have significantly improved the early detection of these conditions.
In conclusion, successful management of these conditions requires a multidisciplinary approach, early diagnosis, and individualized treatment in order to prevent long-term complications and ensure normal musculoskeletal development in children.

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YOU ARE NOT ENTIRELY YOU: MICROCHIMERISM AND THE HIDDEN PERSISTENCE OF FOREIGN CELLS- A SYSTEMATIC REVIEW AND META ANALYSIS

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Abstract

The human body was traditionally considered a self-contained system defined by a single genetic identity; however, this concept of biological unity has been challenged by the phenomenon of microchimerism. Microchimerism was defined as the long-term presence of a small population of genetically distinct cells within a host, most commonly originating from pregnancy, blood transfusion, or organ transplantation. The aim of this review was to synthesize current experimental and clinical evidence in order to evaluate whether microchimeric cells acted as functional contributors to host physiology, remained biologically neutral, or participated in pathological processes such as autoimmunity and cancer. The reviewed studies indicated that microchimeric cells were widely distributed across multiple human tissues and were capable of expressing tissue-specific markers, suggesting potential functional integration within the host. Evidence further showed that microchimerism exhibited a dual role, being associated with protective effects in certain cancers such as breast cancer and papillary thyroid cancer, while also being observed at increased levels in conditions such as colon cancer and autoimmune diseases. In addition, some findings suggested possible involvement in tissue repair, although the underlying mechanisms remained unclear. Published experimental and clinical studies were reviewed, including evidence obtained through cytogenetic and molecular techniques such as FISH, STR analysis, qPCR, ddPCR, and next-generation sequencing (NGS). Overall, the findings suggested that microchimerism challenged the traditional concept of biological individuality by demonstrating that the human body functioned as a dynamic system in which the boundary between self and non-self was not absolute.

Keywords: Microchimerism, immune tolerance, autoimmune disease, carcinogenesis, tissue repair.

Introduction

Biological identity has traditionally been understood as a stable and self-contained system encoded in DNA and confined within the boundaries of the human body.
However, this concept has been challenged by the phenomenon of microchimerism.
The term “microchimerism” refers to the presence of a small population of genetically distinct cells within an individual, most commonly acquired through pregnancy, blood transfusion, or organ transplantation.
Although these cells originate from another individual, they can persist for long periods and may integrate into host tissues. This phenomenon raises important questions regarding the functional role of foreign cells within the human body and their potential impact on health and disease.
The aim of this review was to synthesize current experimental and clinical evidence to evaluate whether microchimeric cells act as functional contributors to host physiology, remain biologically neutral, or participate in pathological processes.
Recent developments in chimerism analysis have introduced more advanced and sensitive molecular techniques, including quantitative polymerase chain reaction (qPCR), droplet digital PCR (ddPCR), and next-generation sequencing (NGS). These methods allow for the detection of very low levels of chimerism, often below 1%, and have improved the ability to monitor engraftment dynamics and identify early signs of disease relapse. Despite their high sensitivity and precision, their overall clinical utility remains under evaluation.

Results suggest that microchimerism may have beneficial roles, such as contributing to tissue repair, but may also have pathological effects, including the development of autoimmune diseases and certain types of cancer.
As research on microchimerism expands, it becomes increasingly important to bring this phenomenon into broader scientific and intellectual discussion because it shows that foreing cells can persist and even function within us.

Origins and types of microchimerism

Microchimerism is a phenomenon which originates from:
Pregnancy
Twin pregnancies
Organ transplantation
Blood transfusion

Pregnancy as a Source of Microchimerism

In 1893, the German pathologist Georg Schmorl became one of the first scientists to propose that fetal cells could enter the maternal body while studying eclampsia in Leipzig. During autopsies of women who died during pregnancy or childbirth, he identified unusual multinucleated giant cells in the lungs. Since these cells are typically associated with bone marrow and placental tissue, and no skeletal damage was observed, Schmorl concluded that they most likely originated from the placenta. Decades later, in 1959, researchers in New York demonstrated that trophoblast cells could also be detected in the blood of healthy pregnant women as early as the eighteenth week of gestation. (Barnéoud, 2025)
Pregnancy-related microchimerism can be further classified into two subtypes based on the direction of cell transfer:
Fetal microchimerism
Maternal microchimerism

Fetal Microchimerism

Fetal microchimerism refers to the long-term persistence of a small population of fetal cells within the maternal body after pregnancy has ended. This phenomenon arises when cells from the developing fetus cross the placental barrier during gestation and enter the maternal circulation. These fetal-derived cells can survive in various maternal tissues, organs, and blood for many years or even decades. The passage of fetal cells into the mother is thought to occur mainly through transcytosis, a process by which cells move across the placental barrier. (Avery, 2026)

Maternal Microchimerism

Maternal microchimerism refers to the presence of maternal cells within the fetal circulation. This phenomenon was first described in the 1960s by Desai et al., who identified maternal leukocytes in the umbilical cord blood of newborns. Further studies have shown that during fetal and early neonatal life, maternal-derived cells can be detected in multiple organs, including the skin, thymus, spleen, liver, and thyroid. These maternal cells have also been implicated in certain pathological processes, including the possible transmission of cancer from mother to fetus. Historical reports of transplacental metastasis involving various maternal

malignancies further support the existence of maternal microchimerism. (Shrivastava, Naik, & Suryawansh, 2019)

Twin Pregnancies as a Source of Microchimerism

The concept of chimerism in pregnancy was first identified in animals in 1916. It had long been observed that when cattle twins consist of one male and one female, the female is typically infertile and is referred to as a freemartin. This condition arises due to vascular connections between the twins in the placenta, allowing the transfer of anti-Müllerian hormone (AMH) from the male to the female fetus, which disrupts normal development of the female reproductive organs. In contrast, the transfer of female hormones to the male twin has no significant effect. In addition to hormonal exchange, cellular transfer between twins can also occur, resulting in XX/XY chimerism. Similar freemartin phenomena have also been documented in other species, including sheep, goats, and llamas. (Draper, 2018)

Monozygotic twins share genetically identical DNA profiles. At specific genetic loci, homozygosity is indicated by a single detectable DNA fragment, while heterozygosity produces two distinct fragments. In a study conducted at the Perinatology and Gynaecology Clinic of the Medical University of Poznan between 2007 and 2009, cord blood samples were collected from 50 consecutive pairs of twins immediately after birth. Analysis of peripheral blood lymphocytes revealed additional DNA fragments in four pairs of monozygotic twins (8%), observed at loci D7S21 and D12S11. (LeBlanc , Cheever, MacPherson, Taft, & Vichinsky, 2013)

Organ Transplantation as a Source of Microchimerism

Starzl et al. proposed that long-term tolerance after organ transplantation may be explained by the exchange of migratory leukocytes between the donor organ and the recipient. According to this hypothesis, the persistence of donor-derived cells in the recipient is associated with immune tolerance and may allow reduction or withdrawal of immunosuppressive therapy. This bidirectional movement of cells between host and graft is considered to have significant implications for transplant outcomes, as cellular migration may contribute to the development of:

Speed up rejection

Graft versus host disease (GVHD)

The basis of tolerance (Saboowala, 2020)

A study was made in Pomeranian Medical University in Szczecin in an attempt to determine the impact of post-transplant microchimerism on the function of the transplanted kidney. The study included 100 kidney transplant recipients, mostly women. All transplanted organs were from opposite-sex deceased donors. Microchimerism was assessed using multiplex PCR. Male DNA was detected in all urine samples from female recipients and in 13/56 blood samples from female kidney recipients. Female DNA was found in 31/44 urine samples from male recipients, but in none of the blood samples. (Brzóska, Wysocka, Mielczarek-Palacz, & Słotwiński, 2023)

Blood Transfusion as a Source of Microchimerism

Blood transfusion is the most common form of allogeneic transplantation.

Early studies in the 1970s, such as those by Schechter et al., showed short-term proliferation of donor leukocytes within days after transfusion, but later research suggested that these cells rarely persisted beyond about six days in immunocompetent recipients. However, these findings were limited by the low sensitivity of earlier detection methods.

Later studies revisited this topic and found that while most transfused donor leukocytes are rapidly cleared, some cases—particularly in trauma patients—show a transient expansion followed by, in some individuals, long-term persistence of donor cells known as transfusion-associated microchimerism (TA-MC). Research indicates that trauma recipients are at higher risk of developing durable TA-MC, possibly due to multiple transfusions and temporary immune suppression after injury.
This altered immune state, involving reduced innate and adaptive responses and changes in cytokine activity, may allow low-level donor cell survival and engraftment.
Genetic factors may also contribute to differences in susceptibility among patients. (Bloch, Jackman, Lee, & Busch, 2013)

Vanishing Twin Syndrome as a Source of Microchimerism

Vanishing twin syndrome refers to the spontaneous loss of one embryo or fetus during the first trimester in a twin or multiple pregnancy.
In most cases, the exact cause of this phenomenon, as well as later reductions in multiple pregnancies, is not well understood.
The outcome of fetal demise depends on when death occurs and how long the tissue remains in the uterus. When loss occurs early in pregnancy, the affected twin may disappear completely without leaving visible structural remnants. However, genetic traces of the lost twin may sometimes be detected as limited placental chimerism. (Creasy, Resnik, Iams, Lockwood, Moore, & Greene, 2022)
A collaborative study conducted by researchers at the Université libre de Bruxelles and INSERM UMR639 described a case of long-term microchimerism originating from a vanished twin, where fetal-derived cells persisted for decades after gestation. The study involved a 40-year-old man with a scleroderma-like condition, whose symptoms resembled graft-versus-host disease, prompting chimerism analysis using fluorescence in situ hybridization (FISH). Female cells were identified in his peripheral blood mononuclear cells, initially suggesting maternal cell origin.
However, further investigation using HLA-specific quantitative PCR excluded maternal microchimerism and instead detected a paternal HLA haplotype that the patient had not inherited. Since the patient had no history of blood transfusion, the researchers proposed that the most plausible explanation was the presence of cells from an unrecognized vanished twin. This case supports the possibility that vanished twins can be a source of long-term microchimerism, although its frequency and any potential link to autoimmune-like disease remain uncertain. (Bianchi, Zickwolf, Weil, Sylvester, & DeMaria, 2010)

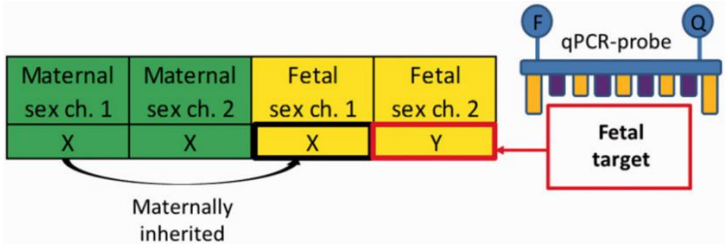
Detection and Methodologies

Chimerism analysis involves identifying and measuring genetic variations, such as polymorphic markers, that can differentiate donor-derived cells from those of the recipient. This approach is used to determine the proportion of donor and recipient hematopoietic cells present in samples such as peripheral blood, bone marrow, and other tissues. Monitoring changes in these proportions over time allows clinicians to assess and track donor engraftment. Although different techniques are available for chimerism monitoring, they are all based on the same fundamental principle of detecting informative genetic polymorphisms that distinguish between donor and recipient cells. (Blouin, Ye, Williams, & Askar, 2021)
Non-molecular methods
Initial non-molecular approaches to chimerism analysis included red blood cell phenotyping and cytogenetic techniques such as fluorescence in situ hybridization (FISH). FISH was

commonly used to detect genetically distinct cell populations by targeting sex chromosomes. Although these methods provided early insights into chimerism, their sensitivity and quantitative accuracy were limited. (Blouin, Ye, Williams, & Askar, 2021)

Classical molecular methods

Classical molecular techniques significantly improved the detection and quantification of chimerism. These methods included restriction fragment length polymorphism (RFLP), variable number tandem repeats (VNTR), and short tandem repeat (STR) analysis. STR analysis, performed using polymerase chain reaction (PCR) followed by fragment analysis, became the most widely used method due to its higher sensitivity (approximately 1–5%), improved reproducibility, and strong clinical applicability. Over time, STR analysis largely replaced earlier molecular techniques in both research and clinical practice. (Blouin, Ye, Williams, & Askar, 2021)

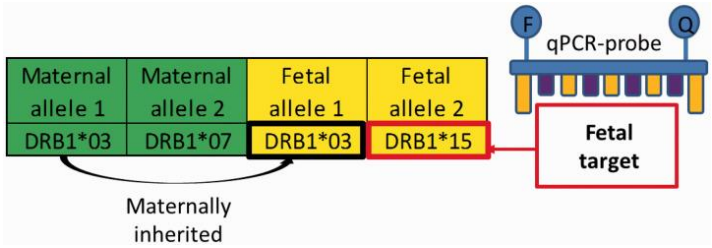


Reproduced from Fjeldstad H.E.S. et al. 2020. Journal of Reproductive Immunology, 139, 103119.

Figure 1- Fetal Y-chromosome is commonly used as a marker for detecting microchimerism. The pregnant woman has two X-chromosomes, whereas the male fetus has one maternally inherited X-chromosome and one paternally inherited Y-chromosome. This genetic difference enables the identification of fetal cells using techniques such as FISH or qPCR that specifically target Y-chromosome sequences. (Fjeldstad, Johnsen, & Staff, 2020)

Advanced molecular methods

More recently, advanced molecular techniques such as quantitative polymerase chain reaction (qPCR), droplet digital PCR (ddPCR), and next-generation sequencing (NGS) have been developed. These highly sensitive methods allow detection of very low levels of chimerism, often below 1%, and are particularly useful for monitoring engraftment dynamics and identifying early disease relapse. However, despite their increased sensitivity and precision, their overall clinical utility and cost-effectiveness in routine practice are still being evaluated. (Blouin, Ye, Williams, & Askar, 2021)



Reproduced from Fjeldstad H.E.S. et al. 2020. Journal of Reproductive Immunology, 139, 103119.

Figure 2- Highly polymorphic human leukocyte antigen (HLA) class II genes, particularly the DRB1 locus, are used to identify fetal-derived cells. A pregnant woman carries two DRB1 alleles, one on each chromosome, while the fetus inherits one maternal allele and one paternal

allele. When the paternal allele differs from the maternal genotype, it can serve as a unique genetic marker for detecting fetal microchimeric cells within maternal tissues. (Fjeldstad, Johnsen, & Staff, 2020)

The dual role of microchimerism in health and pathology

Accumulating evidence indicates that microchimeric cells can contribute to both protective and pathological processes.
The balance between beneficial and deleterious outcomes appears to depend on cell type, tissue localization and the interplay with host genetic and environmental factors. (Index, 2026)

Pathogenic and Protective Roles of Microchimerism in Autoimmune Diseases

Several human and animal studies have suggested that microchimerism may play a role in triggering autoimmune processes.
Early researches focused on detecting microchimeric cells in peripheral blood and examined conditions such as systemic lupus erythematosus, multiple sclerosis, primary biliary cirrhosis, thyroiditis, rheumatoid arthritis, Sjögren's syndrome, and systemic sclerosis.
Sjögren's syndrome, an autoimmune disorder affecting exocrine glands, shows a strong female predominance and often increased incidence following childbirth, which implies a possible link between pregnancy and disease development.
This has led to the hypothesis that fetal microchimerism may contribute to its pathogenesis. (Demir & Görgun, 2021)
At the same time, microchimerism may also have beneficial effects in certain autoimmune conditions, as seen in rheumatoid arthritis, which typically improves during pregnancy in many patients. (Bhattacharya & Stubblefield, 2013)

Role of Microchimerism in Tissue Repair and Regeneration

Microchimerism has been marked as both actively enhancing tissue repair and regeneration.
Fetal stem cells show substantial potential in regenerative medicine and have been investigated in the treatment of myocardial injury, hematopoietic engraftment, and necrotizing enterocolitis models. (Shangaris & El Hoss, 2023)

Pathogenic and Protective Roles of Microchimerism in Cancer

Fetal microchimerism has been reported at lower levels in certain cancers, such as breast cancer and lymphoma, while higher frequencies have been observed in colon cancer.
Microchimeric cells have also been detected in both normal and diseased tissues, as well as in healing and tumour environments.
This has led to the hypothesis that these cells may have dual roles, potentially offering protection against some malignancies while contributing to the development of others.
In humans, microchimeric cells have been found in multiple organs, including the brain, lymph nodes, thyroid, heart, skin, spleen, kidneys, pancreas, liver, gastrointestinal tract, bone marrow, and cervix.
These cells have been shown to express tissue-specific markers such as lymphocyte differentiation antigens and cytokeratins, suggesting functional integration within host tissues.
Epidemiological evidence linking microchimerism with both cancer risk and protection supports the idea that these cells may actively influence carcinogenesis.
Early observations as far back as 1960 suggested a possible role for maternal lymphocytes in Hodgkin lymphoma in offspring. Some studies have reported that women with detectable microchimerism in peripheral blood may have a reduced risk of breast cancer, and male-derived cells have been found more frequently in normal and benign breast tissue than in malignant lesions. Similarly, reduced levels of microchimerism have been associated with

papillary thyroid cancer and certain hematological malignancies, which has been interpreted as a potential protective effect.
In contrast, increased microchimerism has been observed in colon cancer, although the underlying mechanism remains unclear.
In melanoma, microchimeric cells have even been proposed to contribute to tumour progression through effects such as lymphangiogenesis.
Given the many interacting biological and environmental factors involved in cancer development, the precise role of microchimerism remains complex and not fully understood. (Gadi & Nelson, 2014)

Conclusion

Microchimerism has deeply challenged our understanding of the immune system's behavior toward foreign cells. For a long time, it was believed that the human body was determined to keep itself "clean" of them, eliminating them rapidly, if not immediately. However, to our surprise, we now know that these foreign cells can coexist within us for decades.
We know that all of us were carried by our mothers, usually for nine months. What we did not know is that they may continue to carry parts of us for the rest of their lives.
It is undeniable that microchimerism plays a dual role in the organism. It may have a healing role associated with tissue repair, a protective role in certain cancers such as breast cancer, and a pathogenic role in other cancers such as colon cancer, while also contributing to the development of autoimmune diseases.
Microchimerism offers an entirely new perspective on the human organism and the way it functions. It is extremely important for research to continue on the protective, healing, and pathogenic effects it may have within the body, so that those suffering from diseases currently considered incurable are not left without hope indefinitely. Science continuously shows us that what we deny today may tomorrow be accepted as an absolute truth. As Evelyn Fox Keller said, "To know the history of science is to recognize the mortality of any claim to universal truth."

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PREVENTIVE MEASURES FOR RODENT (*RODENTIA*) CONTROL IN THREE DISTINCT URBAN LOCALITIES IN SKOPJE

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Abstract

The main purpose of this study was to analyze rodent activity in three different buildings (companies) that are located in different environmental conditions, have different functions, and also differ in structural characteristics. The research was carried out by monitoring the consumption of poisoned bait placed in certain bait stations, both in the outdoor and indoor areas of these research points.
The monitoring of the activity of rodents was carried out in 4 periods during one year (January 2024, May 2024, September 2024, and January 2025). To determine rodent presence, we implemented a standardized scoring system that measures rodent activity from 0 (no activity) to 4 (high activity, defined as complete bait consumption). At the first study site (Dauti Komerc) in Saraj, data analysis showed the highest peak in January 2024, which is consistent with low environmental temperatures encouraging rodents to seek shelter indoors. The activity of rodents in the interior spaces of this research point resulted in generally lower values, but several high-risk areas were identified that require increased preventive measures. The highest levels of rodent activity in the outdoor spaces in the second research site (Feniks and El Farma - the industrial area in Vizbeg) were during January of 2024 and 2025. Meanwhile, the monitoring of the internal spaces of this point resulted in a minimum level of rodent activity, which was achieved by the effectiveness of deratization. The highest rodent activity was recorded in September and January, at the third research point (Kromberg-Schubert in the Ilinden story), while activity was at its lowest in May. Inside the buildings, evidence of the presence of rodents was limited to some isolated areas.
In summary, the analysis of rodent activity shows a distinct seasonal trend, with increased levels of activity recorded during the colder months, especially in January and September, when rodents seek shelter and food. The first research company had the highest overall rodent activity, both indoors and outdoors, most likely due to the food items being attractive to the pests. Despite the fact that the second company (Kromberg-Schubert) did not possess food products, its location in wide open spaces in nature contributed to the promotion of high rodent activity. Well-maintained and isolated facilities, such as those of Feniks and El Farma, demonstrate in particular the effectiveness of proactive deratization strategies. These results highlight the importance of environmental factors and site-specific management strategies in controlling rodent populations.
Keywords: Rodent Activity, Bait Stations, Deratization Strategies, Seasonal Patterns.

Introduction

The order of rodents (Rodentia) represents one of the most diverse orders of the mammalian class and is characterized by a cosmopolitan distribution, exerting various impacts on forest ecosystems, urban and rural areas, agriculture and crop cultivation, as well as a significant and important impact on public health (Lan *et al.*, 2025*;* Capizz*i et al.*, 2014). The global diversity of all vertebrates numbers 6759 taxa recorded in the Mammalian Diversity Database (www.mammaldiversity.org), and of this total worldwide record, rodents lead with 40.6%, specifically with 2747 species (Burgin *et al.*, 2025). Mainly urban environments, where the human population is high, rats are rodents that have found ideal conditions to reproduce by taking advantage of the abundant food and shelter resources that urbanized areas offer, and all these favorable conditions are also related to the reproductive cycle of rodent species, which is characterized by rapid sexual maturity, short lifespan and a polyestrous cycle, with female individuals often capable of mating immediately after birth. Therefore, favorable climatic conditions, abundant food resources, and the reproduction of small rodents without a specific season often leads to population growth in urban environments and disruption of the ecological

balance (Gratz, 1999; Panti-May *et al.*, 2017; Jurišić *et al.*, 2022). Studying rats in urban environments is essential not only to understand their biology and ecology, but also to develop effective strategies for managing their negative impact. According to Tapia-Ramírez et al (2022), species of the order Rodentia can be grouped into three categories in relation to their frequency in their environments. Even those species in urban environments, responding positively to urbanization, increase their abundance, and are known as "urban residents", permanently inscribed in the urban environment. The rapid increase in the abundance of some species poses economic and public health problems for humans. In addition, the second group includes species that make occasional visits: "urban visitors" and some species belonging to the third category react negatively, seeing their abundance as "urban avoiders".

Among the above-mentioned categories, special emphasis is usually given to urban visitors, including synanthropic species, mainly by the World Health Organization (WHO, 1974), due to their direct impact on public health and harmful urban consequences. In this context, WHO has played a central role in the development of global guidelines for rodent control, publishing a series of documents that provide recommendations on the use of rodenticides, monitoring rodent populations, and evaluating control measures. These guidelines emphasize and highlight the importance of integrating mechanical and chemical approaches, giving priority to the safest and most sustainable methods of rodent control and management.

In accordance with these recommendations, effective management and control of commensal rodents can be achieved by combining environmental hygiene, proper food storage, elimination of shelter, and protection of buildings from rodents with various control methods such as blocking, fumigation, and rodenticides. Although the application of chemical methods is increasingly preferred and the widespread use of anticoagulant rodenticides is also recommended due to their effectiveness, long-term management success must be combined with the improvement of environmental conditions and the implementation of multiple control methods in combination (Brooks et al., 1987). Rodenticides are widely used to control rodents in agriculture and forestry; however, their application and use in amateur settings are strictly regulated throughout Europe due to risks to non-target species, environmental impacts, and the emergence of resistance (Jacob & Tkadlec, 2010).

Numerous initiatives focusing on the use of safer chemicals, the promotion of biological control methods and improved waste management as a strategy to reduce rodent populations have also been undertaken by the Food and Agriculture Organization (FAO) and the United Nations Environment Programme (UNEP). These organisations also stress the need for training local specialists and strengthening capacities to implement international standards at the national level (FAO, 2011). In recent years, faster and more accurate responses to population outbreaks have been achieved as advances in information technology have led to the development of data management systems that help track and analyse rodent infestations.

Therefore, this study aims to assess the effectiveness of preventive measures and the selection of chemical control agents for rodent management in three different companies operating in industrial areas of Skopje, North Macedonia.

Materials and methods

Three companies with different activities and different spatial and structural conditions were selected for the realization of this study, which represent important places for an interesting comparison:

1. Dauti Komerc-Saraj (N: 42.00553, E: 21.31462), a company that deals with the storage and distribution of food products.
2. Feniks and El Farma-Vizbeg (N: 42.03275, E: 21.40005), a pharmaceutical company for the storage and transportation of medicines.

3. Kromberg & Schubert-Ilinden (N:41.99595, E: 21.541), an automotive industry company, producing parts for vehicles (Fig. 1).



Fig. 1. Satellite images of the locations of the companies included in the study (arrows indicate their locations). A-Dauti Komerc (Saraj); B-Feniks and El Farma (Vizbeg); Kromberg & Schubert (Ilinden) (source: https://maps.google.com).

The rodenticides used for this study are well known and tested so far: Brodisa Blue PE in pellet form containing the active anticoagulant substance - brodifacoum (0.005%), Brodisan Blue PF in paraffin block form containing the active anticoagulant substance - bromadiolone (0.005%) and Brodisan Blue MM, a ready-to-use soft bait, containing the active anticoagulant substance (0.0025%) (European Chemicals Agency [ECHA], n.d). Anticoagulant rodenticides act by disrupting blood clotting and causing fatal internal hemorrhage. Compared with acute rodenticides, their advantage is that they are better tolerated by rodents and generally pose lower risks to non-target species when used properly (Bentley,1972; Brooks *et al.*, 1987).
The target rodents of this study were: house mouse (*Mus musculus* Linnaeus, 1758), Norway rat (*Rattus norvegicus* (Berkenhout, 1769)), and black rat (*Rattus rattus* (Linnaeus, 1758)).
Monitoring was carried out in four different time periods within one year: January 2024, May 2024, September 2024, and January 2025. In each period, data from boxes placed with poison baits were observed and recorded, both inside and outside the facilities (Fig. 2, 3).

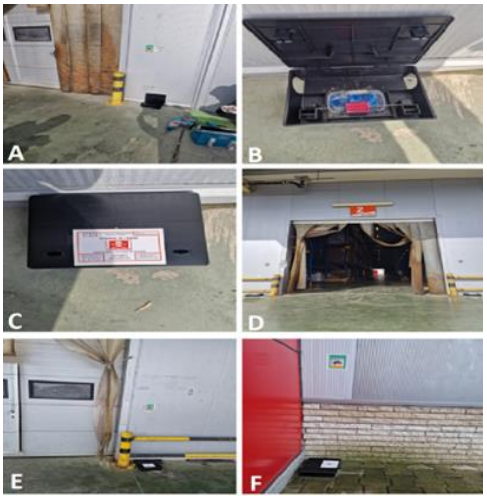


Fig. 2 Dauti Komerc location in Saraj, Skopje and in the companies Feniks and El Farma in Vizbeg, Skopje. The photographs show the way the boxes are mounted outside the buildings (A, B, C) and their correct position (D, E, F).



Fig. 3. Third location of the Kromberg-Shubert Company in the municipality of Ilinden. The photographs show bait boxes placed inside and outside the facility, half-bitten baits, which served to assess the level of activity and the finding of dead mice outside the facility (A, C, H), as well as assessing the level of manifestation (B, D, E, G)

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The activity assessment was carried out according to a standardized monitoring system based on EPPO field guidelines for rodent control (OEPP, 1995), which determines the level of rodent manifestation from 0 (no activity) to 4 (high activity, when the bait is completely consumed). The calculation of the average values for rodent activity was carried out based on the number of boxes and baits consumed.

Results are presented with the help of graphs, in particular for each company. A comparative analysis was also conducted to assess the effectiveness of deratization, the impact of climatic conditions, and the construction structure of each facility, as well as the composition and form of the rodenticides used in each case.

Results and discussion

Dauti Komerc- Company, Saraj

Dauti Komerc is a company that has constant contact with food products, which makes it very susceptible to rodent infestation. 43 bait boxes were placed outside the facility, while 25 were placed inside the facility.

The data analysis indicates that the period of highest activity was January 2024, when temperatures were lower, and rodents sought shelter in such conditions (Fig. 4, a). Within the research facility, activity has been lower, but specific high-risk areas have nevertheless been identified that require ongoing treatment (Fig. 4, b).

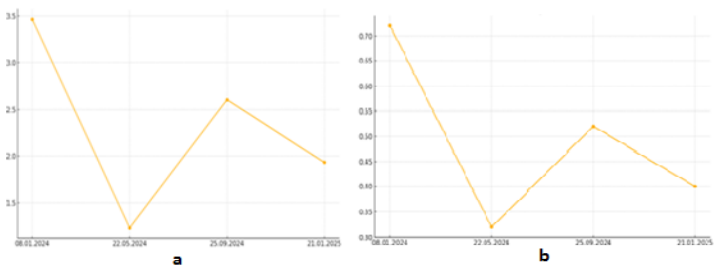


Fig.4 Average rodent activity outside (a) and inside (b) the Dauti Komerc Company premises during the time periods January, May, September 2024 and January 2025.

Feniks and El Farma-Vizbeg

This pharmaceutical company has high safety and hygiene measures, but the outdoor areas still pose a potential risk for infestation. 22 boxes are placed outside the facility and 18 boxes inside the facility. The highest activity outside the facility was recorded in January, September 2024 and January 2025, while in May 2024, activity was lowest (Fig. 5, a). Inside the facility, activity was very low in almost all periods, indicating successful indoor pest control management (Fig. 5, b)



Fig. 5. Average rodent activity outside (a) and inside (b) the Feniks and El Farma company during the time periods January, May, September 2024, and January 2025.

Kromberg and Schubert Company - Ilinden

Kromberg and Schubert Company operates in the technical and industrial sector, where rodent damage can cause serious consequences to equipment or products. 55 boxes have been placed outside the facility, and 30 boxes inside the facility. The highest activity was recorded in January, September 2024, and January 2025, while in May 2024 the activity was lowest (Fig. 6, a). Within the premises of this company, the presence of rodents has only been detected in a few places, mainly in the most isolated places (Fig.6, b).

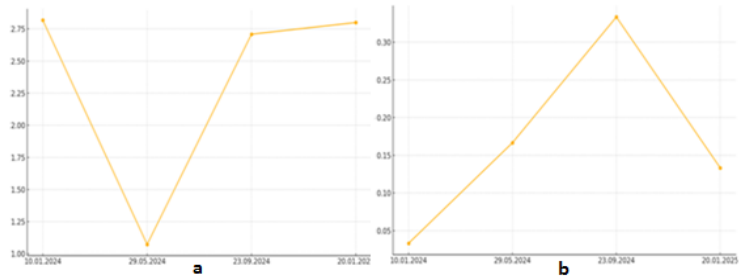


Fig. 6. Average rodent activity outside (a) and inside (b) the Kromberg and Shubert-Ilinden company premises during the time periods January, May, September 2024, and January 2025.

The capture of rodents with mechanical traps and the application of rodenticides were analyzed as control methods; however, certain limitations were identified in the implementation of these methods. Eliminating rodents with traps requires more time and a large number of traps, so rodenticides have shown efficacy in enclosed spaces, compared to their weaker effectiveness in natural environments. The recommendations of the European Chemicals Agency (ECHA), which are also acceptable to the European Committee (2016), emphasize that the dose of these anticoagulants should not exceed 30 ppm or 0.003%, but despite this dose limitation, which has ecological importance in terms of reducing anticoagulant residues, this causes an extension of the consumption time of rodents, specifically a slower mortality that automatically makes these animals in natural outdoor conditions hunted by other predators of the trophic chain, increasing the chances of secondary and tertiary poisoning (Frankova et al., 2019; Blažić et al., 2024).

Regarding the research in different months, the lowest rate of rodent species capture was observed in May in all three localities, both in indoor and outdoor areas. The justification for this result has to do with the abundant presence of food reserves available to rodents in nature (for example, insects) (Kikkawa, 1964). Previous studies (Romanach et al., 2005; Quirici et al., 2010) have also proven that the abundance and mobility of rodents are influenced by key factors such as food availability and environmental climatic conditions. Also, the increase in rodent numbers in September and January is related to the company of this research providing sustainable food sources.

Conclusions

This research shows that the rodent control process must be continuous and specific for different facilities, as rodent activity is affected by seasonal changes, food availability, building conditions, and the presence of the anthropogenic factor itself. Rodenticides, mainly anticoagulants, are used at different levels of effectiveness depending on their formulation and environmental conditions, emphasizing the importance of proper selection and regular monitoring to avoid as many cases of secondary and tertiary poisoning as possible. The protection of public health, safety in the workplace, and the increase in the quality of manufactured products can only be achieved with effective rodent management by alternating continuous controls, training of employees in different companies, and related institutional and scientific efforts.

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HPV VACCINATION: AWARENESS, EDUCATION, VACCINE CONFIDENCE AND EARLY PREVENTION STRATEGIES

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Abstract

Human papillomavirus (HPV) vaccination represents one of the most effective preventive strategies against cervical cancer and other HPV-related diseases. Despite the proven safety and effectiveness of HPV vaccines, vaccination rates continue to be influenced by misinformation, fear, lack of awareness, and limited public confidence. This paper discusses the importance of awareness, education, vaccine confidence, and early prevention in HPV vaccination, with special emphasis on North Macedonia's immunization policies and preventive healthcare strategies. The paper also highlights the role of healthcare professionals, parents, schools, and public institutions in combating misinformation and improving long-term public health outcomes.

Keywords: HPV vaccination, cervical cancer prevention, Gardasil 9, vaccine confidence, misinformation, adolescents, public health, North Macedonia

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide. Persistent infection with high-risk HPV types, particularly HPV 16 and HPV 18, is strongly associated with cervical cancer development. HPV infection is also linked to anal, vulvar, vaginal, penile, and oropharyngeal cancers, as well as genital warts.

Cervical cancer remains one of the leading preventable causes of cancer-related morbidity and mortality among women globally. According to the World Health Organization (WHO), preventive vaccination and screening strategies are essential for the elimination of cervical cancer as a public health problem.

The development of HPV vaccines has transformed preventive medicine by providing effective protection before exposure to the virus. However, fear, misinformation, and insufficient public education continue to influence vaccination acceptance in many countries. Increasing awareness and strengthening trust in vaccines remain essential components of successful immunization programs.

HPV Vaccination and Prevention

HPV vaccination is considered a primary prevention strategy because it prevents infection before disease development. HPV vaccines induce a strong immunological response by stimulating the production of neutralizing antibodies, thereby providing long-term protection against high-risk HPV infections.

Currently, the most widely used vaccine is Gardasil 9, a 9-valent vaccine that protects against nine HPV types, including the most oncogenic strains responsible for cervical cancer. Scientific evidence demonstrates that HPV vaccination significantly reduces HPV infections, precancerous cervical lesions, genital warts, and cervical cancer incidence.

Vaccination is most effective when administered before the initiation of sexual activity. Consequently, adolescents are considered the primary target group for immunization programs. Vaccination of both girls and boys also contributes to herd immunity and reduction of HPV transmission within the population.

Preventive vaccination represents not only a medical intervention but also an investment in long-term public health and quality of life. Choosing HPV vaccination means choosing protection, prevention, and a healthier future.

Educating Adolescents and Parents

Education represents one of the most important determinants of HPV vaccine acceptance. Many adolescents and parents remain insufficiently informed about HPV transmission, cancer risk, vaccine safety, and the benefits of early prevention.
Healthcare professionals, teachers, schools, and public health institutions play a crucial role in providing evidence-based information and promoting preventive healthcare awareness. Educational campaigns should focus on:
• the importance of cancer prevention;
• vaccine safety and effectiveness;
• recommended vaccination age;
• the importance of completing all vaccine doses;
• the role of vaccination in reducing HPV-related cancers.
Parents often make vaccination decisions for adolescents, making parental education especially important. Studies consistently demonstrate that strong physician recommendations significantly increase vaccination rates and improve public trust in immunization programs.

Combating Fear and Vaccine Misinformation

One of the greatest challenges facing modern preventive medicine is the rapid spread of misinformation regarding vaccines. False claims shared through social media and non-scientific sources often create fear, confusion, and distrust among parents and adolescents. Misleading information about infertility, severe complications, or long-term health damage associated with HPV vaccines has no scientific evidence and may negatively influence public health decisions.
Healthcare professionals and public institutions must actively combat misinformation through transparent communication, evidence-based education, and community engagement. Providing accurate scientific information is essential for helping individuals make informed healthcare decisions.
HPV vaccines have undergone extensive clinical testing and continuous international safety monitoring. Organizations such as the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and the European Medicines Agency (EMA) consistently confirm the safety and effectiveness of HPV vaccination.
Most reported side effects are mild and temporary, including pain at the injection site, redness, mild fever, fatigue, headache, dizziness, or nausea. Serious adverse reactions remain extremely rare. The health benefits of preventing cervical cancer and other HPV-related diseases greatly outweigh the minimal risks associated with vaccination.
Fear should never become a barrier to cancer prevention. Promoting scientific literacy, strengthening public trust, and encouraging open communication between healthcare professionals and families are essential steps toward improving vaccine confidence and protecting future generations.
Every missed vaccination represents a missed opportunity for cancer prevention.

HPV Vaccination in North Macedonia

In North Macedonia, the HPV (Human Papillomavirus) vaccine was officially introduced into the National Immunization Program in October 2009. Initially, it was administered as a mandatory vaccine for 12-year-old girls.
Some key points in the timeline:

2009 – Mandatory vaccination for 12-year-old girls began in schools and healthcare centers. The quadrivalent vaccine (Gardasil) was used, protecting against HPV types 6, 11, 16, and 18. At the same time, the government also provided free vaccination for girls aged 9–26 who registered for immunization.
2019 – The immunization calendar was updated, and the quadrivalent vaccine continued to be provided with a 2-dose schedule (0 and 6 months).
2024/2025 – The country switched to the nine-valent vaccine (Gardasil 9), which protects against more HPV types, and the vaccine also began to be recommended for boys aged 12–18.
In 2024, the Ministry of Health introduced the 9-valent HPV vaccine Gardasil 9 into the national immunization program. The vaccination strategy was expanded to include both girls and boys in order to improve population protection and reduce HPV transmission. The vaccine is recommended primarily for children and adolescents aged 9–14 years. Vaccination is organized through public health institutions, vaccination centers, and school healthcare services.
For adolescents aged 9–14 years, a two-dose schedule is generally recommended:
• first dose at month 0;
• second dose after 6–12 months.
For individuals aged 15 years and older, a three-dose schedule is recommended:
• first dose at month 0;
• second dose after 2 months;
• third dose after 6 months.
Although HPV vaccination in North Macedonia is strongly recommended and included within preventive immunization strategies, it is not currently considered strictly mandatory like several childhood vaccines. The Ministry of Health continues to support vaccination through awareness campaigns and preventive healthcare education initiatives.

Conclusion

HPV vaccination represents one of the most effective preventive interventions in modern medicine. Awareness, education, vaccine confidence, and early prevention remain essential for improving vaccination coverage and reducing HPV-related diseases worldwide.
Educating adolescents and parents, combating misinformation, and strengthening public trust in vaccines are critical priorities for successful immunization programs. In North Macedonia, the inclusion of Gardasil 9 in the national immunization calendar represents an important advancement in preventive healthcare and cancer prevention strategies.
Preventing cancer through vaccination is one of the greatest achievements of modern medicine. Strengthening educational campaigns and promoting evidence-based information can contribute significantly toward reducing cervical cancer incidence and protecting future generations from preventable diseases.

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CHARACTERIZATION OF APPLE (*MALUS DOMESTICA*) PROCESSING WASTE: PHYSICOCHEMICAL AND NUTRITIONAL COMPOSTITION

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Abstract

Apple (*Malus domestica*) processing industries generate large quantities of by-products, primarily apple pomace consisting of peels, pulp residues, and seeds. These residues are often discarded or used as low-value animal feed, despite their significant nutritional and functional potential. The present study investigates the valorization potential of apple processing waste through detailed physicochemical characterization and proximate composition analysis. Apple (*Malus domestica*) waste samples were analyzed to determine their basic physicochemical properties and nutritional composition, including protein, fat, carbohydrates, and dietary fiber. According to results, apple pomace typically contains a moisture content ranging from 70–80%, while the dry matter accounts for approximately 20–30%. On a dry weight basis, the protein content ranges between 3.0–5.5%, while the fat content remains relatively low, generally between 1.5–3.5%. Carbohydrates represent the major fraction, accounting for approximately 55–70% of the dry matter, mainly composed of soluble sugars and structural polysaccharides. Importantly, apple processing waste is characterized by a high dietary fiber content, typically ranging from 35–60%, including both soluble fibers such as pectin and insoluble fibers like cellulose and hemicellulose. Additional physicochemical parameters indicate that apple peel waste has a pH between 3.2 and 4.1 and total soluble solids ranging from 10 to 15 °Brix, reflecting its natural organic acid and sugar composition. The relatively high fiber and carbohydrate content highlights the potential of apple waste as a functional ingredient in food formulations, bakery products, and nutraceutical applications. In general, the results demonstrate that apple processing by-products represent a valuable bioresource. Their valorization could contribute to sustainable waste management, promote circular bioeconomy practices, and provide novel ingredients for the development of functional foods with enhanced nutritional value.

Keywords: Apple processing waste, dietary fibers, food waste, functional ingredients

Introduction

The global apple industry represents one of the most significant sectors within fruit production and processing. Apples (*Malus domestica*) are widely cultivated and processed into a variety of products such as juices, ciders, purees, jams, and concentrates (Schwartz et al. 2025). However, industrial processing of apples generates substantial quantities of by-products, primarily apple pomace, which consists of peel, pulp residues, and seeds (Zaky et al. 2024). It is estimated that apple pomace accounts for approximately 20-35% of the total processed fruit mass, making it one of the largest agro-industrial residues generated by the fruit processing sector (Gołębiewska et al. 2022). Traditionally, this by-product has been used as low-value animal feed or simply discarded, leading to environmental concerns and economic inefficiencies. In recent years, increasing attention has been directed toward the sustainable management and valorization of agro-industrial by-products (Lackner & Besharati, 2025). The concept of circular bioeconomy encourages the efficient utilization of biological resources, aiming to transform food processing residues into value-added products (Pal et al. 2024). Apple processing waste represents a promising raw material due to its rich nutritional composition and functional properties. Several studies have reported that apple pomace contains considerable amounts of dietary fiber, carbohydrates, and bioactive compounds, including

polyphenols, flavonoids, and organic acids, which contribute to its potential health-promoting properties (Tsoupras et al.2025). Dietary fiber is one of the most important components of apple processing residues. Apple pomace represents a valuable source of dietary fiber, containing substantial amounts of soluble components such as pectin, alongside insoluble fractions including cellulose and hemicellulose (Díaz-Núñez et al. 2026). These compounds are known to play an important role in human nutrition, contributing to improved digestive health, regulation of blood glucose levels, and reduction of cholesterol concentrations (Chaouch & Benvenuti, 2020). In addition, the presence of natural sugars, minerals, and other phytochemicals further enhances the nutritional and technological value of apple by-products. Because of these properties, apple processing waste has gained increasing interest as a potential ingredient in the development of functional foods, dietary supplements, and nutraceutical products (Korban, 2023). From an environmental perspective, the improper disposal of fruit processing waste can lead to significant ecological issues, including microbial spoilage, unpleasant odors, and increased biochemical oxygen demand in waste streams (Liu et al. 2023). Therefore, the valorization of apple pomace not only provides an opportunity to recover valuable nutrients and bioactive compounds but also contributes to sustainable waste management and environmental protection (Duan et al. 2021). Furthermore, the integration of such by-products into food formulations aligns with current global trends toward sustainable food systems and resource efficiency. Despite the recognized potential of apple processing waste, detailed information regarding its physicochemical properties and nutritional composition remains essential for its effective utilization in food and industrial applications (Pal et al. 2024). Comprehensive characterization of these residues is necessary to determine their suitability as functional ingredients and to support their incorporation into novel food products (de Carvalho et al. 2023).Therefore, the aim of the present study was to investigate the physicochemical characteristics and proximate nutritional composition of apple (*Malus domestica)* processing waste. Particular attention was given to the determination of moisture content, dry matter, protein, fat, carbohydrates, dietary fiber, pH, and total soluble solids. Understanding these parameters is crucial for evaluating the potential of apple pomace as a valuable bioresource and for promoting its application within sustainable food production and circular bioeconomy frameworks.

Materials and Methods

2.1 Sample collection and preparation: Apple processing waste samples were collected from a local fruit-processing facility in Pristina (Kosovo) in the period of March 2026 after the industrial production of apple juice. The waste material mainly consisted of apple peels, pulp residues, and seeds remaining after juice extraction. Immediately after collection, the samples were transported to the laboratory (University for Business and Technology-UBT, Pristina). All the collected samples were packed separately in polyethylene bags and brought to the laboratory for preliminary treatment and analysis. In the laboratory, the samples were homogenized to ensure uniformity. Fresh samples were analyzed for physicochemical properties, while a portion of the material was dried for proximate composition analysis. Drying was performed in a laboratory oven at 60 °C until constant weight was achieved. The dried samples were then ground using a laboratory mill to obtain a fine powder and stored in airtight containers at room temperature until further analysis.

2.2 Determination of moisture content and dry matter

Moisture content was determined using the oven-drying method. Approximately 5 g of fresh apple pomace was weighed in analytical balance (Sartorius Entris II BCA224I-1S, Germany) and dried in a hot-air oven at 105 °C (Memmert UN110, Memmert GmbH, Germany) until a

constant weight was obtained. The moisture content was calculated as the percentage loss in weight relative to the initial fresh sample weight. Dry matter content was determined as the remaining percentage after moisture removal.

2.3 Determination of protein content: The total protein content of the dried apple waste samples was determined using the Kjeldahl method (AOAC. 2000; Method 920.87), which measures the total nitrogen content in the sample. Approximately 1 g of dried sample was digested with concentrated sulfuric acid (99.99%% purity, Sigma-Aldrich, Germany) in the presence of a catalyst. After digestion, the ammonia produced was distilled and titrated. The nitrogen content was converted to protein using the standard conversion factor (N × 6.25). Results were expressed as percentage on a dry weight basis.

2.4 Determination of fat content: Crude fat content was determined using Soxhlet extraction by AOAC, (2000: Method 920.39). Approximately 2 g of dried sample was extracted with petroleum ether for several hours until complete lipid extraction was achieved. After extraction, the solvent was evaporated, and the remaining lipid fraction was weighed. The fat content was calculated as a percentage of the dry sample weight.

2.5 Determination of dietary fiber: Dietary fiber content was determined using the enzymatic-gravimetric method according to McCleary et al. (2012). The procedure involved enzymatic digestion to remove proteins and digestible carbohydrates, followed by filtration and drying of the remaining fiber fraction. The obtained residue was weighed and expressed as percentage of dry matter.

2.6 Determination of carbohydrates: Total carbohydrate content was calculated by difference according to the proximate analysis method. The percentage of carbohydrates was estimated by subtracting the sum of moisture, protein, fat, and dietary fiber contents from the total mass of the sample.

2.7 Determination of pH: The pH of fresh apple pomace was measured using a digital pH meter (Hanna Instruments HI2211, Romania). A sample suspension was prepared by mixing apple waste with distilled water, and the pH electrode was immersed directly into the homogenized mixture. Measurements were performed at room temperature.
2.8 Determination of total soluble solids: Total soluble solids (TSS) were measured using a digital refractometer (Atago PAL-1, Japan) and expressed as degrees Brix (°Brix). A small quantity of fresh apple pomace extract was placed on the refractometer prism, and the value was recorded after stabilization.

2.9 Statistical analysis: All analyses were performed in triplicate, and the results were expressed as mean ± standard deviation (SD). Additional statistical parameters, including standard error (SE), coefficient of variation (CV), minimum and maximum values, and 95% confidence intervals, were calculated to evaluate data variability. Statistical significance was assessed using appropriate statistical tests, and differences were considered significant at $p < 0.05$. Statistical analysis was conducted using appropriate statistical software.

Results and Discussion

Table 1 presents the statistical analysis of the physicochemical properties and proximate composition of apple processing waste. The results demonstrate that apple waste is

characterized by a high moisture content along with considerable levels of dietary fiber and carbohydrates, indicating its potential as a valuable raw material for food and nutraceutical applications. The variability observed among the measured parameters reflects differences in the composition of peels, pulp residues, and seeds present in the pomace. These findings highlight the nutritional richness of apple processing by-products and support their potential utilization within sustainable food systems and circular bioeconomy strategies.

Table 1. Statistical analysis of physicochemical properties and proximate composition of apple processing waste

Parameter	**Unit**	**Mean ± SD**	**SE**	**CV (%)**	**Min**	**Max**	**95% CI**	**p-value**
Moisture content	% (fw)	75.0 ± 3.5	2.02	4.67	70.0	80.0	70.0 – 80.0	0.021
Dry matter	%	25.0 ± 3.5	2.02	14.00	20.0	30.0	20.0 – 30.0	0.021
Protein	% (dw)	4.2 ± 0.9	0.52	21.43	3.0	5.5	3.1 – 5.3	0.034
Fat	% (dw)	2.5 ± 0.7	0.40	28.00	1.5	3.5	1.6 – 3.4	0.041
Carbohydrates	% (dw)	62.5 ± 5.2	3.00	8.32	55.0	70.0	56.0 – 69.0	0.018
Dietary fiber	% (dw)	47.5 ± 8.5	4.91	17.89	35.0	60.0	37.0 – 58.0	0.012
pH	–	3.65 ± 0.30	0.17	8.22	3.20	4.10	3.28 – 4.02	0.027
Total soluble solids	°Brix	12.5 ± 1.8	1.04	14.40	10.0	15.0	10.2 – 14.8	0.036

3.1 Moisture content and dry matter: Moisture content represents one of the most important physicochemical parameters influencing the stability, storage conditions, and potential utilization of agro-industrial by-products. The results obtained in this study indicate that apple processing waste exhibited a mean moisture content of 75.0 ± 3.5%, with values ranging between 70.0% and 80.0%. Consequently, the dry matter content was 25.0 ± 3.5%.These results are consistent with previously reported data in the literature, where apple pomace moisture content typically ranges between 70% and 80%, depending on the apple variety, maturity stage, and processing technology used during juice extraction (Zaky et al. 2024; Akagić & Oras, 2025). The relatively high moisture content explains the limited shelf stability of fresh apple pomace, as high water activity may promote microbial growth and rapid spoilage. The statistical analysis revealed a coefficient of variation (CV) of 4.67% for moisture content, indicating relatively low variability among samples and good reproducibility of the measurements. The statistically significant p-value (0.021) suggests that the measured parameter is reliable and consistent within the experimental dataset. The high moisture content also highlights the necessity for appropriate drying or stabilization methods if apple pomace is intended for further industrial applications. Drying processes can significantly extend shelf life and facilitate its incorporation into food formulations or nutraceutical products.

3.2 Protein content: Protein content is an important nutritional parameter when evaluating the potential use of food processing by-products as functional ingredients. The analysis showed that apple processing waste contained 4.2 ± 0.9% protein on a dry weight basis, with observed values ranging from 3.0% to 5.5%. Although apple pomace is not considered a major protein

source compared with other plant materials, the detected levels are consistent with values reported in previous studies (Naseem et al. 2024). The presence of proteins in apple waste is mainly attributed to cellular components of the fruit pulp and peel. The coefficient of variation for protein content was 21.43%, indicating moderate variability among samples, which may result from differences in apple cultivar, agricultural practices, and fruit maturity. The obtained p-value of 0.034 confirms the statistical significance of the results. From a nutritional perspective, even moderate protein levels can contribute to the overall functional value of apple pomace when used as an ingredient in food products. In particular, apple pomace powders have been incorporated into bakery formulations and dietary supplements, where their nutritional contribution is combined with dietary fiber and bioactive compounds (Aslamet al. 2024).

3.3 Fat content: The fat content of apple processing waste was relatively low, with an average value of 2.5 ± 0.7% (dry weight). The measured values ranged between 1.5% and 3.5%, which is in agreement with previously reported data for apple pomace (Sobczak et al. 2022). The low lipid content reflects the natural composition of apples, which are not typically considered lipid-rich fruits. However, the small fraction of lipids present in apple pomace may originate from apple seeds and cellular membranes. The coefficient of variation for fat content was 28.00%, suggesting higher variability compared to other measured parameters. This variability may be associated with differences in the proportion of seeds present in the pomace fraction, as seeds generally contain higher lipid concentrations than the fruit pulp (Hobbi et al. 2023). Despite the relatively low lipid content, apple pomace remains a valuable raw material for food applications due to its other nutritional components, particularly dietary fiber and carbohydrates.

3.4 Dietary fiber content: Dietary fiber is one of the most valuable components of apple processing waste. The results obtained in this study demonstrated that apple pomace contained 47.5 ± 8.5% dietary fiber on a dry weight basis, with values ranging between 35.0% and 60.0%. The fiber fraction in apple pomace consists of both soluble and insoluble components. Soluble fibers, particularly pectin, are known for their technological applications as natural gelling and thickening agents in food products (Cherian et al. 2024). Insoluble fibers such as cellulose and hemicellulose contribute to digestive health and intestinal function (Guan et al. 2021). The coefficient of variation (17.89%) suggests moderate variability in fiber content among the samples, which may be influenced by apple variety and processing conditions. The obtained p-value of 0.012 confirms the statistical significance of the results. The high dietary fiber content highlights the potential use of apple pomace as a functional ingredient in the development of fiber-enriched foods, including bakery products, cereals, snacks, and dietary supplements (Kauser et al. 2024).

3.5 Carbohydrate content: Carbohydrates represented the major component of apple processing waste, accounting for 62.5 ± 5.2% of the dry matter. The observed values ranged from 55.0% to 70.0%, indicating that carbohydrates constitute the dominant nutritional fraction of apple pomace. The carbohydrate fraction consists mainly of soluble sugars such as glucose, fructose, and sucrose, as well as structural polysaccharides including cellulose, hemicellulose, and pectin. These compounds contribute to both the nutritional and technological properties of apple waste. The relatively low coefficient of variation (8.32%) suggests good consistency in carbohydrate composition among the analyzed samples. Furthermore, the p-value of 0.018 indicates statistically significant results. The high carbohydrate content highlights the potential of apple pomace as a source of fermentable substrates in food processing, bioenergy production, and biotechnological applications. In addition, structural carbohydrates contribute significantly to the dietary fiber content of the material (Selmi et al. 2025).

3.6 pH and total soluble solids: The physicochemical parameters pH and total soluble solids provide important information regarding the acidity and sugar composition of apple processing waste. In the present study, the pH value of apple waste ranged between 3.20 and 4.10, with a mean value of 3.65 ± 0.30. This acidic nature is primarily attributed to the presence of organic acids such as malic acid, which is the predominant organic acid in apples. The coefficient of variation for pH was relatively low (8.22%), indicating consistent acidity among samples. The statistically significant p-value (0.027) further confirms the reliability of the measurements. Total soluble solids were determined to be 12.5 ± 1.8 °Brix, with values ranging from 10.0 to 15.0 °Brix. These values reflect the natural sugar content remaining in the pomace after juice extraction. The presence of soluble solids contributes to the flavor characteristics and potential fermentability of the material. The relatively moderate coefficient of variation (14.40%) indicates acceptable variability in soluble solid content among samples.

3.7 Valorization potential of apple processing waste: The overall results demonstrate that apple processing waste possesses significant nutritional and functional potential. Its high carbohydrate and dietary fiber contents make it a promising raw material for the development of functional foods, dietary supplements, and nutraceutical products. Furthermore, the presence of natural sugars, organic acids, and structural polysaccharides expands its potential applications in fermentation processes, food formulations, and biotechnological industries. The results support the concept that apple pomace should not be considered merely an agricultural waste product but rather a valuable bioresource. The valorization of apple processing by-products aligns with the principles of the circular bioeconomy, promoting sustainable waste management and resource efficiency within the food industry. By converting fruit processing residues into high-value products, both environmental impacts and economic losses associated with food waste can be significantly reduced.

Conclusion

The present study provides a comprehensive evaluation of the physicochemical properties and proximate nutritional composition of apple (*Malus domestica*) processing waste, highlighting its potential as a valuable resource rather than a low-value by-product. The high dietary fiber and carbohydrate content observed in apple processing waste confirms its strong potential as a functional ingredient in food formulations, particularly in fiber-enriched bakery products, functional beverages, and nutraceutical preparations. Furthermore, the physicochemical characteristics identified in this study indicate that apple pomace may serve as a promising raw material for various industrial applications, including fermentation processes, bioactive compound extraction, and the development of value-added food ingredients. From a sustainability perspective, the valorization of apple processing by-products represents an important strategy for reducing agro-industrial waste and promoting resource efficiency within the food supply chain. Transforming apple pomace into functional food ingredients or nutraceutical products not only contributes to waste reduction but also supports the development of circular bioeconomy models in the agro-food sector. Overall, the findings of this study emphasize that apple processing waste should be considered a valuable bioresource with significant nutritional and technological potential. Future research should focus on the optimization of processing techniques, stabilization methods, and the recovery of bioactive compounds in order to fully exploit the industrial and functional applications of apple pomace.

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PHYSICAL SEPARATION OF URBAN PUBLIC TRANSPORT FROM OTHER TRAFFIC FLOWS IN THE CITY OF TETOVO AS A MODERN MOBILITY SOLUTION

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Abstract

The increase in private vehicle ownership and insufficient development of road infrastructure have created serious mobility challenges in the city of Tetovo. Traffic congestion, reduced operational efficiency of public transport, environmental pollution, roadside parking, and travel delays have become major urban transport problems. This paper analyzes the possibility of implementing physically separated bus lanes for urban public transport in Tetovo and evaluates their potential impact on improving mobility conditions, reducing travel time, and increasing public transport reliability. The research is based on traffic flow analysis, field observations, comparative analysis of urban bus routes, and evaluation of the current traffic conditions within the city. The results indicate that dedicated bus infrastructure could significantly improve urban mobility, increase average bus speed, reduce congestion, and contribute to sustainable urban development.

Keywords: urban mobility, public transport, Tetovo, dedicated bus lanes, traffic engineering.

Introduction

Urban public transport systems represent one of the most important components of sustainable urban mobility. Efficient public transport directly affects economic development, environmental sustainability, social mobility, and the quality of urban life. In many European cities, dedicated public transport infrastructure has become a strategic tool for reducing congestion and improving transport efficiency.

The city of Tetovo has experienced a continuous increase in private vehicle ownership during the last decades, while road capacities and traffic infrastructure have remained almost unchanged. As a result, heavy congestion, travel delays, increased fuel consumption, and environmental pollution have become serious urban problems.

Urban buses currently operate under mixed traffic conditions together with private vehicles. This significantly reduces the reliability and efficiency of public transportation systems, especially during peak traffic periods. The lack of dedicated bus lanes additionally reduces the competitiveness of public transport compared to private vehicles.

Therefore, the physical separation of urban public transport from other traffic flows represents a modern and sustainable solution for improving urban mobility conditions in Tetovo.

Research Methodology

The methodology used in this paper is based on literature review, field observation, comparative traffic analysis, and direct evaluation of traffic conditions in Tetovo.

The research methods include:

- traffic flow analysis;
- comparative before/after analysis;
- travel time analysis;

• field observation of critical urban corridors;
• environmental impact evaluation.
Special attention was given to urban corridors characterized by high traffic density, roadside parking, and conflicts between different traffic participants. Traffic photographs and route maps were used to document the current traffic situation and identify the most problematic segments of the urban road network.

Current State Of Traffic Conditions in Tetovo

The current traffic conditions in Tetovo are characterized by insufficient road capacity, uncontrolled roadside parking, mixed traffic flows, and inefficient traffic organization. Field observations indicate that the central urban area is heavily affected by traffic congestion, especially during peak hours. In many locations, parked vehicles reduce the effective width of the roadway and create bottlenecks that significantly affect traffic flow efficiency. The following figures illustrate typical traffic conditions observed in several urban corridors in Tetovo.



Figure 1. High vehicle density and roadside parking in central Tetovo.

The observed traffic conditions demonstrate the lack of effective traffic management measures and the negative impact of uncontrolled parking on urban mobility. Similar conditions are present in several urban corridors within Tetovo, creating delays for both private vehicles and public transport operations.



Figure 2. Traffic conflict caused by mixed traffic conditions.

The observed traffic conditions demonstrate the lack of effective traffic management measures and the negative impact of uncontrolled parking on urban mobility. Similar conditions are present in several urban corridors within Tetovo, creating delays for both private vehicles and public transport operations.



Figure 3. Reduction of effective roadway width due to roadside parking.

The observed traffic conditions demonstrate the lack of effective traffic management measures and the negative impact of uncontrolled parking on urban mobility. Similar conditions are present in several urban corridors within Tetovo, creating delays for both private vehicles and public transport operations.



Figure 4. Urban boulevard suitable for public transport prioritization.

The observed traffic conditions demonstrate the lack of effective traffic management measures and the negative impact of uncontrolled parking on urban mobility. Similar conditions are present in several urban corridors within Tetovo, creating delays for both private vehicles and public transport operations.

Analysis Of Existing Urban Bus Routes

The urban public transport network in Tetovo consists of several main bus lines connecting residential zones with universities, commercial centers, and the city center. These routes represent the primary mobility corridors used daily by students, workers, and citizens.



Figure 5. Bus route: Pallma Mall – SEEU

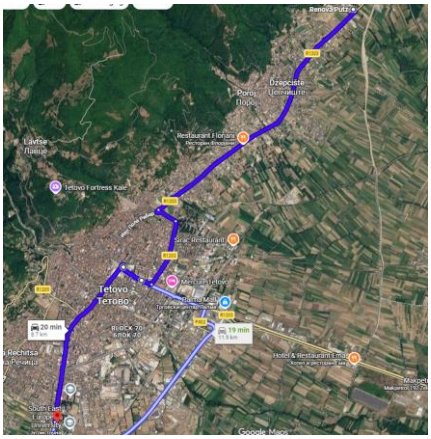


Figure 6. Bus route: Xhepçishtë – SEEU.

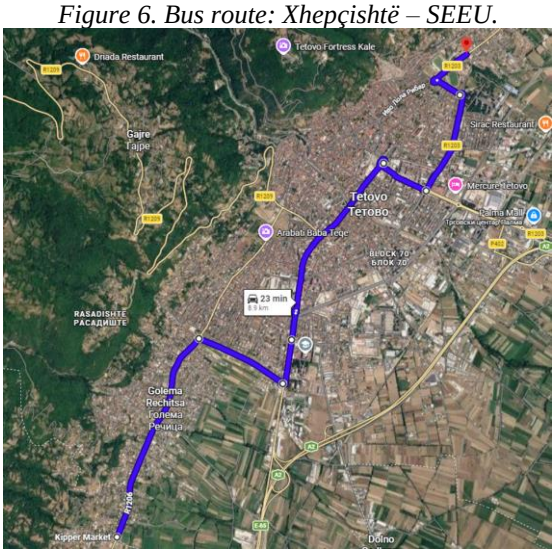


Figure 7. Bus route: Reçicë e Madhe – Pallma Mall.

Analysis of the existing routes indicates that the most problematic segments are located near urban intersections and central corridors with high traffic intensity. During peak hours, travel times increase significantly due to traffic congestion and roadside parking.

Table 1. Existing Urban Bus Lines

Bus Line	Distance	Travel Time	Main Traffic Problem
Pallma Mall – SEEU	4.3 km	25–45 min	Heavy congestion
Xhepçishtë – SEEU	8.7 km	30–50 min	Entrance bottlenecks
Reçicë e Madhe – Pallma Mall	8.9 km	30–45 min	Urban conflicts

Concept Of Physical Separation Of Public Transport

Physical separation of public transport means reserving specific traffic lanes exclusively for buses and public transportation vehicles. Dedicated bus lanes can be implemented through road markings, physical barriers, traffic islands, and traffic signal priority systems. This concept has been successfully implemented in many European cities and has produced positive results in reducing travel time and improving operational efficiency.
The main advantages of dedicated bus infrastructure include:

• increased average bus speed;
• reduced travel time;
• improved schedule reliability;
• reduced congestion;
• lower environmental pollution;
• increased attractiveness of public transport.

Implementation Possibilities In Tetovo

Based on urban structure analysis, several corridors in Tetovo are suitable for the initial implementation of dedicated bus lanes, including the city center–university corridor and the eastern entrance toward the city center. The implementation process could be realized gradually through pilot projects and continuous traffic performance evaluation.

Expected Effects

The implementation of dedicated public transport infrastructure in Tetovo is expected to significantly improve urban mobility conditions. Increased average bus speed and reduced travel time would improve the competitiveness of public transport and reduce dependence on private vehicles.

Table 2. Comparison Before and After Implementation

Parameter	Before	After
Average Bus Speed	14 km/h	24 km/h
Travel Time	30 min	18 min
Schedule Reliability	Low	High
Passenger Demand	Average	Increasing
CO_2 Emissions	High	Lower

Conclusion

Tetovo requires a comprehensive transformation of its urban mobility system. Continued dependence on private vehicles will further increase traffic congestion, environmental pollution, and travel inefficiency. Physical separation of urban public transport from other traffic flows represents a realistic and sustainable solution for improving mobility conditions in the city. Dedicated bus lanes would significantly improve public transport efficiency and contribute to sustainable urban development.

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EVALUATION OF MORPHOLOGICAL AND BIOMETRIC INDICATORS OF SWEET POTATO CULTIVARS (*Ipomea batatas Poir*)

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Abstract

The evaluation of morphological and biometric indicators of sweet potato cultivars (Ipomea batatas Poir) is one of the most important field experimental studies because they create the basis for yield and other production indicators in sweet potato cultivars. The experiment was set up with five variants and four repetitions, during the period May - September 2025 in Sulzotaj, Divjakë. Five sweet potato cultivars were included in the experiment, namely Beauregard, Pepita, Convingation, O'Henry, and Georgia Jet. During the vegetative period, assessments were made for flower color, leaf color, pulp color, skin color, and biometric measurements for shoot length, length of the longest shoot, and the shortest shoot.

Keywords: Cultivar, leaves, shoots, flowers, pulp, skin.

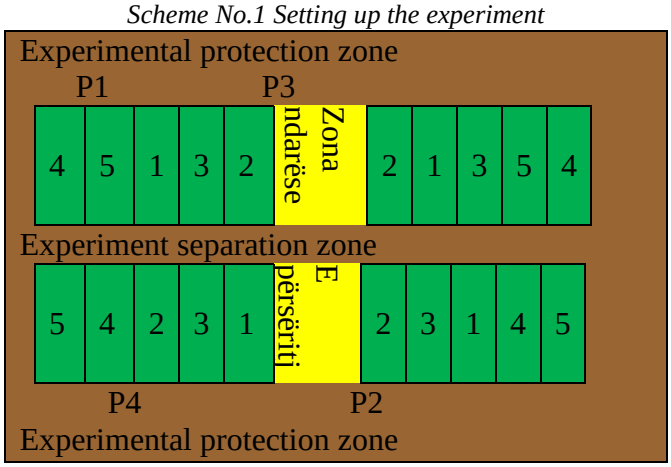
Introduction

Sweet potato is one of the field plants that is being studied and is spreading more and more every year in many countries around the world. This is due to its chemical composition and nutritional values. In Albania, it is unknown and not widespread.

Materials and methods

The study of potato cultivars with the aim of determining the best cultivar for the agroecological and soil conditions of Lushnja was conducted in Divjaka.
Objectives:
1. To evaluate the morphological and biometric indicators of sweet potato cultivars.
2. To evaluate the production indicators of sweet potato cultivars.
3. To evaluate and compare sweet potato cultivars for yield as the main indicator of economic and production evaluation.
4. Conduct chemical analyses for the main chemical indicators for all cultivars and compare them.
To achieve the goal and objectives of this scientific study, an experiment was set up with five sweet potato cultivars:1. Beauregard, 2. Pepita, 3. Convingation, 4. O'henry, 5. Georgia jet.
The experiment was set up with three variants and four repetitions. The variant was designed with dimensions 7 m x 2.4 = 16.8 m2. The soil was worked to a depth of 31 - 35 cm. It was fertilized with organic fertilizer 300 kv/ha, 2 kv/ha potassium sulfate, and 80 kg/ha urea. The previous crop was carrot. During the vegetation, several treatments were carried out: Supplementary fertilization with ammonium nitrate twice with 70 kg/ha, five irrigations were carried out with drip tubes, and were accompanied by liquid fertilizers.
It was not affected by various diseases (early blight and late blight). It was treated only with gastrotox because snails appeared with and without shells.

Scheme No.1 Setting up the experiment



The field experiment was carried out during the period May-September 2025, in Sulzotaj, Divjakë municipality: Five sweet potato cultivars were included in the study, namely; Beauregard, Pepita, Convingaton, O'henry and Georgia jet . The harvest was carried out on September 28, 2025.

2.3. Morphological indicators:1. Number of shoots/plant, 2. Length of shoots/plant (sum), 3. Longest shoot, 4. Shortest shoot, 5. Number of leaves/plant, 6. Leaf color, 7. Flower color, 8. Leaf shape, 9. Tuber shape, 10. Tuber skin color, 11. Tuber pulp color, 12. Bud placement on the tuber.

Results and their interpretation

3.1. Morphological indicators: Descriptions and measurements of indicators were made according to scientific methodology.

3.1.1. Leaf color

Leaf color *Table No. 1*

No.	Cultivars	Leaf color
1	Beauregard	Green
2	Pepita	Light green
3	Convingation	Green with purple veins
4	O'henry	Dark green
5	Georgia jet	Green

The leaf color is different among the cultivars studied. The two cultivars, Beauregard and Georgia Jet, are green, while Pepita is light green and O'Henry is dark green. The Convingation cultivar is unique, with green leaves but purple veins that make it very distinct from the others.

3.1.2. Flower color

Table No.2. Flower color

No.	Cultivars	Flower color
1	Beauregard	Light purple with white crown
2	Pepita	Light purple
3	Convingation	Dark purple
4	O'henry	Light purple
5	Georgia jet	Light purple

Flower color shows less variation between cultivars. The Beauregard cultivar has much more distinctive flowers because the flower is light purple and the corolla is white, while other cultivars have monochromatic flowers in light or dark purple.

3.1.3. Leaf shape

Table No.3. Leaf shape

No.	Cultivars	Leaf shape
1	Beauregard	Heart
2	Pepita	Heart
3	Convingation	Elongated and larger heart
4	O'henry	Heart
5	Georgia jet	Heart

The leaf shape is heart-shaped in four cultivars, while the Convignation cultivar has an elongated and larger heart shape.

3.1.4. Tuber shape

Table No.4. Tuber shape

No.	Cultivars	Tuber shape
1	Beauregard	Elliptical
2	Pepita	Elliptical
3	Convingation	Narrow conical
4	O'henry	Cylindrical – conical
5	Georgia jet	Irregular cylindrical

First, we should mention that all cultivars included in the study are of the hard-pulp type, a type that is more tolerant to storage and has a longer shelf life on the market. The tuber shape is regular and specifically: the Beauregard and Pepita cultivars have an elliptical shape, the Convignation cultivar has a truncated-conical shape, while the O'Henry cultivar has a cylindrical-conical shape. The Georgia Jet cultivar is special, which has an irregular cylindrical shape.

3.1.5. Color of tuber skin

Table No.5 Color of tuber skin

No.	Cultivars	Color of tuber skin
1	Beauregard	Light purple
2	Pepita	Light brown
3	Convingation	Strong purple
4	O'henry	White on yellow
5	Georgia jet	Light brown

The color of the tuber is different and makes the cultivars clearly and precisely distinguishable by the color of the tuber skin. Specifically: The Beauregard cultivar is light purple, the Pepita cultivar is light brown, the Convingation cultivar is a deep purple, the O'henry cultivar is white to yellow, and the Georgia Jet cultivar is light brown.

3.1.6. Color of the tuber pulp

Table No.6 Color of the tuber pulp

No.	Cultivars	Color of the tuber pulp
1	Beauregard	Beige
2	Pepita	Beige
3	Convingation	Bold purple
4	O'henry	White
5	Georgia jet	Beige

The color of the tuber pulp shows less variation between cultivars. The Beauregard, Pepita, and Georgia Jet cultivars have beige pulp, the Convingation cultivar has a bold purple pulp, and the O'Henry cultivar has white pulp.

3.1.7. Placing buds on the tuber

Table No.7 Placing buds on the tuber

No.	Cultivars	Placing buds on the tuber
1	Beauregard	Superficial
2	Pepita	Superficial
3	Convingation	Superficial
4	O'henry	Superficial
5	Georgia jet	Superficial

The placement of the buds on the tuber is the same in all cultivars. The buds are placed superficially, facilitating the peeling mechanism and ensuring a very high pulp utilization rate.

3.1.8. Length of shoots (m)

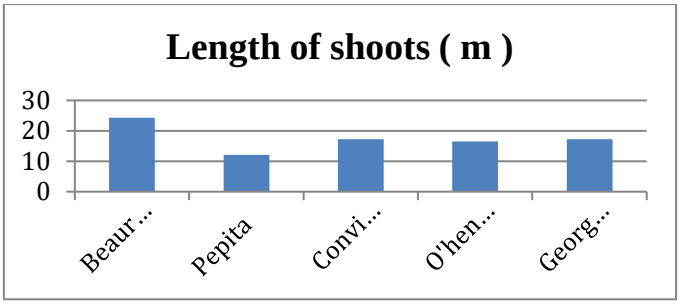


Chart No. 1 Length of shoots of a plant (m)

The length of the shoots varies. The Beauregard cultivar has the longest shoots at approximately 25 m. Three cultivars: Convingation, O'henry and Georgia jet have similar shoot lengths. The Pepita cultivar has the shortest shoots.

3.1.9. The longest shoot (m)

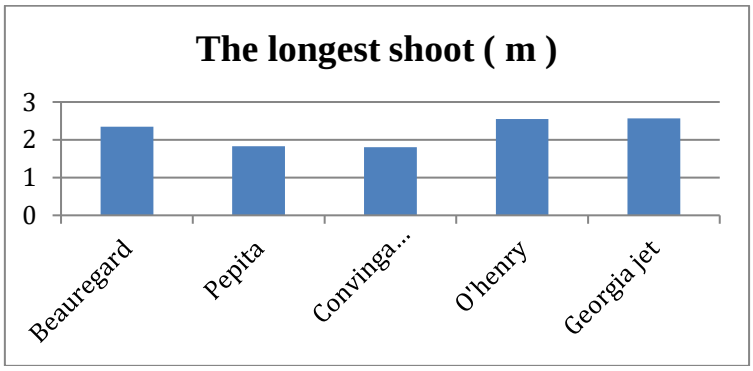


Chart No. 2 The longest shoot (m)

The longest shoots are found in three cultivars: O'henry, Georgia Jet, and Beauregard, while the other two cultivars, Pepita and Convingation, have shorter shoots.

3.1.10. The shortest shoot (m).

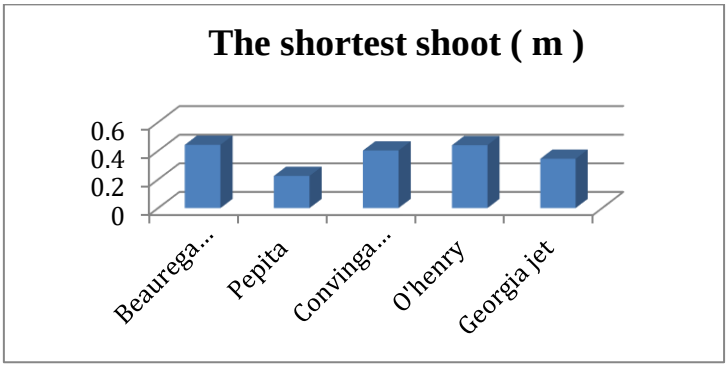


Chart No. 3 The shortest shoot (m)

The shortest shoot is in the Pepita cultivar, while the other four cultivars have smaller differences.

3.1.10. Number of leaves per plant

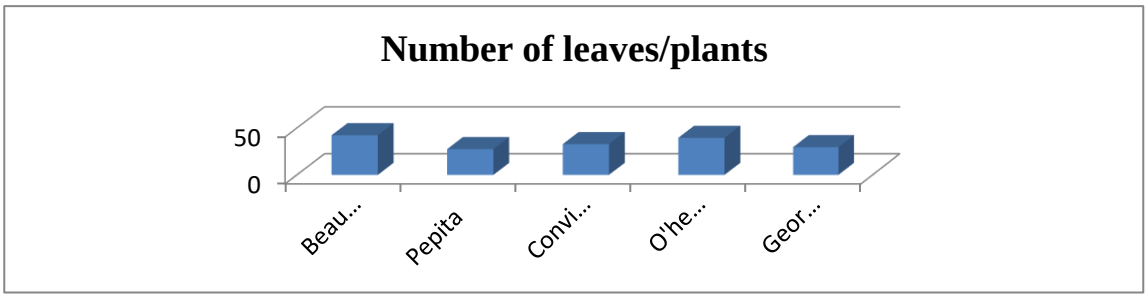


Chart No. 4 Number of leaves per plant

The number of leaves per plant varies, and the ranking of cultivars by number of leaves per plant is as follows: Beauregard, O'Henry, Convingation, Georgia Jet, and Pepita. The number of leaves is distinguished in the field because cultivars with a greater number of leaves completely cover the soil surface, preventing the growth of weeds.

3.1.11. Number of shoots per plant

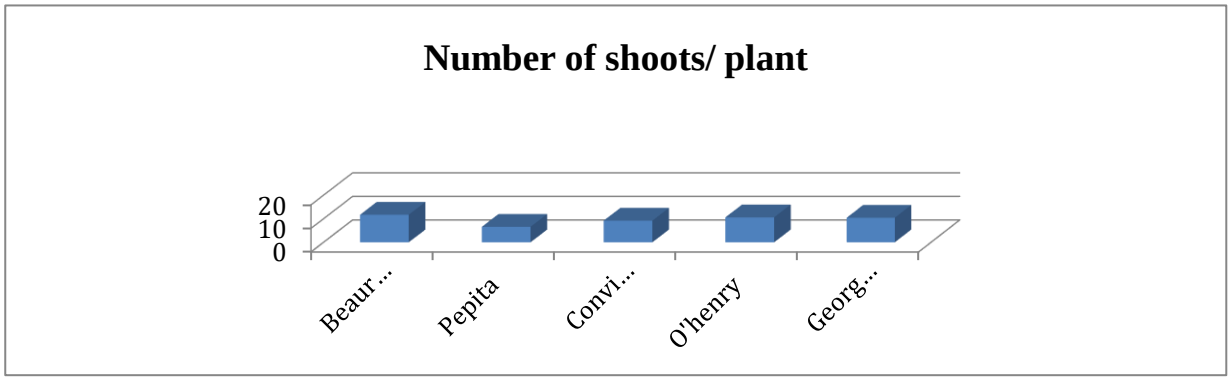


Chart No. 5 Number of shoots per plant

The number of shoots per plant varies; the cultivar with the highest number of shoots is Beauregard, and the cultivar with the lowest number of shoots is Pepita. Two cultivars, O'henry and Georgia jet, have the same number of shoots, while the Convingation cultivar has a lower number of shoots than the two cultivars, O'henry and Georgia jet.

Conclusions and recommendations

From the analysis of morphological and production indicators as well as adaptation to climate and soil, we can draw several conclusions, among which we will mention:

A. Conclusions

Among the conclusions we present, the most important:
1. The color of the leaf varies slightly between cultivars. It is green with dark or light shades. They are cultivars of the same group and very similar.
2. Sweet potatoes have two leaf shapes: lanceolate and palmate (like fig leaves). The lanceolate form is more resistant to blight. All five cultivars have lanceolate leaf shapes.
3. The shapes of the tubers are different, with the narrow conical shape prevailing.
4. The color of the skin and pulp varies from white, purple, and brown.
5. The placement of the buds is on all surfaces, which is more preferable.

B. Recommendations

The evaluation of morphological indicators is of interest in the selection of suitable cultivars according to the zones. We recommend cultivars with heart-shaped leaves that are more resistant to diseases and with superficial bud placement.

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LEVEL'S OF STUDENT'S KNOWLEDGE ACCORDING TO BLOOM'S TAXONOMY ON THE TOPICS OF GRAVITY AND COSMOLOGY IN UPPER SECONDARY SCHOOLS

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Abstract

This study investigates upper secondary school students' conceptual and procedural knowledge in gravitation and cosmology within the framework of Bloom's Taxonomy, encompassing the cognitive domains from remembering to evaluating, in alignment with curriculum standards and competency-based learning outcomes. The study aims to elucidate how the abstract and conceptually demanding nature of these physics domains shapes the development of higher-order thinking skills and scientific literacy. The research addresses cognitive performance across Bloom's levels, comparative understanding between gravitation and cosmology concepts, and persistent conceptual misconceptions in physics education. A mixed-methods research design was implemented, involving 100 students and 4 physics teachers from two secondary schools in Klinë. Data were collected through validated instruments, semi-structured interviews, and qualitative analysis of student-produced artifacts derived from simulations and presentations. Findings indicate alignment with Bloom's Taxonomy, with a predominance of higher-order cognitive processes, particularly analysis and evaluation. The results further indicate that students' performance is significantly influenced by prior knowledge, pedagogical strategies, textbook quality, and the integration of digital learning technologies.

Keywords: Bloom's Taxonomy, conceptual and procedural knowledge, gravitation, cosmology, conceptual misconceptions, physics education.

Introduction

Physics is a fundamental discipline of the natural sciences that studies matter, energy, space, and time as well as their interactions, providing the conceptual foundation for both natural sciences and engineering. In the contemporary curriculum, it is approached through the scientific method as an integrated process that includes empirical observation, hypothesis formulation, controlled experimentation, and data analysis, with the aim of constructing scientific models and laws. Within this framework, physics education aims at developing students' scientific competencies through the integration of experimental experience with conceptual knowledge construction. According to the National Research Council, effective learning is built upon linking prior knowledge with empirical evidence, enabling the development of stable and transferable understandings. In line with this approach, the contemporary curriculum directs the learning process toward the development of critical thinking, scientific reasoning, and problem-solving as key competencies of the 21st century. In modern physics, gravitation is conceptualized in classical mechanics as a universal attractive force between masses, whereas in general relativity it is understood as the curvature of spacetime caused by mass and energy, forming the basis for interpreting cosmological phenomena on a universal scale. Bloom's Taxonomy represents a hierarchical framework for classifying cognitive levels, ranging from remembering and understanding to analyzing, synthesizing and evaluating, and this is widely used in educational planning and assessment. In this study, it serves as an analytical instrument for assessing students' cognitive levels in the topics of gravitation and cosmology, while considering didactic factors such as teaching strategies and prior knowledge. Despite the theoretical importance of these domains, previous studies indicate persistent difficulties in students' conceptual understanding of gravitation and cosmology, particularly regarding abstract representations and the transition from classical to relativistic models, highlighting a gap in effective instructional approaches. Methodologically,

this study employs a mixed-methods research design, combining quantitative data from validated assessment instruments with qualitative insights derived from semi-structured interviews and analysis of student-produced artifacts, ensuring a comprehensive evaluation of cognitive performance and conceptual understanding. This research aims to contribute to the improvement of physics teaching practices by providing an empirical basis for optimizing didactic approaches in alignment with contemporary curriculum requirements. In particular, the findings are expected to inform teacher training, enhance instructional strategies, and support the development of improved curricular and textbook materials in the domains of gravitation and cosmology.

Literature Review

Contemporary learning theories have shifted from behaviorist toward constructivist and socio-cognitive perspectives, emphasizing knowledge construction rather than reproduction. Bransford, Brown, and Cocking argue that meaningful learning occurs through integration of new information with prior knowledge structures, enabling transfer across contexts (Bransford, J .D., Brown, A. L., & Cocking, R. R., 2000). Illeris extends this view by conceptualizing learning as a multidimensional process involving cognitive, emotional, and social dimensions (Illeris, 2018). In this framework, Bloom's taxonomy provides a structured hierarchy of cognitive processes from lower- to higher-order thinking, alongside a classification of knowledge types (factual, conceptual, procedural, metacognitive). From a socio-constructivist perspective, Vygotsky emphasizes socially mediated learning within the Zone of Proximal Development (Vygotsky, 1978), while Bandura highlights observational learning as a mechanism linking cognition and environment (Bandura, 1986). In physics education, research consistently shows that learning is more effective when based on conceptual modelling rather than memorization. McDermott and Redish emphasize mental models, conceptual reasoning, and misconceptions analysis as key components of effective physics learning (McDermott, L. C., & Redish, E. F., 1999). Hestenes further supports a model-based instructional approach. A common misconception in gravitation is the belief that heavier objects fall faster than lighter ones, despite the fact that their acceleration is independent of mass in the absence of air resistance. In modern physics, gravitation is interpreted as a transition from Newtonian force-based description to Einstein's geometric spacetime framework. At the cosmological scale, Weinberg and Mukhanov provide theoretical foundations for cosmic expansion and structure formation. Within science education frameworks such as PISA (OECD, 2019), scientific literacy is defined not as recall of knowledge, but as the ability to interpret, analyze, and apply scientific concepts in real-world contexts. These theoretical perspectives provide the foundation for the present study's analysis of students' conceptual development in gravitation and cosmology.

Methodology

This study is based on Bloom's Taxonomy as a framework for analyzing the teaching and learning of gravitation and cosmology concepts in upper secondary physics education. A mixed-methods research design was employed, integrating quantitative and qualitative approaches to provide a comprehensive evaluation of students' cognitive achievement and conceptual understanding. The research was conducted in the gymnasium "Luigj Gurakuqi" and IAAP "Fehmi Agani" in Klina, involving 100 students and 4 physics teachers. The student sample included learners from grade XI and XII, comprising both female and male participants. In "Luigj Gurakuqi" Gymnasium, the sample consisted of 22 male and 28 female students (ages 16-17) corresponding to 45% male and 55% female participants. In IAAP "Fehmi Agani"

Technical Upper Secondary School, the sample included 30 male and 20 female students (ages 16-17), corresponding to 60% male and 40% female participants. Students were selected through random sampling to ensure equal representation within the study group. Data were collected using multiple instruments, including structured tests, student questionnaires, semi-structured teacher interviews, and analysis of student-produced artefacts generated through simulations and classroom presentations. All instruments were aligned with the national curriculum and structured according to Bloom's Taxonomy, and were reviewed for content validity prior to use. Findings were organized using tables and graphs to support systematic comparison and interpretation of results. The study examined students' cognitive performance across Bloom's levels, variations in understanding gravitation and cosmology concepts, and key factors influencing learning outcomes, including prior knowledge, instructional approaches, textbook quality, and the use of digital technologies in physics education. Quantitative data were analysed using descriptive statistics, including means and frequencies, while qualitative data were coded thematically to identify recurring patterns in understanding and misconceptions. The research addresses persistent difficulties in students' understanding of abstract concepts in gravitation and cosmology, particularly gravitational interactions, relativistic frameworks, cosmic expansion, dark matter, and dark energy.
The main aim of the study is to evaluate students' cognitive achievement according to Bloom's Taxonomy and to examine the role of interactive teaching strategies and digital simulations in enhancing conceptual understanding and scientific reasoning. Ethical approval and informed consent from participants and guardians were obtained prior to data collection.

Results and discussion

The demographic characteristics of research sample, including age, gender, and percentage distribution for each Upper Secondary Schools, are summarized in the following tables. Data are presented separately for "Luigj Gurakuqi" and IAAP "Fehmi Agani" whereas combined graphs are used only when student responses were identical or showed minimal statistical variation. This approach enables clearer interpretation and comparison of students' cognitive achievement in gravitation and cosmology.

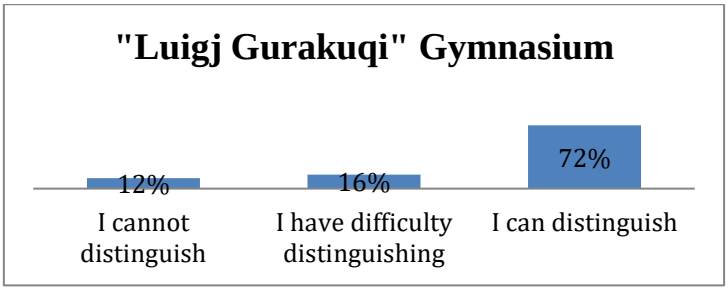


Figure 1. Percentage of students' ability to distinguish between mass and weight at "Luigj Gurakuqi" Gymnasium

Most student 72% can distinguish between mass and weight, 8% report difficulties , while 6% are unable to make the distinction.

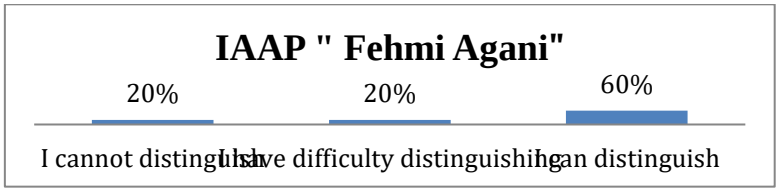


Figure 2. Percentage of students' ability to distinguish between mass and weight at IAAP "Fehmi Agani"

60% of students can distinguish between mass and weight, 10% report difficulties, and 10% are unable to make the distinction.

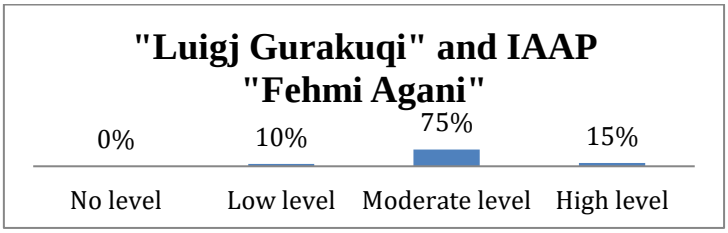


Figure 3. Level of students 'ability to reproduce the universal law of gravitation without textbook assistance

75% of students can reproduce the concept and mathematical formulation without textbook support, 15% show high level, and a 10% a low level.

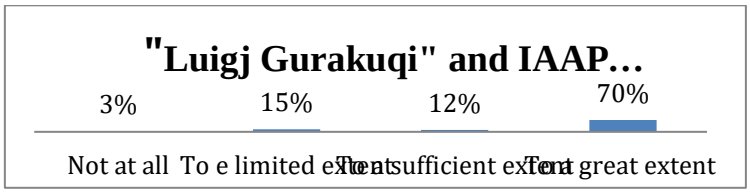


Figure 4. Student' understanding of the attraction of bodies toward Earth's center of mass under the action of gravitational field.

Among the 100 students, 70% reported a very good understanding of the phenomenon, 12% good, 15% sufficient, and 3% no understanding.

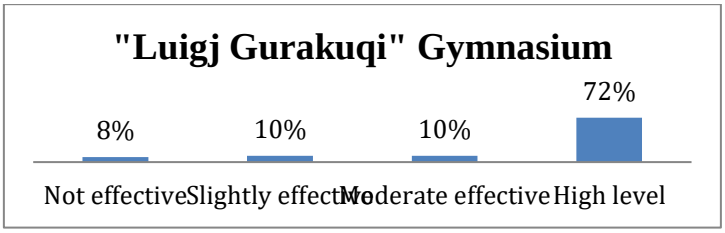


Figure 5. Students' ability to transfer theoretical principles of gravitation to new problem situations.

72% of students' report of being highly effective in applying gravitational principles to new problem situations, 10% moderate, 10% low, 8% are unable to perform this transfer successfully.

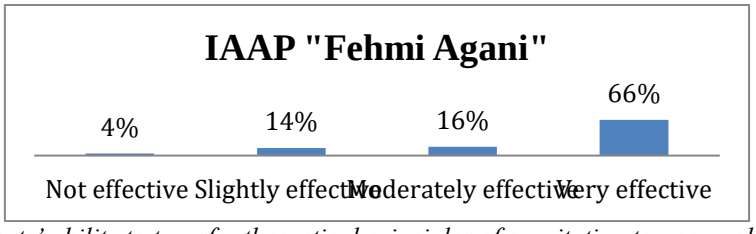


Figure 6. Students' ability to transfer theoretical principles of gravitation to new problem situations.

66% of students from technical track report high effectiveness in applying gravitational principles to new problem situations, 16% moderate, 14% slightly effective, and 4% are unable to perform this transfer successfully.

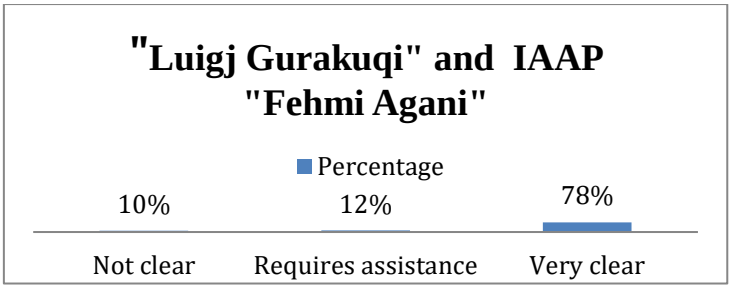


Figure 7. Students' understanding and analysis of how mass and distance influence gravitational force between two objects.

According to the figure 78% of students clearly analyze the effect of mass and distance on gravitational force between two bodies, 12% require assistance, and 10% do not understand the relationship.

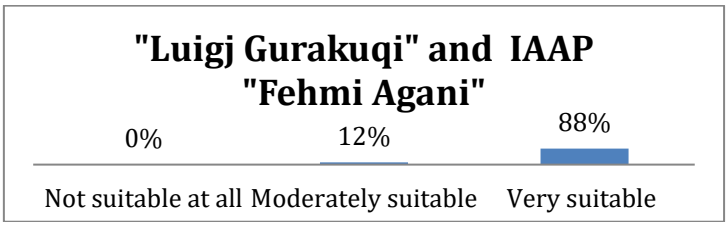


Figure 8. Students' evaluation of the suitability teaching methods for facilitating understanding of gravitation and cosmology concepts.

88% of students consider the teaching methods (simulations, examples, discussions) highly appropriate, while 12% rate the as moderately appropriate.

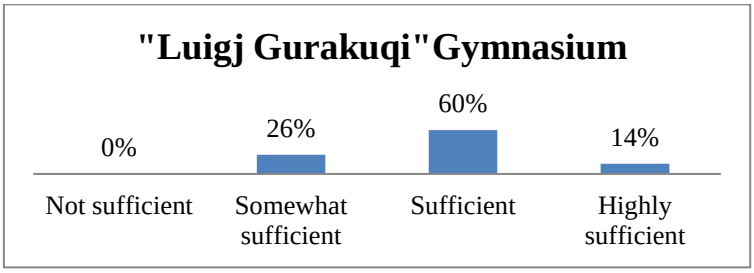


Figure 9. Students' evaluation of textbook clarity and sufficiency for understanding modern theories on the origin of the Universe.

60% of students consider the textbook content sufficiently clear for understanding modern theories on the origin of Universe, 14% find it very clear and adequate, while 26% report that it provides limited information.

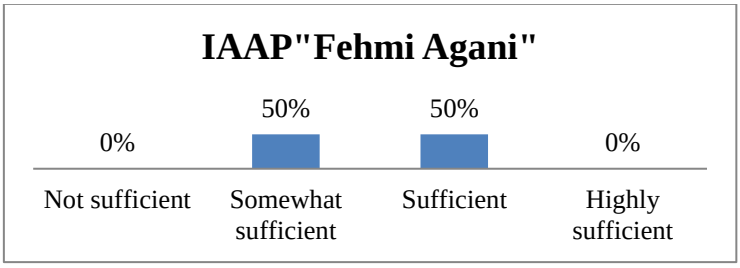


Figure 10. Students' evaluation of textbook clarity and sufficiency for understanding modern theories on the origin of the Universe.

50% of students find the textbook sufficiently clear, while 50% consider it provides limited information.

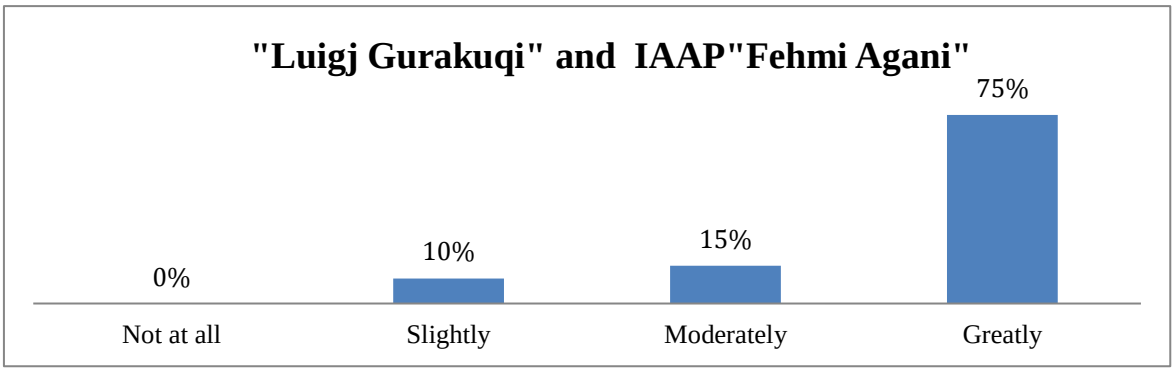


Figure 11. Active teaching methods and conceptual understanding of gravity

75% of students state that active teaching methods greatly support the shift from memorization to conceptual understanding of the law of gravitation, 15% report a moderate effect, and a 10% a low effect.

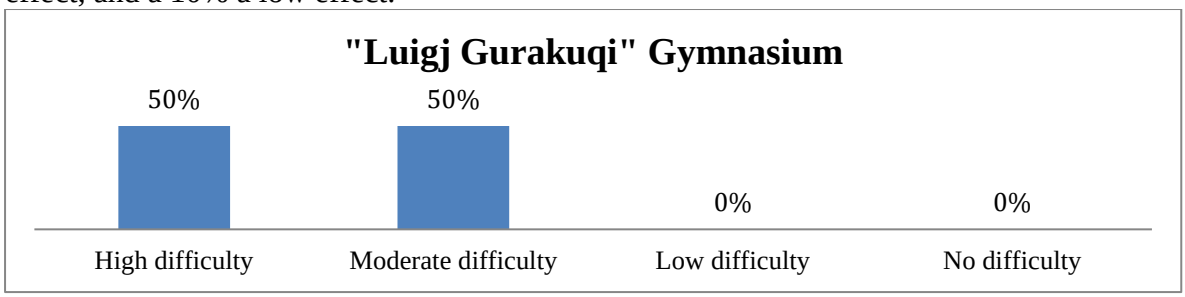


Figure 12.Students' difficulty in visualizing abstract concepts such as space time curvature

60% report moderate difficulties, 20% low, and 20% high difficulties in visualizing and understanding these concepts.

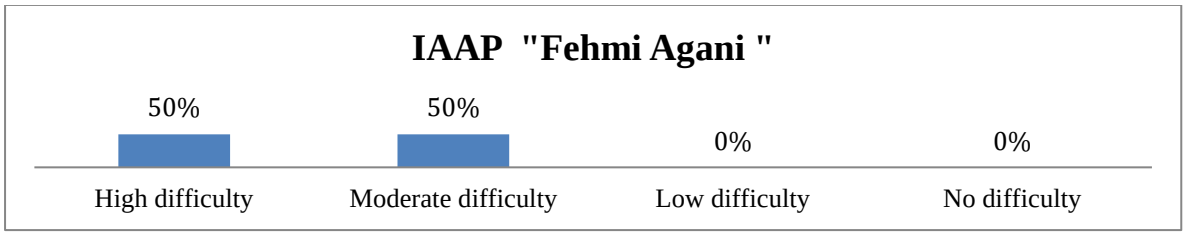


Figure 13. Students' difficulty in visualizing abstract concepts such as space time curvature

50% report moderate and 50% high difficulties, indicating a significant learning challenge requiring improved teaching approach

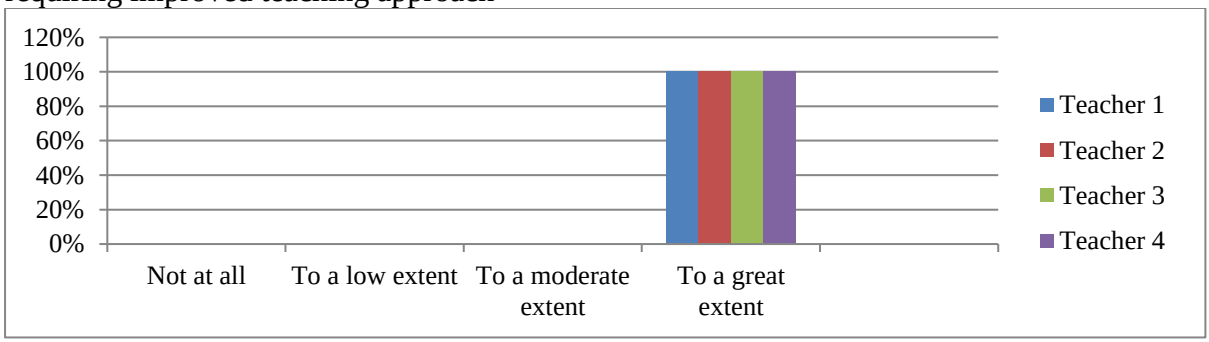


Figure 14. Assessment of the impact of simulations and virtual laboratories

All teachers 100% strongly agree that simulations and virtual laboratories enhance the visualization of abstract phenomena such as space time curvature.

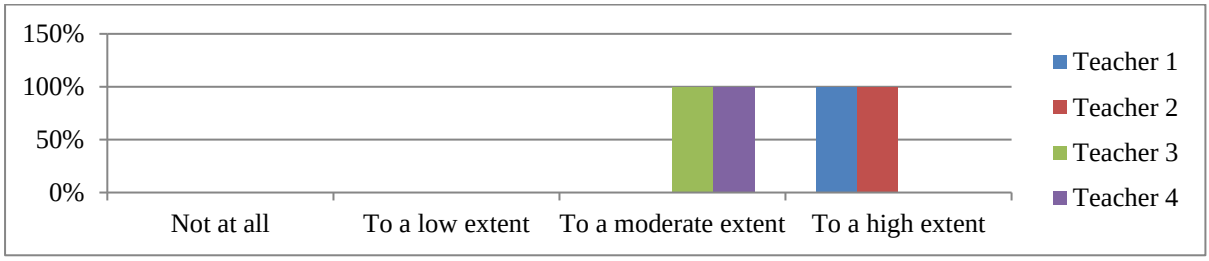


Figure 15. Application of gravitational knowledge in real-life and astrophysical contexts

Teachers at "Luigj Gurakuqi" rate this ability higher, while those at "Fehmi Agani" at a moderate level, both results indicate a positive level of application of gravitational knowledge.

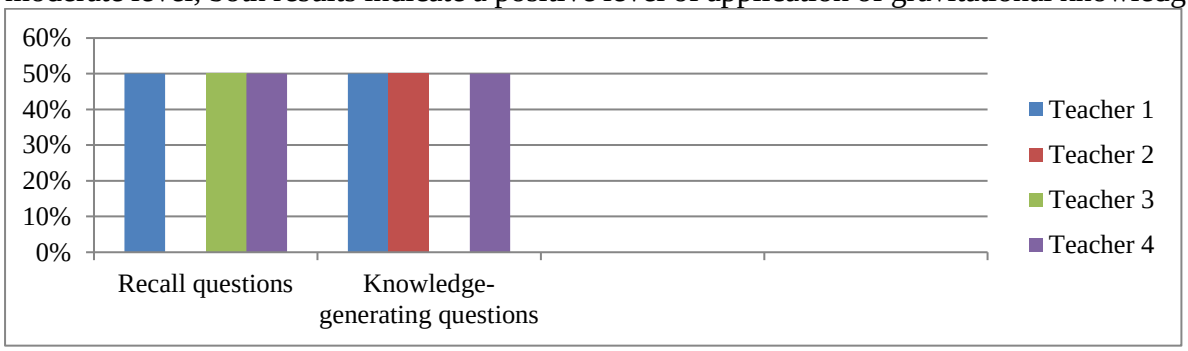


Figure 16. Types of questions for assessing and generating students' knowledge

Two teachers use both types, while two use one type depending on students' needs.
The comparative summary synthesizes the main findings across all indicators, highlighting major similarities and differences between the two schools.
Students from "Luigj Gurakuqi" Gymnasium exhibit slightly higher performance in conceptual understanding and knowledge transfer (72%vs 60%), particularly in distinguishing mass and weight and applying gravitational principles to novel problem situations. Both institutions show strong understanding of core concepts, including the universal law of gravitation (75%) and gravitational field interpretation (70%), indicating a solid shared foundation knowledge. Active teaching methods are highly valued in both institutions (88%), while teachers confirm the effectiveness of digital simulations (100%). However, differences are more evident in abstract reasoning and visualization of complex concepts, where students from IAAP "Fehmi Agani" Technical Upper Secondary School report higher levels of difficulty (up to 50%), suggesting a need for enhanced conceptual and visual support. These variations reflect differences in instructional approaches, curricular emphasis, prior conceptual preparation, and exposure to active learning and visualization-based strategies, which may influence students' ability to construct abstract scientific concepts and transfer knowledge to novel problem solving situations.

Conclusion

Findings of this study indicate generally high levels of students' conceptual understanding of gravitation and cosmology, with strong performance in fundamental concepts and effective application of knowledge in most cases. Active teaching methodologies and digital simulations were identified as highly effective in supporting conceptual learning and visualization of abstract phenomena, while textbooks were considered moderately sufficient depending on

context. However, persistent difficulties were observed in understanding highly abstract concepts, highlighting the need for further didactic support. Overall, the results confirm all research hypotheses, demonstrating that Bloom's Taxonomy-based analysis, combined with interactive teaching strategies, significantly enhances students' cognitive achievement and conceptual development in physics education

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RADIOGRAPHIC METHODS FOR LOCATING & EVALUATING IMPACTED MAXILLARY CANINES USING KUFTINEC, CHAUSHU AND ERICSON & KUROL METHODS

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Abstract

A canine impaction is a very common phenomenon in the everyday dental practice. For the orthodontist to be able to successfully treat an impacted maxillary canine a deep and thorough radiographic evaluation needs to be made almost imminently after the first visit.
The various modern methods are an imperative and must therefore be fully reviewed by the orthodontist before the beginning of treatment.
This paper aims to review cases of bilateral and unilateral canine impaction, their exact location through the most used diagnostic methods in modern orthodontics.

Introduction

Radiographic evaluation

Orthodontic-surgical treatment of impacted teeth is very complex, which is why radiological diagnostics play an important role in therapy, showing their exact localization. Based on the obtained images, the methods for treating the impacted tooth are decided. Several different radiological techniques can be used in diagnostics. The appearance of impacted teeth can be proven through orthopantomogram images, laterolateral and posteroanterior and occlusal and periapical images. It is important to show the position of the tooth, its direction, placement in the bone and relationship to the roots of neighboring teeth. Such images are two-dimensional. They diagnose the presence of impacted teeth, but any analysis is due to distortion, superposition and the appearance of artifacts.
Details such as the exact location of the tooth, the impact on neighboring teeth and structures, and the root anatomy are difficult to distinguish. For this reason, cone beam computed tomography (CBCT) has been used more frequently in recent years, which shows the jaw in three dimensions with the exact position of the impacted tooth, the hard and soft tissues surrounding it (Katalinić et al., 2012), (Jeremias et al., 2016). Radiography is a diagnostic procedure for detection and diagnosis. According to Severin, the X-ray examination contains three moments:
1. Visualization of the impacted tooth.
2. Analysis of the morphology of the impacted maxillary canine, inclination of the impacted maxillary canine and position towards adjacent structures.
3. Assessment of the risk of complications.
The X-ray examination should meet certain criteria: - complete contour of the impacted maxillary canine; - contour of the follicular sac; - contours of bone tissue, as well as of the root of the impacted tooth.
Various radiographic examinations (orthopaedic, lateral, PA, teleradiography, occlusal, computed tomography) have their advantages and disadvantages. The methods differ in the radiation dose, the speed and quality of obtaining information, as well as in the cost-benefit ratio (price). The assessment of which and how many of them will be used depends on the decision of the therapist, individually for each patient. All of these examinations reveal the

position of the canine in relation to the surrounding structures, but also the inclination of the longitudinal axis of the impacted tooth in relation to the reference plane.

Orthopantomogram (OPG)

The use of orthopantomogram examination to localize impacted maxillary canines is the most commonly recommended method, given its relatively low radiation exposure, simple performance, economic acceptability, and wide distribution (Chaushu et al., 1999), (Fox et al.,1995). In case of impactions, orthopantomogram can be used to monitor:
• tooth position (deep or shallow);
• general orientation, horizontal or inclined mesial or distal;
• relationship to neighboring teeth;
• risk of transposition;
• presence or absence of apical resorption of the roots of neighboring teeth.
Lateral radiography
This radiograph allows visualization of the sagittal and vertical position of the canines and their relationship to the floor of the nasal cavity.
The longitudinal axis of the canine should be almost parallel to the longitudinal axis of the incisors.

Frontal radiograph

This radiograph provides a transverse view of the situation. This radiograph can measure the intercanine distance, visualize the abnormal position of the canine tooth bud (germ), and assess the likelihood of impaction. Canines that are about to erupt should be inclined mesially, with their crowns lying below the level of the tips of the lateral incisors and the lateral border of the nasal cavity.

Periapical Radiographs

By using two or more periapical films of the same region with different angulations of the central beam and a conical technique that allows parallelism between the tooth and the film, the orthodontist can determine the exact position of the tooth. Using Clark's rule, it is determined whether the tooth is impacted labially, lingually, or palatally.

Occlusal radiographs

Orthodontists use these radiographs very often, as they are a useful adjunct to other radiological examinations, providing a third horizontal dimension.
Ericson and Kurol sector method

Vertical Parallax

To facilitate the use of vertical parallax with the orthopantomography, the tube should be increased to 70-75 degrees.
a – axial angulation of the canine to the central sagittal plane or medial line.
OL – occlusal line, connects the center point between the two mandibular central incisors with the tip of the buccal tubercle of the first mandibular molar.
Sector 1 – the tip of the maxillary canine is located distal to the root of the lateral incisor

Sector 2 – the tip of the maxillary canine is located in the distal half of the root of the lateral incisor
Sector 3 – the tip of the maxillary canine is located in the mesial half of the root of the lateral incisor
Sector 4 – the tip of the maxillary canine covers the distal half of the root of the central incisor
Sector 5 – the tip of the maxillary canine covers the mesial half of the root of the central incisor.

Kuftinec Method

If the tip of the canine covers the distal half of the root of the lateral incisor, then it is located buccally is more mesial to the root of the lateral incisor then it is located palatal.

Chaushu Method

Canine-Incisor Index, CII; Canine-Canine Index, CCI; Buccal < 1.15 > Palatal.
Aim

The aim of this study is to determine the methods used for location and evaluation of impacted maxillary canines, as well as to determine a detailed position using Chaushu, Kuftinec and Ericson and Kurol sector method.

Materials & Methods

0 patients with impacted maxillary canines were included in this study. For the evaluation and location method OPG was used. Out of patients 5 were males and 5 were females, out of which 8 had a mixed dentition and 2 had permanent dentition. Their age varied from 9-18 years.

Results

6 patients had buccally impacted maxillary canines, out of which 4 were bilateral and 2 unilateral.
4 patients showed palatal impaction out of which only one patient had a bilateral impaction.

Impacted Maxillary Canine			**Unilateral Impacted Maxillary Canine**		
	Number	%		Number	%
13	8	53	13	3	20
23	7	47	23	2	13,33
Bilaterally Impacted Maxillary Canines					
13 & 23		Број		%	
		10		66,6	

Using the Kuftinec method to determine the canine location, it was determined that, in total 10 buccally impacted canines and 5 palatal impacted canines were analyzed.
50% of the patients showed a bilateral impaction out of which 80% were buccal impactions and only 20% palatal.
50 % of the rest showed a unilateral impaction out of which 40% were buccally placed and 60% palatal.

Impaction	Buccally	Palatal	Total
Unilateral	10	5	15
Bilateral	8	2	10
Total	18	7	25

Using the Ericson & Kurol sector method the following was determined:
Out of 10 buccally impacted canines 8 were placed in sector 1, and 2 into sector 2.
Out of 5 palatal impacted maxillary canines 3 were placed into sector 4, and 2 into sector 3.

Sectors	13		23		Total	
1	4	50%	4	57,14%	8	53,33%
2	1	12,5%	1	14,28%	2	13,33%
3	0	0	2	28,57%	2	13,33
4	3	37,5%	0	0	3	20%
5	0	0	0	0	0	0
Total	8	53%	7	47%	15	100%

According to Chaushu method, IKI (Canine-Incisor Index, CII) was used for 7 cases, out of which 5 had a buccal impaction and only 2 showed a palatal impaction, for the rest of 3 an IKK (Canine-Canine Index, CCI) was used, and it showed that 2 had a palatal impaction and only one showed a buccal impaction.

Kuftinec Method				
Position	13		23	
	Nr.	%	Nr	%
Buccal	5	62,5%	5	71,42%
Palatal	3	37,5%	2	28,58%
Total	8	100%	7	100%
Chaushu Method				
Position	13		23	
	Nr.	%	Nr.	%
Buccal	5	62,5%	5	71,42%
Palatal	3	37,5%	2	28,58%
Total	8	100%	7	100%

For us to determine the canine position in relation with midline, measuring alpha angle that is formed between longitudinal central axis and medial sagittal line method was used, we determine whether the position is vertical or horizontal.
We concluded that 5 of the right impacted maxillary canines showed a favorable prognosis, compared to 4 from the left. 3 out of the 8 impacted on the right side showed an average prognosis whereas 3 from the left side showed an average prognosis. We conclude that not a single impacted maxillary canines showed a poor prognosis.

Degree	13	23	Total			
	Nr	%	Nr	%	Nr	%
First 0-15 degrees	5	62,5	4	57,2	9	60
Second 16-30	3	37,5	3	42,8	6	40

Third >31	0	0	0	0	0	0
Total	8	100	7	100	15	100

Conclusion

Panoramic radiography remains the most used diagnostic aid in clinical cases where there is a suspicion of dental impaction of permanent canines, because of its ease of interpretation, low cost, and low radiation.
Clinical examination and ectopic positioning on a panoramic radiograph warrant further radiographic investigations.
The methods used for determining the exact and precise canine locations all correspond and match 100%.
The Chaushu, Clack and Ericson Kurol methods remain a wide field of study and clinical evidence for both locating and evaluating maxillary canine treatment., however for more complicated cases a cbct is preferred.

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DIAGNOSTIC CHALLENGES IN DORSAL HAND MASSES: RHEUMATOID NODULES WITH CONCOMITANT RADIAL NERVE NEUROMA

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Abstract

Soft-tissue masses of the dorsal hand present a diagnostic challenge because they may originate from inflammatory, vascular, tenosynovial, or neoplastic conditions with similar clinical manifestations. Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis; however, involvement of the dorsum of the hand associated with extensor tendon structures is uncommon and may mimic benign or malignant soft-tissue tumors. We present a rare case of concomitant rheumatoid nodule and radial nerve neuroma in a 62-year-old patient with two slowly enlarging masses on the dorsum of the left hand and lateral forearm. The patient experienced progressive difficulty with hand movement due to the size of the dorsal lesion and pain on percussion over the forearm mass. Clinical examination revealed a firm, immobile dorsal hand lesion and a painful forearm tumor-like formation, creating a preoperative diagnostic dilemma regarding surgical management. Both lesions were surgically excised and evaluated histopathologically. The dorsal hand mass was identified as a rheumatoid nodule characterized by inflammatory infiltrates, fibrinoid deposits, and synovial hyperplasia, while the forearm lesion was confirmed as a radial nerve neuroma. At one-year follow-up, no recurrence was observed, and the patient maintained full, painless hand function. This case emphasizes the importance of considering rheumatoid nodules in the differential diagnosis of dorsal hand masses and highlights the essential role of histopathological evaluation in establishing accurate diagnosis and guiding treatment.

Keywords: rheumatoid nodule, dorsal hand mass, radial nerve neuroma, soft-tissue tumor, histopathology, rheumatoid arthritis

Introduction

Soft-tissue masses of the hand represent a heterogeneous group of lesions arising from synovial, tendon, vascular, neural, and connective tissues. Although many of these lesions are benign, their clinical presentation may resemble malignant tumors, making accurate diagnosis difficult. The dorsum of the hand is an uncommon location for tumor-like formations, and the differential diagnosis includes giant cell tumor of the tendon sheath, tenosynovial chondromatosis, osteochondroma, synovial hemangioma, and, more rarely, sarcomatoid tumors of synovial origin. Because of the complex anatomy of the hand and the functional importance of surrounding structures, appropriate preoperative evaluation and surgical planning are essential [2,4,6].

Soft tissue tumors of the hand are relatively frequent, with more than 15% of all soft tissue tumors occurring in this region, and the majority being benign in nature [2,4]. However, their overlapping imaging and clinical features often make diagnosis challenging, and histopathological confirmation is frequently required for definitive classification [6].

Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis and occur in approximately 20–30% of seropositive patients. They are usually located over pressure points such as the olecranon, extensor surface of the forearm, and Achilles tendon. Involvement of the dorsum of the hand, especially in close relation to extensor tendon structures, is uncommon and may clinically mimic other soft-tissue tumors. In some cases, these lesions may lead to tendon irritation, limitation of movement, or tendon rupture [2].

Neuromas of the radial nerve are also rare lesions and are most commonly associated with trauma, chronic compression, or previous surgical intervention. Clinically, they may present with pain, tenderness, or neurological symptoms, which can further complicate diagnosis when occurring simultaneously with other tumor-like lesions [10].
The concomitant presence of rheumatoid nodules and a radial nerve neuroma in different anatomical regions represents a rare diagnostic and therapeutic challenge. In this report, we present a case of rheumatoid nodules located on the dorsum of the left hand associated with a radial nerve neuroma of the forearm, emphasizing the importance of histopathological evaluation in establishing an accurate diagnosis and guiding appropriate surgical management.

Case Report

A 62-year-old patient presented with two slowly enlarging masses located on the dorsum of the left hand and lateral aspect of the left forearm. (Fig. 1). Past medical history included arterial hypertension, benign prostatic hyperplasia, and cholelithiasis. The patient reported progressive enlargement over several months. Before surgery, the patient experienced difficulty with hand movement due to the size of the dorsal hand mass. Additionally, he reported pain on percussion over the lateral forearm lesion.
Clinical examination revealed a firm, immobile mass on the dorsum of the left hand in relation to the extensor tendon structures. A second lesion on the lateral forearm was painful on palpation and percussion, suggesting possible neural involvement.
Computed tomography (CT) of the left forearm and hand demonstrated a heterogeneous predominantly hypodense mass with areas of cystic degeneration located dorsally in the projection of the second, third, and fourth metacarpal bones, extending toward the carpal bones and adjacent extensor tendon group. The lesion showed extension into the radiocarpal and distal radioulnar joint spaces and was radiologically suggestive of a neurofibromatous lesion. Marked osteoarthritic degenerative changes of the carpal and metacarpal skeleton were also present without evidence of traumatic bone lesions. Ultrasound examination additionally confirmed a soft-tissue tumorous lesion in close relation to the extensor tendon apparatus.
Fine-needle aspiration biopsy (FNAB) was performed preoperatively and was classified as cytological Group I.
The presence of two tumorous formations in different anatomical regions posed a surgical challenge. Preoperatively, the biological behavior of the dorsal hand lesion remained uncertain, and malignancy could not be excluded. This created a dilemma regarding the extent of surgical excision, whether to perform radical tumor resection with wider margins or simple extirpation with preservation of surrounding structures, particularly the extensor tendons.
The procedure was performed under local anesthesia utilizing the WALANT (Wide Awake Local Anesthesia No Tourniquet) technique in combination with monitored anesthesia care (MAC). **[3]** The patient was positioned supine, and both operative fields were prepared and draped in a standard sterile fashion. Attention was first directed toward the dorsum of the hand, where a longitudinal skin incision was made directly over the palpable lesion. Sharp and blunt dissection through the subcutaneous tissue was performed with meticulous hemostatic control. Intraoperatively, a well-circumscribed, firm, gelatinous soft-tissue mass was identified. (Fig. 2). Circumferential dissection allowed complete mobilization of the lesion from the surrounding tissues. Particular care was taken to preserve the extensor apparatus; the extensor tendons and associated dorsal structures were identified and remained entirely intact throughout the procedure without evidence of iatrogenic injury. The lesion was excised and submitted for histopathological evaluation. (Fig. 3.)
Attention was subsequently directed to the lateral aspect of the forearm, where a longitudinal incision was performed over the palpable mass. Careful dissection through the subcutaneous

tissue was carried out using combined sharp and blunt techniques. Intraoperative exploration revealed a tumorous mass of the radial nerve. (Fig. 4.) Surgical dissection was undertaken to isolate the lesion while preserving the continuity of the radial nerve. The radial nerve was meticulously protected throughout the procedure, without evidence of mechanical, traction, or thermal injury. Complete extraction of the mass was achieved and the specimen was submitted for histopathological analysis. (Fig. 5.)

Following excision of both lesions, the operative fields were copiously irrigated with sterile saline solution and meticulous hemostasis was achieved. Layered wound closure was performed using 3-0 Vicryl sutures for the subcutaneous tissues and 4-0 Prolene sutures for skin approximation. Sterile compressive dressings were subsequently applied. The patient tolerated the procedure well, and no intraoperative complications were encountered.



Figure 1. Preoperative clinical photograph showing a firm, well-defined mass on the dorsum of the left hand.



Figure 2. Intraoperative photograph showing the dorsal hand mass in situ during surgical exposure.



Figure 3. Intraoperative photograph following removal of the dorsal hand mass, showing a preserved extensor apparatus with exposed extensor tendons.



Figure 4. Intraoperative view: round, well-defined neuroma mass of the radial nerve at the lateral forearm — characteristic smooth, pearly-white appearance.



Figure 5. Lateral forearm: radial nerve isolated with yellow vessel loops for safe neuroma excision.

Histopathological Findings

Histopathological examination of the dorsal hand lesion revealed nodular aggregates composed of inflammatory infiltrate with central fibrinoid necrosis surrounded by palisading histiocytes and synovial hyperplasia. Congo red staining was negative, while PAS staining was positive. These findings were consistent with a rheumatoid nodule.
Histopathological evaluation of the lateral forearm lesion confirmed a radial nerve neuroma.

The two tumor-like formations originated from different tissues and demonstrated distinct histopathological features.

Results / Follow-up

The postoperative course was uneventful. At one-year follow-up, there was no recurrence of either lesion. (Fig. 6). The patient maintained full, painless flexion and extension of the affected hand, with preserved neurological function. Following surgical management, the patient was referred to the Department of Rheumatology. Further evaluation confirmed rheumatoid arthritis, and long-term treatment was started and is ongoing.



Figure 6A.

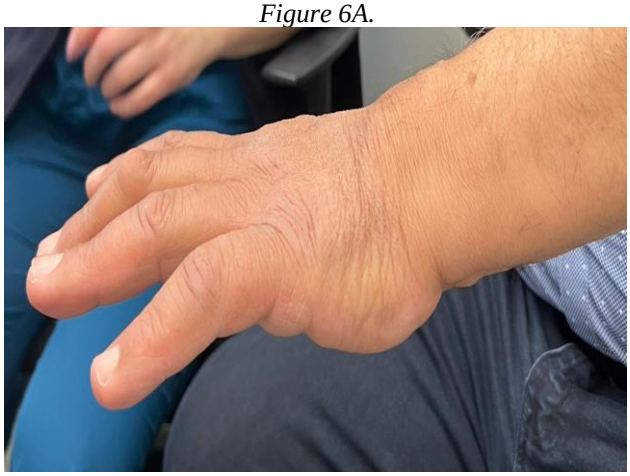


Figure 6B.

Figure 6. One-year postoperative photographs of the hand showing a well-healed surgical site with no clinical evidence of recurrence. (A) Anterior aspect; (B) Lateral aspect.

Discussion

Soft-tissue masses of the hand and forearm are diagnostically challenging due to the wide spectrum of possible etiologies, including inflammatory, vascular, neural, and neoplastic conditions. Clinical and radiological overlap often limits preoperative diagnostic accuracy, particularly in anatomically complex regions such as the dorsum of the hand [4,11].
Rheumatoid nodules are the most common extra-articular manifestation of rheumatoid arthritis but are typically located over pressure points. Dorsal hand involvement is uncommon and may closely mimic benign or malignant soft-tissue tumors, especially when associated with tendon

structures. Their firm consistency and deep location can further obscure clinical differentiation from neoplastic lesions [8].

Radial nerve neuromas are rare and usually post-traumatic or compressive in origin. They commonly present with localized pain and hypersensitivity; however, these features are non-specific and may overlap with other soft-tissue pathologies, particularly when multiple lesions coexist, as in this case [10].

Imaging modalities such as CT and ultrasound are useful for defining lesion extent but are often non-specific in differentiating inflammatory from neoplastic processes. Similarly, fine-needle aspiration may be inconclusive, as demonstrated in this case, highlighting its limited diagnostic value in fibrotic or necrotic lesions [4,7].

Definitive diagnosis relies on histopathological examination, which in this case clearly distinguished a rheumatoid nodule from a radial nerve neuroma. This emphasizes the necessity of tissue diagnosis in atypical or multifocal soft-tissue presentations [11,12].

Surgically, careful dissection with preservation of extensor tendons and neurovascular structures is critical, particularly when malignancy cannot be excluded preoperatively. The favorable functional outcome in this case supports complete excision as an effective and safe approach when guided by intraoperative findings and anatomical preservation principles [13].

Overall, this case highlights the importance of considering rheumatoid nodules in the differential diagnosis of dorsal hand masses and reinforces the essential role of histopathology in guiding definitive diagnosis and management.

Conclusion

This case demonstrates the diagnostic challenges of soft-tissue masses of the hand and forearm, especially when inflammatory and neural lesions coexist. Rheumatoid nodules in atypical locations may closely mimic tumors, while radial nerve neuromas can present with non-specific pain, making preoperative diagnosis difficult.

Imaging and cytology are often inconclusive, so histopathological examination remains essential for definitive diagnosis. Careful surgical excision with preservation of vital structures allows good functional outcomes.

Importantly, preoperative surgical evaluation may also reveal previously undiagnosed internal medical conditions, which can significantly affect overall patient management.

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DIGITAL TRANSFORMATION IN PARLIAMENT OF THE REPUBLIC OF NORTH MACEDONIA

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Abstract

This paper examines the impact of digital transformation on the parliamentary public administration sector in the Republic of North Macedonia. Drawing on an empirical survey conducted in January 2024 among 49 employees in the parliament (13 Albanian-language respondents and 36 Macedonian-language respondents), the study tests two hypotheses: that the widespread integration of digital technologies significantly affects work practices and service delivery, and that digital transformation correlates positively with efficiency gains, service quality improvements, and more responsive governance. Survey results confirm both hypotheses, revealing high levels of digital awareness, broad recognition of technology-driven improvements in public services, and moderate satisfaction with current digitalization levels. Data-privacy and cybersecurity concerns represent the most prominent challenge identified by respondents. The paper situates these findings within the broader Western Balkans context and the North Macedonia Reform Agenda 2024–2027, contributing empirical evidence to the growing literature on digital government in transitional and accession-candidate states.

Keywords: digital transformation, public administration, governance, North Macedonia.

Introduction

The rapid advancement of information and communication technologies has fundamentally reshaped the way governments interact with citizens, process information, and deliver public services. Digital transformation, defined as the systematic integration of digital technologies into all areas of organizational activity, has moved from a strategic option to an operational imperative for public administrations worldwide (Thomas, 2024). Governments are modernizing their administrative frameworks, enabling continuous cross-border mobility and improving digital interactions with citizens (United Nations, 2022).

In the Western Balkans, the trajectory of digital transformation is shaped by both internal reform agendas and external pressures from European Union accession processes. North Macedonia, in particular, has made measurable strides: the European Commission approved its Reform Agenda 2024–2027 in October 2024, unlocking €6 billion from the Reform and Growth Facility to support digitalization, good governance, and energy transition (Metamorphosis Foundation, 2025). The country has emerged at a 'systematic stage' in UNDP's Digital Development Compass, signaling strategic investment in digital public services and skills (UNDP, 2024).

Albeit, empirical evidence from within public institutions about employees' perceptions, experiences, and concerns remains scarce. This paper addresses that gap by reporting on a structured survey conducted in January 2024 among 49 employees of the parliamentary public administration, as a key institution in which digitalization intersects with transparency, accountability, and legislative governance.

The paper is organized as follows. The next section reviews the relevant literature. Section three presents the research problem, hypotheses and describes the methodology. Section four analyzes the survey data. The final section discusses findings and concludes with recommendations.

Literature Review

Digital transformation has become a central strategic priority for public administration, reshaping citizen–government relationships, service delivery, and internal governance (IJAMRS, 2025). The integration of digital technologies enables governments to streamline services and enhance the overall citizen experience, from online portals to mobile applications, while harnessing data for evidence-based decision-making (Thomas, 2024). Automation and digital tools significantly improve the efficiency of administrative processes, allowing institutions to identify trends, allocate resources efficiently, and respond promptly to emerging challenges (Kamoche & Wood, 2023).

A systematic literature review by Tangi et al. (2023), based on 164 studies using the PRISMA method, identified key drivers, implementation processes, and outcomes of digitally-induced change in the public sector. Their findings underscore that digital transformation is not merely technical but organizational, requiring cultural shifts, leadership commitment, and new competency frameworks. Similarly, a bibliometric analysis of Web of Science data found a steadily increasing research volume since 2020, closely linked to the acceleration of digital government adoption during the COVID-19 pandemic (Frontiers in Political Science, 2024).

More recent conceptual contributions include automated administrative decision-making (Roehl & Hansen, 2024), digital public goods and services (Shulz, 2024), and digital resilience as a distinct governance objective (Mamediieva & Moynihan, 2023). These developments point to a maturing field that increasingly recognizes the risks and limits of digitalization alongside its benefits.

E-government which is broadly defined as the use of ICT to deliver government services to citizens, businesses, and other government entities, has evolved substantially over two decades (United Nations, 2022). The United Nations E-Government Survey tracks country progress globally; in 2022, Serbia ranked 40th on the E-Government Development Index, followed by Albania (63rd), Montenegro (71st), and North Macedonia (80th), illustrating the range of development within the Western Balkans (BIRN, 2024).

Citizen-centricity has become the prevailing design philosophy, emphasizing user needs, accessibility, and trust. However, expectations have outpaced delivery in many contexts: citizens increasingly demand always-on, mobile-accessible services (Molleri, 2018), while surveys in the Western Balkans reveal that digital literacy and portal usage rates remain uneven. The European Commission's eGovernment Benchmark 2023 and SIGMA's 2024 assessments using the EU eGovernment Benchmark methodology highlight both progress and structural challenges in user-centric digital public services across the region (SIGMA, 2025; European Commission, 2023).

The Western Balkans region is advancing with the digital transformation of government processes and services, though at varying speeds and with different institutional capacities (SIGMA, 2025). OECD/SIGMA's 2024 assessments, which included mystery-shopper exercises for the whole region for the first time, found that North Macedonia and Albania have evolved into the group of well-advanced administrations in terms of Single Digital Gateway Regulation (SDGR) readiness, while Bosnia and Herzegovina, Kosovo, and Montenegro remain at earlier stages (OECD/SIGMA, 2024).

The World Bank (2025) notes that North Macedonia and Albania stand out for their progress, with Albania's 'E-Albania' portal offering over 95% of government services online. In North Macedonia, 170 public institutions out of approximately 1,300 provide e-services, offering 245 services through the national portal (BIRN, 2024). The Reform Agenda 2024–2027 identifies digitalization of public administration as a key instrument for greater efficiency, transparency, and anti-corruption (Metamorphosis Foundation, 2025).

Open data and cybersecurity remain significant challenges. Montenegro experienced a ransomware attack in August 2022, while Albania's systems were targeted in July and September of the same year, exposing vulnerabilities inherent in rapid digitalization without commensurate security investment (Balkan Insight, 2024). These incidents underscore that technical digitalization must be accompanied by robust cybersecurity infrastructure and digital literacy programs.

The COVID-19 pandemic served as an unprecedented accelerator of digital government adoption. Bibliometric evidence confirms a notable peak in research output on digital governance from 2020 to 2023, closely linked to the pandemic (Frontiers in Political Science, 2024). Governments were compelled to swiftly implement digital solutions to maintain service continuity and coordinate crisis response. This emergency-driven acceleration exposed both the potential and the fragility of existing digital infrastructure, and prompted renewed interest in digital resilience as a governance objective (Mamediieva & Moynihan, 2023).

Research and Methodology

Despite the growing policy commitment to digital transformation in North Macedonia's public sector, empirical evidence about how front-line public administration employees perceive, experience, and engage with this transformation remains limited. Understanding insider perspectives is essential for designing effective implementation strategies, identifying training needs, and addressing barriers such as data-privacy concerns.

The parliamentary public administration represents a strategically important context: it is at the intersection of legislative governance, transparency obligations, and citizen interaction. It is also a multilingual and multicultural workplace, making it a revealing lens for examining whether digital transformation is experienced comparably across linguistic communities.

Two hypotheses guide this study:

H_1: The widespread integration of digital technologies in the public sector significantly affects work practices, the design of public services, and decision-making, fostering a transformative environment.

H_2: The application of digital transformation is positively associated with gains in efficiency, improvement in service quality, and a more responsive and transparent governance framework.

3.1 Research Design: This study adopts an empirical, mixed-methods design combining quantitative survey data with descriptive statistical analysis. A structured questionnaire was used as the primary data-collection instrument, supplemented by analysis of response patterns across linguistic groups to explore potential differential perceptions.

The questionnaire was developed using Google Forms and made available in two languages, Albanian and Macedonian, reflecting the linguistic diversity of the parliamentary public administration. It comprised 10 questions organized into four thematic sections: (1) general perceptions of digital transformation; (2) digital technologies in public service design and delivery; (3) data importance and data-privacy concerns; and (4) digital governance during the COVID-19 crisis.

The target population was the workforce of the parliamentary public administration. A random sampling approach was applied, targeting a 25% representation across departments and hierarchical levels, yielding a total of 49 valid responses: 13 in Albanian and 36 in Macedonian. The survey was distributed electronically via personalized Google Form links in January 2024. Participation was voluntary, informed consent was obtained, and all responses were anonymous.

3.2 Data Analysis: Data were processed using descriptive statistics, frequencies and percentages, to summarize and interpret responses. The Albanian-language group (n=13) was predominantly male (61.5%), while the Macedonian-language group (n=36) was predominantly female (71.4%). In terms of education, 53.8% of Albanian respondents held postgraduate qualifications, compared with 40.0% of Macedonian respondents; 45.7% of Macedonian respondents held undergraduate degrees and 8.6% had completed secondary education only.

Table 1 provides a consolidated overview of survey responses across both language groups for each thematic question.

Table 1. Summary of Survey Results by Language Group

Survey Question / Theme	Albanian (%)	Macedonian (%)
Gender: Male	61.5%	28.6%
Gender: Female	38.5%	71.4%
Postgraduate education	53.8%	40.0%
Knowledge of digital transformation: Somewhat familiar	69.2%	57.1%
Knowledge of digital transformation: Very familiar	23.1%	34.3%
Digital transformation impact on work practices: High	61.5%	71.4%
Digital technologies improved service quality: Agree/Strongly agree	84.7%	94.3%
Digital tech contributed to new value creation: High	46.2%	74.3%
Satisfaction with current digital service delivery: Moderate	53.8%	57.1%
Data as basis for public-sector decisions: Very important/Important	92.3%	94.3%
Privacy/security concerns: High/Extreme	46.2%	45.7%
Digital tech contribution during COVID-19: High	38.5%	57.1%
COVID-19 digitalization accelerated sustainable society: Agree/Strongly agree	76.9%	80.0%

A high proportion of respondents in both groups reported familiarity with digital transformation in the public sector. Among Albanian respondents, 69.2% described themselves as 'somewhat familiar' and 23.1% as 'very familiar', with only 7.7% neutral. Macedonian respondents showed a similar pattern: 57.1% somewhat familiar and 34.3% very familiar, with 8.6% neutral. These figures suggest a baseline of digital literacy sufficient to evaluate transformation experiences, though the relatively low shares of 'very familiar' respondents highlight the need for continued digital upskilling.

Respondents overwhelmingly acknowledged a significant impact of digital transformation on work practices. In the Albanian group, 61.5% rated the impact as 'high' and 15.4% as 'exceptional'; in the Macedonian group, 71.4% rated it as 'high' and 11.4% as 'exceptional'. These results provide strong support for Hypothesis 1, confirming that digitalization has fundamentally altered day-to-day professional activity in parliamentary public administration.

A strong majority in both groups agreed that digital technologies have improved the quality of public services. Among Albanian respondents, 46.2% agreed and 38.5% strongly agreed

(combined 84.7%); among Macedonian respondents, 68.6% agreed and 25.7% strongly agreed (combined 94.3%). Only 7.7% and 5.7%, respectively, disagreed. This finding strongly supports Hypothesis 2, indicating a broad consensus that digitalization has produced tangible service-quality improvements.

When asked about the contribution of digital technologies to value creation in public services, 46.2% of Albanian respondents and 74.3% of Macedonian respondents rated the contribution as 'high'. However, satisfaction with current digital service design and delivery was more modest: a majority in both groups rated their satisfaction as 'moderate' (53.8% Albanian; 57.1% Macedonian), indicating an aspiration gap between what is possible and what has been delivered.

The critical role of data in public-sector decision-making was widely recognized: 92.3% of Albanian and 94.3% of Macedonian respondents rated data as 'very important' or 'important'. At the same time, data-privacy and cybersecurity concerns emerged as a significant challenge: 46.2% of Albanian respondents and 45.7% of Macedonian respondents reported 'high' or 'extreme' concern about personal data privacy when interacting with government digital services. These findings underscore that trust-building and data protection must be integral components of any digitalization strategy.

A majority in both groups recognized a significant contribution of digital technologies to governance processes during the COVID-19 crisis (38.5% 'high' and 15.4% 'exceptional' among Albanian respondents; 57.1% 'high' and 20.0% 'exceptional' among Macedonian respondents). Furthermore, 76.9% of Albanian and 80.0% of Macedonian respondents agreed or strongly agreed that COVID-19-era digital adoption accelerated progress toward a more sustainable and resilient society. These results confirm the pandemic as a pivotal inflection point in digital governance, consistent with the bibliometric evidence in the literature.

Discussion and Conclusions

The survey results collectively provide strong empirical support for both hypotheses. Hypothesis 1, that digital integration significantly affects work practices, service design, and decision-making, is confirmed by the near-universal recognition of transformation impacts across both language groups. Hypothesis 2, that digital transformation correlates with improved efficiency, service quality, and responsive governance, is supported by high agreement rates on service-quality improvements and data-driven decision-making.

The aspiration gap captured in satisfaction scores (majority 'moderate') is consistent with findings from the broader Western Balkans literature: while legal and strategic frameworks are in place and awareness is growing, actual user-side delivery often lags behind expectations (Balkan Insight, 2024; SIGMA, 2025). For North Macedonia specifically, the national e-services portal covers only 170 of approximately 1,300 public institutions, representing substantial room for expansion (BIRN, 2024).

The prominent data-privacy concerns (46% rating them as high or extreme in both groups) warrant particular attention. The 2022 ransomware attacks on Montenegro and Albania demonstrated that digitalization without commensurate cybersecurity investment creates systemic vulnerabilities (Balkan Insight, 2024). As North Macedonia accelerates its digitalization under the Reform Agenda 2024–2027, a parallel investment in cybersecurity infrastructure, institutional capacity, and public trust is essential.

The relatively modest divergences between Albanian and Macedonian respondents suggest that core perceptions of digital transformation transcend linguistic community, at least within the parliamentary public administration context. This is an encouraging finding for multilingual policy design.

This paper contributes empirical evidence on how digital transformation is experienced within parliamentary public administration in North Macedonia, a country at a pivotal juncture between EU accession reform requirements and internal modernization. Key conclusions are:
First, digital transformation is recognized as a significant and positive force shaping work practices and service quality among parliamentary public administration employees. The high rates of agreement across both language groups confirm that digitalization is no longer peripheral but central to institutional functioning.
Second, the aspiration gap between current satisfaction and perceived potential is real and actionable. Moderate satisfaction scores signal that employee recognize the transformative potential of digital tools even as current delivery falls short of that potential.
Third, data-privacy and cybersecurity concerns represent the most prominent risk dimension. Closing the trust gap requires transparent data-governance policies, robust technical safeguards, and sustained citizen and employee education.
Based on these findings, the study provides the following recommendations: (i) invest in digital infrastructure expansion; (ii) prioritize digital skills development; (iii) embed cybersecurity by design; (iv) foster citizen engagement; and (v) monitor and evaluate systematically.

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REDO INGUINAL HERNIA REPAIR WITH POLYPROPYLENE MESH: A CASE REPORT

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Abstract

Recurrent inguinal hernia represents a significant surgical challenge, with reoperation rates varying between 1% and 15% globally. Tension-free mesh repair (Lichtenstein technique) has become the gold standard for both primary and recurrent inguinal hernia repair due to its low recurrence rates and favorable postoperative outcomes. We present a case of a 54-year-old male patient from the Tetova region who underwent a successful redo inguinal hernia repair using a polypropylene mesh. The patient had previously undergone primary hernioplasty and developed a symptomatic recurrence eighteen months postoperatively. Intraoperative findings revealed scar tissue around the previous repair site. The redo procedure was completed without complications, with a total operative time of approximately one hour under spinal anesthesia. The patient was discharged on the second postoperative day and reported no pain or recurrence at the six-month follow-up. This case highlights the feasibility and safety of redo mesh-based hernia repair in a regional hospital setting and is contextualized within current literature reporting success rates exceeding 95% for laparoscopic and open mesh redo procedures.

Keywords: recurrent inguinal hernia, redo hernioplasty, Lichtenstein technique, polypropylene mesh, tension-free repair.

Introduction

Inguinal hernia repair is among the most commonly performed operations in general surgery worldwide, with approximately 20 million procedures conducted annually (Kingsnorth A, et al. 2003). Despite advances in surgical technique, recurrence remains one of the most clinically significant complications, with reported rates ranging from 1% to 15% depending on the technique employed and patient-related factors Amid PK (2004). The introduction of tension-free mesh repair — most notably the Lichtenstein technique — has dramatically reduced primary recurrence rates compared with traditional tissue-based repairs such as the Shouldice procedure (Lichtenstein et al., 1989).

Recurrent inguinal hernia, once considered a technically demanding reoperation reserved for specialized centers, is increasingly being managed in regional and district hospitals. The reoperation presents unique challenges, including altered tissue planes, scar formation, and increased risk of iatrogenic injury to the vas deferens and spermatic cord vessels (Dedemadi, et al., 2006). However, with careful preoperative planning and adherence to established principles of tension-free repair, outcomes comparable to primary repair can be achieved.

The present study describes a successful redo inguinal hernioplasty with polypropylene mesh and situates this single case within the broader context of published success rates and complications of redo mesh repair. The study also reviews the relevant literature to provide a framework for managing recurrent hernia in a regional surgical center.

The aim of this study is to present a case of successful redo inguinal hernia repair with polypropylene mesh, and to review contemporary outcomes data for recurrent inguinal hernia repair, with emphasis on success rates, complication profiles, and implications for surgical practice.

The structure of the study is as follows. The second section provides literature review for recurrent inguinal hernia repair and their results. The third section presents a case report. Then the study offers discussion followed by conclusion.

Literature Review

This section provides literature review by highlighting contemporary outcomes data for recurrent inguinal hernia repair, with emphasis on success rates, complication profiles, and implications for surgical practice. The table below summarizes key findings from the published literature regarding success rates and complications following recurrent inguinal hernioplasty.

Table 1. Selected studies on outcomes of recurrent inguinal hernia repair

Study / Author	Technique	N (patients)	Success Rate	Complications (%)
Dedemadi et al., 2006	Open mesh (Lichtenstein)	186	96.8%	8.2%
Kouhia et al., 2009	Open mesh vs. Laparoscopic (TEP)	200	95.5% / 97.1%	9.0% / 6.5%
Miserez et al., 2012 (EHS)	Open mesh (after tissue repair)	~1500	94–97%	7–12%
Bittner et al., 2015 (IEHS)	Laparoscopic (TAPP/TEP)	~3000	97.2%	5.4%
Bay-Nielsen et al., 2001	Various (nationwide registry)	3128	90–95%	10–15%
Haxhirexha et al., 2018 (CHT)	Open mesh (Lichtenstein)	126 (primary)	89%*	11% (chronic pain)
Present case (Alili, 2026)	Open mesh (Lichtenstein redo)	1 (redo)	100% (6-month f/u)	0%

Source: Author's selection of studies.

As demonstrated in Table 1, success rates for redo inguinal hernia repair using mesh techniques consistently exceed 94% across major series, with complication rates ranging from 5% to 15% depending on definition and follow-up duration (Amid, 2004; Kouhia, et al., 2009; Bay-Nielsen, et al., 2001). The most commonly reported complications include chronic groin pain (inguinodynia), wound seroma, haematoma, and — in rare cases — testicular atrophy secondary to vas deferens or cord vessel injury (Alfieri, et al., 2011).

The European Hernia Society guidelines recommend that recurrent inguinal hernias following prior open repair should preferably be approached laparoscopically (TEP or TAPP) to avoid the scarred tissue planes of the previous operation (Miserez, et al., 2007). However, when laparoscopic expertise or equipment is unavailable — as is the case in many regional centres in the Western Balkans — open Lichtenstein redo repair performed by an experienced surgeon remains an acceptable and effective alternative, as demonstrated by Dedemadi et al. (96.8% success) and our own institutional experience (Lichtenstein, et al., 1989).

Particular attention must be paid intraoperatively to the identification and preservation of the ilioinguinal nerve, iliohypogastric nerve, and the genital branch of the genitofemoral nerve to minimize the risk of chronic neuropathic pain — the most frequent long-term complication of inguinal hernia repair (Kehlet, et al., 2006). In the present case, all three nerves were identified and preserved, which likely contributed to the patient's pain-free outcome at six-month follow-up.

Case Report

A 54-year-old male patient presented with a complaint of a progressively enlarging groin bulge on the right side, associated with intermittent pain aggravated by physical exertion. His medical history was significant for a right-sided inguinal hernioplasty performed eighteen months prior,

using a Shouldice tissue repair technique. The patient denied any systemic comorbidities and had no history of smoking or connective tissue disorders.
Physical examination confirmed an easily reducible right inguinal hernia with no signs of incarceration or strangulation. Ultrasound of the inguinal region confirmed recurrence with a defect measuring approximately 2.1 cm in diameter, with no evidence of bowel involvement. Routine preoperative blood work, ECG, and chest X-ray were within normal limits.
The patient was scheduled for elective redo right inguinal hernioplasty. The procedure was performed under spinal anaesthesia. Intraoperatively, a right inguinal incision was made along the previous scar, and careful dissection was carried out through the dense fibrous adhesions of the prior repair. The spermatic cord was identified and protected throughout. The defect at the medial floor of the inguinal canal was clearly delineated, with evidence of partial breakdown of the previous tissue repair. A standard flat polypropylene mesh (15 × 8 cm, medium weight) was positioned to cover the entire myopectineal orifice and secured with continuous prolene suture to the inguinal ligament and interrupted sutures to the conjoint tendon, in adherence to the Lichtenstein tension-free repair principles. The spermatic cord was replaced above the mesh and the external oblique aponeurosis closed in layers. Total operative time was approximately one hour. Estimated blood loss was less than 30 mL.
The postoperative course was uneventful. The patient was mobilized on the evening of surgery and discharged on postoperative day two with oral analgesics. Wound inspection at day 5 confirmed primary healing with no signs of infection, seroma, or haematoma. At three-month and six-month follow-up appointments, the patient reported complete resolution of preoperative symptoms, full return to daily activities, and absence of any groin discomfort. No clinical evidence of hernia recurrence was detected at either follow-up.

Discussion and Conclusion

This case illustrates several important principles in the surgical management of recurrent inguinal hernia at a regional hospital. First, careful patient selection and thorough preoperative assessment — including imaging to confirm recurrence and exclude incarceration — are essential. Second, the intraoperative strategy must account for distorted anatomy from prior surgery, necessitating meticulous dissection to protect neurovascular structures. Third, adherence to the tension-free mesh repair principle, as codified by Lichtenstein et al. and subsequently refined by the European Hernia Society, provides a reliable framework for achieving durable repair even in the redo setting (Lichtenstein et al., 1989; Miserez, et al., 2007).
The choice of a medium-weight polypropylene mesh in this case reflects current evidence suggesting that heavyweight meshes may increase the risk of chronic pain and mesh-related complications without conferring additional benefit in terms of recurrence prevention (O'Dwyer, et al., 2005). Lightweight and medium-weight meshes have demonstrated equivalent recurrence prevention with a more favourable chronic pain profile, and their use is increasingly advocated in both primary and redo settings (O'Dwyer, et al., 2005).
Redo inguinal hernia repair with polypropylene mesh can be performed safely and effectively at a regional surgical center. The case presented demonstrates that a successful outcome — defined as absence of recurrence, freedom from chronic pain, and full return to activities — is achievable with careful operative technique and adherence to tension-free repair principles. The published literature supports success rates exceeding 95% for mesh-based redo hernioplasty, confirming that recurrent inguinal hernia should not be regarded as a prohibitive surgical challenge. Continued prospective documentation of such cases at our institution will contribute to the regional evidence base for hernia surgery in North Macedonia.

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ARCHITECTURE AS INSTITUTIONAL PRACTICE: DEVELOPMENT MODELS OF PRIMARY SCHOOL BUILDINGS IN NORTH MACEDONIA

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Abstract

This paper examines the institutional framework shaping the development of primary school architecture in North Macedonia throughout the twentieth and early twenty-first centuries. The research traces the evolution of educational systems across three key periods: pre-socialist conditions, socialist Yugoslavia, and post-independence transformation.
Based on historical analysis and statistical data, the study identifies three distinct models of school development. The first model, emerging after World War II, is characterized by mass construction and standardization aimed at eliminating illiteracy. The second model, following the reforms of the 1970s, reflects a shift toward self-management and greater architectural variation within standardized systems. The third model, in the post-1991 period, reveals a lack of coherence between educational reforms and architectural development.
The study suggests that school architecture should be understood as a product of institutional processes rather than purely design-driven decisions. In this context, school architecture can be understood as closely connected to institutional and educational structures.

Keywords: institutional framework, school architecture, primary education, North Macedonia, typology**1.**

Introduction

The development of primary school infrastructure represents a fundamental component of social and spatial organization, particularly in contexts marked by rapid political and institutional transformation. In North Macedonia, the evolution of school architecture cannot be understood independently from the broader educational system and its governing structures (Hörner, Döbert, Reuter, & von Kopp, 2015).
Following the Second World War, the establishment of a state-organized educational system initiated a large-scale process of school construction, directly linked to policies aimed at eliminating illiteracy (Ademi, 2017) and expanding access to education. These changes affected not only the educational system, but also the spatial organization and development of school buildings.
Despite the significance of this development, the relationship between educational policy and architectural production remains insufficiently explored. Existing studies tend to focus either on educational reforms or on individual architectural examples, without addressing their interdependence.
This paper aims to bridge this gap by examining school architecture as a product of institutional processes. By analyzing the evolution of the educational system and its materialization in built form, the research seeks to identify key development models that have shaped primary school buildings in North Macedonia.
Methodologically, the study combines historical analysis, institutional interpretation, and statistical data review to examine the relationship between educational policy and school architecture.

Institutional Framework of Education

2.1 Pre-socialist Conditions (1918–1941): During the period of the Kingdom of Serbs, Croats and Slovenes and later the Kingdom of Yugoslavia, the level of educational development remained significantly limited. As documented in historical records, a large portion of the population lacked access to even basic education, with illiteracy rates reaching over 40% in the early 20th century.

The insufficient number of schools, limited state investment, and widespread poverty resulted in low enrollment rates. Although legislative measures introduced compulsory education, their implementation remained inconsistent, particularly in rural areas. Consequently, the educational system during this period did not generate a coherent architectural framework, as school construction was sporadic and uncoordinated.

2.2 Socialist Transformation (1945–1963): A decisive shift occurred after the Second World War, when the newly established socialist state initiated a systematic reorganization of the educational system. Education was recognized as a key instrument for social transformation, leading to the implementation of policies aimed at universal literacy and compulsory schooling (Kamberski, 1994).

A five-year development plan introduced in 1947 defined clear objectives, including the elimination of illiteracy, expansion of school networks, and establishment of free education. Subsequent legislative reforms, particularly the introduction of compulsory seven- and later eight-year education, reinforced the institutional framework.

These changes had direct architectural implications. The rapid increase in the number of students necessitated the construction of a large number of school buildings within a relatively short period. As a result, standardized design approaches emerged as a practical solution, enabling efficient and economical construction.

2.3 Self-management (1963–1991): In the later phase of socialist Yugoslavia, particularly after the 1970s, the educational system underwent further transformation through the introduction of self-management principles. Schools were no longer centrally controlled entities but were governed by collective bodies composed of teachers, students, parents, and representatives of the local community.

This shift toward decentralization influenced both the organizational structure and the spatial configuration of school buildings. While standardization remained present, greater flexibility was introduced, allowing architectural solutions to respond to local conditions and specific community needs.

At the same time, the expansion of the educational network reached its peak, with a high percentage of school-age population being enrolled in primary education. This period represents a transition from purely functional standardization toward more differentiated architectural expressions within an institutional framework.

2.4 Post-1991 Transition: Following the independence of North Macedonia in 1991, the educational system entered a new phase characterized by legislative reforms and structural adjustments. The introduction of compulsory education laws and later the implementation of a nine-year educational system reflected efforts to align with broader European standards.

However, unlike the previous periods, this phase is marked by a weaker connection between institutional reforms and architectural production. While changes in educational structure were significant, they were not consistently accompanied by corresponding transformations in school design.

This resulted in a fragmented architectural landscape, where new interventions coexist with inherited building stock from earlier periods, often without a unified design approach or long-term spatial strategy.

Development of Educational Infrastructure

The development of educational infrastructure in North Macedonia reflects the broader institutional transformations of the educational system. The expansion of primary education, particularly after the Second World War, required a corresponding increase in the number of school facilities and their spatial capacity (Socijalisticka Federativna Republika Jugoslavija, 1989).

Statistical data indicate a significant growth in both the number of schools and student enrollment during the socialist period (State Statistical Office of the Republic of North Macedonia, 1999–2021). The introduction of compulsory education led to the rapid construction of school buildings, especially in rural areas where access to education had previously been limited.

This expansion was not only quantitative but also organizational. Schools were planned as part of a wider network, responding to demographic distribution and settlement structure. The need to accommodate a growing number of students resulted in the development of buildings with varying capacities, ranging from small rural schools to larger urban institutions.

During the period of intensified construction, architectural solutions increasingly relied on standardized models. These models allowed for efficient implementation across different locations, ensuring consistency in spatial organization while reducing design and construction time. The repeated use of similar layouts and structural solutions suggests that school construction followed a coordinated planning logic.

In the later decades of the socialist period, the expansion of infrastructure reached a level of relative stability. The majority of the population had access to primary education, and the focus gradually shifted from rapid construction to the improvement and adaptation of existing facilities.

Following the transition after 1991, the development of educational infrastructure became less systematic. Although new schools were constructed and existing ones were renovated, these interventions were often fragmented and lacked a unified architectural or institutional strategy. As a result, the current condition of school infrastructure reflects a combination of different historical layers, each corresponding to specific institutional contexts.

Models of School Architecture

The analysis of the institutional development of education and the corresponding expansion of school infrastructure reveals the existence of three distinct models of primary school architecture in North Macedonia. These models are not defined primarily by stylistic characteristics, but by their relationship to institutional frameworks, educational policies, and construction strategies.

4.1 Model 1 – Post-war Standardization (1945-1963)

The first model emerged in the period following the Second World War, when the primary objective of the state was the rapid elimination of illiteracy and the establishment of a universal education system.

This period is characterized by:

- mass construction of school buildings
- strong centralization of planning and decision-making

- emphasis on efficiency and functionality

Architecturally, this resulted in the development of standardized school designs, where spatial organization was defined by basic functional requirements. Buildings were typically simple in form, with linear or corridor-based layouts that allowed for easy replication across different locations.

The primary concern was not architectural expression, but the ability to accommodate a large number of students within limited time and resources. As a result, school architecture in this phase can be understood as a direct materialization of institutional priorities.

4.2 Model 2 – Diversification within Standardization (1963-1991)

The second model corresponds to the period of institutional maturation and the introduction of self-management principles within socialist Yugoslavia.

While standardization remained an important tool, this phase introduced:

- greater flexibility in design
- adaptation to local conditions
- increased participation of local communities in decision-making

Architectural solutions became more varied, reflecting differences in site conditions, settlement structure, and specific programmatic needs. Despite these variations, school buildings continued to follow similar organizational principles.

In this sense, the second model represents a hybrid condition, where standardized systems coexist with localized adaptations. School buildings from this period often display more complex spatial organizations, including articulated volumes and differentiated functional zones.

4.3 Model 3 – Post-socialist Fragmentation (1991-present)

The third model emerges in the post-1991 period, following the transition to an independent state and the restructuring of institutional systems.

This phase is characterized by:

- discontinuity in planning strategies
- absence of a unified architectural framework
- reliance on ad hoc interventions and partial reconstructions

Although educational reforms continued, including the extension of compulsory education, these changes were not consistently translated into architectural development. As a result, school infrastructure evolved in a fragmented manner, combining inherited buildings with new additions that often lack coherence.

Architecturally, this model is defined less by clear typological patterns and more by variability and inconsistency. The absence of a strong institutional framework resulted in a shift away from systematic design toward individualized or situational solutions.

4.4 Comparative Overview

The three identified models illustrate a broader transformation in the relationship between architecture and institutional structures.

The first model demonstrates a direct and systematic relationship between institutional goals and architectural production.

The second model reflects a balance between standardization and adaptation.

The third model reveals a weakening of this relationship, resulting in fragmentation.

This progression highlights the extent to which architectural form is conditioned by institutional frameworks rather than purely design intentions. School buildings, therefore, can be understood as spatial expressions of specific historical and organizational contexts.

Discussion

The analysis of primary school architecture in North Macedonia demonstrates that built form cannot be interpreted independently from institutional frameworks. The three identified models reveal a direct correlation between educational policies, governance structures, and architectural production.

In the post-war period, architecture functioned as an operational tool within a centralized system, where standardization enabled rapid and large-scale implementation. School buildings were conceived as repeatable models, reflecting the urgency of social transformation and the expansion of education.

The subsequent phase introduced a more complex relationship between standardization and local adaptation. The decentralization of decision-making processes allowed for greater variation in architectural solutions, while still maintaining an underlying systemic logic. This period illustrates how institutional flexibility can generate spatial diversity without abandoning structural coherence.

In contrast, the post-socialist period is characterized by a weakening of the connection between institutional planning and architectural development. The absence of a consistent framework resulted in fragmented interventions, where school buildings are shaped by immediate needs rather than long-term strategies.

These findings support the argument that architecture should be understood as a form of institutional practice (Batakoja, 2021/2022). Rather than being driven primarily by formal or stylistic considerations, school buildings emerge as spatial responses to administrative systems, policy decisions, and socio-economic conditions.

Such an approach allows school architecture to be interpreted beyond individual buildings and stylistic analysis.

Conclusions

This paper has examined the development of primary school architecture in North Macedonia through the lens of institutional frameworks. By analyzing historical transformations in the educational system, the research identified three distinct models of architectural development: post-war standardization, diversification within standardization, and post-socialist fragmentation.

The study demonstrates that school architecture is not merely the result of design decisions, but a material expression of institutional structures and socio-political priorities. Each development phase produced different spatial and organizational approaches to school design. The study highlights the importance of examining school buildings through institutional and systemic relationships rather than solely through architectural form.

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HYACINTHUS ORIENTALIS L. SUBSP. ORIENTALIS (ASPARAGACEAE) A NEW TAXON FOR THE FLORA OF NORTH MACEDONIA

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Abstract

Hyacinthus orientalis L. subsp. *orientalis* (Asparagaceae), also known as wild hyacinth, was found at the foot of the Dry Mountain and represents a new taxon for the flora of North Macedonia. Specimens examined: Dry Mountain, near the mountain road to the village of Kunovo, about 6 km from the town of Gostivar: 576 m, 41º 46' 04.83″ N, 20º 55' 52.24″E, April 2026.

Keywords: New taxon, *Hyacinthus orientalis* subsp. *orientalis,* Asparagaceae, Dry Mountain, Republic of North Macedonia.

Introduction

The genus *Hyacinthus* Tourn. Ex L. is comprised of only six species: *Hyacinthus litwinovii* Czerniak, *Hyacinthus transcaspicus* Litv., *Hyacinthus brachypodus* Borbás, *Hyacinthus colchicoides* Delile, *Hyacinthus griseus* Brouss. ex Schult. & Schult. f., and the most famous of them all, *Hyacinthus orientalis* L. These plants were once considered members of the lily family (Liliaceae) but more recent genetic work places them in the asparagus family (Asparagaceae), (Tutin *et al*., 1980), (Heywood, 1980). The native range of this genus is Southern Turkeye to Northern Israel and Southern Turkmenistan. The new taxon for the flora of North Macedonia, presented in this paper, is a subspecies of *Hyacinthus orientalis* L. This species is native to southwest Asia and is cultivated and naturalized in Mediterranean Europe (Hassler, 2022), (Heywood *et al*., 1980). It is a ornamental geophytes, with the cultivation history over 400 years, numerous cultivars were bred with varying morphologies and performance.



Figure 1. Hyacinthus orientalis L. subsp. orientalis (photo by Haziri, April 2026)

The new taxon is wild hyacinth, *Hyacinthus orientalis* L. subsp. *orientalis* (Figure 1), also known by the synonyms: *Hyacinthus brumalis* Haw. Ex G. Don, *Hyacinthus albulus* Jord., *Hyacinthus modestus* Jord. & Fourr., *Hyacinthus praecox* Jord., *Hyacinthus provincialis* Jord., *Hyacinthus rigidulus* Jord. & Fourr. (Grundmann *et al*., 2010), it is a bulbous plant, with a 3–7 cm diameter bulb. The leaves are strap-shaped, 15–35 cm long and 1–3 cm broad, with a soft, succulent texture, and produced in a basal whorl. The flowering stem grows to 25–30 cm (rarely to 35 cm) tall,bearing 1–2 fragrant purple flowers 2–3.5 cm long with a tubular, six-lobed perianth. Perianth segments united about one-half of their length. Fruits more or less

spherical. The native range of this subspecies is Southern Turkeye to Northern Israel. It grows primarily in the temperate biome (Stace, 2019), (Dimopoulos, 2013).

Material and Methods

The new data presented in this paper are based on plant material collected during the field research. Floristic researches in this area was carried out during the spring period of 2025-2026. *Hyacinthus orientalis* L. subsp. *orientalis* plants were observed with flowers, and later, with mature fruits. The distribution locality has been determined precisely through the latitude and longitude coordinates on Google Maps. Herbaized specimens of this taxon are preserved in the private herbarium of the authors and in herbarium of the Department of Biology, Faculty of Natural Sciences and Mathematics, University of Tetova. Taxonomic treatment is based on careful observation of morphological characteristics in herbarium specimens and living populations, and on morphometric data. The morphological and systematic description of the subspecies is based on relevant taxonomic literature. Plant nomenclature and taxonomy is consistent with Euro+Med Plant base (Greuter, 2006).

Results and Discussion

The flora of North Macedonia is known for its large number of species, including many endemic and relict species (Micevski, 1978, 1987). As a result of continuous research, many new taxa have been discovered, as well as new distribution localities for many endemic and relict species. (Matevski *et al*., 2001, 2016, 2022, 2022), (Haziri, 2020, 2022, 2024, 2024).



Figure 2. Locality of Hyacinthus orientalis L. subsp. orientalis, near the mountain road to the village of Kunovo, at the foot of the Dry Mountain (source: Google Earth)

Hyacinthus orientalis L. subsp. *orientalis* (Asparagaceae, formerly Liliaceae), (Vangjeli *et al*., 2000), (Haziri, 2019), also known as wild hyacinth, was found at the foot of the Dry Mountain and represents a new taxon for the flora of North Macedonia. It was found for the first time in 2025, while, as a result of continuous research, its presence at the same location was also determined in April 2026. Specimens examined: Dry Mountain, near the mountain road to the village of Kunovo, about 6 km from the town of Gostivar: 576 m, 41º 46' 04.83″ N, 20º 55' 52.24″E, April 2026 (Figure 2, 3).



Figure 3. Hyacinthus orientalis L. subsp. orientalis, in the locality near the mountain road to the village of Kunovo, in Dry Mountain (photo by Haziri, April 2026)

Conclusions

From what was said above we can conclude that *Hyacinthus orientalis* L. subsp. *orientalis* (Asparagaceae, formerly Liliaceae), also known as wild hyacinth, represents a new taxon for the flora of the Republic of North Macedonia. It was found for the first time in 2025, while, as a result of continuous research, its presence at the same location was also determined in April 2026. Specimens examined: Dry Mountain, near the mountain road to the village of Kunovo, about 6 km from the town of Gostivar: 576 m, 41º 46' 04.83″ N, 20º 55' 52.24″E, April 2026.

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IDENTIFICATION OF PARAMETERS FOR THE ANALYSIS OF STRUCTURAL WEAKNESSES IN IPA INFRASTRUCTURE PROJECTS: LITERATURE REVIEW

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Abstract

The implementation of infrastructure and other projects financed through the European Union Instrument for Pre – Accession Assistance (IPA) in the Republic of North Macedonia is associated with significant deviations from planned schedules, budgets and outcomes that are expected to achieve, indicating the presence of structural weaknesses in project management. The aim of this paper is to identify and systematize the critical parameters influencing the successful implementation of infrastructure projects through a literature review of relevant methodologies and procedures applied by international financial institutions, as well as analyzing available reports and documentation related to IPA projects. The research focuses on parameters associated with phases of the project life cycle, including project initiation and planning, preparation of technical documentation, procurement procedures, contractual condition, implementation, supervision and final project delivery with quality control. The identified parameters are grouped and structured according to project life cycle in order to facilitate a clearer presentation of critical factors that most frequently contribute to time delays, cost overruns and reduced efficiency in project implementation. Furthermore, this study provides a foundation for further empirical analysis and validation through the application of data derived from real implemented infrastructure projects.

Keywords: infrastructure projects, IPA funds, parameters, structural weaknesses, project life cycle

Introduction

The development of a country largely depends on the quality of planning and implementation of infrastructure projects, as a fundamental prerequisite for sustainable development – long term economic and social development, as well as maintaining environmental protection requirements. The aim of this research is to identify and analyze the critical factors that can directly influence the performance of infrastructure project financed through the IPA programs. The analysis encompasses the entire project life cycle, from the early stages – initiation of the project idea, preparation of feasibility study and project documentation, through public procurement procedures and contractual conditions, to the phase of construction, supervision and closure with quality control. Within the scope of the research, critical parameters with potential impact on the success of project implementation are identified, highlighting their role within different project life cycle phases. The transformation of initial project concepts into a complete built environment represent a complex process influenced not only by the needs of society, but also by institutional capacities, planning frameworks and governance structures [1]. In the context of transition economies, including the Republic of North Macedonia, previous experience in the implementation of such projects indicates the existence of systematic weaknesses manifested through low implementation rates, frequent time delays, cost overruns and insufficient utilization of available financial resources [2]. These phenomena negatively affect the performance of public investments, disrupt the continuity of development planning and contribute to increased fiscal pressure. Of particular concern is the fact that such challenges are evident in projects financed through non – repayable funds provided by the European Union and other financial institutions, where the Republic of North Macedonia demonstrates a relatively low level of implantation efficiency. This situation directly affect the dynamics of economic growth and slows down the transformational processes necessary for

successful European integration, because significant share of planned capital investments within national strategic and budgetary documents is expected to be financed through these mechanisms [3].
Sustainable management of capital investments requires timely identification, analysis and control of project weaknesses, as well as continuous monitoring of project performance throughout the entire project life cycle [4]. Emphasizing the importance of informed decision making based on systematic and quantified risk analysis [5]. From the initial stages of project development, it is essential to balance design intentions with institutional capacity in order to achieve sustainability objectives [6]. Structuring the risk according to the phases of project life cycle represent a classical and fundamental element of modern project management, given that risks are not static, but rather evolve and manifest differently throughout the phases of planning, design, public procurement, construction and operation. Such approach enables a clearer identification of risk sources, assessment of their probability and impact within a specific temporal context and selection of appropriate corrective measures [7]. Neglecting or insufficiently addressing any of those challenges may lead to the accumulation of risks, inefficient use of resources and deviation from planned project objectives [8]. The successful implementation of such projects depends on effective leadership and active involvement of competent stakeholders advocating investments in sustainable direction [9]. Furthermore, effective project management represents a fundamental component in the realization of architectural and infrastructural development, not only as a technical framework but also as a crucial aspect of spatial, functional and operational performance [10]. In addition, selection and application of construction materials must comply with relevant legal regulations and technical standards in order to ensure safety, durability and long term operational performance [11].
In order to precisely define and measure the impact of critical risks on project success, it is necessary for such risks to be systematically identified, analyzed and structured according to clearly defined and measurable parameters [12]. This approach enables an objective assessment of both the probability and consequences of risks and provides the basis for their quantification. Particularly significant are the findings confirming that the early phase of project life cycle have decisive influence on the overall success of the project.

Research methodology

In this research, a systematic approach of literature review was applied for the identification of critical parameters with influence on the performance of capital infrastructure projects financed through IPA funds in the Republic of North Macedonia. During the research process the following sources and materials were analyzed:
Scientific literature in the field of architecture and project management, with focus on the analysis of potential risks related to project delays and cost overruns.
PRAG procedures and FIDIC contractual standards which are mandatorily applied from international financial institutions.
Other projects documentation including reports from evaluation committees, audit reports etc. related the IPA infrastructure projects.
Based on this research process, a total of 30 parameters were identified and classified according to the phases of the project life cycle.
Within the scope of the research, the following phases were considered:
Idea – project initiation
Preparation of feasibility study
Preparation of project documentation
Procurement procedures and contractual conditions

Project implementation
Closure with quality control

Results

The following section presents the results of this study obtained through the analyses of selected literature, project documentation, procedures and guidelines used from international financial institutions, as well as applicable national legislation. The research identified a total of 30 parameters with direct influence on the performance of IPA funded infrastructure projects. In order to ensure a clearer analytical structure and facilitate a more comprehensive interpretation of their role in different stages of project management, the identified parameters are grouped into six categories according to the phases of the project life cycle described in the research methodology. For each parameter, the following elements are presented: the parameter name, conceptual explanation – definition of the parameter, the corresponding indicator for its measurement and the relevant literature source from where parameters are identified. Such a structured presentation enables a clear and transparent representation of the identified parameters, while simultaneously providing a consistent analytical framework for their further evaluation.

3.1 Parameters for the project initiation phase: Following table presents the identified parameters related to the project initiation phase, including their conceptual definition, measurement indicators and corresponding literature sources.

Table 1: Identified parameters for the project initiation phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Project justification	Degree to which project objectives, scope, expected benefits and strategic alignment are clearly defined during the initial phase, providing a stable basis for feasibility analysis and subsequent decision making	Degree of completeness of the project justification section, consistency between the problem definition, objectives, scope and preliminary budget	[17], [18], [60]
Institutional readiness	Degree to which the responsible possess adequate organizational capacity, clearly defined roles, decision making authority and human resources for project control throughout the entire project life cycle	Existence of a formal project management structure, availability of dedicated project team, clarity of roles and responsibilities, experience with similar projects	[19], [50], [53]
Stakeholder identification	Degree to which all relevant stakeholders (institutional, technical, financial) are systematically identified, analyzed and documented during initial phase, including their roles, interests and influence on the project	Existence and completeness of a stakeholder register, coverage of key stakeholder categories, analysis, addressing roles, interests and influence	[15], [20], [60]
Financing structure	Degree to which financing sources, financing structures, eligibility conditions, co – financing requirements, cash flow needs and financial risk are systematically analyzed and documented prior to project implementation decisions	Completeness of financing analysis, identification of financing sources, clearly defined co – financing participation and prepared cash flow projections	[21], [53]

Level of political sensitivity	Degree to which project is exposed to political influence or political pressure, public visibility, that may affect the objectivity of decision making process, prioritization or stability of the project throughout its life cycle	Political visibility of project, frequency of political references in official decisions, changes in project scope, schedule, budged influenced from political cycles	[17], [22], [53]
Constraints	Degree to which predefined constraints (technical, institutional, financial, environmental or time related) limit project flexibility and decision making processes and implementation possibilities throughout project life cycle	Number and type of documented constraints, existence of binding legal, budgetary, technical or other limitations affecting project scope and implementation	[15], [23], [50]

3.2 Parameters for the feasibility study phase: Following parameters were identified as critical elements within the feasibility study phase, primarily influencing the reliability of project planning and the accuracy of early strategic and operational decisions.

Table 2: Identified parameters for the feasibility study phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Initial cost estimate	Degree to which the initial project cost estimate (prepared prior to detailed design) is realistic, comprehensive and aligned with the project scope, market condition and identified constraints	Difference (%) between the initial cost estimate and the contracted price	[24], [59], [60]
Initial duration estimate	Degree to which the initial project duration estimate is realistic, comprehensive and aligned with institutional capacity, procurement procedures, technical and financial constraints	Difference (%) between the estimated and actual project duration	[17], [25], [60]
Identification of critical points	Degree to which critical points, risks, sensitive moments within the project implementation are systematically identified, documented and analyzed at an early stage in order to enable preventive planning	Existence of a documented critical path analysis, risk register and identified mitigation measures	[26], [59], [61]
Alignment with administrative capacity and procedures	Degree to which project requirements, deadlines, documentation and procedural complexity are realistically aligned with actual administrative capacity and institutional experience	Evidence of conducted capacity assessments, alignment between procedural complexity and available administrative resources, frequency of procedural delays and repeated procedures	[27], [58]

3.3 Parameters for the preparation of project documentation phase: The parameters presented below reflect the technical quality, consistency and implementation readiness of the project documentation, which are considered essential requirements for successful project execution.

Table 3: Identified parameters for the project documentation phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Maturity of project documentation	Degree to which technical documentation is sufficiently developed, coordinated and verified, ensuring clarity of project scope, quantities, construction feasibility in compliance with applicable standards	Number of unresolved design issues, degree of completeness of the bill of quantities calculations	[17], [28], [61]
Alignment of design with cost and time	Degree to which the technical design is explicitly coordinated with cost estimates and project schedules, ensuring that design solutions are feasible within the approved budged and planned duration	Consistency between the design scope, bill of quantities, cost estimate and baseline project schedule	[14], [29], [59]
Level of innovation	Degree to which the project incorporates new or non - standard technical solutions, construction methods, materials, digital tools or management approaches compared to local practices	Presence of non – standard solutions, innovative design or construction elements, existence of innovation – related risk assessment or pilot validation	[15], [30], [61]
Detected errors	Degree to which errors, inconsistencies, deficiencies in the technical design affect quantity analyses, technical specifications and project implementation	Number of errors during bid evaluation or project execution	[13], [31], [59]

3.4 Parameters for the procurement procedures and contract award phase: The parameters identified in this phase reflect the procedural efficiency, regulatory compliance, contractual structure and marked related factors that may significantly influence the transparency and effectiveness of project implementation.

Table 4: Identified parameters for the procurement procedures and contract award phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Duration of procurement procedures	Total duration required for conducting procurement procedures related to the selection of contractors for technical documentation, supervision services and construction works, including repetitions, cancelations and procedural delays	Duration of each procurement procedure, number of cancelled or repeated tenders	[32], [48], [52]
Technical and financial requirements	The degree to which the technical specifications, qualification criteria and financial requirements defined within the tender documentation are appropriated, clear and aligned with the complexity of the project and market capacity	Lever of compliance with PRAG and FIDIC requirements, number of clarification requests, number of compliant bids, frequency of tender cancellations	[14], [33], [48]

Structural imbalance in participation	Degree to which procurement procedures result in unbalanced participation among bidders, indicating the existence of structural barriers related to financial capacity, technical requirements and experience criteria	Ratio of awarded contracts between domestic and international companies, diversity of bidder participation, representation of subcontracting or consortium participation	[34], [52], [51]
Irregularities in procurement procedures	The occurrence of cancelled, repeated, suspended procurement procedures resulting from procedural errors noncompliance with regulations, audit findings or suspicions for irregularities and frauds	Number of cancelled or repeated tenders, references to procedural noncompliance in official decisions	[35], [48], [52]
Contract type and risk allocation	The degree to which the selected contract type and payment mechanisms appropriately allocate risks and responsibilities among contractual parties	Type of contract used, payment mechanisms, risk allocation matrix frequency of claims , variations and extensions of time	[36], [49], [56]
Transparency among project participants	The degree to which different types of contractual engagement (main contractor, sub-contractor, consortium) create unequal responsibilities and risk exposure	Level of disclosure of sub-contractors and providers of technical and financial capacity during the tendering phase, differences in contractual conditions (prior to contract award versus after contract award)	[37], [49], [54]

3.5 Parameters for the project implementation phase: The parameters associated with the implementation phase primarily address operational, technical, financial and managerial conditions that directly affect the continuity, efficiency and overall performance of project execution.

Table 5: Identified parameters for the project implementation phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Delayed start of implementation	The time difference between the formal commencement date of the contract and the actual start of works, caused by unresolved preconditions, administrative delays or procedural inefficiencies	Number of days between the planned and actual commencement of works and reasons for delay documented in official reports	[17], [38], [59]
Technical and financial capacity of contractor	The degree to which the selected contractor possesses adequate technical expertise, human resources equipment and financial stability to execute the contracted works in accordance with project requirements	Compliance with qualification criteria, financial indicators, relevant references, key personnel and equipment	[14], [39], [58]
Unforeseen conditions and additional works	Degree to which unforeseen site conditions, deficiencies in technical solutions or external factors require additional works, modifications or variations	Number and value of variation orders, justifications for additional works, documented unforeseen conditions	[15], [40], [59]
Currency risk	Changes in exchange rates between the contract currency and the local currency affect project	Exchange rate fluctuations during the contractual period, existence of price adjustment or foreign exchange risk clauses	[41], [58]

	costs, payments, cash flow during project implementation		
Material supply	The degree to which the availability, timeliness of delivery, logistics and reliability of construction material supply affect project implementation including import dependency and market shortages	Delays in material delivery, number of work interruptions caused by material shortages, changes in material prices , meeting eligibility requirements	[16], [42], [59]
Effectiveness of supervision	The degree to which the supervising authority effectively manages , coordinates and response to unplanned events , ensuring timely decisions in order to mitigate impact on time and cost	Response time to unplanned events, number of unresolved issues quality of site instruction , impact of unplanned evens on schedule and costs	[13], [43], [58]

3.6 Parameters for the project closure and quality control phase: The following parameters are associated with the final phase of the project life cycle and are intended to evaluate the effectiveness of project completion, quality assurance processes and long term performance after formal project delivery.

Table 6: Identified parameters for the project closure and quality control phase

PARAMETERS	DEFINITION	INDICATOR	LITERATURE
Completion within planned time and budged	The degree to which the project is formally completed and accepted in accordance with the originally approved schedule, budget and quality requirements without unresolved defects or significant deviations	Difference between the planned and actual completion date, final cost deviation, number of defects identified during handover	[16], [44], [55]
Defects liability and warranty period performance	The effectiveness with which defects and performance related issues identified during the defects liability period are addressed , corrected and resolved in accordance with contractual requirements	Number of defects reported during the warranty period , response time for defect correction, unresolved defects after the expiration of the warranty period	[45], [55], [57]
Rework and corrective works	The degree to which completed works require repetition , correction or modification do to defects , errors or changes , indicating inefficiencies in design , execution or quality control processes	Percentage or reward relative to the total value of works, cost and time impact of corrective works	[14], [46], [55]
Post completion quality complains	The degree to which formal compliance related to quality defects or performance deviations are submitted after formal project completion and handover, indicating deficiencies in construction quality or control processes	Number of formal quality complains after handover, type of complaints, required corrective measures	[47], [55], [57]

4. Conclusion

This research provides a systematic identification and structuring critical parameters that can influence the performance of IPA funded infrastructure projects in the Republic of North Macedonia. Through the analysis of scientific literature and other documentation as a different regulatory frameworks, a total list of 30 parameters were identified and classified according to six phases of project life cycle. The proposed analytical framework enables a clearer understanding of the institutional, managerial, technical and procedural factors that contribute to project delays, cost overruns and reduced implementation efficiency. By structuring the identified parameters according to the project life cycle phases, the research establishes a consistent methodological basis for the identification of critical points and weaknesses throughout project implementation.

Identified parameters present a foundation for further empirical validation and expert based evaluation, with the aim to develop a more objective and comprehensive approach for assessing the performance of infrastructure projects financed through international financial assistances.

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TRANSFORMATION OF THE DAIRY INDUSTRY (2000–2030): FROM A TRADITIONAL FOOD SYSTEM TO MOLECULAR AND DIGITAL PRECISION

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Abstract

This paper presents an overview of the structural, technological, and bioindustrial evolution of the dairy industry during the period 2000–2030, with a particular focus on its transformation from a traditional food system into a biotechnologically and digitally integrated production model. The analysis encompasses the transitional phase from 2000 to 2010, characterized by the intensive development of membrane technologies, advanced separation processes, and the industrial standardization of dairy components into functional ingredients with high added value. The period from 2010 to 2020 was marked by the expansion of the circular economy concept, the valorization of dairy by-products, and the development of functional dairy matrix systems based on interactions between nutrients and the biological activity of food. During the 2020–2030 phase, the industry has been transforming toward a "Dairy 4.0" model, founded on the integration of artificial intelligence, digital technologies, precision fermentation, biofractionation, and automated production management systems. In conclusion, the contemporary development of the dairy sector indicates an intensive convergence of nutritional science, biotechnology, and digital systems aimed at improving the functional properties of dairy products, resource efficiency, and the long-term sustainability of production.

Keywords: Dairy matrix, Dairy 4.0, precision fermentation, circular economy, milk processing, functional food.

Introduction

From a historical perspective, milk and dairy products have represented one of the fundamental elements in the development of human nutrition and civilization, providing a significant source of energy and nutritional security since the Neolithic period and the emergence of early agrarian communities (Evershed et al., 2008; Dunne et al., 2012). Archaeological and bimolecular evidence indicates that the introduction of dairy consumption constituted an important adaptive strategy in human evolution, enabling continuous access to high-quality proteins, lipids, and essential micronutrients, thereby contributing to improved nutritional status, demographic expansion, and the development of early agricultural populations (Leonardi et al., 2012).

In the traditional context, milk was predominantly valued as a concentrated source of calcium, phosphorus, vitamins, and highly bioavailable proteins, essential for growth, skeletal development, and the maintenance of physiological and metabolic functions in the human body (Auestad & Layman, 2021; Mulet-Cabero et al., 2024). However, contemporary scientific research has substantially broadened this perspective, with dairy products now being described as complex biological systems exhibiting pronounced functional and nutritional effects on human health (Huppertz et al., 2024). Particular attention has been devoted to the bioactive components of milk, including protein fractions, bioactive peptides, and lipid structures, which may influence a wide range of metabolic, immunological, and physiological processes (Clare & Swaisgood, 2000; Korhonen & Pihlanto, 2006).

Within contemporary dairy science, the concept of the "dairy matrix" has emerged as a key paradigm emphasizing the interactions among nutritional components within their natural structural organization. According to this concept, the health effects of dairy products cannot be fully explained solely by their individual nutrients, but rather arise from their complex

structural, physicochemical, and functional interrelationships (Mulet-Cabero et al., 2024; Huppertz et al., 2024). Recent studies further indicate that the structural organization of the dairy matrix may significantly influence nutrient bioavailability, postprandial metabolism, and the physiological effects of food, representing a substantial shift in the understanding of the role of dairy products in nutrition and public health (Thorning et al., 2017; Lovegrove & Givens, 2022).

Parallel to this scientific evolution, technological advancements in the dairy industry have enabled a transition toward more precise, automated, and biotechnologically advanced systems for production and processing. These transformations include improved membrane separation processes, fractionation technologies, bioprocessing strategies, and the functional modification of dairy components, aimed at optimizing their nutritional, technological, and biological value (Smithers, 2008; Mistry, 2020). During the last decade, the dairy sector has increasingly evolved toward the "Dairy 4.0" concept, which involves the integration of digital technologies, artificial intelligence, automated production control systems, precision fermentation, and sustainable circular economy models (Balthazar et al., 2021; Kapoor & Metzger, 2023).

The transformation of the dairy industry during the period 2000–2030 does not merely represent a process of technological modernization, but rather a systemic shift in the understanding of milk—from a traditional nutritional raw material to a biologically functional and digitally optimized nutritional system. In this context, the present paper analyzes the evolution of the dairy sector, from traditional processing approaches to contemporary concepts of molecular precision, functional nutrition, and digitally integrated production systems.

Evolution of the dairy industry: From industrial standardization to Dairy 4.0

2.1. Industrial standardization and functional transformation of the dairy sector (2000–2010):

The period from 2000 to 2010 represents a pivotal transitional phase in the development of the dairy industry, during which traditional processing technologies were gradually transformed into highly standardized systems oriented toward food safety, functional nutrition, and industrial efficiency (Bintsis & Papademas, 2022). In this context, the global emphasis on hygiene and quality control culminated in the implementation of the ISO 22000 standard in 2005, which integrated HACCP principles throughout the entire food production and distribution chain (ISO, 2005).

In parallel with regulatory standardization, technological advances in membrane processing, ultra-high-temperature (UHT) treatment, and industrial separation technologies enabled substantial improvements in the stability, shelf life, and nutritional controllability of milk, which increasingly came to be regarded as a functional carrier of bioactive compounds (Kumar et al., 2013; Dhillon & Singla, 2024; Blasi & Verardi, 2024). This technological progress contributed to the redefinition of milk from a "fresh food product" into a highly controlled nutritional system with precisely managed properties.

One of the most significant structural shifts during this period was the industrial valorization of whey, which evolved from a by-product of cheese production into a highly valuable raw material for the manufacture of functional ingredients. The isolation and concentration of whey proteins (WPC/WPI) enabled the development of novel applications in sports nutrition, clinical nutrition, and functional foods, thereby laying the foundation for the contemporary understanding of the "dairy matrix" as an integrated nutritional system (Pires et al., 2021; Soumati et al., 2023; Mulet-Cabero et al., 2024).

At the same time, scientific interest became increasingly focused on the selection and industrial application of probiotic microorganisms, particularly strains such as *Lactobacillus rhamnosus* GG and various species belonging to the genus *Bifidobacterium*, with the aim of modulating the gut microbiome and supporting immune function (Reid, 2008; Özer & Kirmaci, 2010;

Marsh et al., 2014). This development led to a significant expansion of the market for fermented functional dairy products, which experienced the fastest growth within the dairy industry during this period.

Concurrently, the period was also characterized by the dominance of the "low-fat" trend, driven by nutritional recommendations advocating reduced intake of saturated fats. This resulted in the intensive development of delipidation technologies, as well as the increased use of hydrocolloids and stabilizers to preserve the texture and sensory properties of dairy products (Knips, 2005; Haug et al., 2007; Zhao et al., 2023).

2.2. Nutritional revolution, the dairy matrix, and the circular bioeconomy (2010–2020): The period from 2010 to 2020 is characterized as one of the most intensive phases in the evolution of the dairy industry, marked by a clear transition from conventional processing toward the molecular and functional engineering of dairy components (Granato et al., 2022). This transformation was supported by advances in nutritional science, process engineering, and systems-based food analysis.

One of the most influential market and technological phenomena during this period was the global expansion of Greek yogurt, which, through the application of advanced separation processes and ultrafiltration technologies, enabled the development of products with high protein density, improved textural stability, and a "clean label" profile (Aryana & Olson, 2017; Paredes Valencia et al., 2018; Lange et al., 2020). This trend further stimulated the industry toward intensified use of membrane technologies for the fractionation of casein and whey protein fractions, aiming at their precise nutritional and functional application.

Simultaneously, substantial scientific progress was achieved in understanding bioactive peptides and their role in metabolic and physiological processes, supported by developments in metabolomics and advanced analytical techniques (Meleti et al., 2025; Luparelli et al., 2025; Waqar et al., 2026). These investigations reinforced the concept of milk as a dynamic source of biologically active molecules rather than merely a static nutritional system.

In parallel, a significant expansion was observed in the valorization of whey as a functional raw material, as well as in the integration of agro-industrial by-products rich in dietary fibers, such as inulin and pectin, enabling the development of a new generation of synbiotic dairy matrices with enhanced health-promoting properties (Ivanović et al., 2017; Iriondo-DeHond et al., 2018; Fluerasu et al., 2025; Mota et al., 2026). This approach represents an important step toward a circular bioeconomy in the food sector, in which waste streams are increasingly transformed into biologically and nutritionally valuable ingredients.

During the same period, a substantial revision of the scientific perception of dairy fats also occurred. Meta-analyses and systematic reviews indicated that the context of the "dairy matrix" significantly modulates the metabolic response, suggesting that dairy fats are not directly associated with increased cardiometabolic risk and may exert neutral or potentially protective effects in certain populations (Thorning et al., 2017; Astrup et al., 2020; Lordan et al., 2020; Bruno et al., 2021).

Toward the end of the decade, the integration of Industry 4.0 concepts gradually began to transform the dairy sector through digitalization, automation, and predictive analytics. The implementation of big data systems, cloud-based production platforms, and sensor technologies enabled more precise monitoring of product quality, production efficiency, and food safety, thereby laying the foundation for contemporary models of personalized nutrition and intelligent management of nutritional systems (Wolfert et al., 2017; Hassoun et al., 2023; Islam et al., 2025).

2.3. Dairy 4.0: Precision nutrition, digital integration, and sustainable production (2020–2030): The period 2020–2030 is characterized as a phase of intensive digital and

biotechnological integration within the dairy sector, in which the focus progressively shifts from mass production toward molecular precision, functional personalization, and enhanced environmental sustainability (Arena et al., 2023; Kaura et al., 2026). In this context, the concept of "Dairy 4.0" describes the synergy between artificial intelligence (AI), the Internet of Things (IoT), sensor systems, and advanced data analytics, enabling continuous monitoring, predictive modelling, and real-time optimization of productivity, animal health, and resource efficiency (Serrano-Torres et al., 2025; Sabale et al., 2026).

Contemporary AI systems in the dairy industry are applied for productivity forecasting, animal behavior analysis, and early disease detection. The application of machine learning and computer vision enables a transition from reactive to predictive farm management based on real biological and environmental data, significantly improving animal welfare and operational efficiency (Hao et al., 2024; García-Méndez et al., 2024).

Table 1. Integrated technological and biotechnological advances in Dairy 4.0 systems (2020–2030)

Technological domain	Key outcomes and scientific contributions	Source
Precision Livestock Farming (AI, IoT, biosensors)	Real-time optimization of nutrition, improved feed conversion efficiency, early detection of metabolic disorders, and significant reduction of methane emissions.	Norton et al. (2019) Benaissa et al. (2020);
AI and IoT monitoring systems	Machine learning for disease detection (including lameness), behavior analysis of livestock and environmental conditions, and optimization of farm decision-making.	Halachmi et al. (2019); Kamilaris & Prenafeta-Boldú (2018)
Precision feeding models	Individualized nutrition leading to reduced methane emissions (5–15%) and improved productivity and nutritional efficiency.	Nielsen et al. (2021); Dijkstra et al. (2018)
Machine learning for production prediction	High predictive accuracy ($R > 0.80$) for milk yield and quality based on climatic and physiological parameters.	Feldmann et al. (2020); Fuentes et al. (2018)
Precision fermentation	Production of casein and whey proteins with structural and functional identity to animal-derived proteins, without the use of animals.	Huang et al. (2021); Gosling et al. (2020)
LCA and sustainability assessment	Significant reduction in greenhouse gas emissions, water use, and land occupation compared to conventional production systems.	Smetana et al. (2022)
AI-based climate and production optimization	Balancing productivity and environmental footprint through integrated models for sustainable livestock management.	Hristov et al. (2018)

In this direction, by 2030 the dairy industry is increasingly positioned as an integrated biotechnological and digital system combining nutritional personalization, automated analytics, molecular precision, and sustainable production.

2.3.1. Future perspectives in clinical nutrition and dairy systems: In future perspectives of nutritional science, it has been proposed that research should further explore the interaction between pharmacologically induced body weight reduction and nutritional strategies aimed at preserving fat-free mass. In particular, in therapies based on glucagon-like peptide-1 (GLP-1) receptor agonists, including semaglutide (Ozempic), clinical studies indicate that a substantial proportion of weight loss may involve reductions in lean mass, representing a potential risk for muscle function and metabolic stability (Batsis & Zagaria, 2018; Ordovas et al., 2018; Rossi et al., 2026).

In this context, it is emphasized that pharmacologically induced weight reduction requires an integrated approach that includes adequate intake of high-quality proteins and structured physical activity, particularly resistance training, in order to maintain muscle protein synthesis

and minimize the loss of fat-free mass (Devries & Phillips, 2015; Phillips & Van Loon, 2011; Morton et al., 2018). Whey proteins, due to their high biological value and richness in essential amino acids - particularly leucine - represent a key nutritional factor in the preservation of lean mass during caloric restriction and rapid weight loss.
Furthermore, contemporary clinical evidence suggests that optimal outcomes in pharmacological weight reduction are achieved through a combined approach integrating pharmacotherapy, nutritional supplementation, and physical activity, thereby improving body composition and reducing the risk of sarcopenia (Morton et al., 2018; Rossi et al., 2026).

Conclusions

The evolution of the dairy industry demonstrates a clear transition from a traditional food system toward a digitally and biotechnologically integrated model. During the period 2000–2030, the development of AI, IoT, precision fermentation, and advanced processing technologies has enabled a transformation toward "Dairy 4.0," which is based on data-driven decision-making, sustainability, and molecular precision.
These innovations significantly enhance production efficiency, animal welfare, and the environmental performance of the industry. In parallel, contemporary nutritional science emphasizes the need for integrated approaches to maintaining body composition, particularly in the context of pharmacologically induced body weight reduction.
Overall, the dairy sector is evolving toward a highly integrated system that combines nutritional science, biotechnology, and digital intelligence with the aim of improving human health and sustainability.

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HEPATOTOXICITY OF ANTIBIOTICS IN DIFFERENT AGE GROUPS

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Abstract

Drug-induced liver injury (DILI), also referred to as drug - induced hepatotoxicity, constitutes a major clinical problem, which has become the leading cause of acute liver failure. This research aims to identify the main antibiotics that can cause liver damage and discuss their presentation, type and consequences including frequency and severity. Hepatotoxicity caused by antibiotics is usually asymptomatic, reversible, associated with only mild liver damage. However, in rare cases, the need for liver transplantation and death from acute liver failure have been reported. Hepatotoxicity is an uncommon adverse effect of the drug and the main cause of drug discontinuation. Most patients with liver injury associated with use of antibiotics have a favorable prognosis. However, patients with jaundice have approximately 10% risk of death from liver failure and/or require liver transplantation. In this regard, it is essential that doctors and patients are aware of and monitor possible symptoms for early detection of hepatotoxicity.

Keywords: Drug Induced Liver Injury (DILI), Antibiotics, Hepatotoxicity.

Introduction

During the last decade, liver toxicity has been one of the most frequent reasons for pharmacovigilance safety reports and withdrawal from the market of an approved drug. The liver is a major organ involved in the detoxification and secretion of many endogenous and exogenous substances. Liver dysfunction challenges not only healthcare professionals, but also pharmaceutical industries and drug regulatory agencies. Drug-induced liver injury (DILI), also referred to as drug-induced hepatotoxicity, constitutes a major clinical problem, which has become the leading cause of acute liver failure. Drug-induced **hepatotoxicity is one of the leading causes of acute and chronic liver disease and is also the most common side effect that halts the development of a new drug or leads to the withdrawal of approved drugs from the market (**Dass E. 2020) . **According to World Health Organization (WHO) statistics, DILI is ranked as the 5th leading cause of death worldwide (**Lu RJ, Zhang, et al 2016). **Maintaining a healthy liver is vital to the overall health of human beings. The liver is the largest and most complex internal organ of living systems, involved in the intermediary metabolism of proteins, fats and carbohydrates, acts as a storehouse of protein, glycogen, vitamins (**Das A., Biswas P. et al 2011). **Most drugs must pass through the liver, as it is the main site for their metabolism. Since in the liver, enzymes convert prodrugs to active metabolites or convert active drugs to inactive forms, the liver's primary mechanism for metabolizing drugs is via cytochrome P-450. However, the process is slower in some people and in these people there is a risk of liver damage. Hepatotoxicity is defined as liver damage or impairment of liver function caused by drugs or other non-pharmacological agents. (**Paniagua, **et al 2017). Many drugs can cause liver damage, but people react differently to different drugs. Some people may have an adverse reaction to certain drugs and may experience liver damage, while others may not. In rare cases, hepatoxicity can lead to chronic damage and bile duct obliteration syndrome (**Einar S. Björnsson. 2017)**. Antibiotics are considered the most common causes of hepatotoxicity.Antibiotic-induced hepatotoxicity is usually asymptomatic, transient, and associated with only mild liver damage. However, serious injury requiring liver transplantation has been reported in some cases (**Andrade RJ,.**2011) Hepatocytes,**

cholangiocytes, Kupffer cells, ductal and endothelial cells are involved in the mechanisms by which drugs cause hepatotoxicity that have direct effects on cellular organelles such as mitochondria, endoplasmic reticulum, or nucleus. Drug metabolites generated in the liver through biotransformation can cause liver damage due to the formation of toxic or reactive substances such as free radicals and thus a breakdown of a variety of chemical reactions can occur. These mechanisms can generate necrosis, apoptosis, or both (Paniagua et al **2017)**. Various environmental factors including age, gender, alcohol consumption, comorbidities and genetic factors are involved in each step and the degree of liver damage is different. If liver damage heals within 6 months, it is known as acute liver damage and if it persists for more than 6 months, it is known as chronic liver damage (Jeong III Suh, 2020). Chronic drug-induced liver injury defined as DILI with persistent liver injury is a global challenge with major difficulties in determining the cause and establishing effective treatment. Hepatotoxicity may be considered chronic when liver enzymes do not return to normal or baseline values after drug withdrawal and/or signs and symptoms of liver disease persist six months after the onset of DILI. Risk factors are important and may be useful for early detection of chronic liver damage. Elderly patients may be considered a risk factor due to reduced metabolic function. Chronic damage manifests as persistent inflammation of the bile ducts that progresses to cirrhosis and eventually requires a liver transplant. However, research on chronic DILI over the past decades is still lacking, and the incidence, phenotypes, mechanisms, risk factors, and treatment are not fully understood (Qiaoling Wang 2021). Drug-induced liver damage is usually reversible and is considered benign and improves after the drug is withdrawn. However, it sometimes progresses to liver failure, requiring a liver transplant or causing death. It is important to recognize and remove the suspected agent as soon as possible to prevent progression to chronic liver disease and/or fulminant hepatic failure (Stefan David 2010). Drug-induced liver damage presents a challenge to the clinician and hepatologist David E. Kleiner (2014).. Clinical features are an important basis for the diagnosis of drug-induced liver diseases. Since there are no specific diagnostic tests or specific biomarkers for idiosyncratic hepatotoxicity, its diagnosis is made after strictly excluding other causes of liver disease, evaluating the temporal relationship between drug use, abnormal liver tests, and evaluating improvement in liver tests after drug withdrawal. Hepatotoxicity caused by antibiotics can often be detected early by elevations of liver enzymes, Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GGT) (Andrade RJ, 2011 ; Singh A, Bhat TK, Sharma OP. 2011; Stefan David 2010). The main aim of the study is to identify antibiotics that can cause hepatotoxicity and to highlight this side effect of widely used antibiotics, their frequency and severity.

Materials and methods

In order to realize the purpose and objectives of the study, the analysis-causal method was selected where all the specific elements of the study are presented, starting from the type of data, the cases analyzed and the development of the topic based on the general and specific objectives using the histories of the patients' illnesses from the mother doctors.In this study, a total of 29 patients of different genders and age groups from the Center for Family Medicine - Clinical Hospital of Tetova - of the Pollog Region were analyzed. Outpatients who were prescribed antibiotics for the treatment of bacterial infections by their primary care physician were analyzed, as well as hospitalized patients who were treated with antibiotics for various diagnoses. Carefully following the patient's history, the therapy he uses, the duration of antibiotic use, the time of their initiation and cessation. Biochemical data analyzed from (patient history): alanine aminotransferase (ALT), aspartate aminotransferase (AST), gammaglutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels. The study was

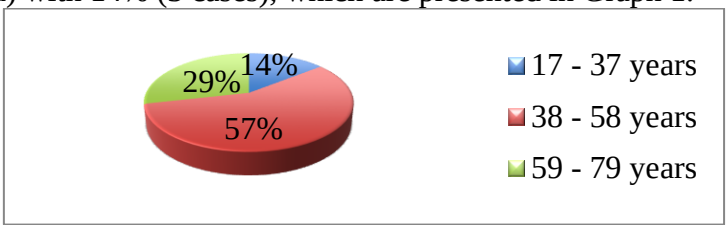
conducted according to a protocol designed in accordance with the ethical principles of the Declaration of Helsinki for medical research involving humans. Patients were informed in advance about the purpose of the study, about privacy, assuring them that the data collected from them would be anonymous and would not be identifiable (World Medical Association , 2001).

Statistical data processing

The results were processed and presented in tabular and graphical form using Microsoft Office Excel 2007.

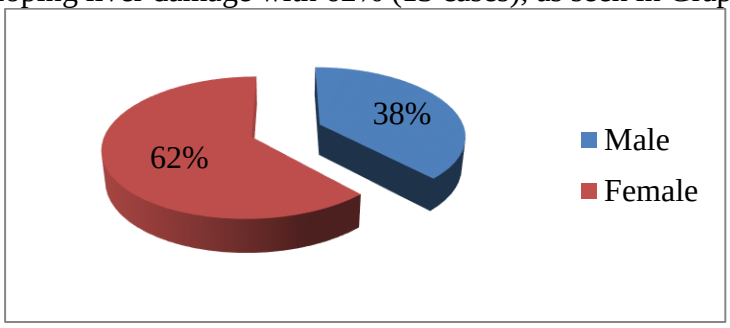
Results and discussion

This study analyzed a total of 29 patients of different age groups. In continuous follow-up of liver enzymes, only 21 patients resulted in hepatotoxic effects and only the results of patients in whom increased liver enzyme values were detected are presented below.
Of the cases included in the study, the most affected is age group II (38 - 58 years old) with 57% (12 cases), followed by age group III (59 - 79 years old) with 29% (6 cases) and age group I (17 - 37 years old) with 14% (3 cases), which are presented in Graph 1.



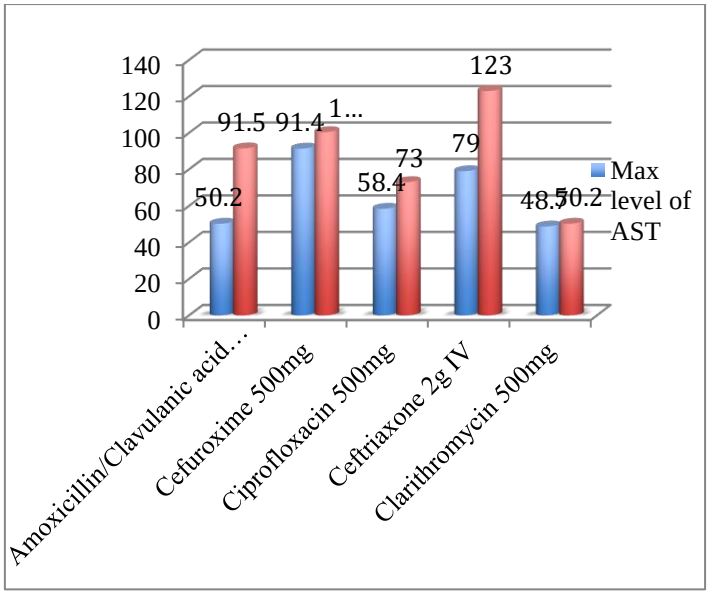
Graph 1. Incidence of hepatotoxicity according to age groups

Overall, compared to male patients comprising 38% (8 cases), female patients are at greater risk of developing liver damage with 62% (13 cases), as seen in Graph 2.



Graph 2. Susceptibility to hepatotoxicity according to gender

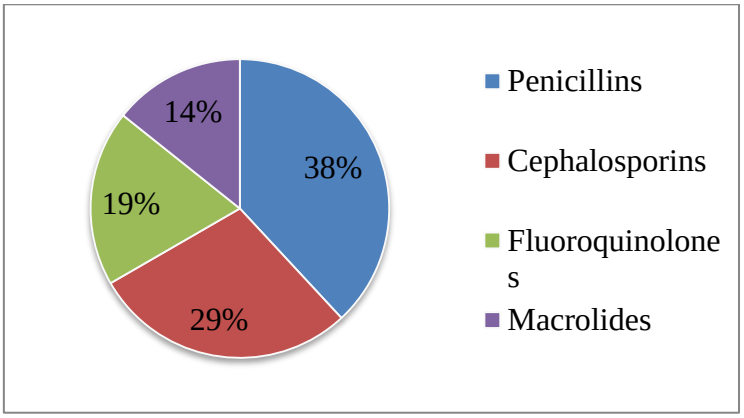
24% of patients (5 cases) who were treated with Amoxicillin/Clavulanic acid 1000 mg showed that the maximum level of AST is 50.2 U/L (0-31) and ALT 91.5 U/L (0-34). 10% of patients (2 cases) treated with Cefuroxime 500 mg and 14% (3 cases) with Ciprofloxacin 500 mg showed that the maximum level of AST in patients who were treated with Cefuroxime is 91.4 U/L (9-43) while ALT 100.4 U/L (10-41). In patients treated with Ciprofloxacin the maximum level of AST is 58.4 U/L and ALT 73.0 U/L. 9% of patients (2 cases) treated with Ceftriaxone 2 g IV showed a peak level of AST of 79.0 U/L and ALT of 123.0 U/L. 10% of patients (2 cases) treated with Clarithromycin 500 mg showed minimal increases in AST and ALT. The maximum level of AST is 48.7 U/L and ALT 50.2 U/L, which are shown in Graph 3.



Graph 3. The rate of increase in liver enzymes from the most prescribed antibiotics

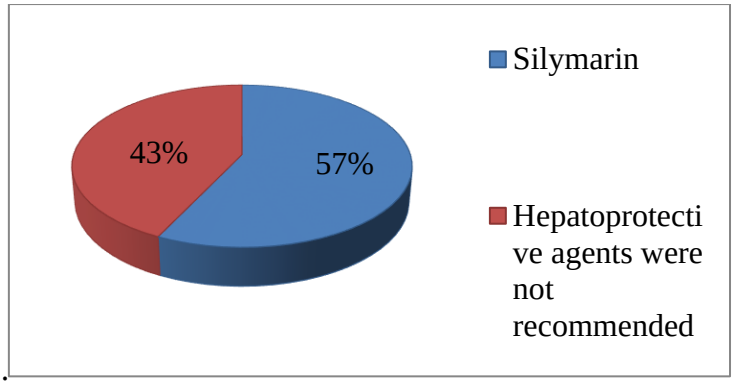
From the obtained results, it can be observed that slight, transient increases in aminotransferases appeared in patients treated with Fluoroquinolones and Macrolides, while patients treated with Penicillins, Cephalosporins developed increases in aminotransferases above twice the upper normal limit

The causative agents that developed liver enzyme values above the upper normal limit include Penicillins with 38% of patients (8 cases), followed by Cephalosporins 29% (6 cases), Fluoroquinolones 19% (4 cases), Macrolides 14% (3 cases), which are presented in Graph 4



*Graph **4. Groups of antibiotics that caused hepatotoxic** effects*

Among the hepatoprotective agents, mainly herbal preparations including Silymarin were recommended in 57% (12 cases), while in 43% (9 cases) no hepatoprotective agents were recommended, which are shown in Graph **5**



*Graph **5.** Use of hepatoprotective agents*

In this study, a wide variety of antibiotics resulted in hepatotoxic effects. Penicillins and Cephalosporins were the most common antibiotics that developed asymptomatic elevations of liver enzymes. Analysis of 29 cases showed that Amoxicillin/Clavulanic acid (Amoksiklav) was one of the most common antibiotics prescribed to outpatients that caused hepatotoxic effects after the end of treatment. Among the 6 patients who were treated with Amoxicillin/Clavulanic acid only 1 of them did not develop elevated liver enzymes. In cases of increased levels of liver enzymes that exceeded twice the upper limit of normal, doctors have recommended supportive therapy to patients - hepatoprotective agents to prevent progressive liver damage. Our results correspond to the data of (Raúl J. Andrade et al 2005) and others in the study conducted in Spain that was registered in the Spanish Registry of Hepatotoxicity where the analysis of 461 cases over a 10-year period showed that Amoxicillin/Clavulanic acid was the most common drug involved in hepatotoxicity

Conclusion

Antibiotics resulted in hepatotoxic effects. Penicillins and Cephalosporins were the most common antibiotics that developed asymptomatic elevations of liver enzymes
Elevated liver enzymes, fatigue, fever and jaundice are the most common symptoms.
Since Amoxicillin/Clavulanic acid is a widely used antibiotic, it is essential to highlight this side effect so that patients and medical professionals become more aware of its existence. By doing so, we hope to spare patients unnecessary examinations, which can be invasive and have potentially serious complications.
Some patients are asymptomatic and the identification of liver damage is based only on increased levels of liver enzymes; therefore, monitoring of liver tests is important to prevent serious effects. In addition, knowing the risk factors can prevent hepatotoxicity in a possible case because the process is reversible and the situation improves after withdrawal of the drug

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ACUTE DIARRHEA IN CHILDREN OF EMIGRANTS DURING SUMMER VISITS TO THE COUNTRY OF ORIGIN:A CLINICAL, ETIOLOGICAL AND THERAPEUTIC ANALYSIS OF 24 PEDIATRIC CASES (MAY–OCTOBER 2025)

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Abstract

Background. Acute diarrhea remains one of the most frequent causes of pediatric presentation during the warm months, and children of emigrant families returning to their country of origin constitute a particularly high-risk subgroup (pediatric VFR — visiting friends and relatives). Abrupt changes in dietary regimen and water quality, variable hygienic-sanitary conditions and exposure to local enteric pathogens markedly increase the incidence of infectious gastroenteritis in this population.
Aim. To analyze the etiological factors, clinical manifestations, laboratory and imaging findings, treatment delivered and clinical course of acute diarrhea in children of emigrants who presented during the summer season, and to identify modifiable predisposing factors.
Materials and methods. A retrospective descriptive study was carried out on 24 children aged 2–16 years (14 girls, 10 boys) treated for acute diarrhea between May and October 2025. Demographic data, exposure history, laboratory work-up (complete blood count, CRP, electrolytes, stool culture, parasitological examination), imaging findings (abdominal ultrasound, plain abdominal radiography), treatment and clinical course were analyzed.
Results. Infectious etiology predominated: viral gastroenteritis 41.7%, bacterial infection 29.2%, foodborne intoxication 16.7%, intestinal parasitosis 8.3%. The most frequent bacterial pathogens were *Salmonella* spp., enteropathogenic *Escherichia coli* and *Campylobacter jejuni*. Dominant symptoms were watery diarrhea (100%), abdominal pain (79.2%) and vomiting (62.5%). Mild-to-moderate dehydration was documented in 37.5% of cases. Eighteen patients (75%) were managed on an outpatient basis; 6 (25%) required short-term hospitalization (mean 2.3 days). No serious complications occurred.
Conclusion. Diarrhea in children of emigrants during summer visits is mostly of infectious origin transmitted via the fecal-oral route and is closely related to dietary exposures in uncontrolled household settings. Pre-travel counseling, food and water hygiene and early oral rehydration are the cornerstones of prevention and treatment.

Keywords: acute diarrhea, children of emigrants, VFR, gastroenteritis, rehydration, Salmonella, Rotavirus, Norovirus, food hygiene.

Introduction

Acute pediatric diarrhea continues to be one of the leading causes of morbidity and emergency consultations worldwide, particularly during the summer months, when high ambient temperatures, easier spoilage of food and increased population mobility together create favorable conditions for the fecal-oral transmission of enteric pathogens. Although mortality has fallen substantially in middle- and high-income countries, diarrhea still represents a considerable burden in terms of outpatient visits, pediatric hospitalizations and healthcare expenditure.
Within the pediatric population, children of emigrant families who travel periodically to their country of origin to visit relatives and friends — referred to in the international literature as "pediatric VFR travelers" (Visiting Friends and Relatives) — represent an epidemiologically distinct subgroup with elevated risk of travel-associated infectious diseases (Hagmann et al., 2010; CDC, 2024). Unlike conventional tourists, these children stay for prolonged periods in rural or family settings, eat and drink in domestic environments outside standard hygienic

control, rarely attend pre-travel consultations and have lower coverage with vaccines recommended for the destination risk profile (Han et al., 2012; Bui et al., 2015).
Traveler's diarrhea (TD) is reported as the most frequent health problem among these children, with rates ranging from 13.5% to 39% of pediatric trips, depending on destination, length of stay and age (Stauffer et al., 2002; Mattila et al., 2013). Young children, especially those under five, are particularly vulnerable due to smaller fluid and electrolyte reserves, a proportionally larger weight share of gastrointestinal losses and the inability to communicate symptoms early (Guarino et al., 2014). VFR children born outside their parents' country of origin lack natural immunity to local pathogens, which makes them as — or sometimes more — susceptible than their accompanying adults (CDC, 2024).
The etiological spectrum of summer diarrhea is predominantly infectious. Enteric viruses, mainly Rotavirus and Norovirus, remain the leading agents of acute pediatric gastroenteritis throughout Europe, although the introduction of anti-rotavirus vaccination in some countries has modified the epidemiological picture (Payne et al., 2013; Yang et al., 2022). Among bacterial pathogens, enteropathogenic / enterotoxigenic *E. coli*, non-typhoidal *Salmonella* spp., *Campylobacter jejuni* and *Shigella* spp. account for the most frequent causes, while parasites such as *Giardia lamblia* and *Cryptosporidium* remain relevant in rural settings where water supply is uncontrolled (Sakran et al., 2020; Fischer Walker et al., 2012; Diallo et al., 2008). VFR children have also been shown to face an increased risk of typhoid fever and hepatitis A, underscoring the need for vaccination-status review prior to departure (Angell & Cetron, 2005; CDC, 2024).
In the specific context of the Balkans and South-Eastern Europe — the region of origin of many emigrant families now living in Western Europe, Scandinavia, North America and Australia — the seasonal summer return is regularly associated with the consumption of traditional dishes prepared at home, unpasteurized dairy products, grilled meat at family picnics, and drinking water of variable quality. This clinical reality is well known to local pediatricians but remains insufficiently documented in the domestic scientific literature. The present study aims to contribute to filling this gap.

Aim of the study

The primary aim of this study was to describe the clinical, etiological and therapeutic characteristics of acute diarrhea in children of emigrants seen at the pediatric service during the 2025 summer season.
Specific objectives were:
to identify the most frequent etiological factors (viral, bacterial, parasitic, alimentary);
to analyze clinical manifestations and signs of dehydration in relation to etiology;
to evaluate the role of laboratory and imaging investigations (abdominal ultrasound and plain radiography) in diagnostic management;
to analyze therapeutic management — with emphasis on rehydration and selective antibiotic use — and clinical course;
to identify modifiable predisposing factors that may serve as targets for preventive intervention before travel and during the stay in the country of origin.

Materials and methods

3.1. Study design and population: The study was designed as a retrospective descriptive analysis of clinical data from cases of acute pediatric diarrhea presenting at the pediatric service between 1 May and 31 October 2025. Twenty-four children aged 2–16 years (14 girls, 58.3%; 10 boys, 41.7%) were included, all with a history of long-term residence abroad (primary

residence in a Western European country) and seasonal return to the country of origin during the summer months.

3.2. Inclusion and exclusion criteria: Inclusion criteria were: age 2–16 years; an acute episode of diarrhea (≥3 loose stools within 24 hours) starting within 7 days of arrival in the country of origin; residence abroad for ≥6 months prior to the current episode; complete clinical documentation.
Children with chronic gastrointestinal disease (inflammatory bowel disease, celiac disease), patients with primary or secondary immunodeficiency, those with chronic metabolic disease, and cases with incomplete documentation were excluded.

3.3. Data collected and diagnostic procedures: For each patient the following were recorded: age, sex, length of stay abroad, time interval between arrival and onset of symptoms, suspected dietary exposures (water, food, setting of consumption), clinical symptoms, physical examination findings, grading of dehydration (mild / moderate / severe according to clinical criteria), laboratory parameters (complete blood count, CRP, serum electrolytes, urea, creatinine), stool culture and parasitological stool examination. Abdominal ultrasound was performed in cases with marked abdominal pain or suspicion of additional pathology; plain abdominal radiography was performed when clinically indicated.

3.4. Ethical considerations and analysis; Data were collected anonymously from clinical records, in accordance with the principles of the Declaration of Helsinki. Analysis is descriptive, with results expressed as absolute numbers and percentages, mean values and age range.

Results

4.1. Demographic characteristics: Of the 24 patients enrolled, 14 were girls (58.3%) and 10 were boys (41.7%). Mean age was 8.4 years (range 2–16 years). The age-group distribution is shown in Table 1. The largest concentration was in the 6–10-year age group (37.5%), followed by the preschool group of 2–5 years (33.3%).

Table 1. Distribution of patients by age group (n = 24)

Age group	Number of patients	Percentage (%)
2–5 years	8	33.3
6–10 years	9	37.5
11–16 years	7	29.2
Total	24	100

4.2. Etiological factors: Infectious etiology accounted for the predominant cause (87.5% of cases). The distribution of identified causes is shown in Table 2.

Table 2. Etiological factors of acute diarrhea (n = 24)

Etiological factor	Number of cases	Percentage (%)
Viral gastroenteritis (Rotavirus, Norovirus)	10	41.7
Bacterial infection (Salmonella spp., E. coli, Campylobacter jejuni)	7	29.2
Foodborne intoxication	4	16.7
Intestinal parasitosis (Giardia lamblia)	2	8.3
Undetermined	1	4.1
Total	24	100

Among viral infections, the clinical picture most often suggested Rotavirus and Norovirus as the likely agents. Among bacterial infections, stool culture isolated *Salmonella* spp. in 3 cases, enteropathogenic *Escherichia coli* in 2 cases and *Campylobacter jejuni* in 2 cases. Parasitological examination identified *Giardia lamblia* in 2 patients with subacute–persistent diarrhea.

4.3. Predisposing factors: The dietary history most often revealed: consumption of unfiltered water from family wells or private boreholes; meat or unpasteurized dairy products; ice cream or food bought in open-air settings; and consumption of traditional dishes (savory pastries, meat dishes, salads) prepared at home and kept for several hours at ambient temperature during family gatherings. In 15 cases (62.5%) consumption of food prepared ≥3 hours before being eaten, without adequate refrigeration, was documented. Sixteen families (66.7%) reported that they had not consulted a pediatrician before departure for advice on food hygiene and vaccination status.

4.4. Clinical manifestations: Symptoms began on average 24–72 hours after arrival in the country of origin. Watery diarrhea was present in all patients; abdominal pain — predominantly periumbilical and in the lower quadrants — was reported by 79.2%; vomiting by 62.5% and fever >38°C by 54.2% (Table 3). In patients with bacterial etiology, fever was more pronounced and diarrhea was more often associated with mucus or blood.

Table 3. Clinical manifestations reported by the patients (n = 24)

Symptom / sign	Number of cases	Percentage (%)
Watery diarrhea	24	100
Abdominal pain	19	79.2
Vomiting	15	62.5
Fever (>38°C)	13	54.2
Loss of appetite	12	50.0

Symptom / sign	Number of cases	Percentage (%)
Mild–moderate dehydration	9	37.5
Asthenia (general weakness)	8	33.3
Diarrhea with mucus	5	20.8
Bloody diarrhea	2	8.3

4.5. Laboratory and imaging findings: The complete blood count showed leukocytosis in 9 patients (37.5%), with neutrophil predominance in bacterial cases and relative lymphocytosis in viral cases. CRP was elevated (>20 mg/L) in 11 patients (45.8%). The most frequent electrolyte disturbances were mild hyponatremia and hypokalemia, mainly in patients with repeated vomiting.
Abdominal ultrasound was performed in 8 patients (33.3%) because of marked abdominal pain or suspicion of additional pathology. The most common findings were intestinal meteorism, mesenteric lymphadenitis and mild thickening of the bowel wall; no case revealed pathology requiring surgical intervention. Plain abdominal radiography was performed in 5 patients and showed intestinal distension with minimal air-fluid levels and no signs of obstruction.

4.6. Treatment and clinical course: Oral rehydration with hypo-osmolar solutions was the mainstay of treatment in most cases, in accordance with the ESPGHAN/ESPID guidelines (Guarino et al., 2014). In 6 patients (25%) with oral intolerance or moderate dehydration, intravenous rehydration with normal saline and Ringer's lactate was administered, with careful electrolyte correction. Symptomatic therapy included antipyretics (paracetamol), probiotics (Saccharomyces boulardii and Lactobacillus rhamnosus GG) and ondansetron in patients with repeated vomiting. Refeeding was resumed within 4–6 hours of rehydration, in accordance with current recommendations.
Antibiotic therapy was used selectively in 7 patients (29.2%) with suspected or confirmed invasive bacterial infection. Regimens included azithromycin (first-choice agent for suspected *Campylobacter* or *Shigella*), parenteral ceftriaxone in febrile patients with a more severe course, and trimethoprim/sulfamethoxazole in selected cases. Both children with *Giardia lamblia* received oral metronidazole for 7 days.
Eighteen patients (75%) were managed as outpatients; 6 patients (25%) required short-term hospitalization with a mean length of stay of 2.3 days. Mean duration of symptoms was 3–5 days. No patient developed serious complications (sepsis, acute renal failure, intestinal obstruction, severe dehydration) and none required intensive-care treatment. All patients recovered fully.

Discussion

Our study confirms that acute diarrhea among children of emigrants during summer visits to their country of origin is mostly of infectious etiology and presents with a clinical profile consistent with the international literature on pediatric traveler's diarrhea (Shah et al., 2009; Mattila et al., 2013). The predominance of viral gastroenteritis (41.7%), followed by bacterial causes (29.2%), reproduces the distribution reported in European and Asian studies of the past decade (Payne et al., 2013; Yang et al., 2022; Gastañaduy et al., 2013).

Rotavirus and Norovirus remain the two most frequent agents of pediatric gastroenteritis. Although rotavirus vaccination has substantially reduced its relative weight in developed countries, VFR children often have an incomplete vaccination schedule or are vaccinated late in the host country; the result is a vulnerable population travelling to destinations with active viral circulation (Han et al., 2012; Bui et al., 2015). In many developed settings Norovirus has become the leading agent following anti-rotavirus vaccination, and is characterized by prolonged fecal viral shedding that promotes secondary household transmission (Payne et al., 2013).

Among bacterial pathogens, the isolation of non-typhoidal *Salmonella* spp., enteropathogenic *E. coli* and *Campylobacter jejuni* is consistent with data reported from the Mediterranean region and the Middle East, where these organisms represent the leading causes of pediatric bacterial enteritis during the warm months (Sakran et al., 2020; Diallo et al., 2008). The seasonality of non-typhoidal salmonellosis, with a clear peak between May and September, is well documented in the literature and is linked to increased consumption of eggs, poultry and dairy products stored under suboptimal conditions (Cheng et al., 2019). The identification of *Giardia lamblia* in two of our cases is a reminder that intestinal parasitoses must be considered, particularly in subacute or persistent diarrhea, when conventional stool culture is negative (Fischer Walker et al., 2012).

An important finding of our study is the marked impact of behavioral and dietary factors: 62.5% of patients reported eating food kept at room temperature for several hours, and 66.7% of families had not received pre-travel counseling. This is consistent with the literature documenting that VFR families are the group least covered by pre-travel services (Hagmann et al., 2010; Han et al., 2012). The reasons are complex and include: the misperception that returning "home" poses no health risk, language and economic barriers, the lack of specialized travel-medicine consultations, and prolonged stays in rural conditions (CDC, 2024).

Despite clinical similarities, VFR children may be at higher risk than tourist children for several documented reasons: longer exposure (2–6 weeks rather than a few days), accommodation in family homes in rural areas with limited hygienic-sanitary infrastructure, direct consumption of non-commercial food and water, and close contact with the local population (CDC, 2024; Angell & Cetron, 2005). As a consequence, beyond classical gastroenteritis they also face an elevated risk of typhoid fever, hepatitis A, malaria (in endemic destinations) and tuberculosis — a consideration that should be reflected in pre-travel care plans (Han et al., 2012).

The treatment applied in our series followed the current ESPGHAN/ESPID 2014 guidelines, which recommend oral rehydration with hypo-osmolar solutions as first-line therapy and reserve the intravenous route for cases with severe dehydration or oral intolerance (Guarino et al., 2014). Adjunctive interventions — selective probiotics (Lactobacillus rhamnosus GG, Saccharomyces boulardii) and ondansetron for vomiting — have solid support in clinical trials and have been shown to reduce both the duration of diarrhea and the need for hospitalization (Szajewska et al., 2014; Freedman et al., 2014).

Antibiotic therapy in acute pediatric diarrhea remains an area of narrow consensus: it is recommended only in cases of suspected or confirmed invasive infection (dysenteric diarrhea with high fever, systemic toxicity, risk factors) or for specific pathogens (*Shigella*, *Campylobacter* in protracted diarrhea, *Salmonella* in infants <3 months or immunocompromised patients). Azithromycin is gaining ground as the preferred empirical agent because of rising *Campylobacter* resistance to fluoroquinolones and its good safety profile in children (Riddle et al., 2017; CDC, 2024). We used antibiotics in 29.2% of cases, a proportion in line with the series reported by Sakran et al. (2020) in children hospitalized for bacterial gastroenteritis.

Stronger collaboration between the host-country pediatrician and the pediatrician in the country of origin is essential. Pre-departure counseling should include: review of vaccination status

(including rotavirus, hepatitis A and typhoid fever where indicated), education on hand and water hygiene, preparation of a “travel kit” containing oral rehydration solution (ORS) and paracetamol, and a simple algorithm for parents indicating when to seek medical care (high fever, blood in stool, marked dehydration, symptoms lasting >72 hours) (Stauffer et al., 2002; CDC, 2024).

Limitations of this study include the relatively small sample size (n = 24), its retrospective and single-center character, the absence of advanced molecular testing (multiplex PCR) for the identification of viral pathogens, and the inability to follow patients after they had left the country of origin. Nevertheless, the results provide a useful clinical overview and serve as a basis for further prospective studies with larger samples and molecular diagnostics.

Conclusion

Acute diarrhea in children of emigrants during summer visits to their country of origin is overwhelmingly of infectious origin, with a predominance of viral (Rotavirus, Norovirus) and bacterial (*Salmonella*, *E. coli*, *Campylobacter*) gastroenteritis. Modifiable dietary and hygienic factors — unfiltered water, food kept at unsuitable temperatures, lack of pre-travel counseling — play a decisive role in the pathogenesis of these cases.

Clinical course is predominantly benign when diagnosis is established early and oral rehydration is started promptly. The limited and well-targeted use of antibiotics, combined with symptomatic treatment and selective probiotics, constitutes an effective therapeutic strategy.

We recommend: (i) systematic education of emigrant families before departure on food hygiene, vaccination and the “travel kit” including ORS; (ii) closer collaboration between the host-country pediatrician and the pediatrician in the country of origin; (iii) expansion of molecular diagnostics in local pediatric centers for better etiological characterization; and (iv) prospective studies with larger samples that would allow the formulation of clinical guidelines specific to this population, which has distinct epidemiological features.

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MANAGEMENT OF HIGH-RISK IMPACTED MANDIBULAR THIRD MOLARS USING SURGICAL METOHOD OF CORONECTOMY: A CASE REPORT

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Abstract

Impacted mandibular third molars, due to their proximity with the mandibular canal, often are categorized as high-risk tooth for surgical intervention and may be accompanied by postoperative neurosensory deficit. The management of these situations, show better results by performing coronectomy, as a technique for surgical extraction of these teeth and prevention of potential neuropathy. This paper focuses on the importance of using coronectomy as an alternative surgical technique in cases with impacted mandibular third molars with high risk of nerve injury, in order to minimize possible postoperative complications. Case presentation: a 26 years old female patient presented with vertical impacted mandibular third molar, and a radiographic evaluation of a close proximity with the inferior alveolar nerve. CBCT confirmed the position. The procedure of coronectomy was performed, sectioning the crown and leaving the roots in situ. The follow-up time included radiographic evaluation of the root migration in 6 and 12 months after the coronectomy. The postoperative complications, including injury of inferior alveolar nerve, postoperative pain, swelling, trismus and wound infection, were followed the first week after the surgical procedure. There were no signs injury of IAN, infection or exposure of the roots. The root migration was visible in radiographic imaging after 6 and 12 months after the surgery. Postoperative morbidity consisted on moderate pain, trizmus and swelling. Coronectomy is a safe method for surgical extraction of impacted mandibular molars for patients who demonstrate elevated risk for injury to the inferior alveolar nerve. This surgical method minimizes the incidence of damage to the inferior alveolar nerve and is safer than complete extraction in situations in which the root of the impacted mandibular third molar are in close proximity to the mandibular canal.

Keywords: coronectomy, mandibular third molar, impaction, inferior alveolar nerve, radiography, CBCT.

Introduction

Tooth impaction is a developmental anomaly, with a multicausal etiology, and is caused by various local and general factors. It can affect any morphological group of teeth, in both jaws, on deciduous and permanent teeth; it commonly the most involves the last teeth to erupt in the dental arch, such as mandibular third molars, maxillary third molars, maxillary canines. [1]
Impacted mandibular third molars have different positions considering the bone depth, occlusal plane, and angulation. Determining these elements is of clinical importance, since the position of the impacted tooth determines the risk of adjacent tooth caries, pain, pericoronitis, and mandibular angle fracture. Furthermore, it has been demonstrated that the position of the impacted mandibular third molar determines the level of difficulty of its surgical extraction and the occurrence of postoperative complications. [2-6]
Impacted third molars have a predisposition to cause various pathologies, such as: pericoronitis, periodontal diseases of the second molar, orofacial infections, caries, resorption of the root of the adjacent tooth, cystic changes, changes in the bone structure, problems with the temporomandibular joint [1]
The extraction of the impacted mandibular third molar is a challenge for oral surgeons, and the relationship of the intervention with intraoperative and postoperative complications is particularly important. These complications are due to the position of the impacted tooth, as well as the proximity of important anatomical-morphological structures, such as the

mandibular canal, i.e. its neuro-vascular content (n.alveolaris inferior, a.et v.alveolaris inferior) [7]

The most common and severe complications of third molar extraction surgery include dry socket, postoperative infection, alveolar bone fracture, damage of inferior alveolar nerve or lingual nerve and, in rare cases, mandibular fracture. Therefore, intentional coronectomy is a well-established technique where the root/roots of the wisdom tooth are left in situ and only the crown is sec-tioned and removed [8].

Before performing surgical extraction, an important initial step is to determine the exact position (localization, depth in the jawbone, inclination of the longitudinal axis and relationship to adjacent anatomical-morphological structures) of the impacted mandibular third molar. For this purpose, generally accepted and validated classification systems are used, according to George Winter, Pell & Gregory and Sisk.[9]

The Winter classification defines the deviation of the eruption of the impacted third molar from the normal position of the tooth in the dental arch, i.e. the angle formed between the average longitudinal axis of the second and third mandibular molar.Classification according to Pell and Gregory, determines the relationship of the tooth to the ramus mandibulae and the second molar, also the depth of the impacted molar in relation to the occlusal plane. [9]

In oral and maxillofacial surgery, panoramic radiography is primarily used to evaluate the position of impacted mandibular third molar and assess the risk of injury to the inferior alveolar nerve. However CBCT can provide more accurate information in this regard, allowing for better treatment planning and safer surgical extraction in cases with severe impaction.

To minimize the risk of nerve injury during surgical extraction of impacted mandibular third molars Knuttson K. in 1989 proposed the technique of coronectomy [10]. In recent years, this technique has been indicated in cases characterized by a close contact relationship between the mandibular third molar and the inferior alveolar nerve, where complete removal could cause injury to the nerve [11]

In recent years, less invasive therapeutic alternatives have been implemented.

Laser therapy has shown promising results. Less invasive approaches offer several practical advantages, including reduced intraoperative bleeding, shorter procedural time, lower postoperative discomfort, and faster healing of the wound.[12]

Material and methods

This report presents a case of coronectomy with clinical and radiographic follow-up. The selection of patients in the research sample was limited by certain criteria for patient selection.

Criteria for inclusion in the study:

Patients with an impacted mandibular third molar with a vertical, mesioangular and distoangular position

Patients with an impacted mandibular third molar in close relation to the mandibular canal.

Patients with subjective and objective complaints related to an impacted mandibular third molar

ASA I (normal, healthy patient)

Exclusion criteria from the study

Horizontally positioned impacted mandibular third molar (along the direction of the mandibular canal), where there is a high risk of injury to the inferior alveolar nerve during tooth separation

Acute infection present in the oral cavity or in the immediate vicinity of the tooth that is subject to coronectomy

The planned therapeutic procedure was carried out by implementing the basic surgical principles in relation to conventional operative extraction and the method of coronectomy, i.e.

surgical principles for working in soft and bone tissue. Local block anesthesia was applied for n.alveolaris inferior, n.lingualis and n.buccalis, with 2% lidocaine hydrochloride with 1:100 000 adrenaline.
The procedure includes: elevation of a mucoperiosteal flap with adequate flap design, osteotomy, separation of the tooth crown immediately below the enamel-cementum boundary at an angle of 45°, removal of the tooth crown, reduction of the root fragment 2-3mm below the crestal bone ridge, buccally/lingually, dressing of the surgical wound and closure of the surgical area (per primam) by placing individual sutures with non-absorbable Silk 3-0 thread.
A postoperative panoramic radiograph is performed to visualize the root fragments after the coronectomy. The chosen medical treatment includes ibuprofen 600 mg (one tablet every 12 hours for 3 days) as anti-inflammatory and analgesic therapy. A soft and cold diet is recommended for 24 hours, with local application of cold compresses placed on the cheek in the surgical region for during the first hour after surgery. Oral hygiene measures are also recomended (rinsing with 1% Betadine (Povidonum iodinatum) three times a day until the sutures sre removed one week after surgery).

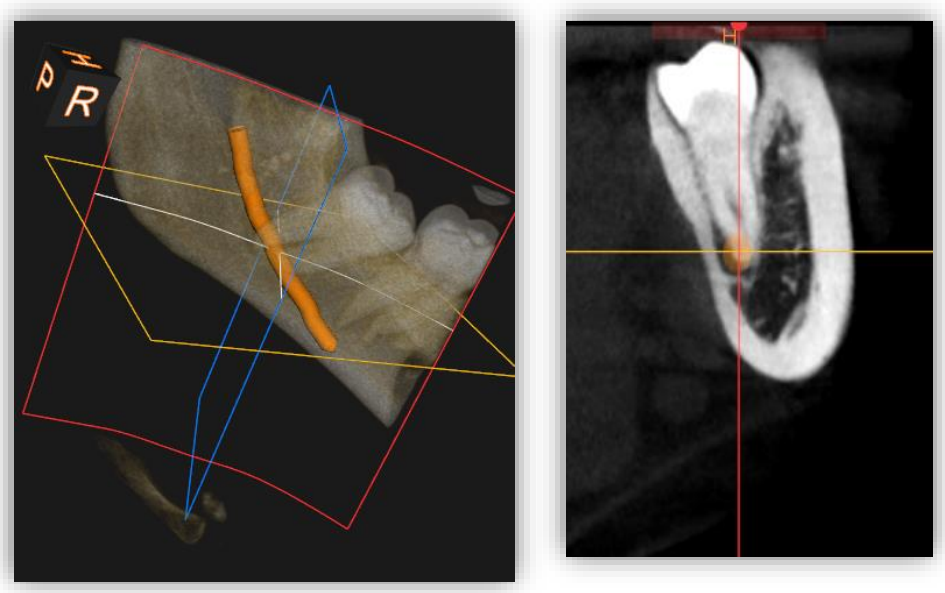
Case presentation

A twenty-six year-old female patient complained about pain in the right posterior region of mandible. With clinical examination and radiographic imaging we could witness the presence of impacted mandibular third molar in close proximity with mandibular canal. CBCT was performed to confirm the direct contact of the roots of the impacted mandibular third molar with the mandibular canal.
Ortopantomography imaging of the current patient shows a vertical positioned impacted mandibular third molar where the roots of the tooth are in close relationship with the mandibular canal.



Picture1. Ortopantomography shows the position of the right impacted mandibular third molar

Cone beam computed tomography (CBCT) has significantly expanded the possibilities for clinical assessment of the three-dimensional relationship between the mandibular third molars and the mandibular canal and for more accurate assessment of the risk of injury to the inferior alveolar nerve. Although CBCT does not completely eliminate surgical risk; it primarily contributes to better anatomical understanding and more adequate case selection. Studies comparing panoramic findings with CBCT consistently indicate superior detection and better characterization of the root-canal relationship when CBCT is applied in appropriately selected cases. [13]
In the presented case CBCT confirms the close relationship between the roots of the right impacted mandibular molar and the mandibular canal, showing the canal which passes between the two roots of the tooth. (Picture 2 and 3.)



Picture 2. CBCT – custom slicing Picture3.CBCT – oblique slicing

Methods of work

The method of coronectomy is presented in the literature as a surgical technique that reduces the risk of injury to the inferior alveolar nerve. The basis of this method is the removal of the crown of the impacted lower third molar, leaving the roots in situ, that way avoiding direct or indirect injury to the inferior alveolar nerve.[14]
When performing the method of coronectomy we applied the following principles [15]
Applying and elevation of a triangular mucoperiosteal flap
Buccal, occlusal and distal osteotomy
Separation of the crown from the root of the tooth, immediately below the enamel - cement border

Complete cutting of the crown at an angle of 45°
Removal of the crown with a suitable instrument
Reduction of the root fragment 2-3mm below the crestal bone ridge, buccal and lingual
Suturing the wound primary with vertical mattress sutues



Picture 4. Elevation of mucoperiosteal flap



Picture5.Crown sectioning, remaining roots



Picture6. Suture of the wound



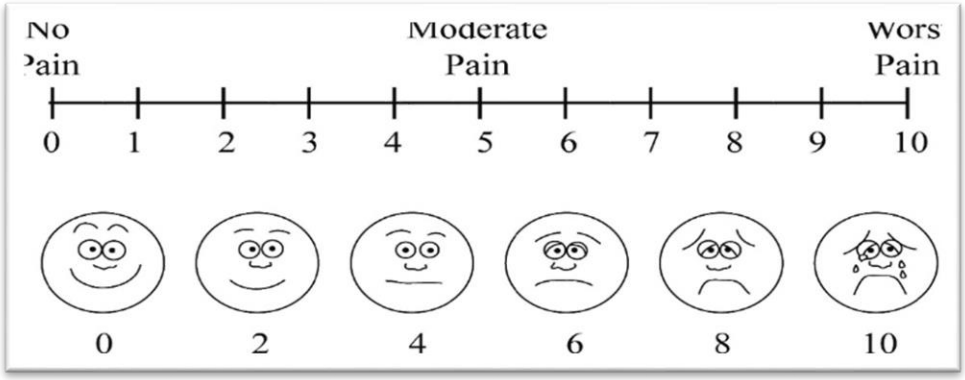
Picture 7. The separated crow

The firs week after surgical treatment the patient was observed for early postoperative morbidity, including pain, swelling and trizmus.

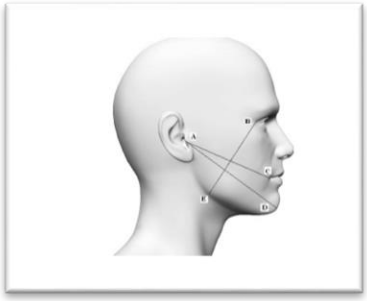
Trismus is most often evaluated by measuring the reduction in maximum interincisal opening of the mouth, and is evaluated: absence of trismus - 0, mouth opening >76% - 1, mouth opening < 75% - 2, mouth opening < 50% and > 26 % - 3, mouth opening < 25% - 4. [16]

The pain evaluation was realized through a horizontal VAS scale to determine the intensity of pain from 1 to 10 by the patient on the first, third and seventh day postoperatively Kaczmarzyk T. et al. [17] (Picture 8).

Picture 8. VAS scale – pain intensity



The swelling evaluation was realized by measuring the distance of certain points in the face, tragus (point A), labial commissure (point C), pogonion (point D), lateral angle of mandible. [18] (Picture 9.)



Picture 9. Swelling measurement by certain points in the face

The swelling the first day after coronectomy is presented at the patient of that participated in this surgical procedure, where it can be seen a moderate swelling on the right cheek. (Picture 10).

The results showed that swelling after applying the method of coronectomy is comparable to the outcomes of cases where is performed conventional extraction of impacted mandibular third molar.



Picture 10. Swelling on the right cheek, first postoperative day

Except the first week, we also followed the long term postoperative morbidity after coronectomy, including the presented case, like root migration, new bone generated above the remained tooth, root eruption. Rradiograph imaging is performed 6 month and 12 months after coronectomy (Picture 9, 10 and 11)



Picture 10. 6 months after coronectomy



Picture11.12 months after coronectomy

Results

The patient was followed up for a 12-month period, where a clinical and radiographic evaluation was conducted. The patient showed a small discomfort after surgery, including moderate pain and swelling, and a light trizmus (mouth opening >76% - 1), there was not registered any deficit in sensitive nerve function for the anticipated follow-up period. The migration of the remaining roots was evident after 6 months of surgery, while the difference between 6 and 12 months was insignificant. The distance of root migration from the mandibular canal from the initial position and after 12 months follow up was measured 1.6 mm.

Discussion and conclusion

The combination of radiographic imaging and CBCT findings has significant clinical value and directly contributes to better decision-making, aiming to reduce the risk of neurosensory complications and optimize surgical outcomes.

According to two systematic reviews coronectomy appears to be safer than total extraction in terms of lower risk of injury to the inferior alveolar nerve during surgical treatment of impacted mandibular third molars. [19,20] The study by Bernabeu-Mira JC et al. [21] showed only one case (2.56%) of temporary paresthesia. The inferior alveolar nerve was not affected. Several factors have been identified that influence the incidence of nerve injury: the anatomical position of the tooth to be extracted, the age of the patient, the exposure of the nerve, the applied extraction access technique and the experience of the surgeon.[22]

One of the most characteristic features of coronectomy is the postoperative migration of the roots left in situ. The majority of long-term radiographic studies have shown that the greatest root migration occurs in the first 6–12 months, with minimal additional migration beyond 24 months 94. [23]

The success rate of coronectomy depends on the survival of the retained root fragments, i.e., the successful formation of bone tissue over the roots, and the absence of symptoms.

The analysis of the available literature and the discussed results from a clinical and radiographic aspect, we can conclude that the method of coronectomy is a scientifically based and clinically justified surgical method for the treatment of impacted mandibular third molars with a high risk of injury to the inferior alveolar nerve.
Coronectomy shows a clear advantage in terms of preserving the neurosensory function of the inferior alveolar nerve, significantly reducing the risk of temporary and permanent consequences of injury to it compared to conventional extraction in high-risk cases.

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ACADEMIC BURDEN AND BEHAVIORAL ADAPTIONS : A STUDY OF DIETARY AND STIMULANT USE AMONG MEDICAL STUDENTS

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Abstract

For many years, medicine has been considered one of the most challenging academic disciplines. Maintaining both academic success and personal well-being is made extremely difficult by the demanding curriculum, extended study sessions, ongoing clinical exposure, and regular patient interactions. Prior studies have repeatedly shown that medical students high levels of stress, sleep deprivation, and burnout are caused by the demanding nature of medical training.
In order to investigate this association, the current study surveyed 162 students about their lifestyle choices and how these behaviors changed during times of high and low academic stress in various academic years.
The purpose of the study was to investigate how academic pressures affects students; coping mechanisms and physical and mental health. Students are frequently expected to constantly perform at a high level despite ongoing stress and exhaustion
due to the precision and responsibility required in medical practice. Despite the known negative consequences of stimulants, the study also took into account students; use of them as a possible way to improve cognitive performance.

Keywords: Medicine, academic burden, medical students, student wellbeing, behavioral adaptations

Introduction:

Medicine has been known through times as one of the, if not the most difficult study majors. Between the extensive curriculum, prolonged study hours, continuous clinical exposure, and the contact with patients every day, it is widely understood that the relationship between maintaining a good academic life and a healthy one is a tough sport. It is not hard to find in other research papers similar to ours, that due to medical training being academically and physically demanding, students experience sleep deprivation, stress and burn-out (Dyrbye et al., 2006; Frajerman et al., 2019). To asses this specific relationship we have decided to survey a number of 162 students on their lifestyle choices, and differences one may find in periods of high and low levels of stress across academic years.
Because of the precise nature of medicine, one that does not allow mistakes, it is almost impossible to be able to perform at your potential each and every day, taking into consideration too the burn-out that chronic stress can cause. Therefore we found it important to add to the study the possibility of students using stimulants as a way to enhance their cognitive performance even with the known side affects.

Behavioural changes

From the problem mentioned above, from which our research paper is centered we have decided to find and highlight the differences in 5 main aspects of their lifestyle :
Dietary Behaviours
Sleep
Energy Drink, Caffeine / Supplement Use
Physical Activity
Nicotine Use

Dietary changes

Because of the long hours of studying, many students as you will see later in the paper find it easier to eat less healthier as a faster option compared to cooking healthy food. Long study hours and limited time for meal preparation often encourage the consumption of fast food, high-calorie snacks, and nutritionally inadequate meals (Almojali et al., 2017; Fares et al., 2016). In addition, many students reported to skipping at least one meal or relying on convenience foods during examination periods . In many cases students have decided on the usage of high caloric snacks just to get a few more hours of studying (Mikolajczyk et al., 2009).

Sleep

As of sleep, it is not surprising to find that a high number of medical students choose to sacrifice a good number of hours of sleep everyday in order to keep their high academic performance, despite evidence demonstrating the negative effects of poor sleep quality on cognitive performance and mental health (Almojali et al., 2017).

Nicotine use

Nicotine products use among medical students unfortunately presents an important paradox: future healthcare professionals using a substance whose harms they are trained to counsel patients against. The relationship between nicotine use and academic stress is well established(Kinnunen et al., 2016). Substance use, especially tobacco is recognized as a maladaptive coping
mechanism for psychological distress. Although in this study as you will see later not a high number of students reporting to using nicotine products, all those who did use them reported to using them as a way of relieving stress.

Energy Drinks/ Supplement Use

The use of stimulants was a shocking find because interestingly enough not a high number of students voted to using energy drink or stimulants to enhance their cognitive performance. Those who did use them, reported to using energy drinks no more than 1-2 times a week and as of taking supplements, the supplement with the highest number of votes between creatine, ashwagandha, omega-3 and Vitamin B Complex was the latter .
Vitamin B being the highest used supplement is actually seen in many other studies such as ‘Aoki S, Endo T, Hasegawa H, Nakaji S, Sugawara K, Totsuka M. [Dietary patterns and intake of
nutrients, energy, and dietary fiber in medical students]. Nihon Koshu Eisei Zasshi. 1996 Aug;43(8):632-43, which specifically states “The nutrients that showed a higher intake in males than in females were energy, protein, fat, carbohydrates, and vitamins B1 and B2” .
Concerning to this finding was that a number of students voted to experiencing common side effects such as : tachicardia, anxiety, panic attacks, insomnia, and abdominal irritation after using caffeine or energy drinks (Richards & Smith, 2016).

Physical Acitivity

Even though physical activity is consistently identified as a protective factor against burnout, depression and anxiety in medical students (Warburton & Bredin, 2017), during this study we found that almost none choose physical activity as a coping mechanism to the high stress.

Unfortunately from all domains physical activity seemed to be the first domain students seem to change/decrease (Fares et al., 2016).

Methodology

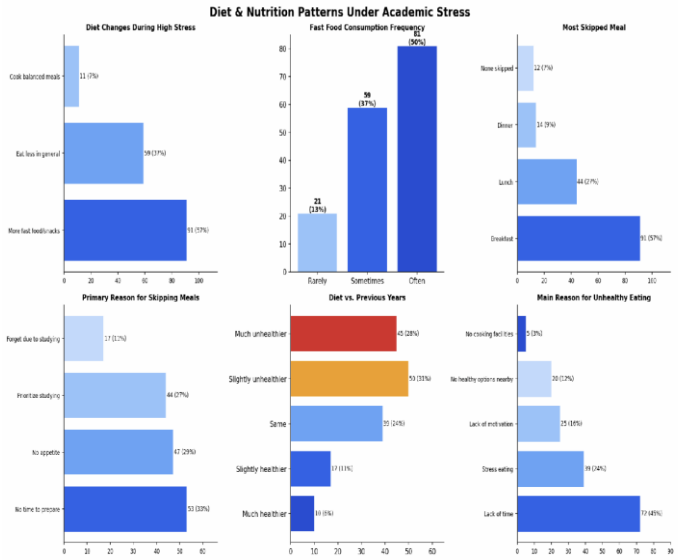
In order to support our hypothesis that academic burden significantly influences dietary behaviors and stimulant use among medical students, we conducted a cross- sectional observational study among medical students using and anonymous questionnaire-based survey. The survey was written in Albanian and covered these main domains:
Demographics
Academic Burden
Dietary Behaviour
Nicotine Use
Caffeine/ Energy Drink Use
Supplement Use
Physical Activity
The number of participants was 162 students from the first to sixth academic year at "University of Tetovo".

Results

Demographics:
The sample was predominantly female with a total of 76.2% compared to male respondents with only 23.6%. The majority of the respondents were aged 21-23 years (57.8%) which corresponds to them representing mostly Years 2 and 3 of the academic years, followed by 18-20 years with 26.7% and the lowest percentage covering age 24-26 years with 14.3%.
As of the academic status, 63.4% were reported as regular students, 32.9% are repeating one or more subjects and only 3.7% were in their final year of studies.

Academic Burden and Stress

As expected academic stress was rated highly in all question related to it in the survey. 41.0% of the students selected a rating of 4 as 'Highly Stressful', 39.8% selected a rating of 5 'Extremely Stressful', and 18.6% selected a rating of 3 as 'Moderately Stressful" , with no students selecting a rating of 1, and only 1 student or 0.6% rated medicine as a 2 'low stress'.
Related to the percentages above, 85.1% reported to feeling overwhelmed by academic responsibilities with 72.7% of students reporting an extreme increase in workload during exams.
Sleep Sacrifice was the most highlighted behaviour with a number of 76.4% students. As of the number of hours students study daily , 51.6% reported to studying 3-4 hours per day and 34.8% reported to studying five or more horse daily. This also point to 86.4% working extra hours on top of their regular classes.



Dietary Behavior

Dietary Behaviour based on the samples we got from the survey tented to lean towards unhealthy patterns. The most common pattern was the increased consumption of fast foods and snacks with a reported 56.5% followed by a 36.6% of students who reported eating less in general with breakfast being the most frequently skipped meal with a total of 56.5% followed by lunch 27.3%. Only 7.5% of students reported to never skipping a meal.

As of the reason for skipping meals wether it be breakfast or lunch, 32.9 % of students reported it being the lack of time to prepare food, 29.2% experiencing loos of appetite during periods of high stress and 27.3% choosing studying a few more hours over eating. 10.6% also reported to forgetting because of studying.

We decided to also test if wether or not these dietary behaviour changes got worse or better during academic years. 59.0% rated their diet as worse, this percentage was a combination of students who reported to their diet being slightly unhealthier 31.1% and 28.0% much unhealthier.

A percentage of 24.2 students reported to perceiving no change and only 16.8% reported improvement in their diet.

Because of these dietary changes a total of 65.2% of students reported to experiencing reduced concentration and energy while 71.4% admitted to feeling a brief energy boost followed by fatigue when using high-sugar foods mostly during exams.

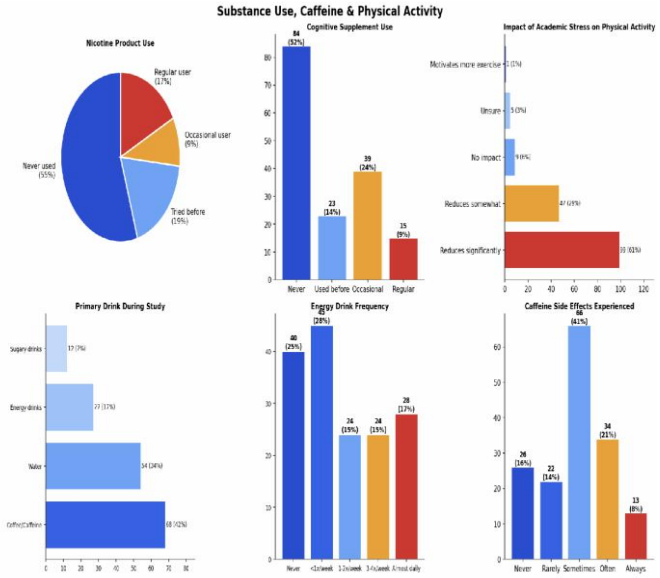
Caffeine/ Energy Drink and supplement use

During study sessions and periods of high stress caffeine-containing beverages were the most used drinks reported so by 42.2% of students, 33.5% reported to using water and only 16.8% reported to using energy drinks.

Overall, the usage of energy drinks was pretty low with only 17.4% of students reporting to using them nearly daily and 14.9% consumed them 3-4 times per week.

The reason for using energy drinks was predominantly for staying awake as reported by 44.1%, followed by improving concentration by 15.5% which correlated to 50.3 % of students reporting neutral when asked if caffeine improved their academic performance , and reducing fatigue for only 8.1% of students.

Unfortunately, from the students who consumed such drink, caffeine side effects were commonly experienced with a total of 29.2% of students reporting feeling them often/always and only 16.1% having never experienced them.



Nicotine Use

The reason to using nicotine as a part of this survey was because of the wide known fact as seen in many studies nicotine usage is mainly used as means to relief stress. Interestingly enough 54.7% of students reported to never having used nicotine products while 26.7% were current users and 18.6% of students having tried nicotine in the past but not longer used it. It is important to cite that from the total number of students who admitted to used nicotine 74.5% reported that their usage was partially linked to academic stress by 51.6% and strongly linked by 33.9%.

Physical Activity

During this survey we recognized that academic stress has a profound effect on physical activity with 61.5% of students reporting a significnat decrease in physical activity and 29.2% reported only a small decrease. None the less, combined 90.7% reported to a exercise reduction. Only one student reported to feeling more motivated by stress to practice physical activity more .

Contradictory is the fact that 64.6% of students rated physical activity as important for their mental well being, a percentage that reveals a substantial gap between what students believe in and their behavior .

Supplement Use

It is not rarely cited that a number of people use different supplements in order to enhance their performance. We decided to test this citation in medical students whos academic perfomance has to be in an all time high. Only 33.5% of students reported to currently using cognitive supplements and 14.3% reported to having used them in the past .

As mentioned in the introduction Vitamin B takes the lead as the most used supplement reported by 32 students, Omega-3 by 16 students, Creatine and Aschawaganda 9 students .

Conclusion

The findings of the study demonstrate that academic burden significantly influences the lifestyle behaviours of medical students. High levels of perceived stress and academic workload were consistently associated with disrupted sleep patterns, irregular dietary habits, reduced physical activity, and increased reliance on stimulants such as caffeine and energy drinks.

Putting this aside the study also revealed an important discrepancy between students awareness of healthy behaviours and their ability to maintain them under academic pressure. While most respondents recognized the importance of physical activity and balanced nutrition for mental and physical well-being, academic stress frequently interfered with the maintenance of these habits.

Overall, the results suggest that academic stress in medical education extends beyond psychological strain and contributes to broader behavioral and lifestyle adaptions that may negatively affect student health and long-term well-being.

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MORPHOLOGICAL AND ANATOMICAL VARIATIONS OF THE BASILAR ARTERY AND THEIR INFLUENCE ON CEREBRAL CIRCULATION

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Abstract

The basilar artery (Basilar artery BA) is one of the arteries that supplies the brain with oxygen-rich blood. It is formed by the union of the left and right vertebral arteries at the junction between the medulla oblongata and the pons, near the abducens nerves (CN VI) [1,2].The basilar artery represents the principal vessel of the posterior cerebral circulation and plays a major role in the vascularization of the brainstem, cerebellum, and occipital regions. ogether with the two vertebral arteries, it forms the vertebrobasilar system (VBS), which supplies blood to the posterior part of the Circle of Willis and connects with the blood supply of the anterior part of the circle provided by the internal carotid arteries [3,4,5].Anatomical variations of the BA, such as hypoplasia, dolichoectasia, tortuosity, and others, may contribute to disturbances in cerebral circulation, including hypoperfusion of the brainstem and cerebellum, as well as the development of neurological deficits. These may manifest clinically as headache, vertigo, ataxia, visual disturbances,transient ischemic attacks, and other symptoms [6,7,8].

Keywords: Morphological variations of the basilar artery (BA), cerebral circulation

Introduction

The vertebrobasilar system (VBS) is one of the most important vascular systems of the brain and is responsible for supplying blood to the brainstem, cerebellum, thalamus, and occipital lobe. The BA as a component of the VBS, is formed by the fusion of the left and right vertebral arteries and represents the main arterial vessel of the posterior cerebral circulation [9,10].Anatomical variations of the BA, such as hypoplasia, asymmetry, and dolichoectasia, have considerable clinical significance because they may lead to hemodynamic disturbances, transient ischemic attacks, and cerebrovascular stroke [11]. Hypoplasia is most commonly defined as an arterial diameter of less than 2 mm, whereas dolichoectasia is characterized by dilation and elongation of the artery with a diameter greater than 4 mm (Bruneau et al., 2006).Clinical pathological disorders involving the BA may manifest as cranial nerve deficits, cerebellar dysfunction, motor and sensory impairment, altered consciousness, vertigo, and clinical syndromes such as the “top-of-the-basilar syndrome” and the „locked-in syndrome” [12,13,14].Several anatomical variations in the distribution of the BA artery have been documented. The posterior inferior cerebellar artery, which usually arises from the vertebral artery, may originate from the BA in approximately 10% of cases. The most common variation is basilar artery fenestration, resulting from incomplete embryological fusion of the primitive longitudinal arteries. Another relatively frequent variation is the aberrant origin of cerebellar branches,including trifurcation and quadrifurcation, which together account for more than 10% of cases.Variations in arterial diameter may also be observed, such as hypoplasia and vertebrobasilar dolichoectasia, which are characterized by elongation, tortuosity, and dilatation of the basilar trunk. These morphological features are of clinical importance because they may affect the hemodynamics of the posterior circulation and may be associated with an increased risk of neurovascular compression or ischemic events in the posterior cerebral circulation

[15,16,17, 18].Anatomical variations of the BA, including fenestration, hypoplasia, dolichoectasia, atypical branching patterns,and others, are clinically important because they may alter cerebral hemodynamics, thereby increasing the risk of posterior circulation stroke, aneurysm formation, and vertebrobasilar insufficiency (VBI) [19,20].Modern radiological techniques, such as Magnetic Resonance Angiography(MRA),Computed Tomo-graphy Angiography(CTA), and color Doppler sonography, enable precise visualization and analysis of anatomical variations in cerebral blood vessels.

Purposse of the work

The aim of this study was to analyze the frequency of anatomical variations of the BA according to sex and age, to assess the measurements of the basilar artery diameter and their influence on cerebral circulation in patients with different clinical manifestations, and to compare the obtained results with data reported in international studies.

Materials and Methods

In this retrospective observational study, 60 patients were analyzed, including 25 women (41.67%) and 35 men (58.33%), with a mean age of 45.00 ± 12.00 years. Of the total number of patients (n = 60), 33.3% were younger than 45 years, whereas 67.7% were older than 45 years.The patients were examined and hospitalized in the Department of Traumatology and Neurosurgery at the Clinical Hospital Tetovo during a one-year period. They were admitted for various conditions, including head injuries, neck injuries, traffic accidents, vertigo, and other neurological complaints, and were grouped according to sex and age.The patients underwent evaluation using Computed Tomography (CT), Magnetic Resonance Angiography (MRA), and color Doppler sonography. The analysis included measurement of the basilar artery diameter, as well as assessment for the presence of hypoplasia, dolichoectasia, and normal anatomical morphology. Our results were compared with data reported in internationally.

Statistical Analysis

Descriptive statistical methods were used, including the arithmetic mean and standard deviation (X ± SD). Comparative statistics of lipid parameters between groups were analyzed using Student's *t*-test for independent and dependent samples, as well as non-parametric tests according to the Mann–Whitney U test. The results were processed using SPSS software version 26.

Table number 1: number of patients by gender and mean age ± SD

Total number of patients	60 (100 %)	mean age ± SD
Male	35 (58.33 %)	45.00±12.00 years
Females	25 (41.67 %)	45.00±12.00 years

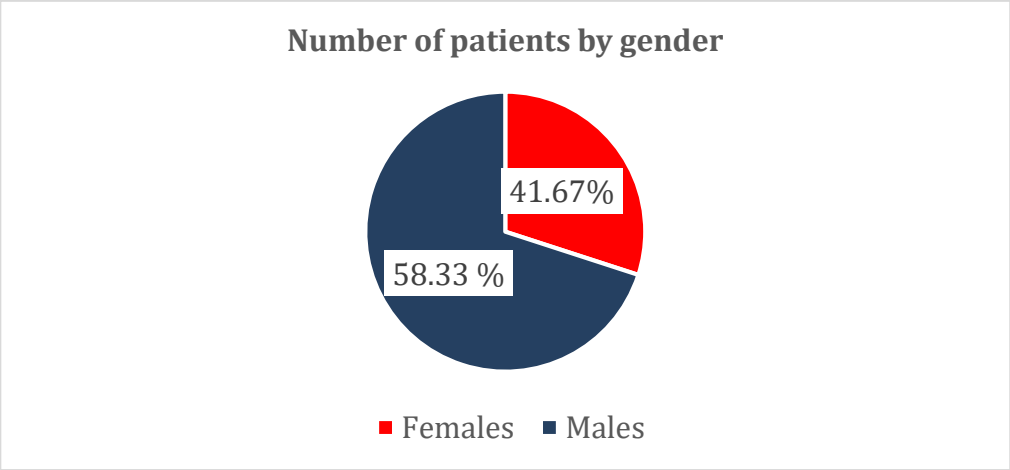


Table 2. Distribution of patients by age

Age	Men (n=350	Wome(n=25)
<45 years	14 (40%)	10 (40%)
>45 year	21 (60%)	15 (60 %)

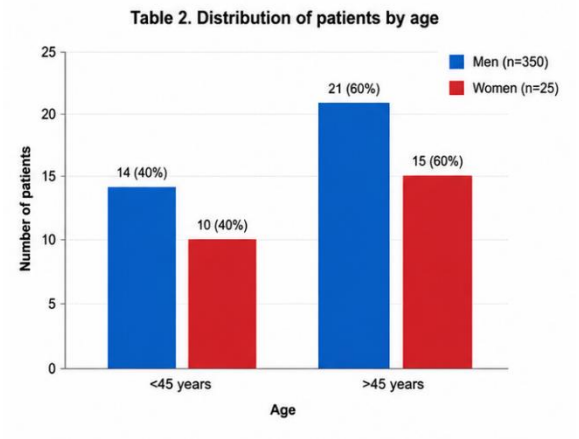
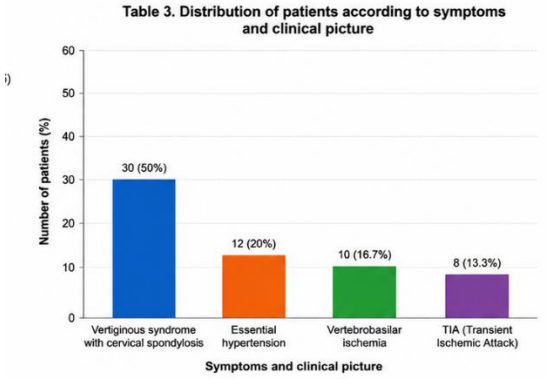


Table 3: Distribution of patients by symptoms and clinical picture

Symptoms	Number of patients (60-100%)
Vertigo syndrome with cervical spondylosis	30 (50 %)
Essential hypertension	12 (20 %)
Vertebrobasilar ischemia	10 ((16.7 %)
TIA (Transient Ischemic Attack)	8 (13.3 %)



Results

In the female population, normal morphology of the basilar artery was observed in 64% of patients, hypoplasia in 32%, and dolichoectasia in 4%. In the male population, normal morphology was present in 74.3% of cases, hypoplasia in 17.1%, and dolichoectasia in 8.6%. The mean arterial diameter in patients with hypoplasia ranged from 1.80 mm to 1.95 mm, while in the case of dolichoectasia it was 4.0 mm.

Table 4. Distribution of anatomical variations Basilar Artery in women

Anatomical Variations Female %	Women	%
Normal morphological anatomy	16	64.0
Hypoplasia	8	32.0
Dolichoectasia	1	4.0
Total	25	100

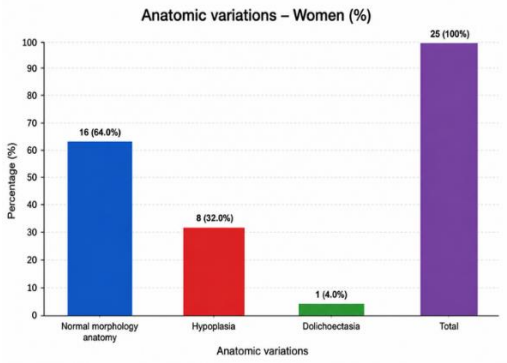
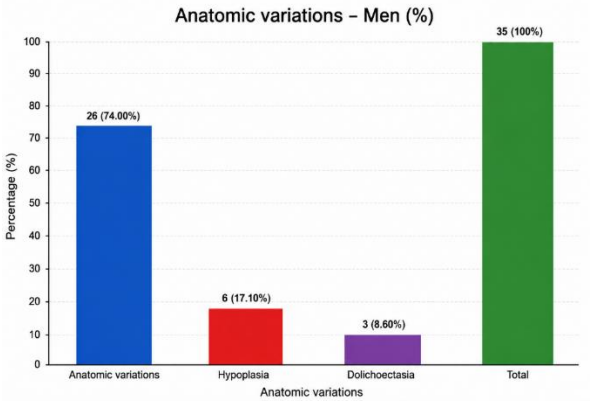


Table 5. Distribution of anatomical variations in men

Anatomical variations	Men	%
Anatomical variations	26	74.00
Hypoplasia	6	17.10
Dolichoectasia	3	8.60
Total	35	100



In the male sex, normal anatomical morphology was present in 26 patients (74.0%), hypoplasia in 6 patients (17.10%), and dolichoectasia in 3 patients (8.6%).In patients with hypoplasia, the diameter ranged between 1.80 mm and 1.95 mm, while in dolichoectasia it was over 4.0 mm.

Discussion

In our study, significant anatomical variations of the basilar artery (BA) were identified, with hypoplasia being the most frequent variation, particularly in the female population. In females, hypoplasia was registered in 32% of patients, while in males it was present in 17.1%. On the other hand, dolichoectasia was more common in males (8.6%).Our findings are consistent with recent international studies indicating that anatomical variations of the vertebrobasilar system significantly influence cerebral hemodynamics and are associated with ischemic disturbances in the posterior cerebral circulation [21]. It has been shown that the geometry and morphological variations of the vertebrobasilar system (VBS) are directly related to the formation of atheromatous plaques and reduced flow in the basilar artery.Hypoplasia was defined as a vessel diameter of less than 2 mm, according to the criteria described by Smoker et al.-1986 [22,23], while dolichoectasia was defined as arterial dilatation with a diameter greater than 4 mm (Passero & Rossi, 2008[30].In the study by Cao S, Zhai M, et al. [24], it was demonstrated that dolichoectasia of the basilar artery significantly increases the risk of infarction in the posterior circulation, especially in patients older than 60 years. The authors emphasized that such anatomical changes lead to turbulent flow and hemodynamic instability.Similar findings were reported by Catalano et al. [25], who highlighted that both congenital and acquired variations of the BA play an important role in the development of neurological symptoms,transient ischemic attacks(TIA), vertebrobasilar insufficiency, and ischemic stroke.In our study, patients with hypoplasia had BA diameters ranging from 1.80 mm to 1.95 mm. These values are comparable with the results of Chuang et al. [26], who demonstrated that hypoplastic arteries with a diameter of less than 2 mm represent a risk factor for vertebrobasilar cerebrovascular events.Hsu et al. [27] also showed that bilateral vertebral artery hypoplasia is associated with acute ischemic stroke and impaired posterior circulation. Dong et al. [28], through hemodynamic analysis, found that variations of the basilar artery cause changes in cerebral blood flow, further confirming the importance of these anatomical variations in the pathophysiology of cerebral ischemia.Due to the absence of a control group in our study, the obtained results were comparatively analyzed with data from international studies and publications in the fields of neuroangiography and radiology [29].Modern imaging techniques, especially MRA and CTA, enable early and precise detection of such anatomical variations. According to current neuroradiological recommendations, these methods play an important role in assessing the risk of cerebrovascular diseases and planning further treatment.

Conclusion

Anatomical variations of the BA are relatively common and represent an important factor in the disturbance of cerebral circulation. They may be associated with neurological deficits and a wide spectrum of neurological symptoms.Early detection of these variations using modern radiological methods is of great importance for the prevention of cerebrovascular complications and timely patient management.In conclusion, we can state that anatomical variations of the BA, as well as the VBS, are key elements in the diagnosis, prevention, and management of vertebrobasilar disorders and symptoms, and have significant clinical importance in predicting surgical and interventional outcomes.

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EXPERIMENTAL OPTIMIZATION AND CHARACTERIZATION OF AN O/W COSMETIC CREAM BASED ON A NON-IONIC SELF-EMULSIFYING SYSTEM

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Abstract

Non-ionic self-emulsifying bases have gained attention in cosmetic formulation because they are less irritating than ionic surfactants, stable across a wide pH range, and capable of forming liquid crystalline gel networks that improve cream consistency and long-term stability.
The aim of this study was to experimentally optimize an O/W cosmetic cream by varying the concentration of a non-ionic self-emulsifying base that further be used to incorporate Niacinamide as Cosmetic Active.
The Experimental Matrix included three levels of the Emulsifying Base (4%, 6% and 8%). Three test formulations were prepared with different levels of emulsifying compound and evaluated for Organoleptic properties, pH, Density, Spreadability and Physical Stability under Accelerated Conditions.
Among the prepared formulations, F2 exhibited the most favorable balance of physicochemical properties and physical stability exhibiting appropriate viscosity for topical application, homogeneous appearance with no phase separation under accelerated conditions, wider diameter of spreadability in plate and smaller droplet size compared to other formulations, indicating efficient emulsification.
Key words: Non-Ionic Self-Emulsifying System, O/W Cosmetic Cream,Cosmetic Formulation

Introduction

Oil-in-water (O/W) cosmetic creams remain one of the most widely used topical delivery systems due to their light skin feel, ease of spreading, and ability to incorporate both active ingredients with hydrophilic and lipophilic character. The physical stability and sensory properties of these systems are strongly influenced by the type and concentration of the emulsifying agent used. Non-ionic self-emulsifying bases have gained attention in cosmetic formulation because they are less irritating than ionic surfactants, stable across a wide pH range (Aultron's Pharmaceutics, 2013), and capable of forming liquid crystalline gel networks (Seppic, 2025) that improve cream consistency and long-term stability. Examples include Polawax, Emulsifying Wax NF, and Ceteareth-20/Cetearyl Alcohol systems. However, the final texture, viscosity, and stability of the cream are highly dependent on the concentration of the Emulsifying Base used. Insufficient emulsifier leads to phase separation, while excess amounts can produce a heavy, waxy, or soapy after-feel that reduces consumer acceptance (RAHN, 2026).
Despite the widespread use of non-ionic self-emulsifying systems, limited data are available on the systematic optimization of emulsifier concentration in relation to physicochemical properties and stability of O/W creams intended for cosmetic use. Suppliers provide us with range as well as limits for emulsifiers use however, to determine the “Sweet Spot” experimental studies are required. Therefore, the aim of this study was to experimentally optimize an O/W cosmetic cream by varying the concentration of a non-ionic self-emulsifying base.
The Experimental Matrix included three levels of the Emulsifying Base (Low 4%, Middle 6% and High 8%). Three test formulations were prepared with different levels of emulsifying

compound and evaluated for organoleptic properties, pH, density, spreadabilityand physical stability under accelerated conditions (Elham Y Al-Barghouthy, 2025), (Ana Simões, 2020), (Zahra Mirzapou, 2025).
For the test formulations, the majority of the O/W emulsion ingredients (listed in the table below) were kept at consistent levels; conversely, the non-ionic emulsifier was considered as the primary variable.

Table 1.General example of O/W cream formulation (Roger L McMullen, 2014)

Ingredients	**Ranges**
Water Phase	qs to 100%
Oil Phase	10-35%
Emulsifier Systems	3-5% (Depends on Emulsifier type)
Stabilizers/Thickeners	0.5-2%
Humectants	3-5%
Preservative	0.5-1% (Depends on Preservative type)
Vitamin E	0.5-1%
EO or Aroma	0.5-1%

Materials And Methods

Materials

Deionized Water was obtained from the Deionizer Apparatus of Faculty of Mathematical and Natural Sciences, Univeristy of Tetovo; Emulsifying Base for preparation of Cosmetic Creams - Emulgade SE-PF (Glyceryl Stearate, Ceteareth-20, Ceteareth-12, Cetearyl Alcohol, and Cetyl Palmitate)Manufactured by BASF Personal Care and purchased from Galafarm DOO Skopje, Republic of North Macedonia; Cetyl Alcohol produced by Riedel-de Haen;n-Propyl p-hydroxybenzoate Manufactured by Sigma-Aldrich Chemie GmbH, Darmstadt, Germany; Methyl 4-hydroxybenzoate Manufactured by Fluka Chemicals; Glycerin (1,2,3-Propanetriol), Prunus Amygdalus Dulcis Oil (Almond Oil) and Cinnamomum zeylanicum Essential Oil were purchased from Fitofarm DOO Skopje, Republic of North Macedonia.

Methods

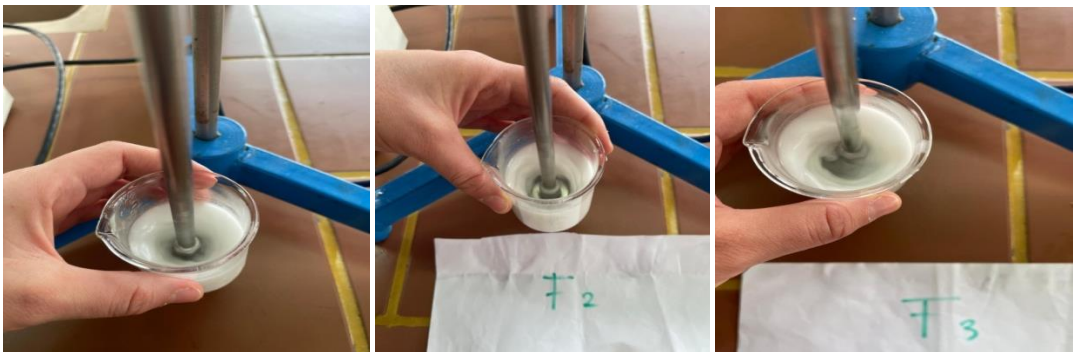
2.2.1. Formulation Development of Test Cosmetic Creams: With aim on finding the so called "Sweet Spot" or the optimal ratio of Emulsifying Base that gives the best properties to the Cream Formulation, three formulations were developed. Further in this paper, formulations are coded as: F1, F2 and F3, corresponding to each formulation of the study.In the following tables are displayed the ingredients and amounts of three of the formulations in this experimental work.

Table 2.Test Formulations Ingredients and their Amount

Ingredients	F1	F2	F3	Role in Formulation	Limits of use
Phase A	-	-	-	-	-
Deionized Water	37.62 g	36.62 g	35.62 g	Water Phase	≈ 60%
Glycerin	1.5 g	1.5 g	1.5 g	Humectant	2-5%

Methyl Paraben	0.085g	0.085g	0.085g	Preservative	0.4%
Propyl Paraben	0.04 g	0.04 g	0.04 g	Preservative	0.14%
Phase B	-	-	-	-	-
Sweet Almond Oil	7.5 g	7.5 g	7.5 g	Oil Phase	15-25%
Cetyl Alcohol	1 g	1 g	1 g	Co-Emulsifier	0.5-6%
Emulgade SE-PF	2 g	3 g	4 g	Emulsifier	2-8%
Phase C	-	-	-	-	-
Cinnamon EO	0.25 g	0.25 g	0.25 g	Fragrance	0.5-1%

Fig 1.Homogenization of O/W test formulations F1(left),F2(middle) and F3(right)



In the formulation process an Analytical Measuring Balance (Mettler Toledo PM300) it utilized to measure the exact amount of the ingredients in three of the formulations. Since the formulation is biphasic, two different beakers are used with aim of preparing both phases, subsequently, the beakers are added to Water Bath previously heated to 60 ˚ C until the Oil Phase (Phase B) is totally melted. Following that, the Water Phase (Phase A) was slowly added to Oil Phase while passing it in Homogenizer (Glas-Col GKH GT Motor Control) for 3 minutes at 2000 rpm. At last, after temperature reaches 40 ˚ C we add Cinnamon EO since it is unstable at higher temperature (Jiageng Guo 1, 2024).

2.2.2. Organoleptic Characterization: It is well known that Organoleptic Characterization, of diverse Cosmetic Cream formulations, evaluates sensory attributes such as: Color, Odor, Appearance and Homogenity in Appearance as well as Texture of the Cream Formulation (Johnny Bullón, 2021) (Magdalena Bîrsan, 2025).
All of these parameters were checked for F1, F2 and F3 and displayed in the results part.

2.2.3. pH Measurement; pH value for all three formulations were checked in two different manners in order to deliver more accurate results. We used Universal Indicator Paper (pH 1-14) as well as Semi Solid Test Pen (pH range 0.00-14.00, Accuracy 0.1 pH) that was previously calibrated using three calibration buffers including here: 4.00, 6.86 and 9.18. After every calibration process, the pH meter probe was rinsed with Deionized Water and Blotted with tissue paper. Method as described by (Carli, 2025) suggests that pH of Cosmetic Cream formulation should be measured by Universal Indicator Paper and pH meter without diluting it previously with water as it can affect the final results. (Muthanna F. Abdulkarim, 2010) as well, in their study have conducted pH measurement without dilution of sample. The paper was immersed into the cream formulation for 15 seconds and after that we read the results. As it

pertains to pH meter, the probe was immersed into the formulation until it reached stability in the showing result. pH Value is measured at 21-22 ˚C that complies with room temperature, in which the formulations are recommended to be stored.



Fig 2.pH meter and Buffer Solutions

2.2.4. Density Measurement : Density is defined as the ratio of the mass of a substance to the volume it occupies at a given temperature and pressure (Ojeda, NA). Based on Archimedes Equation, ρ=m/V, regarding density (Hughes, 2006) has used previously to measure diverse liquids so we applied this principle to measure density for three of our formulations in the absence of a specific density checking device. The temperature of the ambience where we conducted the measurements was 22 ˚ C which complied with the requirements of measuring the density in room temperature. First and foremost, an analytical balance (0.01 g) is mandatory for this measurement as well graduated cylinder. The empty graduated cylinder wasmeasured in the analytical scale and afterwards tared. Then the graduated was filled with 10 ml of cream then tapped it into plain surface for 5 times to get it leveled to 10 ml and remove air bubbles. At last, we checked the weight of the cream formulations in the graduated cylinder and calculated the density utilizing Archimedes Equation given above.



Fig 3.Graduated Cylinder with Cream on the Analytical Balance

2.2.5. Spreadability in Plate: With aim on assessing cream formulation Spreadability, Parallel-Plate Method was employed (Elham Y Al-Barghouthy, 2025). A total of 1 gram cream formulation was added into flat surface then covered with square-shaped glass plate. Spreadability was tested after adding diverse weights: 50g,100g, 150g and 200g above the plate for 1 minute each. Afterwards, the diameter was measured by ruler in three different sides and SD from the Mean was calculated using Microsoft Excel 2016.



Fig 4.Cream Spreadability tested in Parallel-Plate Method

2.2.6. Spreadability in Skin: Spreadability in skin was tested immediately after formulation process. Small amount of the cosmetic cream was applied in the upper part of the hand, gently with circular movements.Subsequently, the time of full skin absorption was assessed.

*2.2.7. Accelerated Stability Study :*Accelerated Stability study for F1, F2 and F3 were carried out utilizing Centrifugation Method. Three samples from all formulations were added to centrifuge tubes and labeled with codes. The tubes were placed in parallel manner in order to balance the rotor and ensure safe operation. As we had three samples, we added an empty tube to balance the last. An Eppendorf Centrifuge 5415 C was utilized to carry out the Accelerated Stability Study with parameters, 3000 rpm for 30 minutes as described by (Zahra Mirzapou, 2025), (Anđela Dragićević, 2023), (Ivana Arsić, 2012).The samples were checked both, Visuallyas well leveraging Optical Microscope.



Fig 5.Centrifuge(Left)and Centrifuge tubes filled with test formulations(Right)

2.2.8. Microscopic analysis: Optical Microscope model Nikon Eclipse E100 was used to analyze three samples of the formulations after Centrifuge Operation. Magnification of 40X/0.65 and distance ≈0.6mm, droplet dispersion was assessed. Samples were placed into microscopic glass slide using Cotton Swab and the amount was minimal, 2 drops of the formulation.

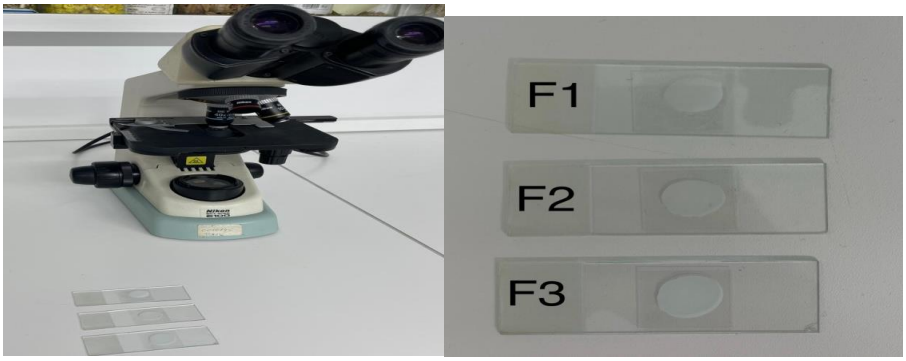


Fig 6.Optical Microscope (Left) and Glass Slides with test formulations (Right)

2.2.9. Hypersensitivity Reaction (Patch Test): With the purpose of assessing Hypersensitivity Reaction of the formulations, a skin patch test was employed (Kaushal K. Verma, 2020). Three tapes filled with cream in the middle and coded as F1, F2 and F3 were stuck in the forearm and left for 12 hours to assess a possible early allergic reaction on the skin. Visual inspection of the skin was conducted to check for possible side effects of the formulations on the skin.



Fig 7.Skin performed Patch Test

Results

3.1.*Organoleptic Characterization :* The characteristics of three visually inspected formulations are listed below in the table.

Table 3. Organoleptic Characterization of Test Formulations

Formulations	Color	Odor	Appearance and Texture
F1	White	Mildly Cinnamon	White, soft cream, Homogeneous.
F2	White	Mildly Cinnamon	White, milky cream, Smooth and Homogeneous.
F3	White	Mildly Cinnamon	White, Thick-Viscous cream, Holding its shape.

3.2. pH Measuremen: As initially, the Paper Indicator was used to assess the pH range of the cream, from the color change it is clear that three of the formulations fall between 6-7 pH range as the color is orange- slightly green.



Fig 8.pH measurement by Universal Paper Indicator. F1 (Left), F2 (Middle) and F3 (Right

On the other hand, results obtained by utilizing the calibrated pH meter are displayed below:

Table 4.pH measurements

Formulation	pH Value
F1	6.47
F2	6.32
F3	6.29

3.3.*Density Measurement;* Density of the three test formulations was mathematically calculated, leveraging Archimedes Equations thus, we obtained the results as below:

Table 5.Density measurements

Formulation	Mass	Volume	Result
F1	11.61 g	10 mL	ρ= 11.61/10=1.161 g/mL
F2	12.18 g	10 mL	ρ=12.18/10=1.218 g/mL
F3	13.42 g	10 mL	ρ=13.42/10=1.342 g/mL

3.4.Spreadability in Plate and on Skin

Table 6. F1 Spreadability in Plate

Measurements	Weight of Glass Plate	50g	100g	150g	200g
M1	6 cm	6.6 cm	6.7 cm	7.1 cm	7.5 cm
M2	5.8 cm	6.6 cm	6.9 cm	7 cm	7.4 cm
M3	6.2 cm	6.6 cm	6.9 cm	7 cm	7.3 cm
Mean	6	6.6	6.833333	7.033333	7.4
SD	0.163299	8.88178E-16	0.094281	0.04714	0.08165

Table 7. F2 Spreadability in Plate

Measurements	Weight of Glass Plate	50g	100g	150g	200g
M1	7.1 cm	7.6 cm	8 cm	8.4 cm	8.6 cm
M2	7.1 cm	7.9 cm	8 cm	8.3 cm	8.7 cm
M3	7.6 cm	8 cm	8 cm	8.5 cm	8.8 cm
Mean	7.266667	7.833333333	8	8.4	8.7
SD	0.235702	0.169967317	0	0.08165	0.08165

Table 8. F3 Spreadability in Plate

Measurements	Weight of Glass Plate	50g	100g	150g	200g
M1	5.4 cm	5.6 cm	6.1 cm	6.5 cm	6.7 cm
M2	5.5 cm	6.0 cm	6.2 cm	6.4 cm	6.8 cm
M3	5.5 cm	5.9 cm	6.2 cm	6.6 cm	6.9 cm
Mean	5.466667	5.833333333	6.166667	6.5	6.8
SD	0.04714	0.169967317	0.04714	0.08165	0.08165

As it can be observed from the tables displayed above, three measurements of diameter were carried out for each weight addition on the plate, to ensure more accurate results. As it pertains to spreadability on skin, all of the formulations were absorbed successfully in the skin 1 minute after applying.

3.5.Accelerated Stability Study and Microscopic Analysis

No visual change was observed after Centrifugation process, all of the test formulations remained intact visually. On the other hand, microscopic analysis shows that after Centrifugation process, the most stable product is F2, exhibiting smaller dispersed oil droplets into water phase and lacking big droplets that were observed in F1 and F3.

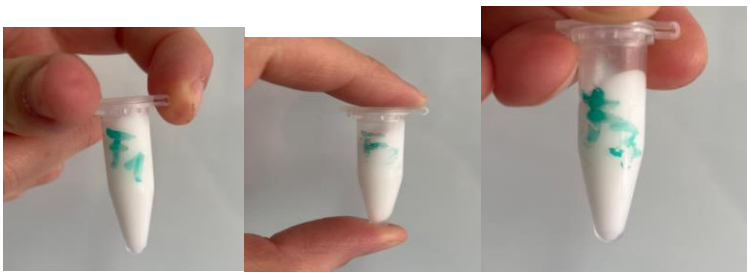


Fig 9. Test Formulations in Centrifugal tubes

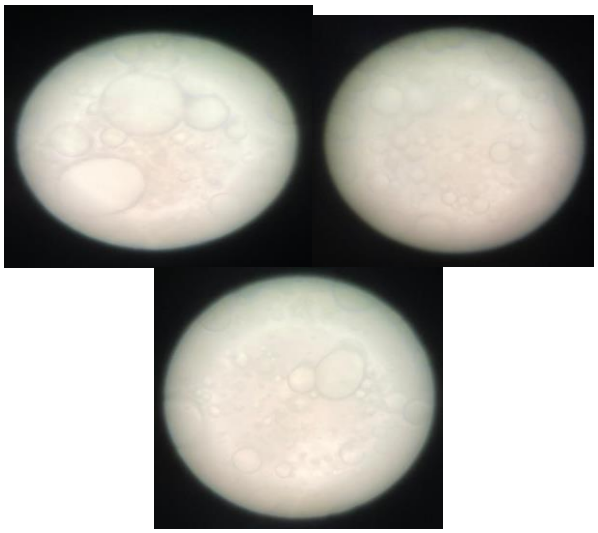


Fig 10. Optical Microscope Visualisation of F1(Left), F2(Midde) and F3 (Right)

3.6.Hypersensitivity Reaction (Patch Test): From the patch test, no visible changes in skin were detected after 12 hours.



Fig 11. Skin Patch test after 12 hours

Discussion And Conclusion

As Manufacturer suggests, Emulgade SE-PF use is recommended to be between 2 - 8% of the total formulation for Cosmetic Creams (BASF). The range seems to be quite wide thus, the

physico-chemical properties changes in the cream formulations can be witnessed. Therefore, our Designed Matrix in three levels of our independent variable, considered the self-emulsifying system in three points as mentioned in the Introduction part, all falling within the tolerated limits for this ingredient. Other ingredients levels remained intact, thus, their role in the formulation is not to be discussed in this article.

In table 2, the levels of all ingredients are included with aim on delivering safe product from the formulation development stage hence, all the three formulations are safe and their amounts are justified. Temperature of preparation is adjusted based on Oil Phase ingredients melting points and the stability of the ingredients in this temperature was also considered to ensure higher quality of the products.

Organoleptic characteristics suggested that the most appropriate test formulation is F2 since it exhibited better texture and appearance considering the purpose of this formulation, incorporation of Niacinamide as an active. F1 and F2 exhibited softer and better Cream texture compared to F3.

pH values of all of formulations were not falling into the preferred range of pH for Cosmetic Face Cream (4.5-5.5) (Saba M. Ali, 2013) (H Lambers, 2006), however Citric Acid solution (50:50, Citric Acid/Water) was prepared to modify pH level of the formulations. On the other side, literature suggests that Niacinamide Cream formulations, in order to improve its activity, pH of formulation should remain between 5.0 to 7.0, more precisely pH 6 (Chem, 2026). Below 4.5, Niacinamide may convert into nicotinic acid (Thomas Sjöberg, 2026, p. NA), which can cause irritation and flushing.

The amount of Parabens in this product is within the tolerated limits by Regulatory Authorities,<0.8% for mixture of parabens (NA, 2008) (Commission, 2009) and the pH of the formulation is appropriate with their antimicrobial and antifungal activity (2-8) (E. Mani-López, 2016).

It is pivotal to mention that the measurement of Density is not conducted by specialized device thus the values are approximate. Density value areincreasing from F1 to F3 that may be attributed to its ability of the emulsifier to create Lamellar Crystal structure (Seppic, 2025) that prevent oil droplets from coalescing and separating.

When it comes to spreadability in plate optimal values, 5-7 cm (Aryan, 2024) are the optimal values that are reached by all of the test formulations however is evident that F2 exhibits better spreadability properties than the other formulations. Skin spreadability is better in F1 and F2 since they got absorbed quickly in skin and didn’t leave oily stains after application.

All three formulations resulted stable after Centrifugation Process, however, Microscopic Analysis suggests that the most stable formulation is F2 since the Oil Droplets were more uniform and smaller. The ones containing larger droplets may be subjected to system disbalance faster. In this case it is also suggested to adjust Homogenization time and speed in order to get more uniform and smaller dispersed droplets in Water Phase (Zahra Rahma Namira, 2021).

Lastly, an early hypersensitivity reaction was not observed by any of the test formulations however, it is worth mentioning that Hypersensitivity reactions can happen after 24, 48 and 72 hours (Antonino Romano, 2008) thus more detailed studies are preferred.

This study demonstrated the experimental optimization of an O/W cosmetic cream using different concentrations of a non-ionic self-emulsifying base. Among the prepared formulations, F2 exhibited the most favorable balance of physicochemical properties and physical stability. It showed appropriate texture for topical application, homogeneous appearance with no phase separation under accelerated conditions, and smaller droplet size compared to other formulations, indicating efficient emulsification. Formulations with lower emulsifier levels lacked sufficient structure and displayed early signs of instability (Bigger oil droplets dispersed in water phase), while higher levels resulted in excessive viscosity and an

undesirable waxy after-feel. Based on these findings, F2 was selected as the optimal base for further development and incorporation of Actives. As (Sousa, 2022) states in his article, O/W emulsions are the preferred ones compared to W/O types as they offer a light texture that is easy to rinse off and suitable for moisturizer formulations (as in our case) due to improved release of active ingredients to the skin (Rahmat Muliadi, 2025). Future work will focus on incorporating Niacinamide as a model active ingredient to evaluate the system's ability to deliver functional benefits while maintaining stability.

In addition, the role of the co-emulsifier will be re-assessed by preparing a modified version of F2 lacking co-emulsifier, in order to simplify the formula and investigate whether the primary non-ionic self-emulsifying base alone can provide adequate stability, texture and spreadability. Overall, the results provide a rational basis for selecting emulsifier concentration in non-ionic O/W cream systems and establish a suitable platform for subsequent formulation of active-containing cosmetic products.

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CONNECTING UNDERUSED PUBLIC SPACES THROUGH GREEN INFRASTRUCTURE: A FRAMEWORK FOR ENHANCING PUBLIC SPACE QUALITY

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Abstract

Underused public spaces are increasingly recognized not merely as residual or deficient urban fragments, but as spatial conditions characterized by latent potential for social, ecological, and spatial transformation. This paper investigates how green infrastructure can function as a multidimensional connectivity mechanism capable of reactivating and integrating such spaces within broader urban systems. The research develops a theoretical framework that conceptualizes underused public spaces as relational and socially produced conditions emerging from disconnections between spatial form, accessibility, programmatic structure, and everyday practices. Building upon theories of urban voids, relational urbanism, landscape urbanism, and public space theory, the study argues that the latent potential of underused spaces can be operationalized through systems of connectivity.

The paper positions green infrastructure not solely as an ecological strategy, but as an operative urban design mechanism structured through spatial, ecological, social, and perceptual connectivity. To operationalize this relationship, the research develops a typology of connectivity strategies consisting of linear, nodal, and hybrid systems, demonstrating how fragmented and underperforming spaces may function as connective elements within urban networks. Furthermore, the study establishes an integrated analytical framework linking connectivity dimensions to public space quality dimensions, including spatial, functional, social, and perceptual qualities.

The framework suggests that public space quality emerges relationally through interactions between urban systems rather than through isolated site characteristics alone. The study contributes to contemporary urban design and landscape urbanism discourse by redefining green infrastructure as a relational framework through which latent spatial potential can be transformed into active urban performance and distributed public space quality.

Keywords: underused public spaces; latent spatial potential; green infrastructure; connectivity; public space quality; landscape urbanism; urban networks; relational urbanism.

Introduction

Contemporary cities increasingly contain fragmented, residual, and underperforming public spaces that remain disconnected from broader systems of urban life. Traditionally described through terms such as urban voids, lost spaces, leftover landscapes, or terrain vague, these spaces have often been interpreted as signs of spatial failure, functional deficiency, or incomplete urbanization (Trancik, 1986). However, recent urban theory has progressively shifted this perspective, reframing underused public spaces not as passive residual conditions, but as spaces characterized by unrealized spatial, social, ecological, and relational capacities.

This shift reflects broader transformations within urban design and planning discourse, where cities are increasingly understood as dynamic and networked systems rather than collections of isolated objects. Within this framework, the quality and performance of public spaces depend not only on their internal characteristics, but also on their relationships with surrounding urban structures, ecological systems, movement networks, and social practices. Consequently, underuse can no longer be interpreted solely as an absence of activity, but rather as a relational condition emerging from spatial disconnection, programmatic mismatch, limited accessibility, or weak integration within the urban fabric. At the same time, contemporary landscape urbanism and green infrastructure theory have emphasized the importance of connectivity as a structuring principle capable of reorganizing fragmented urban environments. Green infrastructure, understood as a strategically planned network of natural and semi-natural spaces, has evolved beyond its ecological origins into a multidimensional urban design framework that integrates environmental, spatial, social, and perceptual functions within

interconnected systems (Benedict and McMahon, 2006; Mell, 2017). Within this interpretation, underused spaces are no longer perceived as isolated anomalies, but as potential nodes, corridors, or connectors capable of reinforcing urban continuity and public life. Despite the growing recognition of connectivity within urban theory, the relationship between green infrastructure connectivity and public space quality remains insufficiently operationalized. Existing literature frequently addresses public space quality and connectivity as parallel concepts, without clearly defining the mechanisms through which connectivity contributes to qualitative spatial outcomes. Furthermore, many studies continue to focus primarily on large-scale parks or ecological corridors, while smaller, fragmented, and underused public spaces remain underexplored within broader networked systems.

This research addresses this gap by developing a theoretical and analytical framework that links underused public spaces, green infrastructure connectivity, and public space quality. The study is structured around four main objectives:

(1) to conceptualize underused public spaces as spatial conditions characterized by latent potential;

(2) to define green infrastructure connectivity as a multidimensional urban design mechanism;

(3) to develop a typology of connectivity strategies consisting of linear, nodal, and hybrid systems; and

(4) to establish an integrated framework linking connectivity dimensions to public space quality dimensions.

The paper argues that connectivity functions as the critical mediating mechanism through which latent spatial potential becomes active urban performance. Through this perspective, public space quality is redefined not as a fixed attribute of isolated sites, but as a relational condition emerging through interactions between spatial systems, ecological processes, social practices, and perceptual experiences. By repositioning green infrastructure as a multidimensional connectivity framework, the research contributes to contemporary urban design and landscape urbanism discourse, offering a conceptual basis for understanding how fragmented and underused public spaces may be transformed into active components of resilient and interconnected urban systems.

1. Conceptualizing underused public spaces as a spatial condition with latent potential

Underused public spaces have increasingly been examined within urban theory not merely as residual or deficient elements, but as spatial conditions embedded within broader socio spatial systems. Traditionally described through terms such as *urban voids*, *lost spaces*, or *terrain vague*, these spaces include vacant lots, abandoned sites, leftover infrastructures, and poorly activated public environments (Trancik, 1986; Hwang and Lee, 2019). Rather than being neutral or passive, such spaces are now understood as products of urban processes, reflecting shifts in planning paradigms, socio-economic transformations, and spatial mismatches within the city.

Recent literature reframes these spaces as sites of unrealized capacity, where the absence of intensive use does not indicate absence of value, but rather a condition of latent potential for spatial, social, and ecological transformation (Rossi, 2025; Iannizzotto, 2023). These perspectives emphasize that underused spaces occupy critical positions within the urban fabric and can contribute to urban resilience, connectivity, and public life when appropriately reinterpreted and reintegrated .

This reconceptualization requires a shift from static definitions toward a process-oriented understanding, where underuse is not a fixed category but an outcome of dynamic interactions between spatial form, social practices, and institutional frameworks. Within this context, three interrelated theoretical positions are essential: underuse as a relational mismatch, space as socially produced and dynamic, and latent potential as a basis for transformation.

Empirical work supports this framing. Research on schoolyards in North Macedonia demonstrates that hard surfaces, limited greenery, and low functional diversity restrict meaningful use to brief intervals, despite strong user demand for green play areas, outdoor classrooms, and varied activity zones (Dehari et al., 2022). These findings highlight both the constraints and the unrealized capacity inherent in underutilized environments.

1.1 Underuse as a relational mismatch: Urban studies literature demonstrates that public spaces function through complex interactions involving accessibility, program, perception, and social inclusion. When these elements are not aligned, spaces fail to reach their intended or potential levels of use (Li, 2022). For example, a space may be physically accessible but socially exclusive, or spatially adequate but programmatically deficient, resulting in underuse despite apparent availability .

This relational understanding is further supported by the concept of "everyday urbanism", where spaces become meaningful through lived practices rather than design intentions alone. Margaret Crawford argues that underused or informal spaces often emerge from a mismatch between planned functions and actual social appropriation, where users redefine space through everyday activities . In this sense, underuse reflects not simply inactivity, but a disjunction between imposed spatial order and lived spatial practices. (Crawford, 1999).

Similarly, theories of urban voids identify underused spaces as products of structural and morphological fragmentation, often resulting from modernist planning approaches that prioritize objects (buildings) over relational spatial systems (Trancik, 1986). These spaces are therefore not accidental but are generated through systemic processes that disrupt spatial continuity and social engagement.

Thus, underuse can be conceptualized as a condition arising from the misalignment between spatial form, accessibility, programmatic structure, and social practices, resulting in a gap between a space's potential capacity and its actual use.

1.2 Space as a socially produced and dynamic construct

The second key theoretical foundation lies in understanding space not as a passive container, but as a socially produced and dynamic construct. This perspective is grounded in the work of Henri Lefebvre, who argues that space is continuously produced through the interaction of physical structures, social relations, and symbolic meanings (Lefebvre 1991). According to Lefebvre, space operates through a triadic structure: perceived space, conceived space, and lived space. Within this conceptualization, underused spaces emerge when these three dimensions are out of sync. For instance, a space may be well-designed (conceived space) but poorly integrated into everyday routines (spatial practice), or it may lack symbolic meaning for users (lived space), resulting in diminished engagement.

Further support comes from place theory, which emphasizes the role of cognitive and affective relationships between users and spatial environments. Research shows that user behavior in public space is shaped by perception, memory, and emotional response to spatial qualities, indicating that spatial use is deeply tied to experiential and cultural factors (SAIDI QAZIMI, 2025; Saidi et al., 2021; Saidi et al. 2024).

Additionally, urban design theory, particularly through Carmona's multidimensional framework, reinforces the idea that spatial performance is shaped by interacting morphological, functional, social, perceptual, and temporal dimensions (Carmona et al., 2010). Underuse, therefore, cannot be attributed to a single factor but must be understood as a multi-dimensional condition embedded in dynamic urban systems.

This leads to the understanding that underused public spaces are not static failures, but temporally evolving spatial conditions, shaped by shifting socio-spatial relations, governance structures, and patterns of use.

1.3 Latent potential as a basis for transformation: The third conceptual dimension reframes underused spaces as sites of latent potential, emphasizing their capacity for transformation rather than their current limitations. This perspective is central to contemporary urban design and planning approaches that prioritize adaptability, resilience, and incremental transformation.

Urban voids and residual spaces are increasingly recognized as strategic resources for regeneration, offering opportunities for ecological integration, social activation, and spatial connectivity (Hwang and Lee, 2019).

The concept of *terrain vague* further reinforces this idea, describing abandoned or undefined spaces as hybrid environments where urban, natural, and social processes intersect. These spaces are valued precisely for their indeterminacy, which allows for experimentation, adaptability, and alternative forms of occupation. Similarly, contemporary planning discourse highlights the role of community appropriation and informal practices in activating underused spaces. Residual spaces can become collective resources when reclaimed by communities, demonstrating that transformation does not always require formal redevelopment but can emerge through bottom-up processes. Importantly, the latent potential of underused spaces is not only spatial but also relational and systemic. These spaces often occupy critical positions within urban networks between infrastructures, neighborhoods, or ecological systems, allowing them to function as connective elements that enhance urban continuity and public space quality. Thus, latent potential can be defined as the embedded capacity of underused spaces to accommodate new functions, relationships, and meanings, enabling their transformation into active components of the urban system.

From latent spatial potential to connectivity

The reconceptualization of underused public spaces as relational, socially produced conditions with latent potential establishes a critical theoretical foundation for understanding how such spaces can be activated within the urban system. However, while this perspective reveals the *existence* of unrealized capacities, it does not in itself provide a mechanism for their activation or integration. The question that emerges, therefore, is not only *what underused spaces are*, but *how their latent potential can be operationalized within the broader urban fabric*.

This transition requires a shift from diagnosis to strategy, from identifying underuse as a spatial condition to defining processes capable of transforming and reconnecting these spaces. Within contemporary urban theory and practice, green infrastructure has increasingly been positioned as such a mechanism, offering a framework through which fragmented, residual, and underperforming spaces can be re-integrated into coherent spatial, ecological, and social networks (Benedict and McMahon, 2006; Mell, 2017).

2.1 Connectivity as the missing link between potential and performance: As established in the previous section, underused spaces are characterized by a mismatch between spatial capacity and actual use. This mismatch is often not solely a result of internal deficiencies, but of disconnection from surrounding urban systems, from flows of movement, and from networks of activity and meaning. In this sense, underuse can be interpreted as a symptom of spatial isolation, where spaces remain physically present but functionally and relationally detached (Ferati et al., 2019). Research on Tetovo's hidden urban network demonstrates how informal threshold systems generate alternative forms of spatial continuity and social connectivity beyond formal urban infrastructure (Limani, 2023).

Urban design theory has long emphasized the importance of connectivity in shaping spatial performance. Jane Jacobs highlights how active urban life depends on continuous networks of movement, visibility, and interaction (Jacobs, 1961), while Kevin Lynch demonstrates that

legibility and use are strongly influenced by the structural coherence of urban systems (Lynch, 1960). When such continuity is disrupted, spaces tend to become marginalized, underused, or socially disengaged.
From this perspective, the latent potential of underused spaces is not only embedded within their internal spatial qualities, but also within their capacity to be reconnected. Connectivity, therefore, becomes the critical mediating concept that links *potential* to *performance*, transforming isolated fragments into active components of a larger system.

2.2 Connectivity as an operative principle in urban systems: The emphasis on connectivity aligns with broader urban theory, which conceptualizes cities as networked systems rather than collections of isolated objects. Manuel Castells describes the contemporary city as structured through flows of information, people, and resources (Castells, 1996), while James Corner highlights the role of landscape in organizing these flows through flexible, adaptive systems (Corner 2006).
Within this framework, underused public spaces previously defined as relational mismatches with latent potential can be understood as disconnected nodes within urban networks. Their transformation, therefore, depends not only on internal redesign but on their repositioning within systems of connectivity.

Green infrastructure as connectivity: A multi dimensional urban design mechanism

Green infrastructure provides a conceptual and operational framework through which this reconnection can occur. Defined broadly as a strategically planned network of natural and semi-natural spaces, green infrastructure integrates ecological, social, and spatial functions within a unified system (Benedict and McMahon, 2006).
Importantly, green infrastructure is not limited to large-scale parks or ecological corridors. Contemporary interpretations emphasize its multi-scalar and multi-functional nature, encompassing a wide range of spatial elements, including small, residual, and underused spaces, when they are connected into a broader network (Mell, 2017). This makes it particularly relevant for addressing the condition of underused public spaces, which often exist as fragmented and discontinuous elements within the urban fabric. Within this framework, connectivity operates across multiple dimensions: Spatial connectivity, ecological connectivity, social connectivity, perceptual connectivity. These dimensions align closely with the multi-dimensional nature of underuse identified earlier (Carmona et al., 2010), suggesting that green infrastructure can address not only physical fragmentation but also functional, social, and perceptual disconnections.

3.1 Reinterpreting underused spaces as nodes within green networks: A key conceptual shift enabled by green infrastructure is the reinterpretation of underused spaces from isolated residual fragments into potential nodes within a networked system. Rather than requiring complete transformation or redevelopment, these spaces can be incrementally integrated through connective strategies that enhance their accessibility, visibility, and functionality (Ferati et al., 2019).
This perspective resonates with landscape urbanism approaches, which emphasize the role of landscape as an organizing structure for urban systems, capable of accommodating change over time (Waldheim, 2006). Within this approach, underused spaces are not anomalies to be erased, but opportunities to extend and reinforce spatial continuity. Furthermore, the concept of "loose space" (Franck and Stevens, 2007) suggests that the openness and indeterminacy of underused spaces can be an asset within networked systems, allowing for flexible and adaptive uses. When connected through green infrastructure, such spaces can support diverse forms of occupation,

contributing to both everyday urban life and ecological performance. Also informal threshold systems may function as micro-connective elements that strengthen social interaction and spatial permeability within neighbourhood structures (Limani, 2025).

3.2 Typology of green infrastructure connectivity strategies: To operationalize green infrastructure as a connectivity mechanism, it is necessary to define distinct yet complementary spatial strategies. Based on urban design and landscape theory, three primary typologies can be identified: linear, nodal, and hybrid connectivity.

3.2.1 Linear Connectivity; Linear connectivity refers to continuous spatial systems that link multiple urban elements through corridors or pathways. These may include greenways, ecological corridors, pedestrian routes, or riverfront systems. The key characteristics are intended to enable continuity and directionality, movement oriented structure and linking of dispersed elements.



Fig. 1: Linear green infrastructure corridor integrated within the dense urban fabric of Bucheon, South Korea. Adapted from By Beatrice Ch'ng, Ecomobility Officer, ICLEI – Local Governments for Sustainability.

Linear systems align with Kevin Lynch's concept of *paths* as primary structuring elements of urban experience, as well as ecological corridor theory, which emphasizes continuity for biodiversity and environmental flows (Lynch, 1960). Underused spaces can be integrated as segments within linear systems, transforming isolated fragments into active connectors within the city.

3.2.2 Nodal Connectivity: Nodal connectivity focuses on strategic points of concentration, where activities, flows, and interactions converge. These include squares, schoolyards, parks, and community hubs. This type of connectivity detects the concentration of activity, and connection between them attempts for social interaction and gathering.

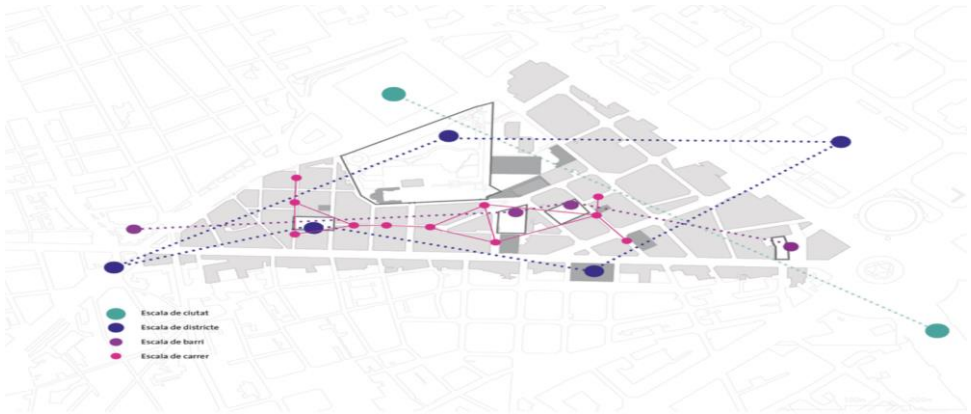


*Fig.1 Nodal connectivity within the urban public space network in Barcelona. Adapted from konstantina (2020). Qualitative analysis of Sants-Hostafrancs public realm - *estel.*

Nodes correspond to Lynch's *nodes* and to Jane Jacobs's emphasis on intensity and diversity of use as drivers of urban vitality. (Lynch, 1960;Jacob, 1961) Underused spaces can be reactivated as nodes, serving as anchors within a broader network, particularly at the neighbourhood scale.

3.2.3 Hybrid Connectivity: Hybrid connectivity combines linear and nodal systems into integrated networks, where corridors connect multiple nodes, and nodes reinforce the network structure.



Fig.3: Madrid Río as a hybrid connectivity system. Adapted from: Madrid Río Project Documentation.

This typology aligns with landscape urbanism (Corner, 2006; Waldheim, 2006), which views urban space as relational fields rather than discrete objects. Hybrid systems allow underused spaces to function simultaneously as: destinations (nodes) and connectors (links).

Connectivity and public space quality: Toward an integrated analytical framework

4.1 From connectivity to quality: While green infrastructure has been widely discussed as a strategy for enhancing urban environments, its role as a mechanism for improving public space quality remains insufficiently operationalized. Existing literature often addresses connectivity and quality as parallel concepts, without explicitly defining the relational mechanisms through which connectivity produces qualitative spatial outcomes (Carmona et al., 2010; Gehl, 2011). Building on the previous chapters where underused public spaces were conceptualized as latent spatial potential, and green infrastructure was defined as a multi-dimensional connectivity mechanism, this chapter establishes a framework that directly links connectivity to public space quality. The central argument is that connectivity is not merely a spatial property, but a structuring condition that enables, enhances, and redistributes public space quality across the urban system. This chapter therefore shifts the analytical focus from what spaces are to how they perform within networks, providing a tool for evaluation, comparison, and design intervention.

4.2 Defining public space quality as a multi-dimensional construct: Drawing on Carmona and Gehl , public space quality can be structured through four interrelated dimensions:
1. Spatial (Morphological) quality
Clarity of form, spatial continuity, enclosure, and integration within the urban fabric
2. Functional quality
Diversity of activities, accessibility, adaptability, and intensity of use
3. Social quality

Inclusivity, interaction, safety, and capacity for collective life
4. Perceptual quality
Legibility, identity, comfort, and sense of place, (Carmona et al., 2010; Gehl, 2011).

4.3 Connectivity as a structuring condition of quality: Connectivity fundamentally reshapes how public space quality is produced and distributed. Rather than emerging solely from internal design characteristics, quality is increasingly understood as relational, dependent on how spaces are positioned within broader networks.
Urban theory supports this relational perspective. Jane Jacobs demonstrates that vibrant public life depends on continuous systems of movement and interaction (Jacobs, 1961), while Jan Gehl emphasizes that accessibility and connectivity are prerequisites for sustained social activity (Gehl, 2011). Within this framework, connectivity operates through several key mechanisms: access, flow, linkage and integration. Thus, connectivity can be understood as a relational mechanism that enhances the capacity of public spaces to support use, interaction, and environmental performance.

4.4 Framework structure: linking connectivity to public space quality To operationalize this relationship, the framework is structured as a matrix that links connectivity dimensions with public space quality dimensions.

4.4.1 Connectivity Dimensions; Rather than functioning as isolated green interventions, the findings indicate that green infrastructure operates through interconnected forms of connectivity that directly correspond to the multidimensional structure of urban space quality articulated by Carmona. Within this framework, four interrelated dimensions of connectivity can be identified:
Spatial connectivity, supporting continuity, permeability, and accessibility across the urban fabric
Ecological connectivity, enabling environmental flows, biodiversity support, and microclimatic regulation
Social connectivity, facilitating movement, interaction, inclusivity, and collective urban life
Perceptual connectivity, reinforcing legibility, identity, spatial coherence, and sense of place

Tab.1: Evaluation matrix linking connectivity to corresponding dimensions of public space quality

Connectivity	Quality			
	Spatial quality	Functional quality	Social quality	Perceptual quality
Spatial Connectivity	Enhances continuity and integration	Improves accessibility and usability	Supports movement and encounter	Strengthens spatial legibility
Ecological Connectivity	Improves environmental structure	Supports climate-responsive use	Enhances comfort and wellbeing	Reinforces natural identity
Social Connectivity	Activates spatial interfaces	Increases diversity of activities	Strengthens interaction and inclusion	Enhances sense of belonging
Perceptual Connectivity	Clarifies spatial organization	Supports intuitive use	Reduces perceived insecurity	Strengthens imageability

4.4.2 Framework matrix: The framework suggests that connectivity should be understood as a relational mechanism through which different dimensions of urban space interact and reinforce one another. From this interpretation, three key insights emerge:

1. Public space quality as a relational condition

The framework indicates that public space quality cannot be evaluated only through the internal characteristics of individual sites. Instead, quality emerges through the relationships that spaces establish with surrounding urban systems, movement networks, ecological structures, and social activities. In this sense, urban spaces do not operate as isolated entities, but as interconnected components within broader relational systems.

2. Connectivity as a multi-dimensional performance multiplier

Connectivity has the capacity to simultaneously enhance multiple dimensions of spatial performance. A single intervention such as a green corridor, pedestrian linkage, or ecological pathway may improve accessibility, strengthen ecological continuity, encourage social interaction, and reinforce perceptual coherence at the same time. Connectivity therefore operates as a multiplier through which spatial, environmental, social, and experiential qualities become mutually reinforcing.

3. Underused spaces as strategic nodes within urban systems

The findings further reveal that through integration into systems of spatial, ecological, social, and perceptual connectivity, these fragmented or underperforming spaces can transition from residual conditions into active urban components. Their latent potential lies precisely in their capacity to reinforce continuity and establish new relationships across the urban fabric.

The framework developed through this research departs from conventional approaches that evaluate public space primarily through the internal qualities of individual sites. Instead, it proposes that public space quality emerges relationally, through the interaction between spatial systems, ecological processes, movement structures, social practices, and perceptual experiences. In this sense, quality is not treated as a fixed or isolated attribute, but as a dynamic condition produced through connections operating across multiple urban dimensions. Within

this interpretation, connectivity functions as the central operative mechanism through which latent spatial potential becomes active urban performance. The framework therefore repositions green infrastructure beyond its conventional ecological role, redefining it as a multidimensional urban design system capable of organizing relationships across the urban fabric.

At the same time, the framework acknowledges that connectivity does not automatically generate quality. The effects of connectivity depend on the balance between spatial integration, programmatic activation, ecological performance, and social appropriation. Highly connected spaces may still remain underused when lacking meaningful activities, symbolic identity, or experiential qualities. The study therefore contributes to contemporary urban design and landscape urbanism discourse by redefining green infrastructure as a system of multidimensional connectivity through which public space quality is produced, distributed, intensified, and sustained across the urban fabric.

Conclusion

This research set out to investigate how underused public spaces can be reinterpreted and transformed through green infrastructure connectivity in order to enhance public space quality. Moving beyond conventional understandings that frame underused spaces as residual deficiencies or inactive urban fragments, the study conceptualized these environments as relational spatial conditions characterized by latent potential. Through this perspective, underuse was understood not as a fixed or inherent property of space, but as a condition emerging from disconnections between spatial form, accessibility, social practices, ecological systems, and urban networks.

Building upon this theoretical foundation, the research identified connectivity as the critical mechanism capable of activating and operationalizing latent spatial potential. The study demonstrated that the limitations of underused public spaces frequently stem not only from internal spatial deficiencies, but from broader forms of fragmentation and isolation within the urban fabric. Consequently, the transformation of such spaces depends not solely on localized redesign interventions, but on their reintegration into systems of movement, ecology, perception, and collective urban life.

Within this context, green infrastructure was redefined as a multidimensional urban design mechanism structured through spatial, ecological, social, and perceptual connectivity. Rather than functioning exclusively as an environmental strategy, green infrastructure was positioned as a relational framework capable of organizing interactions across urban systems. Through the development of linear, nodal, and hybrid connectivity typologies, the study illustrated how fragmented and underused spaces may function simultaneously as connectors, destinations, ecological interfaces, and social anchors within broader urban networks.

The analytical framework developed through the research further demonstrated that public space quality emerges relationally through connections operating across multiple dimensions of urban space. Spatial continuity, ecological integration, social interaction, and perceptual coherence were shown to function not as isolated qualities, but as interdependent conditions reinforced through connectivity. In this sense, connectivity acts as a multidimensional performance multiplier, enabling a single intervention to generate simultaneous spatial, environmental, social, and experiential benefits.

Importantly, the research also acknowledges that connectivity alone does not automatically guarantee quality. The effectiveness of connectivity depends on the balance between accessibility, programmatic activation, ecological performance, social appropriation, and experiential meaning. Highly connected spaces may still remain underused when lacking identity, inclusivity, or meaningful forms of occupation. Therefore, the production of public

space quality requires not only physical integration, but also the capacity to support diverse forms of urban life and collective experience.

The contribution of this study lies in redefining green infrastructure beyond its conventional ecological interpretation and positioning it as a multidimensional relational system through which public space quality can be produced, distributed, intensified, and sustained across the urban fabric. By linking latent spatial potential, connectivity, and public space quality within a unified framework, the research provides a conceptual and analytical basis for future urban design strategies aimed at transforming fragmented and underused public spaces into active and interconnected components of resilient urban systems.

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PLANT-BASED EXPRESSION SYSTEMS IN BIOPHARMACEUTICAL PRODUCTION: A COMPREHENSIVE REVIEW

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Abstract

The development of biotechnology has given rise to a paradigm shift in the field of pharmaceutical production, which is the transgenic plant for the synthesis of bioactive substances that play a role in the production of drugs and more. It is known as molecular agriculture, which uses plant genetic technology to produce certain proteins with therapeutic functions, including monoclonal antibodies, hormones, vaccines and other biologically active components. The most important methods are additional methods of minimal cost and potential biosafety. Unlike traditional production systems (cells, bacteria or yeast), plants on a flexible and workable platform, the characteristics of most of the decentralized biological drugs. The techniques of other technologies are glucocerebroside (elements for the treatment of Gaucher disease) in transgenic carrot cells, as well as recombinant treatments against Ebola, HIV and influenza, such as plants such as Nicotiana benthamiana or corn. These results demonstrate the potential in the true nature of plants that they convey in addressing the challenges of the global health situation. However, it is not difficult to undertake, as it is important, it is important to control the products of the biosynthesis, to identify the products of the biosynthesis, to know that it is mandatory for the educational process, the capacity to record the post-protection of the proteins and the factors of the rules and ethics that are related to the GMO in the care of a specialist. The rules and precise rules are also related to the integration of this technology into pharmaceutical systems.

Keywords: transgenic plants, genetic engineering, pharmaceutical production.

Introduction

Transgenic plants are plants whose DNA has been modified using genetic engineering techniques. The aim is to introduce a new trat into the plant that does not occur naturally in the species. A transgenic plant contains a gene or genes that have been artificially inserted into it. The sequence of the inserted gene is known as a transgene and can come from an unrelated plant or from an entirely different species. The goal of introducing a combination of genes into a plant is to make it more useful and productive. This approach offers advantages such as improved longevity, higher yield, improved quality, resistance to pests, resistance to heat, cold and drought, and to a range of biotic and abiotic stresses. Transgenic plants can also be produced in such a way that they express foreign proteins of industrial and pharmaceutical value (Paul *et al*, 2011).

Plants engineered to produce vaccines or antibodies (Plantibodies) are free from human diseases, thus reducing the costs of screening for viruses and bacterial toxins. The first transgenic plants were reported in 1983. Since then, many recombinant proteins have been expressed in several agronomically important plant species, including tobacco, corn, tomatoes, potatoes, bananas, alfalfa, and canola. In general, tobacco plants have been used most, although potatoes and bananas are also being considered for human purposes (Albiri et al, 2015&Fisher et al 2015).

Genetically modified plants are created in a laboratory by altering the genetic makeup, usually by adding one or more genes to the genome of a plant. The nucleus of the plant cell is the target for the new transgenic DNA. Most genetically modified plants are created by the biolistic method (particle gun method) or by the Agrobacterium tumefaciens-mediated transformation method (Shrawat et al, 2006).

The "Gene Gun" method, also known as "Micro-Projectile Bombardment" or the "Biolistic" method, is most commonly used in species such as maize and rice. In this method, DNA is attached to small particles of gold or tungsten, which are then fired at plant tissues or single plant cells, under high pressure using a gun. The accelerated particles penetrate both the cell wall and membranes. The DNA is separated from the coated metal and integrated into the plant genome within the nucleus. This method has been successfully applied to many crops, especially monocotyledons, such as wheat or maize, for which transformation using Agrobacterium tumefaciens has been less successful. This technique is considered relatively safe and efficient. The only disadvantage of this process is that serious damage to the cell tissue can occur (Chawla et al, 2000).

The other method used to develop genetically modified plants is the "Agrobacterium" method. It involves the use of soil-dwelling bacteria known as Agrobacterium tumefaciens. It has the ability to infect plant cells with a portion of its DNA. The portion of DNA that infects a plant is integrated into a plant chromosome via a tumor-causing plasmid (Ti plasmid). The Ti plasmid can control the plant's cellular machinery and use it to make many copies of its own bacterial DNA. The Ti plasmid is a large circular piece of DNA that replicates independently of the bacterial chromosome. This plasmid is important because it contains DNA transfer regions (tDNA), where a researcher can insert a gene, which can be transferred into a plant cell through a process known as “flower dipping”. A flower dipping involves immersing flowering plants in a solution of Agrobacterium carrying the gene of interest, followed by transgenic seeds, which are collected directly from the plant. This process is advantageous because it is a natural method of transfer and is therefore considered a more acceptable technique. In addition, Agrobacterium is able to transfer large fragments of DNA very efficiently. One of the major limitations of Agrobacterium is that not all important food crops can be infected by these bacteria. This method works particularly well for dicotyledonous plants such as potatoes, tomatoes and tobacco plants (Meagher 2000&Koornef et al, 2010).

Methodology

For the preparation of this paper, various scientific sources published in international peer-reviewed journals, academic books and relevant reports in the field of pharmaceutical biotechnology were used. The literature search was conducted through electronic databases such as PubMed, Scopus and Google Scholar. Keywords such as “transgenic plants”, “plant molecular farming”, “biopharmaceuticals”, and “recombinant proteins” were used. The sources were selected based on scientific relevance, methodological quality and their contribution to understanding current developments, applications and challenges related to the use of transgenic plants in the production of biopharmaceuticals.

Results and discussion

Transgenic plants contain inserted genes that are derived from other species. The inserted genes can come from species within the same kingdom (plant to plant) or between kingdoms (bacteria to plant). In many cases, the inserted DNA must be modified in order to be expressed correctly and efficiently in the host organism. Transgenic plants are used to express proteins, such as the cry toxins from Bacillus thuringiensis, herbicide resistance genes, and antigens for vaccinations.

Cisgenic plants consist of the use of genes, found within the same species or in a closely related species, where conventional plant breeding can occur. Some breeders and scientists argue that cisgenic modification is useful for plants that are difficult to cross by conventional means (such

as potatoes). These plants in the cisgenic category should not require the same level of regulatory control as other genetically modified organisms (Flack et al, 1999).
GM technology has been used to produce a wide range of crops. As the global population continues to expand, food security remains a major concern. Genetically modified foods offer significant benefits by improving crop yields, reducing transportation costs, and increasing nutrient content. Developments, resulting in commercially produced varieties in countries such as the US and Canada, have focused on conferring resistance to insects, pests, or viruses, and on producing tolerance to specific herbicides. While these traits have had benefits for farmers, the benefits for consumers have been less apparent beyond these. In limited cases, a reduced price due to reduced cost and increased ease of production. Several genetically modified crops for malnutrition are expected to be available for cultivation in the next five to ten years (Davies, 2007).

Transient expression platform

It usually takes six months to a year, or more, to produce transgenic plants. Several generations are required to create plants that are homozygous for the transgene. Most transformation technologies also result in the random insertion of genes into the plant genome. This random insertion, together with the need to identify regulatory elements (promoters) that enable high levels of expression of foreign genes, often results in low production of the recombinant protein, even in stably transformed plants.
The time required to use a standard PMF approach is inadequate for dealing with sudden viral epidemics, such as the Ebola, SARS (Severe Acute Respiratory Syndrome) or MERS-CoV outbreaks. Transient expression systems can be used as an alternative to produce recombinant proteins within three to five days.
Several viral vectors have been developed for small- to medium-scale production of proteins via PMF. For example, Huang Z et al. (2010) developed a highly efficient DNA replication system based on bean yellow mosaic virus (BeYDV), incorporating multiple replication cassettes into a single vector. They were able to produce 0.5 mg of an antibody per gram of leaf (fresh weight) in tobacco leaves within four days of infiltration.
Using a similar methodology, Mapp Biopharmaceutical Inc. transiently expressed humanized antibodies, MB-003 and ZMab, in tobacco leaves. Later, these two antibodies were combined and named ZMapp. The use of these antibodies as a pharmaceutical drug was successful in curing 100% of rhesus monkeys infected with Ebola (Qiu et al, 2014).

Bioreactor platforms - plant cell culture system

Currently, bioreactors based on plant cell culture represent more potential than traditional plant molecular farming (PMF) platforms that use whole plants for drug production. Similar to bioreactors used for microbial or animal cells, plant cells are cultured in closed and sterilized vessels, free from human pathogens or soil contamination. This approach helps eliminate biosafety concerns associated with unintended pollen dispersal and cross-fertilization.
Cultivated plant cells require only simple nutrients, which makes the operating cost much lower compared to microbial or animal systems. The purification and processing of recombinant proteins is also simpler, due to the absence of complex plant fibers and numerous secondary metabolites – significantly reducing the overall cost of production (Fox, 2012). To date, over 20 recombinant proteins have been produced using plant cell culture systems. Tobacco varieties such as BY-2 and NT-1 are among the most widely used PMF as bioreactor cell lines. The recombinant protein can be programmed to be secreted directly into the culture medium, to simplify the purification process. However, the pore size of the plant cell wall may prevent the

secretion of some foreign proteins, depending on their size and spatial structure. In addition, proteolytic activity in cultured cells can cause a decrease in antibody yield (Spok et al.2008).

Moss culture

Currently, moss, a non-seed plant, is being studied as a promising candidate for the production of pharmaceutical proteins in bioreactors. The ability of moss cells to photosynthesize in culture significantly reduces the cost of nutrients required for cultivation.
Similar to yeast and plant cell cultures in suspension, recombinant proteins in moss cells can be engineered to be secreted into the culture medium, which greatly facilitates the process of purification and processing of the produced proteins.
Through genetic manipulation, moss cells can produce humanized forms of glycosylated proteins, such as the Lewis Y-specific monoclonal antibody MB314, reducing common concerns associated with plant-specific glycosylation, which can negatively impact drug functionality in humans (Huang et al, 2012).
The moss culture Physcomitrella patens (P. patens) is the most widely used plant material in this technology for protein production in bioreactors. A German biopharmaceutical company, Greenovation Biotech GmbH, has developed a P. patens-based platform, called Bryo-Technology, for large-scale, high-quality production of recombinant proteins. Examples of products from this platform include:
Moss-GAA for Pompe disease,
Moss-GBA for Gaucher disease,
and Moss-AGAL for Fabry disease.
Of these, Moss-AGAL has completed preclinical trials and is in the process of entering phase I clinical trials (Orrellana et al, 2015).

Algal bioreactors

Microalgae cultures have been used for years for both biofuel production and the production of foreign proteins. Microalgae have a very simple structure and can be unicellular, colonial, or filamentous. They are able to produce large amounts of biomass within a very short period of time, due to their very short life cycle.
The purification and processing process of recombinant proteins in algae is similar to that used for yeast and bacteria, and is therefore less expensive compared to systems using whole plants (Mathieu-Rivet et al, 2014).
However, recombinant proteins produced by algae do not undergo several post-translational modifications, which may negatively affect their use for the production of glycoproteins. For example, algae may not be able to produce human forms of glycosylated proteins, due to the lack of specific enzymes required for these modifications.
Despite this, a variety of recombinant therapeutic and diagnostic proteins, including vaccines, enzymes, and antibodies, have been successfully produced in algal system (Gong Y et al, 2011).
An optimized microalgae production system has been developed by the American company PhycoBiologics, which uses specialized bioreactors for this purpose. In this system, it has been possible to obtain quantities of recombinant proteins that constitute up to 20% of the total soluble proteins, which makes the algal platform a very promising opportunity for the commercial production of pharmaceutical drugs (Teng C et al, 2002).
Seed-based platform for recombinant protein production
One of the main challenges in plant-based pharmaceutical drug production (PMF) is the stability of recombinant proteins during storage and purification of harvested material.

Currently, most pharmaceutical proteins are synthesized in green parts of plants to maximize biomass, but proteins in leaves are susceptible to rapid proteolytic degradation after harvest. Also, long-term storage of leaf material is a major challenge, as proteins lose their activity over time (Lu Z, et al, 2012).

In this context, the seed-based protein production platform is becoming a very promising alternative. If foreign proteins are intended to be produced in seeds, they have higher stability and can be stored for long periods (up to 3 years) at ambient temperature without significant loss of activity. Furthermore, seeds have lower levels of native proteins, secondary metabolites, and phenolic compounds that can complicate purification, making the process simpler and more economical (Ou J et al, 2014).

The seed-based platform has been successfully developed in several plant species, such as Arabidopsis, tobacco, rice, and maize. For example, in Arabidopsis, the use of a seed-specific regulatory sequence for common bean (fasciatus) has enabled the achievement of high levels of recombinant proteins—up to 36.5% of the total soluble protein in the seeds. In transgenic rice, human lysozyme was achieved to constitute 1% of the seed weight, while in tobacco seeds, single-chain variable fragments (scFV) reached up to 25% of the total protein when linked to elastin-like polypeptides (Huang N. 2004).

Another major advantage of the seed-based platform is the possibility of targeting proteins to different compartments within the cell, such as the endoplasmic reticulum (ER), which contains very few proteases, reducing degradation and increasing protein yield. For this purpose, the KDEL signal is used, which helps to retain proteins in the ER (Scheller J et al, 2006).

Biopharmaceutical Manufacturing: Proteins, Antibodies, and Vaccines

The market for recombinant protein biopharmaceuticals is large and growing rapidly, with almost all major pharmaceutical companies reporting an increasing share of their revenues from these products rather than small molecule drugs (Goodman M, 2009). Typically, these pharmaceuticals are manufactured using mammalian or bacterial cell-based systems, which are complex to operate and inherently susceptible to contamination with human pathogens. Manufacturing facilities must comply with current good manufacturing practices (cGMP), they require large capital expenditures, and they involve considerable financial risk. Plant biotechnology has the potential to overcome some of these limitations, but several hurdles remain before this new industry can compete effectively in the pharmaceutical sector. Interest in the potential of plants as co-biofactors for recombinant proteins of pharmaceutical importance was first stimulated by the report of a tobacco line engineered to synthesize a functional murine monoclonal antibody (mAb) (Hiatt, A et al, 1989).

Range of plant production platforms

Technological developments in this field have led to an expansion of the number of well-developed systems available for the production of recombinant pharmaceuticals in plants. Many plant species are now amenable to genetic manipulation (Sourrouille C et al, 2008).

Plant-made pharmaceuticals (PMPs) from plant tissues

The first recombinant protein products from plant biotechnology to reach the market were not pharmaceuticals, but enzymes and diagnostic reagents. The production and purification of egg white avidin and bacterial beta-glucuronidase for commercial purposes were first reported in 1998 (TwymanR et al 2003 &Hood et al, 1999) and both were commercialized at one point through a collaboration between the former biotechnology company Prodigene (College Station, TX, USA) and Sigma-Aldrich (St. Louis, MO, USA). However, despite active research and development efforts and venture capital, new non-pharmaceutical products entering the market have remained rare. Both of these precursor products were expressed in a transgenic food crop (maize) in an open field environment, in order to take advantage of the high protein

yields of this crop and the scalability and economics of conventional agronomic practices (Evangelista et al, 1998) The use of food crops for recombinant protein production has been associated with negative sentiment among consumer groups and the food industry, leading to the adoption of a "zero tolerance" policy by the US Food and Drug Administration (FDA) for the release of GMP transgenes and contamination of food crops in the current draft GMP guidance documents for industry. The high-profile loss of content experienced by Prodigene has led the United States Department of Agriculture/Animal and Plant Health Inspection Service to impose additional requirements for all future field releases of GMP crops in the US. These factors have led to a notable shift from open-field transgenic food crops to fully enclosed non-food culture systems for the production of PMPs. Unfortunately, this has left the field off the established path to commercialization defined by these non-pharmaceutical precursors (FDA).

Three broad classes of drugs have received particular attention from the PMP community.

The first class is therapeutic antibodies and antibody-derived proteins. The production of antibody PMPs is now supported by a set of well-developed technologies that can offer excellent yields and unique technical advantages. Indeed, plants remain the only viable production platform for the production of SIgA molecules. Antibodies produced in plants have been approved for topical use in the EU (CaroRXTM, Planet Biotechnology) and are progressing through clinical trials for systemic use in the US (NHL scFvs). Transgenic tobacco, either in an open field or closed greenhouse environment, offers a cost-effective production route that is currently used in the production of antibodies for topical use (e.g., CaroRXTM and mAb 2G12), as well as an antibody used in the downstream processing of a hepatitis B vaccine. The involvement of the EU Pharma-Planta consortium in bringing mAb 2G12 to the brink of a phase I clinical trial has put clear regulatory guidelines in place for the production of PMPs in greenhouses from whole plant biomas (Pujol M et al, 2005). The second class are subunit vaccine antigens. Noninvasive immunization by oral administration is an attractive route of immunization, and plant expression hosts have been associated with oral administration since the inception of the technology. Several edible "vaccines" have progressed to phase I clinical trials, although important issues regarding dose standardization and food chain contamination, as well as the efficacy of oral vaccination, remain to be further investigated. Oral vaccine antigens produced by plants may find greatest relevance as booster components of heterologous prime-boost strategies, as has been demonstrated for measles and hepatitis B vaccines (Thanvala Y et al, 2005). The rapid production of vaccine antigens in transiently transfected leaves of N. benthamiana offers a further potential advantage of plant-based production of vaccine antigens. This approach is illustrated by the seasonal and pandemic influenza vaccines currently in Medicago-sponsored clinical trials (Webster D et al 2002).

The third class of PMPs are therapeutic enzymes. At least initially, PMPs in this class are likely to be "biosimilars" such as insulin (SBS-100, SemBioSys Genetics), glucocerebroside (UP-LYSO, Protalix), and interferon-alpha (LocteronR, Biolex Thera-peutics. The use of PMP technologies could allow the commercialization of biosimilar versions of drugs with existing patent protection in other manufacturing systems. However, given the extensive manufacturing capacity in the generics sector, GMPs must also rely on the advantages of a plant production platform to compete effectively (Thanavala Y et al, 2005)

Conclusions

In conclusion, it can be said that transgenic plants represent one of the most important developments in modern biotechnology, with a profound impact on agriculture, the food industry and medicine. They offer great potential for improving crop quality, increasing

resistance to biotic and abiotic stress, as well as for the production of substances of high pharmaceutical value (such as vaccines and therapeutic enzymes).

However, despite the obvious benefits, the use of transgenic plants remains a controversial topic, due to environmental, ethical and socio-economic concerns. Issues such as the impact on biodiversity, the development of resistance in insects and weeds, as well as the monopoly of corporations on modified seeds, require special attention and a careful approach from stakeholders.

To maximize the benefits and minimize the risks, an integrated approach is necessary, where scientific research, public policy and consumer education go hand in hand. In addition, advances in new genetic modification technologies, such as CRISPR/Cas9, offer opportunities to overcome some of the ethical and technical limitations of traditional transgenic methods.

In the future, the role of transgenic plants is expected to deepen not only in terms of more sustainable food production, but also in addressing global challenges such as climate change, food shortages and the development of new herbal medicines. Therefore, this field remains not only scientifically challenging, but also of strategic importance for the future of humanity.

Transgenic biotechnology presents a wide range of opportunities, ranging from improving the quality and quantity of food to preventing and treating diseases, but there are some potential risks, so some issues that need to be taken into account are:

Consumer safety and health. There are concerns about the production of recombinant proteins that may cause allergic reactions, unpredictable levels of toxicity or long-term effects in humans. Organizations such as the Royal Society and the National Academy of Sciences advise on a transparent and rigorous system of evaluations for potential allergens and toxins. The concept of "substantial equivalence" is used to assess whether a transgenic product is biologically the same as its natural counterpart.

Risk of genetic contamination and loss of biodiversity. Controlling the outcrossing of transgenic genes into wild plants or other seeds remains an ecological and ethical challenge. Exposure to herbicide resistance genes could lead to the development of "superweeds" that threaten natural ecosystems.

Unexpected allergies to foreign proteins. There is a history of concerns when genes from allergenic sources are introduced, such as genes from Brazil nuts into soybeans, which were more sensitive to people allergic to nuts.

Intellectual property control and access for developing countries. Patents on transgenic crops lead to economic dependence; farmers cannot save seeds and must buy them every year. This phenomenon raises ethical dilemmas about the fairness of access and benefit-sharing at the global level.

Patient/consumer autonomy and information. The decision to use transgenic drugs should be based on informed consent. The need for transparency in labeling is critical. Some countries require labeling for "bioengineered" products, supported by standards such as the FFDCA and the concept of substantial equivalence.

Ethical manipulation of genetic material. Some philosophical approaches consider genetic modifications to be unethical interventions in nature, challenging the principles of "respect for life" and the limits of natural equity.

Socio-economic impacts and global justice. Transgenic technology has the potential to improve food and health security, but without ethical intervention it could exacerbate social inequalities. The global need to address food security for all coincides with the values of inequality of access.

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BIOTECHNOLOGICAL ROUTES FOR INSULIN PRODUCTION

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Abstract

Insulin is a peptide hormone produced by β-cells of the Islets of Langerhans in the pancreas and plays a central role in regulating blood glucose homeostasis. Historically, insulin therapy relied on extraction from animal pancreases, but this approach was limited by supply constraints, variable purity, and immunogenic reactions. The introduction of recombinant DNA technology in the late 20th century transformed insulin production by enabling biosynthesis in microorganisms such as *Escherichia coli* and *Saccharomyces cerevisiae*. These advances allowed the large-scale production of highly purified human insulin and eliminated dependence on animal sources.
This study reviews the evolution of insulin production methods, from animal-derived extraction to recombinant biosynthetic approaches, including the development of proinsulin-based systems and yeast expression platforms. Furthermore, it examines the structural and functional properties of insulin, its biosynthesis, receptor interactions, and metabolic effects on carbohydrates, lipids, and proteins. Special attention is given to insulin analogues, including rapid-acting (Humalog, NovoLog, Apidra) and long-acting (Lantus, Levemir) formulations, which were developed through targeted amino acid modifications to improve pharmacokinetic profiles and therapeutic outcomes.
Recombinant insulin and its analogues have significantly improved diabetes management by providing greater safety, consistency, and flexibility in treatment. Additionally, innovations such as insulin pens and advanced delivery systems have enhanced patient adherence. Overall, the development of recombinant insulin represents a major milestone in biotechnology and has fundamentally reshaped modern diabetes therapy.

*Keywords:*Insuline, yeast, gene modiffication

Introduction

Since the 1920s, insulin production relied heavily on large quantities of animal pancreases, primarily from cattle and pigs. Advances in chromatographic purification techniques during the 1970s enabled manufacturers to produce more purified insulin, thereby reducing the risk of developing anti-insulin antibodies, which had been shown to contribute to insulin resistance in a significant number of patients. However, these improved purification methods also required even greater amounts of glandular tissue per unit of insulin (IU). By 1981, the production of one kilogram of insulin required approximately 8,000 kg of pancreatic glands derived from around 23,500 animals—yet this quantity was sufficient to treat only about 750 diabetic patients for one year. Because insulin production was so heavily dependent on animal-derived glands, both supply and cost were closely tied to their availability (Zion Market Research, 2021*)*. During the 1970s, the supply of pancreatic glands in the United States declined significantly, while the prices of beef and pork fluctuated considerably, raising concerns about potential insulin shortages. These concerns were alleviated by a groundbreaking scientific advancement that utilized innovations in gene splicing developed in the mid-1970s. In 1978, scientists at City of Hope National Medical Center and Genentech developed a method for producing biosynthetic human insulin (BHI) using recombinant DNA (rDNA) technology *(FDA*). This multi-step process involved isolating and manipulating the two polypeptide chains (A and B) that constitute the human insulin gene, and then inserting them into a common bacterium, which was genetically engineered to produce large quantities of insulin. Eli Lilly and Company subsequently entered into an agreement with Genentech to commercialize human insulin using rDNA technology. On October 28, 1982, after only five months of review, the Food and Drug Administration approved **Humulin**, the first biosynthetic human insulin product and the first approved medical product of any kind derived from recombinant DNA technology (Ratner *et al,* 2000).The development of biosynthetic human insulin not only

addressed the instability of supply and pricing associated with animal-derived insulin, but also enabled the design of more efficient production protocols, achieving higher purity and improved standardization. Perhaps more importantly, the introduction of synthetic insulin marked a paradigm shift in diabetes therapy, paving the way for the development of non-animal-derived insulin products.These advancements led to the creation of insulin analogs with varying pharmacokinetic profiles, including rapid-acting analogs such as **Humalog** (approved by the FDA in 1996) and long-acting analogs such as **Lantus** (approved in 2000) (Hemmingsen *et al,*2021). This diversification of insulin products provided patients with a broader range of therapeutic options and greater flexibility in managing diabetes. From the 1980s onward, the insulin market increasingly focused on addressing both the clinical and lifestyle needs of patients with diabetes. This shift led to the introduction of innovations such as insulin pens and inhalable insulin formulations. While some of these products achieved greater commercial success than others, all were developed with the aim of improving patient adherence and enhancing the overall management of diabetes (Heinmann *et al,* 2000).

Material and methods

The data for this paper were collected from original and peer-reviewed scientific publications that can be found in online scientific libraries.The literature was searched based on the study topic, authors, and various journals. During the literature review, emphasis was placed on researching specific questions related to this topic. The literature was analyzed starting from general sources and progressing to articles directly related to this issue.The collected data were then corrected, organized, and compared with information obtained from the FDA.

Results

Insulin is a protein hormone. Its name originates from the Latin word *insula* ("island"), since it is secreted by groups of endocrine cells called the Islets of Langerhans in the pancreas.In general, insulin enables glucose metabolism by activating glycolysis, promoting the storage of glucose in the liver in the form of glycogen, and favoring fat storage. Insulin is a polypeptide hormone produced by the β-cells of the Islets of Langerhans in the pancreas, which play a role in regulating blood glucose levels (Mastick *et al,* 1998).

In addition to its effect on glucose metabolism, insulin also affects protein and lipid metabolism. Mitogenic activity has been observed at high insulin concentrations *in vitro,* which is considered to be mediated by insulin-like growth factor 1 (IGF-1). The main stimulus for insulin secretion from the pancreas is elevated blood glucose levels. However, insulin is also involved in other metabolic processes, such as stimulating the transport of glucose, amino acids, potassium ions (K^+), and other nutrients into cells. Insulin can stimulate the dephosphorylation of several regulatory enzymes involved in major catabolic and anabolic processes. Furthermore, insulin can cause changes in the transcription levels of various genes, most of which encode metabolic enzymes (Schwartz *et al,* 1997).

Insulin is a small peptide composed of two chains:

The A chain, consisting of 21 amino acid residues

The B chain, consisting of 30 amino acid residues (Drejer *et al,* 1991)

The two peptide chains are connected by two disulfide bonds at positions A7–B7 and A20–B19, while the A chain also contains an intramolecular disulfide bond between residues A6 and A11.The overall charge of the insulin molecule results from the ionization of acidic and basic functional groups of its amino acids. Insulin has an isoelectric point (pI) of 5.3 in its denatured state, meaning that at neutral pH it carries a negative charge. This property is important for insulin formulation development (Bornfeldt *et al,* 1991). Active insulin exists as

a dimer, but it is synthesized as a single molecule called preproinsulin, which is converted into proinsulin after leaving the endoplasmic reticulum. Proinsulin then undergoes proteolysis in secretory granules, producing active insulin and a connecting peptide (C-peptide), which consists of 34 amino acid residues.In the body, insulin is stored in pancreatic β-cells in the form of Zn-insulin hexamers, where it is stabilized by two zinc atoms. Each zinc ion is coordinated with histidine residues from three neighboring monomers (Rossana *et al*, 2010).

Insulin binds to the cell surface through a specific receptor. The insulin receptor is a tetrameric integral membrane glycoprotein composed of two α-subunits and two β-subunits. Binding of insulin to its receptor triggers the autophosphorylation of three specific tyrosine residues within the tyrosine kinase domain. The first method used to obtain insulin using recombinant DNA technology was from the company Genentech who consisted in inserting a gene encoding the synthesis of the A and B chains of insulin into *E. coli* cells (Owens *et al*, 2001). After culturing and growing the cells in large bioreactors, the product (either the A chain or the B chain separately) is purified using chromatographic methods. Furthermore, the two chains are incubated under oxidative conditions to form the disulfide bonds characteristic of insulin. Another example of DNA technology is the production of proinsulin who plays a crucial role in the insulin biosynthesis pathway, and its proper processing is essential for maintaining proper glucose homeostasis (Nidhi Sharma, 2022). The method of obtaining insulin with two separate chains was later modified by producing only one fused insulin–β-galactosidase protein, which can be cleaved in a single step to release mature insulin. This method consists of synthesizing proinsulin cDNA from mRNA by modifying its sequence through the addition of a codon at the 5^{th} position for methionine synthesis (Seo MJ, *et al* 2011). The modified cDNA is then inserted into plasmid genes and amplified in bacteria. The proinsulin produced in bacteria is subsequently separated from the β-galactosidase enzyme by degrading the methionine residue. The chain then tends to fold, allowing the formation of disulfide bridges, and the C-peptide is removed through an enzymatic reaction that produces the mature protein. Another metod was pthe production of insuline from yeast, Novo Nordisk S/A was the first company to produce proinsulin secreted by the yeast Saccharomyces cerevisiae (Son Y *et al*, 2007). To simplify the purification process, scientists decided to create a method in which insulin would be secreted directly into the culture medium after being produced inside the cell. For this reason, they used yeast instead of bacteria. Yeast is a eukaryote, meaning an organism that has a nucleus and is therefore capable of completing the maturation process of human insulin (Heinse T, 2021). The proinsulin sequence is inserted into a plasmid, and the recombinant plasmid is transformed into yeast. At this point, the yeast can produce proinsulin, which is processed in the same way as in humans. Proinsulin folds into a closed structure, and the disulfide bridges between cysteine residues can form normally. The 33-amino-acid pro-sequence is removed, releasing the mature protein. The development of recombinant technology enabled the production of different types of human insulin and its analogues (Thomas Kjeldsen *et al*, 2024):

Rapid-acting recombinant insulin- In the formulation of these insulins, modifications made to the amino acid sequence responsible for dimerization and oligomerization—namely, the substitution of these amino acids—ensure repulsion between molecules and prevent the formation of oligomers. Such insulins are absorbed 2–3 times faster after subcutaneous (s.c.) administration.

Humalog (insulin lispro)- is the first such preparation and is produced in *E. coli* through the proinsulin pathway. It differs from human insulin by the modified sequence LysB28–ProB29 (Buchbinder *et al*, 2000).

Novolog (insulin aspart) is another short-acting insulin analogue that differs in that the proline at position B28 is replaced by aspartic acid. With this modification, oligomer formation is reduced, ensuring a faster action.

Apidra (insulin glulisine) is an analogue with a modified amino acid sequence, in which aspartic acid at position B3 is replaced with lysine, and lysine at position B29 is replaced with glutamic acid, providing rapid action (Hemmingsen *et al*, 2021).
Long-acting recombinant insulin-the first registered preparation of this type is Lantus (insulin glargine and others), which has a structural modification (GlyA21, ArgB31, ArgB32). Specifically, in the A chain there is a substitution of asparagine at A21 with glycine, while in the B chain two arginine molecules are added. It is produced in *E. coli*.The modification of several amino acids contributes to increased stability and changes in the isoelectric point, so this insulin dissolves at acidic pH and is less soluble at neutral pH (in subcutaneous tissue). It is a clear solution with an acidic pH of 4.0 and contains zinc and m-cresol. After injection, it is immediately deposited in subcutaneous tissue, thereby providing prolonged action. Due to these properties, this insulin should not be mixed or diluted with other forms of insulin (Hemmingsen *et al*,2021. Levemir (insulin detemir) is another analogue of human insulin with a modified amino acid sequence LysB29(N-tetradecanoyl) and B30. (Hemmingsen *et al*,2021).

Discussion

The development of recombinant DNA technology marked a major advancement in the treatment of diabetes mellitus. Before the introduction of biosynthetic human insulin, insulin production depended mainly on animal pancreases obtained from cattle and pigs. Although animal-derived insulin was effective, its production faced several limitations, including limited availability of pancreatic tissue, unstable supply, high production costs, and the possibility of immune reactions caused by impurities. As the number of diabetic patients increased during the twentieth century, the need for a safer and more reliable method of insulin production became increasingly important (Mudaliar *et al,* 1999). The introduction of recombinant DNA technology in the late 1970s revolutionized insulin manufacturing. Genentech developed the first method for producing human insulin by inserting genes encoding the A and B chains of insulin into *E. coli* bacteria. This innovation demonstrated that human insulin could be produced on a large scale without relying on animal sources. The approval of Humulin by the FDA in 1982 represented a milestone in both biotechnology and diabetes therapy, as it became the first recombinant DNA-derived therapeutic product approved for clinical use.An important improvement in insulin production was the development of the proinsulin synthesis method. Instead of producing the A and B chains separately, scientists produced a single proinsulin molecule that could later be converted into mature insulin through enzymatic processing (Kurtzhals *et al*, 2021). This method simplified the manufacturing process, improved production efficiency, and enabled easier large-scale production. In addition, the correct folding of proinsulin and formation of disulfide bonds ensured the production of biologically active insulin similar to natural human insulin. Another advancement was the use of yeast, particularly *Saccharomyces cerevisiae*, in insulin production. Unlike bacteria, yeast is a eukaryotic organism capable of performing more complex protein processing. Novo Nordisk successfully developed a system in which proinsulin was secreted directly into the culture medium, simplifying purification and reducing production costs. The use of yeast further improved the quality and efficiency of recombinant insulin production. (Marlena *et al,* 2022) Recombinant DNA technology also enabled the development of insulin analogues with modified pharmacokinetic properties. Rapid-acting insulin analogues such as Humalog, NovoLog, and Apidra were designed to prevent insulin molecule aggregation, resulting in faster absorption after subcutaneous injection.(Gauarav *et al,* 2020) These analogues improved postprandial glucose control and provided patients with greater flexibility regarding meal timing. Long-acting insulin analogues such as Lantus and Levemir were developed to provide prolonged and stable insulin action. Structural modifications in these analogues altered their

solubility and absorption, allowing them to maintain blood glucose control over an extended period. These preparations reduced fluctuations in glucose levels and decreased the risk of hypoglycemia, especially during the night. The development of recombinant insulin and insulin analogues significantly improved diabetes management and patient quality of life. Modern insulin therapy allows more individualized treatment approaches adapted to patients' clinical and lifestyle needs. In addition, innovations such as insulin pens and inhalable insulin have contributed to improved treatment adherence and convenience. Despite these advancements, challenges still remain, particularly regarding the high cost of insulin products and their accessibility worldwide. Nevertheless, recombinant DNA technology has transformed insulin therapy by enabling the production of highly purified human insulin and advanced insulin analogues, greatly improving the safety and effectiveness of diabetes treatment. (Hemmingsen *et al*,2021).

Conclusion

The development of recombinant DNA technology revolutionized insulin production and significantly improved the treatment of diabetes mellitus. Before the introduction of recombinant insulin, production relied on animal pancreases, which created challenges related to limited supply, impurities, and the risk of immune reactions. The use of genetically engineered microorganisms such as *Escherichia coli* and *Saccharomyces cerevisiae* enabled the large-scale production of highly purified human insulin with greater safety and consistency. Furthermore, recombinant technology allowed the development of insulin analogues with different pharmacokinetic profiles, including rapid-acting and long-acting formulations. These innovations improved glycemic control, reduced the risk of hypoglycemia, and provided patients with greater flexibility in diabetes management. Recombinant insulin also reduced dependence on animal-derived products and opened new possibilities in biotechnology and pharmaceutical research. Overall, recombinant DNA technology has had a major impact on modern diabetes therapy and continues to contribute to advancements in patient care and treatment outcomes.

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AUTOMATION OF INDUSTRIAL PRODUCTION PROCESSES FOR MATERIAL AND ENERGY EFFICIENCY IN SUSTAINABLE DEVELOPMENT

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Abstract

During industrial production processes, the primary elements with the greatest impact are raw materials and energy. Throughout these processes, starting from the procurement of raw materials to the completion of production with the final products, waste is generated, representing both material and energy losses. This occurs mainly as a result of inefficient processes; therefore, there is a growing tendency for these anthropogenic processes to approach natural processes, which are considered more optimized. The reduction of material and energy losses in production processes enables the rational and efficient use of raw materials, contributes to the preservation of environmental resources over a longer period, supports environmental protection from pollution, and leads to improved economic outcomes, thereby moving closer to the objective of sustainable development. This can be most effectively achieved through the application of automation in production processes.

This paper examines the role of automation in production processes as a key factor in achieving sustainable development in modern industry. The increasing global demand for efficient resource utilization has intensified the need to reduce material waste and energy consumption while maintaining productivity and product quality. In this context, automation technologies such as sensor-based monitoring systems, programmable logic controllers (PLC), and real-time process control are essential for improving industrial sustainability.

The study presents a theoretical analysis of selected industrial cases where automation has contributed to achieving sustainability objectives, including reductions in material waste, energy consumption, and defect rates. Although automated systems require electrical energy for operation, they improve overall sustainability by reducing the need for reprocessing, minimizing machine idle time, and eliminating inefficient process conditions, thereby reducing the material and energy requirements per unit of production.

The results indicate that automation is a decisive factor in sustainable industrial development, particularly when integrated with intelligent monitoring and control systems.

Keywords: Sustainable development, industrial production processes, automation, material and energy efficiency

Introduction

Contemporary human activity is defined as dynamic, intensive and voluminous, being very efficient at exhausting and using up the means designed to maintain and uphold itself. Since the Industrial Revolution, this phenomenon has been exponentially more present, and considering the rate at which human numbers are increasing, and by extension, human industry is developing, this actuality is expected to intensify. In an attempt to satisfy consumer demands, ranging from basic necessities to recreational needs, all human industry, but specifically the manufacturing industry, has amplified its rate of production, striving to meet industry demands, oftentimes neglecting the environmentally detrimental byproducts and waste, generated with any production process which, if left unaddressed, inhibit society's ability to achieve a more sustainable approach towards consumer demands and economic, technological growth.

Manufacturing processes generally can be defined as transformation systems in which material and energy inputs are converted into useful products through controlled mechanical and thermal operations. However, these processes unavoidably generate material losses, as well as energy losses in the form of heat and other inefficiencies. (Kalpakjian & Schmid, 1989). Figure 1 presents a diagram of the elements of these transformative systems.

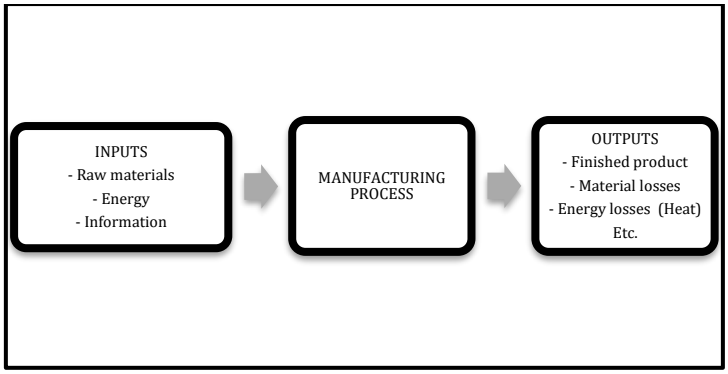


Figure 1. Diagram of manufacturing processes' elements

Addressing these losses in output methodically is imperative for achieving a sustainable approach to manufacturing, which serves not only an ecological purpose, but also achieves a more efficient, higher quality and inexpensive product.

1.1 Concept of "Sustainable Development" : One of the longest standing scientific and engineering approaches to any problem has been to draw inspiration from the natural systems and biological processes, this approach is called "Biomimicry". In many natural biological processes, a byproduct of a process which could be considered "waste", often serves a different purpose once it appears in the physical world, often times being reutilized to facilitate another biological process, this time as an input to the following process. This principle, which is observed in ecosystem cycles, reflects a high level of resource management efficiency and minimal accumulation of waste, and in turn provides a conceptual foundation for sustainable approaches in industrial systems, one of them being sustainable development in production industries.

Sustainable development is generally defined as development that meets the needs of modern generations, without compromising the ability of future generations to meet theirs. (World Commission on Environment and Development, 1987). In a manufacturing context, it is the attempt to minimize, any and all factors which impact a production processes material and energy efficiency, starting from the initial resources needed to initiate production, all the way until the finishing processes before the product hits the market. This approach to manufacturing, is done to ensure energy and material efficiency, resource preservation, lower manufacturing costs, punctual production, all while preserving product quality and consumer satisfaction.

1.2 Automation as a means of achieving sustainable development: As discussed above, biomimicry is an approach that seeks sustainable solutions to human challenges by emulating nature's time-tested patterns and strategies. (Biomimicry Institute, 2006). Many biological systems in nature execute processes very efficiently, achieving desired outcomes while minimizing energy and resource consumption. This efficiency in said systems is enabled by built-in closed-loop control systems, in which sensory inputs, internal decision-making mechanisms, and actuating responses interact and communicate continuously. Through this feedback, the system controls relevant variables and respectively adjusts its behavior to ensure the most efficient response towards achieving the desired result. Good examples of these processes would be homeostasis in humans, or stomatal regulation in plants. This phenomenon in biological systems is why they present prime examples of sustainable systems, capable of fulfilling process needs efficiently with minimal waste generated.

In the pursuit of improved efficiency, consistency, control, and safety, engineering practices have increasingly adopted automation as a key approach in modern manufacturing. Beyond

these aforementioned advantages, automation can also be examined from a sustainability perspective. Through biomimicry, a conceptual parallel can be drawn between closed-loop control systems in manufacturing processes and similar feedback mechanisms found in living organisms. In both of these cases, continuous monitoring and adaptive response enable the system to achieve the most optimal outcome while minimizing inefficiencies and reducing the loss of material and energy resources.

This conceptual analogy is the foundation upon which the present research is based, as it attempts to quantify the extent to which automation benefits manufacturing processes in their pursuit of efficiency and ultimately of achieving sustainable development in industrial production processes. The following sections present the methodology used to assess the impact of automation, followed by an analysis of selected industrial case studies.

Analysis of automation in production processes for sustainable development

2.1 Sources of energy and material losses and their mitigation through automation: Having established the nature of manufacturing processes, it is understood that no such process occurs without the presence of material and energy losses throughout. The Law of Conservation of Energy states that energy cannot be created or lost, it only transforms from one form to another. In an ideal system, the entirety of energy going into a process should be converted into useful work and all materials in their entirety, should contribute directly to the output; when applied to the concept of manufacturing, this would mean that the total amount of any and all inputs going into the process should all be entirely useful to the process, with no input transforming into waste by the end of the process; the process should yield the desired output only, with no residue or energy inefficiency. In manufacturing processes, a portion of the energy input is dissipated as heat due to friction or other inefficiencies, while a part of the material input is lost as waste. As a result of this, any manufacturing processes inevitably produces undesired losses. This relationship can be expressed through an energy balance model:

$$E_{in} = E_{useful} + E_{loss} \quad (1)$$

which for metal-cutting processes can more specifically expanded as:

$$E_{in} = E_{cutting} + E_{friction} + E_{heat} + E_{idle} \quad (2)$$

The same logic and model can be applied to raw material waste, with losses in material as scrap, reworked parts, etc.

The sustainable approach to manufacturing processes is to utilize methods and technologies which minimize said energy losses and material waste, by removing any part of the process which creates energy inefficiencies or causes the generation of raw material losses. The processes analyzed in the actual research are processes pertaining to the metalworking industry of manufacturing, and as such the main issues which lead to inefficiencies in these processes are:

Inconsistency in production – In manual or semi- manual production there is variability in the cutting speed, feed rate, temperature control and operator decisions throughout the work process. This leads to material waste, unsatisfactory product quality, the need for reworking parts etc. (Kalpakjian & Schmid, 1989)

Inefficient machine operation – The machines are operated at non-optimal loads and are sometimes idled unnecessarily, generating heat losses and causing excessive energy consumption. (Groover, 2020)

Lack of real-time process control – In the absence of process control, traditional manufacturing systems cannot react quickly to deviations, cannot perform real time process inspection and

control, which results in errors being detected late. This causes energy and material waste. (Åström & Murray, 2008)
Human error – Human involvement oftentimes causes measurement errors, incorrect inputs of parameters and settings, inconsistencies in repetitive work processes etc.; all contributing towards material losses and energy efficiencies. (Khatib & Sicilano, 2008)
Introducing automation to manufacturing processes the mitigates these issues by replacing open, operator-dependent processes with closed-loop control systems, where sensors continuously monitor process variables and gather data, controllers process said data, and actuators adjust machine behavior accordingly for maximum efficiency.
Automation enables precise regulation of parameters such as speed, feed rate, temperature, and force, significantly reducing variability between production cycles throughout the production process. Furthermore, automated systems enhance energy efficiency by optimizing machine operation, minimizing idle time, and ensuring that equipment operates only under conditions that are considered productive, thereby reducing unnecessary energy loss. The use of robotics and programmable systems also eliminates many forms of human caused inconsistencies, improving repeatability and reducing defect rates. In addition, real-time monitoring allows immediate detection and correction of deviations during the process, preventing the accumulation of errors that would otherwise result in large-scale material waste.
Collectively, these mechanisms enable the transformation of manufacturing from a reactive process—where defects are often identified in conclusion of the production process —into a proactive and adaptive system that continuously optimizes itself. As a result, automation significantly reduces both material and energy losses while simultaneously improving productivity and aligning industrial operations more closely with the objectives of sustainable development.
Having discussed the advantages of automation in reducing material losses and energy inefficiencies in theory, the degree to which these improvements introduced by automation translate into measurable, quantifiable outcomes in real industrial environments remains dependent on analyzing specific instances where automation technologies and processes have actually been implemented. Therefore, it is necessary to move beyond mere descriptions and examine the actual impact of these effects in practice.
This research looks into this aspect by analyzing three selected industrial case studies in which automation technologies have been implemented in production systems. The objective is to identify and compare quantifiable improvements in terms of material waste reduction, energy efficiency, and overall process optimization. Through this comparative analysis, the study aims to evaluate the practical impact of automation and assess its effectiveness as a tool for advancing sustainable development in industrial manufacturing.

2.2 Energy optimization in CNC machining through intelligent process control: One of the clearest examples of automation contributing to sustainable manufacturing can be found in the study conducted by Johnatan Cardona Jiménez and colleagues, where the energy consumption behavior of CNC machining centers was analyzed and optimized using advanced computational control methods. The objective of the study was to determine how automated optimization of machining parameters could reduce electrical energy consumption while maintaining acceptable machining quality, specifically surface finish.
The experimental study was conducted using two industrial CNC vertical machining centers: the Haas UMC-750 and the Leadwell V-40iT. Both of these machines were used to perform controlled metal cutting experiments under different machining conditions. The researchers focused on three controllable machining variables that significantly influence machining performance and power consumption:
Depth of cut (mm) – the thickness of material removed in a single pass

Feed rate (mm/min) – the speed at which the cutting tool advances through the material
Spindle speed (rpm) – rotational speed of the cutting spindle
These variables were selected because they directly affect cutting force, tool- work piece interaction, machining time, and consequently the total electrical energy consumption.
To better visualize the relationship between machining parameters and energy consumption in CNC operations, a nonlinear model was developed to generate a surface graph of the process:

$$E(f,n) = k1n^2 + \frac{k2}{f} + k3f + k4n + E_{base} \qquad (3)$$

The model inputs spindle speed and feed rate as the primary controllable machining variables affecting total energy demand, while also accounting for the baseline machine energy consumption, needed to simply keep the machine operational. Unlike a linear approximation, this model incorporates both quadratic and reciprocal terms to better represent real machining behavior. The quadratic spindle-speed term accounts for increasing rotational and frictional losses which appear at higher spindle speeds, while the reciprocal and linear feed-rate terms represent the energy penalties that are associated with both very low feed rates, which result in longer machining times and very high feed rates, which result in increased cutting loads. The coefficients used in the energy model follow empirical machining energy models described by (Diaz, Helu, Jarboe, & Dornfeld, 2011). As a result, the model produces a nonlinear energy surface containing a minimum energy region, highlighting optimal machining conditions.

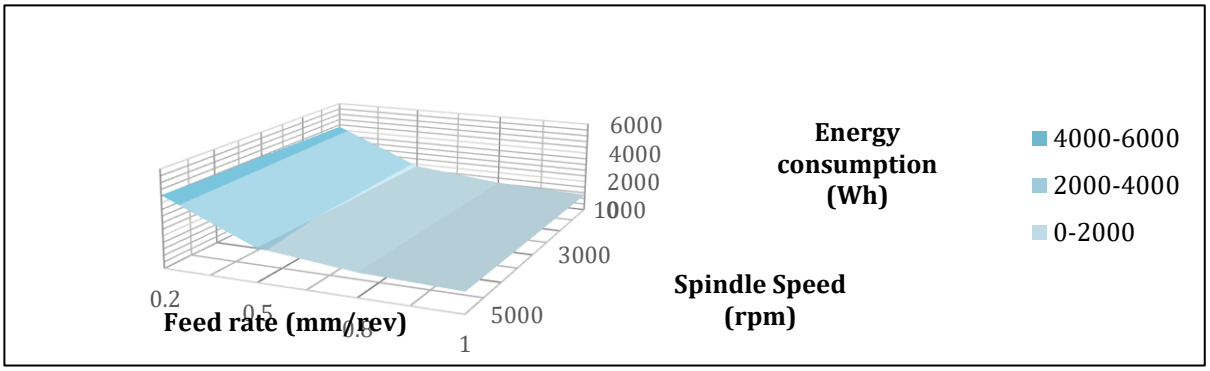


Figure 2. Nonlinear response surface of CNC machining energy consumption as a function of feed rate and spindle speed (model-based analysis)

In order to be able to quantify the relationship between these variables and machine performance, the researchers used a factorial experimental design, which is a method where multiple machining parameters are varied in different possible combinations instead of being tested one at a time, which allows the researchers to see, not only how each parameter in isolation affected the process, but also how the parameters interacted with one another. The factorial experimental design was combined with a Bayesian Seemingly Unrelated Regression (SUR) model. This model allows the simultaneous analysis of two outputs which are affected by the same input parameters; in this case these were parameters critical to the study, namely: Electrical power consumption (energy demand) and surface roughness (machining quality). This is important because simply minimizing energy is not sufficient if that causes the product quality to deteriorate. Therefore, both outputs had to be optimized together, hence the simultaneous analysis.
After developing predictive models for both machining centers, the researchers implemented an automated optimization method using a genetic algorithm combined with quasi-Newton derivative optimization. These methods represent a form of intelligent automation, where the

system itself iteratively searches for machining conditions that minimize energy consumption while preserving surface quality.
The optimization process produced several important findings:
Feed rate was identified as the most influential variable affecting machine power consumption.
Depth of cut was found to have the strongest influence on the roughness of the surface.
The optimization algorithm narrowed down the best operating conditions after approximately 20 generations of iterative search. (Cardona Jiménez, et al., 2022)
The predictive accuracy of the optimized model was extremely high, with an error of less than:
0.01% for the Leadwell V-40iT
0.03% for the Haas UMC-750. (Cardona Jiménez, et al., 2022)
These results demonstrate that automation in the form of intelligent process control can accurately identify the most energy-efficient machining conditions without impacting production quality. Instead of operating under fixed or parameters selected by the operator, which often lead to excessive power usage, longer machining times, and unnecessary tool wear, the automated system continuously determines the most optimal cutting conditions based on process feedback and statistical prediction.
From a sustainability perspective, this has significant meaning, because by minimizing unnecessary spindle load, reducing inefficient cutting conditions, and shortening effective machining time, the automated system lowers the electrical energy used for each manufactured component. In large-scale industrial production, optimizations like these can help achieve substantial reductions in total energy consumption, lower carbon emissions, and more efficient use of industrial resources, directly supporting sustainable manufacturing objectives.

2.3 Energy reduction in CNC milling through automated toolpath optimization: A second example of automation contributing directly to sustainable manufacturing can be found in the study done by Ampara Aramcharoen and Paul T. Mativenga, which investigated the impact of machining strategy and toolpath selection on the energy consumption of CNC milling operations. The objective of this research was to identify how machine-tool energy consumption changes under different automated machining conditions and to determine whether optimization of the tool movement could reduce overall electrical energy consumption during metal cutting.
The study focused on CNC milling processes, where electrical energy is consumed not only during actual material removal, but also during non-cutting machine states such as spindle acceleration, axis movement, coolant circulation, tool repositioning, and standby operation. One of the most important findings of the study was that, in machining operations, a significant portion of total machine energy consumption does not come from cutting itself, but from these movements and non-productive machine activities. The authors note that in mechanical machining, more than 90% of environmental impact is associated with direct electrical energy demand of machine tools. (Aramcharoen & Mativenga, 2014)
To investigate this, the researchers developed a detailed energy demand model for CNC milling. The methodology involved separating machine energy consumption into different operational states:
Basic machine energy – energy required to keep the machine operational
Spindle energy – energy required for rotational motion of the spindle
Axis movement energy – energy used during linear tool movement
Cutting energy – energy directly involved in material removal
By isolating these energy demands, the researchers were able to identify which portions of the machining cycle contributed most to unnecessary energy consumption. (Aramcharoen & Mativenga, 2014)

The experimental phase involved analyzing multiple NC-programmed toolpaths for milling operations. Different machining trajectories were programmed and they were executed under identical cutting conditions, which allowed the authors to isolate the influence of toolpath geometry and machine movement on total power consumption. Parameters such as spindle speed, feed rate, cutting distance, rapid positioning movements and idle motion sequences were all evaluated.

The results demonstrated that toolpath used during the cutting process had a major influence on total machine energy demand. Toolpaths that contained excessive repositioning movements and unnecessary non-cutting motions, significantly increased the electrical consumption. Then, by applying optimized CNC toolpaths with the use of computer-aided manufacturing systems, the researchers identified major opportunities for energy demand reduction, primarily by minimizing non-cutting machine movement, reducing idle spindle operation, and shortening total machining cycle time. The study also identified that machine "ready-state" energy, which is the power required simply to keep the CNC machine operational, made up a large portion of overall energy demand, meaning that reductions in machining time directly reduced total energy usage. (Aramcharoen & Mativenga, 2014)

From an automation perspective, this study demonstrates that sustainability improvements are not achieved only by automating physical machine movement, but also by automating process planning and toolpath optimization; in essence, how the machine moves. Rather than relying on manually selected machining strategies, CAM-based automated path generation allows the system to determine the most energy-efficient movement patterns before machining even begins. This approach reduces unnecessary machine movement, lowers electrical consumption per component, which then improves the overall energy efficiency of production.

From a sustainable development perspective, these findings show that automation and optimization of the machining process in its entirety, can significantly reduce the environmental footprint of CNC machining by optimizing how energy is used across the entire production cycle, rather than focusing solely on the cutting process itself.

2.4 Optimization of a Robotic Spot Welding Manufacturing Line in Automotive Metal Production: A third example of automation contributing to manufacturing efficiency and sustainability can be found in the industrial study carried out by Lopes, Sikora, Schibelbain, & Molina, which investigated the optimization of a fully automated robotic spot welding line in an automotive manufacturing factory operated by Renault in Curitiba, Brazil.

The objective of this study was to determine whether intelligent automation and the balancing of the production-line could reduce inefficiencies caused by excessive robotic movement, uneven distribution of workloads, and non-productive machine time in large-scale sheet metal welding operations.

The manufacturing line which was analyzed in this study was responsible for welding automotive body structures during the final body assembly stage. The production line consisted of: 42 industrial welding robots, which were distributed across 13 production stations, performing over 700 individual spot welds per vehicle body. Although the line was already automated, the researchers identified inefficiencies caused by uneven distribution of welding tasks between robots, unnecessary robotic travel distances between weld points, robot interference in multi-robot stations and extended cycle times caused by poor station balancing.

To address these issues, the researchers developed a Mixed Integer Linear Programming (MILP) optimization model. This model works by searching the most efficient outcome of the combination of different types of inputs or variables; one input of continuous value, such as time or energy and the other, whole number or yes/no values, such as robot assignments. This mathematical optimization model was designed to automatically reorganize welding tasks among the robots while also considering constraints throughout the process such as the

accessibility of the robots to the welding points, physical movement time between welding locations, possible collision/interference between adjacent robots, cycle-time requirements of the production line etc. (Lopes, Sikora, Schibelbain, & Molina, 2017)
The model was validated using empirical production data collected directly from the industrial welding line. After optimization, the system automatically generated better and improved task distributions and movement strategies for the robots and the results were significant:
Production cycle time was reduced by up to 6.6%
Workload balancing between robotic stations improved substantially
Non-productive robotic movement was minimized
Idle time between welding operations was reduced. (Lopes, Sikora, Schibelbain, & Molina, 2017)
These results demonstrate that automation can improve sustainability not only through direct machine control, but also through optimization of the production flow in its entirety. By reducing unnecessary robotic movement and shortening production cycle time, the total electrical energy consumed per welded component is reduced. Additionally, shorter cycle times increase machine utilization and reduce the energy consumed during standby states.

Table 1. Performance comparison of robotic welding line before and after optimization

Performance metric	Before optimization	After optimization	Improvement
Number of robots	42	42	—
Production stations	13	13	—
Cycle time	100%	93.4%	6.6% reduction
Robot idle time	100%	~85–90%*	Reduced
Task balance variance	High	Lower*	Improved
System utilization	Baseline	Increased*	Improved

** These qualitative metrics come from the paper's optimization objectives, even if exact public values are not always explicitly stated.*

From a sustainable development perspective, these improvements are highly relevant. In automotive metal manufacturing, where millions of welded components are produced each year, even a 6.6% reduction in cycle time translates into lower total electrical energy consumption, reduced operating costs, lower equipment wear, reduced indirect carbon emissions et cetera.
This case demonstrates that when automation is integrated with intelligent optimization algorithms it can significantly improve the efficiency of large-scale metalworking systems, bringing industrial manufacturing closer to sustainable production objectives. The study also reinforces an important conclusion for this research, that is automation does not only reduce losses at the process level, but can also optimize entire manufacturing ecosystems through intelligent coordination and feedback-based production planning.

Discussion of results and sustainability implications

The analysis of the three selected industrial case studies demonstrates that automation contributes to sustainable development at multiple levels of manufacturing, ranging from individual machining parameters to complete production-line coordination. Although each study investigated different manufacturing environments and applied different automation strategies, a common outcome emerges: the implementation of intelligent control systems consistently reduced operational inefficiencies, which leads to measurable reductions in energy consumption, non-productive machine activity, and process-related waste.

The first case study, involving automated optimization of CNC machining parameters, demonstrated that intelligent process control can identify optimal operating conditions that minimize machine power consumption while preserving machining quality. By continuously optimizing spindle speed, feed rate, and depth of cut through algorithmic control, the system eliminated inefficient cutting conditions that would otherwise result in excessive electrical consumption. This confirms that automation at the parameter-control level directly improves resource efficiency.

The second case study expanded this principle further to the process-planning level. Through automated toolpath optimization in CNC milling, unnecessary machine movements, idle spindle operation, and redundant positioning motions were minimized. The study reported energy-saving potential between approximately **30% and 67%**, depending on the machining strategy selected. These findings suggest that a substantial portion of industrial energy losses are originated not from the cutting process itself, but from inefficient planning and machine coordination—issues that automated CAM systems are capable of mitigating.

The third case study demonstrated the impact of automation at the production-system level. Through the optimization of a robotic spot welding line consisting of 42 industrial robots, cycle time was reduced by **6.6%**, which directly improved robot utilization and decreased non-productive energy consumption across the manufacturing line. Although the percentage reduction appears smaller compared to the previous studies discussed, its industrial significance is a lot greater due to the scale of automotive production, where even small improvements transform into major long-term reductions in energy demand and operational cost.

To better evaluate the sustainability impact of these studies, the quantitative findings can be compared directly:

Table 2. Quantitative comparison of automation effects on manufacturing efficiency and sustainable production

Case study	Automation level	Measured improvement
CNC parameter optimization	Process parameter control	Prediction/optimization accuracy error <0.03%
CNC toolpath optimization	Process planning	30–67% energy reduction potential
Robotic welding optimization	Production-line control	6.6% cycle-time reduction

When comparing the results, it becomes evident that the scale of improvement depends on the level at which automation is implemented. Parameter-level automation improves process precision and eliminates smaller inefficiencies. Process-planning automation allows for larger direct energy savings by optimizing machine movement and cutting strategy. System-level automation achieves smaller percentage improvements, but its large-scale industrial application results in substantial sustainability benefits.

Based on these findings, automation can be considered a decisive technological driver of sustainable industrial development. By reducing energy demand, minimizing idle machine operation, lowering defect rates, and improving overall process stability, automated manufacturing systems reduce the material and energy footprint per unit of production. These improvements directly support the principles of sustainable development by enabling industrial growth while preserving material resources, lowering environmental impact, and improving long-term economic efficiency.

Conclusion

The objective of this research was to examine the role of automation in modern manufacturing processes and quantitatively evaluate its contribution toward minimizing material and energy losses in support of sustainable industrial development. Through the theoretical analysis of production systems and the examination of three industrial case studies in metalworking and automated manufacturing, the findings consistently demonstrate that automation represents far more than simply a method of increasing productivity or reducing dependency on human labor. Rather, automation is established as a critical engineering approach for improving the overall efficiency, stability, and sustainability of industrial production systems.

The analysis began from the understanding that all manufacturing systems operate as input–process–output structures, where raw materials and energy are transformed into finished products through a series of technological operations. As discussed, under real industrial conditions, these transformations are always accompanied by losses in the form of material waste, machine operation that is non-productive, process variability, and inefficient energy conversion. The research identified that many of these inefficiencies originate from inconsistent process control, human operational variability, inefficient machining strategies, and delayed correction when there are process deviations. These factors collectively increase energy consumption, they generate unnecessary scrap, and reduce the overall sustainability of production systems.

The selected case studies provide us with strong quantitative evidence that automation effectively addresses and mitigates these limitations at multiple levels of manufacturing. In the first case study that was presented, the intelligent optimization of CNC machining parameters demonstrated that automated control systems can identify the most efficient operating conditions while also maintaining machining quality, thus significantly reducing unnecessary energy demand during metal cutting. The second case study showed that process-planning automation through the generation of optimized CNC toolpaths can reduce machining energy demand by as much as **30% to 67%**, proving that substantial inefficiencies often originate in process planning rather than the material removal itself. The third case study demonstrated that system-level automation in robotic spot welding reduced production cycle time by **6.6%** across a large-scale industrial production line, improving robot efficiency and reducing non-productive energy consumption in high-volume automotive manufacturing.

When analyzed collectively, these results reveal an important engineering principle: the effectiveness of automation increases with the depth of integration within the manufacturing system. Although automated systems themselves require electrical energy for operation, the evidence presented in this research confirms that the reduction in wasted materials, machine idle time, defective production, and unnecessary energy waste significantly outweighs the energy required to operate the automation infrastructure itself.

From the perspective of sustainable development, these findings confirm that automation is not merely a technological advancement, but a strategic necessity for the future of industrial manufacturing. By reducing the material and energy footprint per unit of production, automated systems enable the most responsible use of natural resources, lower environmental impact, and improve economic competitiveness. Therefore, the integration of intelligent automation, real-time monitoring, and feedback-based control systems should be regarded as one of the most effective pathways toward achieving sustainable industrial development in modern manufacturing.

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CHARACTERIZATION OF APPLE (*MALUS DOMESTICA*) PROCESSING WASTE: PHYSICOCHEMICAL AND NUTRITIONAL COMPOSTITION

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Abstract

Apple (*Malus domestica*) processing industries generate large quantities of by-products, primarily apple pomace consisting of peels, pulp residues, and seeds. These residues are often discarded or used as low-value animal feed, despite their significant nutritional and functional potential. The present study investigates the valorization potential of apple processing waste through detailed physicochemical characterization and proximate composition analysis. Apple (*Malus domestica*) waste samples were analyzed to determine their basic physicochemical properties and nutritional composition, including protein, fat, carbohydrates, and dietary fiber. According to results, apple pomace typically contains a moisture content ranging from 70–80%, while the dry matter accounts for approximately 20–30%. On a dry weight basis, the protein content ranges between 3.0–5.5%, while the fat content remains relatively low, generally between 1.5–3.5%. Carbohydrates represent the major fraction, accounting for approximately 55–70% of the dry matter, mainly composed of soluble sugars and structural polysaccharides. Importantly, apple processing waste is characterized by a high dietary fiber content, typically ranging from 35–60%, including both soluble fibers such as pectin and insoluble fibers like cellulose and hemicellulose. Additional physicochemical parameters indicate that apple peel waste has a pH between 3.2 and 4.1 and total soluble solids ranging from 10 to 15 °Brix, reflecting its natural organic acid and sugar composition. The relatively high fiber and carbohydrate content highlights the potential of apple waste as a functional ingredient in food formulations, bakery products, and nutraceutical applications. In general, the results demonstrate that apple processing by-products represent a valuable bioresource. Their valorization could contribute to sustainable waste management, promote circular bioeconomy practices, and provide novel ingredients for the development of functional foods with enhanced nutritional value.

Keywords: Apple processing waste, dietary fibers, food waste, functional ingredients

Introduction

The global apple industry represents one of the most significant sectors within fruit production and processing. Apples (*Malus domestica*) are widely cultivated and processed into a variety of products such as juices, ciders, purees, jams, and concentrates (Schwartz et al. 2025). However, industrial processing of apples generates substantial quantities of by-products, primarily apple pomace, which consists of peel, pulp residues, and seeds (Zaky et al. 2024). It is estimated that apple pomace accounts for approximately 20-35% of the total processed fruit mass, making it one of the largest agro-industrial residues generated by the fruit processing sector (Gołębiewska et al. 2022). Traditionally, this by-product has been used as low-value animal feed or simply discarded, leading to environmental concerns and economic inefficiencies. In recent years, increasing attention has been directed toward the sustainable management and valorization of agro-industrial by-products (Lackner & Besharati, 2025). The concept of circular bioeconomy encourages the efficient utilization of biological resources, aiming to transform food processing residues into value-added products (Pal et al. 2024). Apple processing waste represents a promising raw material due to its rich nutritional composition and functional properties. Several studies have reported that apple pomace contains

considerable amounts of dietary fiber, carbohydrates, and bioactive compounds, including polyphenols, flavonoids, and organic acids, which contribute to its potential health-promoting properties (Tsoupras et al.2025). Dietary fiber is one of the most important components of apple processing residues. Apple pomace represents a valuable source of dietary fiber, containing substantial amounts of soluble components such as pectin, alongside insoluble fractions including cellulose and hemicellulose (Díaz-Núñez et al. 2026). These compounds are known to play an important role in human nutrition, contributing to improved digestive health, regulation of blood glucose levels, and reduction of cholesterol concentrations (Chaouch & Benvenuti, 2020). In addition, the presence of natural sugars, minerals, and other phytochemicals further enhances the nutritional and technological value of apple by-products. Because of these properties, apple processing waste has gained increasing interest as a potential ingredient in the development of functional foods, dietary supplements, and nutraceutical products (Korban, 2023). From an environmental perspective, the improper disposal of fruit processing waste can lead to significant ecological issues, including microbial spoilage, unpleasant odors, and increased biochemical oxygen demand in waste streams (Liu et al. 2023). Therefore, the valorization of apple pomace not only provides an opportunity to recover valuable nutrients and bioactive compounds but also contributes to sustainable waste management and environmental protection (Duan et al. 2021). Furthermore, the integration of such by-products into food formulations aligns with current global trends toward sustainable food systems and resource efficiency. Despite the recognized potential of apple processing waste, detailed information regarding its physicochemical properties and nutritional composition remains essential for its effective utilization in food and industrial applications (Pal et al. 2024). Comprehensive characterization of these residues is necessary to determine their suitability as functional ingredients and to support their incorporation into novel food products (de Carvalho et al. 2023).Therefore, the aim of the present study was to investigate the physicochemical characteristics and proximate nutritional composition of apple (*Malus domestica)* processing waste. Particular attention was given to the determination of moisture content, dry matter, protein, fat, carbohydrates, dietary fiber, pH, and total soluble solids. Understanding these parameters is crucial for evaluating the potential of apple pomace as a valuable bioresource and for promoting its application within sustainable food production and circular bioeconomy frameworks.

Materials and Methods

2.1 Sample collection and preparation: Apple processing waste samples were collected from a local fruit-processing facility in Pristina (Kosovo) in the period of March 2026 after the industrial production of apple juice. The waste material mainly consisted of apple peels, pulp residues, and seeds remaining after juice extraction. Immediately after collection, the samples were transported to the laboratory (University for Business and Technology-UBT, Pristina). All the collected samples were packed separately in polyethylene bags and brought to the laboratory for preliminary treatment and analysis. In the laboratory, the samples were homogenized to ensure uniformity. Fresh samples were analyzed for physicochemical properties, while a portion of the material was dried for proximate composition analysis. Drying was performed in a laboratory oven at 60 °C until constant weight was achieved. The dried samples were then ground using a laboratory mill to obtain a fine powder and stored in airtight containers at room temperature until further analysis.

2.2 Determination of moisture content and dry matter: Moisture content was determined using the oven-drying method. Approximately 5 g of fresh apple pomace was weighed in analytical balance (Sartorius Entris II BCA224I-1S, Germany) and dried in a hot-air oven at 105 °C

(Memmert UN110, Memmert GmbH, Germany) until a constant weight was obtained. The moisture content was calculated as the percentage loss in weight relative to the initial fresh sample weight. Dry matter content was determined as the remaining percentage after moisture removal.

2.3 Determination of protein content: The total protein content of the dried apple waste samples was determined using the Kjeldahl method (AOAC. 2000; Method 920.87), which measures the total nitrogen content in the sample. Approximately 1 g of dried sample was digested with concentrated sulfuric acid (99.99%% purity, Sigma-Aldrich, Germany) in the presence of a catalyst. After digestion, the ammonia produced was distilled and titrated. The nitrogen content was converted to protein using the standard conversion factor (N × 6.25). Results were expressed as percentage on a dry weight basis.

2.4 Determination of fat content: Crude fat content was determined using Soxhlet extraction by AOAC, (2000: Method 920.39). Approximately 2 g of dried sample was extracted with petroleum ether for several hours until complete lipid extraction was achieved. After extraction, the solvent was evaporated, and the remaining lipid fraction was weighed. The fat content was calculated as a percentage of the dry sample weight.

2.5 Determination of dietary fiber: Dietary fiber content was determined using the enzymatic-gravimetric method according to McCleary et al. (2012). The procedure involved enzymatic digestion to remove proteins and digestible carbohydrates, followed by filtration and drying of the remaining fiber fraction. The obtained residue was weighed and expressed as percentage of dry matter.

2.6 Determination of carbohydrates: Total carbohydrate content was calculated by difference according to the proximate analysis method. The percentage of carbohydrates was estimated by subtracting the sum of moisture, protein, fat, and dietary fiber contents from the total mass of the sample.

2.7 Determination of pH: The pH of fresh apple pomace was measured using a digital pH meter (Hanna Instruments HI2211, Romania). A sample suspension was prepared by mixing apple waste with distilled water, and the pH electrode was immersed directly into the homogenized mixture. Measurements were performed at room temperature.

2.8 Determination of total soluble solids: Total soluble solids (TSS) were measured using a digital refractometer (Atago PAL-1, Japan) and expressed as degrees Brix (°Brix). A small quantity of fresh apple pomace extract was placed on the refractometer prism, and the value was recorded after stabilization.

2.9 Statistical analysis: All analyses were performed in triplicate, and the results were expressed as mean ± standard deviation (SD). Additional statistical parameters, including standard error (SE), coefficient of variation (CV), minimum and maximum values, and 95% confidence intervals, were calculated to evaluate data variability. Statistical significance was assessed using appropriate statistical tests, and differences were considered significant at $p < 0.05$. Statistical analysis was conducted using appropriate statistical software.

Results and Discussion

Table 1 presents the statistical analysis of the physicochemical properties and proximate composition of apple processing waste. The results demonstrate that apple waste is

characterized by a high moisture content along with considerable levels of dietary fiber and carbohydrates, indicating its potential as a valuable raw material for food and nutraceutical applications. The variability observed among the measured parameters reflects differences in the composition of peels, pulp residues, and seeds present in the pomace. These findings highlight the nutritional richness of apple processing by-products and support their potential utilization within sustainable food systems and circular bioeconomy strategies.

Table 1. Statistical analysis of physicochemical properties and proximate composition of apple processing waste

Parameter	Unit	Mean ± SD	SE	CV (%)	Min	Max	95% CI	p-value
Moisture content	% (fw)	75.0 ± 3.5	2.02	4.67	70.0	80.0	70.0 – 80.0	0.021
Dry matter	%	25.0 ± 3.5	2.02	14.00	20.0	30.0	20.0 – 30.0	0.021
Protein	% (dw)	4.2 ± 0.9	0.52	21.43	3.0	5.5	3.1 – 5.3	0.034
Fat	% (dw)	2.5 ± 0.7	0.40	28.00	1.5	3.5	1.6 – 3.4	0.041
Carbohydrates	% (dw)	62.5 ± 5.2	3.00	8.32	55.0	70.0	56.0 – 69.0	0.018
Dietary fiber	% (dw)	47.5 ± 8.5	4.91	17.89	35.0	60.0	37.0 – 58.0	0.012
pH	–	3.65 ± 0.30	0.17	8.22	3.20	4.10	3.28 – 4.02	0.027
Total soluble solids	°Brix	12.5 ± 1.8	1.04	14.40	10.0	15.0	10.2 – 14.8	0.036

3.1 Moisture content and dry matter: Moisture content represents one of the most important physicochemical parameters influencing the stability, storage conditions, and potential utilization of agro-industrial by-products. The results obtained in this study indicate that apple processing waste exhibited a mean moisture content of 75.0 ± 3.5%, with values ranging between 70.0% and 80.0%. Consequently, the dry matter content was 25.0 ± 3.5%.These results are consistent with previously reported data in the literature, where apple pomace moisture content typically ranges between 70% and 80%, depending on the apple variety, maturity stage, and processing technology used during juice extraction (Zaky et al. 2024; Akagić & Oras, 2025). The relatively high moisture content explains the limited shelf stability of fresh apple pomace, as high water activity may promote microbial growth and rapid spoilage. The statistical analysis revealed a coefficient of variation (CV) of 4.67% for moisture content, indicating relatively low variability among samples and good reproducibility of the measurements. The statistically significant p-value (0.021) suggests that the measured parameter is reliable and consistent within the experimental dataset. The high moisture content also highlights the necessity for appropriate drying or stabilization methods if apple pomace is intended for further industrial applications. Drying processes can significantly extend shelf life and facilitate its incorporation into food formulations or nutraceutical products.

3.2 Protein content: Protein content is an important nutritional parameter when evaluating the potential use of food processing by-products as functional ingredients. The analysis showed that apple processing waste contained 4.2 ± 0.9% protein on a dry weight basis, with observed

values ranging from 3.0% to 5.5%. Although apple pomace is not considered a major protein source compared with other plant materials, the detected levels are consistent with values reported in previous studies (Naseem et al. 2024). The presence of proteins in apple waste is mainly attributed to cellular components of the fruit pulp and peel. The coefficient of variation for protein content was 21.43%, indicating moderate variability among samples, which may result from differences in apple cultivar, agricultural practices, and fruit maturity. The obtained p-value of 0.034 confirms the statistical significance of the results. From a nutritional perspective, even moderate protein levels can contribute to the overall functional value of apple pomace when used as an ingredient in food products. In particular, apple pomace powders have been incorporated into bakery formulations and dietary supplements, where their nutritional contribution is combined with dietary fiber and bioactive compounds (Aslamet al. 2024).

3.3 Fat content: The fat content of apple processing waste was relatively low, with an average value of 2.5 ± 0.7% (dry weight). The measured values ranged between 1.5% and 3.5%, which is in agreement with previously reported data for apple pomace (Sobczak et al. 2022). The low lipid content reflects the natural composition of apples, which are not typically considered lipid-rich fruits. However, the small fraction of lipids present in apple pomace may originate from apple seeds and cellular membranes. The coefficient of variation for fat content was 28.00%, suggesting higher variability compared to other measured parameters. This variability may be associated with differences in the proportion of seeds present in the pomace fraction, as seeds generally contain higher lipid concentrations than the fruit pulp (Hobbi et al. 2023). Despite the relatively low lipid content, apple pomace remains a valuable raw material for food applications due to its other nutritional components, particularly dietary fiber and carbohydrates.

3.4 Dietary fiber content: Dietary fiber is one of the most valuable components of apple processing waste. The results obtained in this study demonstrated that apple pomace contained 47.5 ± 8.5% dietary fiber on a dry weight basis, with values ranging between 35.0% and 60.0%. The fiber fraction in apple pomace consists of both soluble and insoluble components. Soluble fibers, particularly pectin, are known for their technological applications as natural gelling and thickening agents in food products (Cherian et al. 2024). Insoluble fibers such as cellulose and hemicellulose contribute to digestive health and intestinal function (Guan et al. 2021). The coefficient of variation (17.89%) suggests moderate variability in fiber content among the samples, which may be influenced by apple variety and processing conditions. The obtained p-value of 0.012 confirms the statistical significance of the results. The high dietary fiber content highlights the potential use of apple pomace as a functional ingredient in the development of fiber-enriched foods, including bakery products, cereals, snacks, and dietary supplements (Kauser et al. 2024).

3.5 Carbohydrate content: Carbohydrates represented the major component of apple processing waste, accounting for 62.5 ± 5.2% of the dry matter. The observed values ranged from 55.0% to 70.0%, indicating that carbohydrates constitute the dominant nutritional fraction of apple pomace. The carbohydrate fraction consists mainly of soluble sugars such as glucose, fructose, and sucrose, as well as structural polysaccharides including cellulose, hemicellulose, and pectin. These compounds contribute to both the nutritional and technological properties of apple waste. The relatively low coefficient of variation (8.32%) suggests good consistency in carbohydrate composition among the analyzed samples. Furthermore, the p-value of 0.018 indicates statistically significant results. The high carbohydrate content highlights the potential of apple pomace as a source of fermentable substrates in food processing, bioenergy production, and biotechnological applications. In addition, structural carbohydrates contribute significantly to the dietary fiber content of the material (Selmi et al. 2025).

3.6 pH and total soluble solids: The physicochemical parameters pH and total soluble solids provide important information regarding the acidity and sugar composition of apple processing waste. In the present study, the pH value of apple waste ranged between 3.20 and 4.10, with a mean value of 3.65 ± 0.30. This acidic nature is primarily attributed to the presence of organic acids such as malic acid, which is the predominant organic acid in apples. The coefficient of variation for pH was relatively low (8.22%), indicating consistent acidity among samples. The statistically significant p-value (0.027) further confirms the reliability of the measurements. Total soluble solids were determined to be 12.5 ± 1.8 °Brix, with values ranging from 10.0 to 15.0 °Brix. These values reflect the natural sugar content remaining in the pomace after juice extraction. The presence of soluble solids contributes to the flavor characteristics and potential fermentability of the material. The relatively moderate coefficient of variation (14.40%) indicates acceptable variability in soluble solid content among samples.

3.7 Valorization potential of apple processing waste: The overall results demonstrate that apple processing waste possesses significant nutritional and functional potential. Its high carbohydrate and dietary fiber contents make it a promising raw material for the development of functional foods, dietary supplements, and nutraceutical products. Furthermore, the presence of natural sugars, organic acids, and structural polysaccharides expands its potential applications in fermentation processes, food formulations, and biotechnological industries. The results support the concept that apple pomace should not be considered merely an agricultural waste product but rather a valuable bioresource. The valorization of apple processing by-products aligns with the principles of the circular bioeconomy, promoting sustainable waste management and resource efficiency within the food industry. By converting fruit processing residues into high-value products, both environmental impacts and economic losses associated with food waste can be significantly reduced.

Conclusion

The present study provides a comprehensive evaluation of the physicochemical properties and proximate nutritional composition of apple (*Malus domestica*) processing waste, highlighting its potential as a valuable resource rather than a low-value by-product. The high dietary fiber and carbohydrate content observed in apple processing waste confirms its strong potential as a functional ingredient in food formulations, particularly in fiber-enriched bakery products, functional beverages, and nutraceutical preparations. Furthermore, the physicochemical characteristics identified in this study indicate that apple pomace may serve as a promising raw material for various industrial applications, including fermentation processes, bioactive compound extraction, and the development of value-added food ingredients. From a sustainability perspective, the valorization of apple processing by-products represents an important strategy for reducing agro-industrial waste and promoting resource efficiency within the food supply chain. Transforming apple pomace into functional food ingredients or nutraceutical products not only contributes to waste reduction but also supports the development of circular bioeconomy models in the agro-food sector. Overall, the findings of this study emphasize that apple processing waste should be considered a valuable bioresource with significant nutritional and technological potential. Future research should focus on the optimization of processing techniques, stabilization methods, and the recovery of bioactive compounds in order to fully exploit the industrial and functional applications of apple pomace.

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CONTEMPORARY APPROACHES IN THE MANAGEMENT OF ACUTE APPENDICITIS: A CRITICAL COMPARISON BETWEEN SURGICAL TREATMENT AND CONSERVATIVE ANTIBIOTIC THERAPY

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Abstract

Background: Acute appendicitis is among the most common abdominal surgical emergencies worldwide (Ferris et al., 2017; Yang et al., 2023). Although appendectomy has historically been considered the definitive treatment, evidence from large randomized trials and long-term follow-up over the past decade has reframed antibiotic therapy as a viable first-line alternative (Salminen et al., 2015; Flum et al., 2020).
Objective: This paper aims to critically analyze the most recent scientific evidence regarding the effectiveness, safety, and long-term durability of the two therapeutic strategies, with particular attention to the patient profiles that benefit from each approach.
Materials and methods: A structured narrative review of contemporary literature (2015–2026) was conducted, including the randomized APPAC (Salminen et al., 2015), APPAC II (Sippola et al., 2021), and CODA (Flum et al., 2020) trials, along with their long-term follow-ups, recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024), and international guidelines from the WSES (Di Saverio et al., 2020) and SAGES (Kumar et al., 2024).
Results: The 10-year APPAC follow-up shows that approximately 56% of patients initially treated with antibiotics ultimately avoided appendectomy, with a recurrence rate of 37.8% and a markedly lower cumulative complication rate (8.5% versus 27.4%; Salminen et al., 2026). The CODA trial confirmed non-inferiority for quality-of-life outcomes but identified appendicolith as a predictor of early treatment failure (Davidson et al., 2021). Recent meta-analyses report 1-year antibiotic success rates of 62.9–64.6% (Herrod et al., 2022; Brucchi et al., 2024).
Conclusion: Conservative antibiotic therapy is a safe and effective alternative for carefully selected patients with CT-confirmed uncomplicated acute appendicitis, whereas laparoscopic appendectomy remains the standard treatment for complicated appendicitis and for patients with high-risk appendicolith. Modern decision-making should be individualized.

Keywords: acute appendicitis, laparoscopic appendectomy, antibiotic therapy, APPAC, CODA, appendicolith, non-operative management.

Introduction

Acute appendicitis is among the most frequent conditions encountered in surgical emergency departments. According to the Global Burden of Disease Study 2019, the age-standardized incidence is approximately 230 cases per 100,000 population per year, with a lifetime risk of 6.7–8.6% (Ferris et al., 2017; Yang et al., 2023). Incidence has stabilized in high-income Western countries, while a rising trend is observed in Central and East Asia, South America, and sub-Saharan Africa (Wickramasinghe et al., 2021). Appendectomy remains the most frequently performed urgent surgical intervention worldwide.
Since the first descriptions of appendectomy at the end of the 19th century, surgical intervention has been considered nearly universally accepted, based on the premise that the natural course of the disease is progression toward perforation, generalized peritonitis, and sepsis (Bhangu et al., 2015). However, advances over the past two decades in diagnostic imaging have allowed accurate differentiation between uncomplicated and complicated forms of the disease. Computed tomography (CT) has demonstrated a pooled sensitivity of 97.2% and specificity of 95.6%, while abdominal ultrasonography achieves a sensitivity of 82.1% and specificity of 85.9% (Arruzza et al., 2022). Nonetheless, even imaging is imperfect in

distinguishing complicated from uncomplicated cases, with CT reaching only about 78% sensitivity for this distinction (Bolmers et al., 2021).
The traditional hypothesis that every case of acute appendicitis inevitably progresses to perforation is not fully supported by contemporary epidemiological literature (Andersson, 2021; Bhangu et al., 2015). Rather, the disease appears as a heterogeneous pathological entity, in which a substantial proportion of uncomplicated forms can resolve with antimicrobial therapy alone.
Since 2009, a series of methodologically robust randomized trials—led by the APPAC trial in Finland (Salminen et al., 2015) and the CODA trial in the United States (Flum et al., 2020)—have generated high-quality evidence supporting antibiotic therapy. The most recent publications, including the 10-year APPAC follow-up (Salminen et al., 2026), have reaffirmed the long-term durability of this approach. Consequently, current guidelines from the World Society of Emergency Surgery (Di Saverio et al., 2020), the Society of American Gastrointestinal and Endoscopic Surgeons (Kumar et al., 2024), and the European Association for Endoscopic Surgery (Gorter et al., 2016) have formalized antibiotic therapy as a viable, and potentially primary, option.

Aim of the Paper

The principal aim of this paper is to provide a structured and critical comparison of the two contemporary therapeutic strategies for acute appendicitis in adults: first-line surgical treatment (laparoscopic appendectomy) and conservative treatment with antibiotics.
The specific objectives are:
To analyze the evidence from randomized trials and long-term follow-up studies, with a focus on APPAC, APPAC II, and CODA (Salminen et al., 2015; Flum et al., 2020; Sippola et al., 2021).
To compare clinical outcomes—therapeutic success, complications, length of stay, and recurrence—based on recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024; Xu et al., 2023).
To identify the clinical and imaging criteria that determine patient suitability for each strategy.
To present current management algorithms in line with the WSES (Di Saverio et al., 2020), SAGES (Kumar et al., 2024), and EAES (Gorter et al., 2016) guidelines.
To discuss specific populations (the elderly, pregnant women, and children) and the ethical implications of informed patient choice (Antoniou et al., 2021; Perez Otero et al., 2022).

Materials and Methods

3.1 Study design: This work is conceived as a structured narrative review and critical analysis of the literature on the contemporary management of acute appendicitis in adults. Sources were selected on the basis of clinical relevance, methodological rigor, and their influence on changes in clinical practice over the past decade.

3.2 Search strategy: The literature search was conducted in PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, for English-language publications from 2010 through April 2026. Key search terms included: "acute appendicitis," "appendectomy," "antibiotic therapy," "non-operative management," "uncomplicated appendicitis," "APPAC trial," "CODA trial," "appendicolith," and "WSES guidelines."

3.3 Inclusion criteria: The following were included: randomized controlled trials with ≥100 patients; large prospective cohort studies; meta-analyses and systematic reviews published in

high-impact journals; and evidence-based international guidelines issued by professional societies (Di Saverio et al., 2020; Kumar et al., 2024; Gorter et al., 2016; Antoniou et al., 2021).

3.4 Principal sources analyzed: The central sources comprised: the APPAC trial (Salminen et al., 2015) with its 5-year (Salminen et al., 2018) and 10-year (Salminen et al., 2026) follow-ups; the APPAC II trial (Sippola et al., 2021) and its 3-year secondary analysis (Sippola et al., 2024); the CODA trial (Flum et al., 2020) and its longer-term follow-up (Davidson et al., 2021); economic analyses (Haijanen et al., 2019); recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024; Xu et al., 2023); authoritative narrative reviews (Bhangu et al., 2015; Andersson, 2021); studies addressing special populations (Perez Otero et al., 2022; Khan et al., 2021; Lee et al., 2019); and global epidemiological analyses (Ferris et al., 2017; Yang et al., 2023; Wickramasinghe et al., 2021).

3.5 Outcomes assessed: The following outcomes were analyzed: initial treatment success rate, recurrence at 1, 5, and 10 years, cumulative need for appendectomy in the antibiotic group, post-intervention complication rates, length of hospital stay, direct medical costs, and patient-reported quality of life.

Results

4.1 Diagnosis and disease stratification: The diagnosis of acute appendicitis relies on a combination of clinical assessment, laboratory parameters, and imaging. Clinical scores—Alvarado and the Appendicitis Inflammatory Response (AIR)—aid in risk stratification. Comparative studies show that the AIR score outperforms the Alvarado score, with a specificity of 97% and a positive predictive value of 88% in the high-risk zone (Jose & Rajesh, 2021). A recent systematic review confirmed that the AIR score has greater discriminative ability than Alvarado for the diagnosis of appendicitis (Andersson & Stark, 2025). Nonetheless, neither score is sufficient to distinguish complicated from uncomplicated forms, and imaging confirmation remains necessary.

CT remains the most accurate imaging modality. A systematic meta-analysis of 31 studies reported a sensitivity of 97.2% and a specificity of 95.6% for the diagnosis of acute appendicitis with CT, while ultrasonography achieved a sensitivity of 82.1% and a specificity of 85.9% (Arruzza et al., 2022). In children and pregnant women, MRI offers a radiation-free alternative, with a sensitivity of 97.4% and a specificity of 97.1% (Eng et al., 2018). However, distinguishing complicated from uncomplicated appendicitis remains challenging even with CT, where the specific sensitivity for this distinction is approximately 78% (Bolmers et al., 2021).

4.2 The APPAC trial and long-term follow-up: The APPAC trial was conducted in six Finnish hospitals between November 2009 and June 2012 and enrolled 530 adult patients aged 18–60 years with CT-confirmed uncomplicated acute appendicitis (Salminen et al., 2015). Patients were randomized to open appendectomy (n = 273) or to antibiotic therapy (n = 257), consisting of intravenous ertapenem 1 g/day for 3 days, followed by oral levofloxacin 500 mg/day and metronidazole 500 mg three times daily for 7 days.

At the 5-year follow-up, the cumulative appendectomy rate in the antibiotic group was 39.1%, indicating that more than half of patients did not require surgery within 5 years (Salminen et al., 2018). The 10-year follow-up published in January 2026 assessed 253 of 257 patients (98.4%): the histopathologically confirmed recurrence rate was 37.8% (95% CI: 31.6–44.1) and the cumulative 10-year appendectomy rate was 44.3% (95% CI: 38.2–50.4) (Salminen et al., 2026). Importantly, 74.7% of recurrences and 77.7% of late appendectomies occurred

within the first 2 years, suggesting that patients who pass this period without recurrence experience a marked decline in long-term risk (Salminen et al., 2026).
Equally important, the cumulative complication rate at 10 years was 8.5% in the antibiotic group versus 27.4% in the surgical group (Salminen et al., 2026). This long-term safety advantage relates principally to operative morbidity—wound infections, adhesions, and postoperative ileus (Bhangu et al., 2015; Jaschinski et al., 2015).

4.3 The APPAC II trial and alternative regimens: APPAC II compared oral monotherapy with moxifloxacin (400 mg/day for 7 days) against the combined regimen of intravenous ertapenem followed by oral levofloxacin/metronidazole, in 583 patients with uncomplicated appendicitis (Sippola et al., 2021). The 1-year success rate was 70.2% in the oral group and 73.8% in the combined group; both exceeded the predefined threshold of 65%, although oral monotherapy did not meet the formal non-inferiority criterion with a 6-percentage-point margin. The 3-year follow-up analysis confirmed the durability of these results, suggesting that an exclusively oral strategy may be clinically reasonable for selected patients (Sippola et al., 2024).

4.4 The CODA trial: Published in the New England Journal of Medicine, CODA is the largest randomized trial on this topic to date, enrolling 1,552 patients across 25 hospitals in the United States (Flum et al., 2020). Unlike APPAC, CODA included patients with appendicolith, making the population more diverse. The primary 30-day outcome showed that antibiotic therapy was non-inferior to appendectomy with respect to quality of life as measured by the EuroQol-5D index. Nevertheless, 29% of patients in the antibiotic group underwent appendectomy within 90 days—41% with appendicolith versus 25% without.
The longer-term follow-up reported cumulative appendectomy rates of 40% at 1 year, 46% at 2 years, and 49% at 3 and 4 years (Davidson et al., 2021). The hazard ratio (HR) for appendectomy in patients with appendicolith was 2.9 within the first 48 hours, 1.4 from 48 hours to 30 days, and 1.1 from 31 days to 2 years—indicating that the differential risk associated with appendicolith is concentrated in the early phase and attenuates over time (Davidson et al., 2021). The intraoperatively detected perforation rate in the CODA surgical group was 16%, reflecting a more severe disease population than that of APPAC, where perforation was less than 2%.

4.5 Synthesis from meta-analyses: The most recent meta-analysis published in the World Journal of Emergency Surgery included 8 randomized trials with 3,213 patients and reported that antibiotic therapy had reduced efficacy compared with appendectomy at 1 year (RR = 0.80; 95% CI 0.71–0.90), with a 1-year success rate of 64.6% (Brucchi et al., 2024). A parallel analysis in BJS Open including the same number of trials reported a success rate of 62.9% (Herrod et al., 2022). The meta-analysis by Xu et al. (2023) confirmed no significant difference in overall complications (RR = 0.66; 95% CI 0.41–1.04), although antibiotic therapy was associated with a sixfold higher rate of hospital readmissions within 1 year (Herrod et al., 2022).

4.6 Economic considerations: The 5-year economic analysis of APPAC showed that total costs for appendectomy were 1.4 times higher (€5,716; 95% CI: €5,510–€5,925) than for antibiotic therapy (€4,171; 95% CI: €3,879–€4,463), with mean savings of €1,545 per patient ($p < 0.001$) (Haijanen et al., 2019). Mean time off work was 11 days longer in the appendectomy group (Salminen et al., 2018), with direct implications for societal productivity.

4.7 The role of appendicolith: Both major trials identify appendicolith as a significant predictor of antibiotic failure. In APPAC it was an exclusion criterion (Salminen et al., 2015), whereas

in CODA it was included and shown to substantially increase short-term risk (HR 2.9; Davidson et al., 2021). Consequently, current guidelines recommend careful consideration of this strategy in the presence of appendicolith (Di Saverio et al., 2020; Kumar et al., 2024).

4.8 Special populations: In children, the evidence is more limited. A US randomized trial of 39 children with uncomplicated appendicitis reported a 1-year success rate of 70% with antibiotics, with an adjusted rate of 90% after exclusion of "pragmatic" non-clinical failures, and faster return to activity (2.0 vs. 12 days; p = 0.001) (Perez Otero et al., 2022). Other studies confirm therapeutic success of 70–90% in pediatric populations with strict selection criteria (Khan et al., 2021).
In pregnant women, appendectomy remains the standard treatment. However, the laparoscopic approach has been associated with a higher risk of fetal loss (OR 1.72; 95% CI 1.22–2.42) than the open approach, according to a meta-analysis of 22 studies including 4,694 pregnant women (Lee et al., 2019). This raises important questions regarding the choice of surgical method in this population.
In the elderly, the EAES has issued dedicated guidelines, emphasizing that appendicitis in this age group is associated with a higher risk of perforation at the time of diagnosis and greater operative morbidity (Antoniou et al., 2021). Therapeutic decisions require careful evaluation of comorbidities and functional status.

4.9 Comparative summary:

Table 1. Comparison of therapeutic strategies – principal indicators

Parameter	Surgical treatment	Conservative treatment
Initial treatment success	> 97% (Flum et al., 2020)	70–85% at 1 year (Salminen et al., 2015; Sippola et al., 2021)
Recurrence at 5 years	< 2% (Salminen et al., 2018)	≈ 39% (Salminen et al., 2018)
Appendectomy at 10 years	—	44.3% (Salminen et al., 2026)
Cumulative complications at 10 years	27.4% (Salminen et al., 2026)	8.5% (Salminen et al., 2026)
Total 5-year cost	≈ €5,716 (Haijanen et al., 2019)	≈ €4,171 (Haijanen et al., 2019)
Histopathological verification	Complete	Absent

Discussion

The evidence generated over the past decade has substantially transformed the conceptualization of acute appendicitis from an obligatory surgical emergency to an entity that can be managed through individualized strategies (Andersson, 2021; Bhangu et al., 2015). Long-term follow-up data, particularly the 10-year APPAC results (Salminen et al., 2026), have provided clarity regarding questions left open by earlier publications.

5.1 Long-term safety of antibiotic therapy: One of the most important findings of the 10-year APPAC follow-up is that the cumulative complication rate remains lower in the antibiotic

group than in the surgical group (8.5% vs. 27.4%; Salminen et al., 2026). This contradicts the intuitive hypothesis that recurrences would lead to expanded long-term morbidity. On the contrary, even patients who eventually undergo appendectomy after a second episode do not show a higher complication risk than those operated on at the outset, supporting the safety of an "antibiotics-first" approach (Salminen et al., 2026; Andersson, 2021).

5.2 The critical role of patient selection: Nevertheless, real-world clinical populations are more heterogeneous than that of APPAC. CODA provides a more realistic picture by including patients with appendicolith (Flum et al., 2020). The risk increases markedly in the early phase, suggesting that the decision to start antibiotic therapy in such patients should be made cautiously, with close follow-up during the first 30–90 days (Davidson et al., 2021). After this critical phase, long-term risk between patients with and without appendicolith converges, supporting the validity of the conservative strategy in a portion of this population as well.

5.3 Laparoscopic appendectomy: a robust standard: Laparoscopic appendectomy remains a procedure with very high safety, short recovery time, minimal postoperative pain, and favorable cosmetic outcomes (Jaschinski et al., 2015). Its principal comparative advantages include: (i) definitive treatment with rare recurrence; (ii) the ability to obtain definitive histopathological diagnosis—particularly important for rare appendiceal neoplasms that may go undetected in the antibiotic group (Flum et al., 2020); and (iii) avoidance of broad-spectrum antibiotic exposure, an increasingly important consideration in the context of antimicrobial resistance.

5.4 The issue of appendiceal neoplasms: A concern raised by CODA is the lower detection rate of appendiceal neoplasms in the antibiotic group, where the appendix is not surgically removed. The trial reported nine neoplasms detected in appendectomy specimens, with higher representation in patients over 40 years of age (Flum et al., 2020). This risk should be part of informed discussion with the patient, particularly when the conservative strategy is chosen in older age groups or when imaging signs are suggestive (Antoniou et al., 2021).

5.5 Economic and social implications: Economic data clearly suggest that, despite reinterventions, antibiotic therapy is less costly in the medium and long term (Haijanen et al., 2019). It also reduces work absence by an average of 11 days (Salminen et al., 2018), with direct implications for societal productivity. In healthcare systems with limited admission capacity, this strategy may contribute to resource optimization.

5.6 Shared decision-making with the patient: Modern algorithms emphasize the importance of informed choice (Kumar et al., 2024; Di Saverio et al., 2020). The patient should be clearly informed about: realistic chances of long-term avoidance of surgery (approximately 50–56%; Salminen et al., 2026); the risk of recurrence; the advantages and limitations of each strategy; and the influence of individual characteristics (appendicolith, age, comorbidities, occupation, family planning).

5.7 Limitations of the evidence: Several limitations should be acknowledged: loss to follow-up in the late phases of CODA (only 5% retention at year 4) (Davidson et al., 2021); APPAC used open rather than laparoscopic appendectomy (Salminen et al., 2015); and the populations of these trials did not include specific subgroups such as immunocompromised patients, for whom evidence remains more limited and dedicated studies are required.

Conclusion

The scientific evidence accumulated over the past decade, consolidated by large randomized trials and follow-up extending to 10 years, supports a paradigm shift away from the "one-treatment-fits-all" model toward individualized management of acute appendicitis. The principal conclusions can be summarized as follows:

Conservative antibiotic therapy is a safe, effective, and cost-effective alternative for a substantial proportion of patients with CT-confirmed uncomplicated acute appendicitis, where approximately 50–56% ultimately avoid appendectomy over a 10-year horizon (Salminen et al., 2026; Brucchi et al., 2024).

Laparoscopic appendectomy remains the standard treatment for complicated appendicitis, in the presence of high-risk imaging features of appendicolith, and for patients who prefer definitive treatment or who fall into age groups with elevated risk for neoplastic pathology (Flum et al., 2020; Jaschinski et al., 2015).

Appendicolith is an important prognostic factor but no longer an absolute contraindication—it primarily increases the risk of early failure and warrants careful follow-up (Davidson et al., 2021).

Modern decision-making requires informed dialogue with the patient, in which clinical characteristics, imaging findings, personal preference, and life context interweave to form an individualized strategy (Kumar et al., 2024; Di Saverio et al., 2020).

The responsibility of the contemporary surgeon is no longer to make a unilateral decision about whether to operate, but rather to provide accurate, evidence-verified information and to support the patient through a shared decision-making process that respects autonomy and maximizes long-term clinical outcomes.

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FROM PRIMARY TRAUMATIC DISLOCATION TO CHRONIC SHOULDER INSTABILITY: ARTHROSCOPIC BANKART REPAIR IN A YOUNG ACTIVE PATIENT

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Abstract

Anterior shoulder dislocation is the most common major joint dislocation and is seen particularly in young active adults. Recurrent instability may develop after a first traumatic dislocation, especially in patients treated conservatively. This paper presents the case of a 28-year-old male patient with recurrent anterior instability of the right shoulder associated with a Bankart lesion.

The patient experienced his first traumatic anterior shoulder dislocation while swimming recreationally. Closed reduction was performed, followed by conservative treatment and temporary immobilization. During the following year, he experienced several recurrent dislocations after minimal trauma, including a fall from bed during sleep and shoulder movement while taking off his clothes. Over time, the patient reported increasing fear of shoulder movement and limitation during daily activities.

Clinical examination showed findings consistent with chronic anterior shoulder instability, including positive apprehension testing. Magnetic resonance imaging (MRI) demonstrated an anteroinferior labral tear compatible with a Bankart lesion.

Because of recurrent low-energy dislocations and persistent functional limitation, arthroscopic Bankart repair using suture anchors was performed. Postoperatively, the shoulder was immobilized for a short period, followed by a structured physiotherapy and rehabilitation program with gradual return of range of motion and strengthening exercises.

At 18-month follow-up, the patient had regained full shoulder function without further episodes of instability. He successfully returned to normal daily and recreational activities and reported significant improvement in shoulder confidence and quality of life.

This case demonstrates the progression from primary traumatic anterior shoulder dislocation to recurrent instability in a young active patient. It also highlights the importance of MRI evaluation in recurrent cases and the role of timely surgical stabilization when conservative treatment fails.

Keywords: anterior shoulder dislocation, recurrent instability, Bankart lesion, arthroscopic Bankart repair, shoulder instability.

Introduction

Anterior shoulder dislocation represents the most common major joint dislocation encountered in orthopedic and emergency practice, accounting for approximately 90–95% of all shoulder dislocations. The glenohumeral joint possesses the greatest range of motion of any joint in the human body, allowing mobility in multiple planes but consequently predisposing it to instability and dislocation. Young active males represent the highest-risk population, particularly individuals participating in sports and activities involving overhead arm motion or trauma.

The stability of the shoulder joint depends on a complex interaction between static stabilizers — including the glenoid labrum, capsule, and glenohumeral ligaments — and dynamic stabilizers such as the rotator cuff musculature. Traumatic anterior shoulder dislocation frequently results in injury to the anteroinferior glenoid labrum, classically known as a Bankart lesion. Additional associated injuries may include Hill-Sachs lesions, capsular stretching, and rotator cuff injuries.

One of the major clinical concerns following primary anterior shoulder dislocation is recurrent instability. Recurrence rates vary significantly according to patient age, sex, and activity level, but young active males have recurrence rates reported as high as 70–90% following

conservative treatment. Repeated episodes of instability may lead to progressive capsulolabral damage, chronic pain, decreased shoulder function, and degenerative joint changes.
Although first-time dislocations are often initially managed conservatively through closed reduction and immobilization, increasing evidence supports early surgical stabilization in selected high-risk patients. Arthroscopic Bankart repair has become one of the most widely utilized procedures for recurrent anterior instability because of its minimally invasive nature, favorable functional outcomes, and relatively low recurrence rates.
The present paper describes a case of recurrent anterior shoulder instability in a young active adult who progressed from an initial traumatic dislocation to repeated low-energy redislocations associated with chronic instability and Bankart lesion formation. The case highlights the clinical importance of early recognition of instability progression, the diagnostic role of MRI, and the effectiveness of arthroscopic stabilization combined with structured rehabilitation.

Aim of the paper

The aim of this paper is to present and analyze a clinical case of recurrent anterior shoulder instability associated with a Bankart lesion in a young adult patient, and to discuss the diagnostic and therapeutic approach in the context of contemporary orthopedic literature.
More specifically, the objectives of this paper are:
To describe the clinical presentation and progression from first-time traumatic dislocation to chronic recurrent instability;
To emphasize the role of magnetic resonance imaging (MRI) in the evaluation of recurrent shoulder instability;
To illustrate the indications and outcomes of arthroscopic Bankart repair in recurrent anterior shoulder dislocation;
To discuss the importance of rehabilitation and postoperative physiotherapy in restoring shoulder function;
To compare the clinical findings and treatment outcomes of this case with current literature regarding recurrent anterior shoulder instability.

Literature review

Anterior shoulder dislocation is among the most frequent traumatic injuries encountered in orthopedic practice. Epidemiological studies indicate that the incidence is highest among young males involved in contact sports, overhead athletic activities, or physically demanding occupations. The mechanism of injury most commonly involves forced abduction, extension, and external rotation of the arm, leading to displacement of the humeral head anteriorly relative to the glenoid cavity.
The majority of anterior shoulder dislocations are associated with soft tissue injuries, particularly Bankart lesions involving detachment of the anteroinferior glenoid labrum. Hill-Sachs lesions, consisting of compression fractures of the posterolateral humeral head, may also occur due to impaction against the anterior glenoid rim during dislocation.
Recurrence after primary anterior shoulder dislocation remains a major clinical problem, especially in young active adults. Multiple studies have demonstrated significantly higher recurrence rates in patients younger than 30 years who undergo conservative treatment alone. Risk factors for recurrent instability include younger age, male sex, sports participation, ligamentous laxity, and associated labral injuries.
Magnetic resonance imaging (MRI) plays an important role in evaluating recurrent shoulder instability. MRI provides superior visualization of soft tissue structures including the glenoid

labrum, capsule, rotator cuff tendons, and associated ligamentous injuries. Identification of Bankart lesions and associated pathology is essential for planning surgical treatment.
The management of recurrent anterior shoulder instability has evolved significantly over recent decades. While conservative treatment remains appropriate for selected low-risk patients, arthroscopic stabilization procedures have become increasingly favored in young active individuals because of improved functional outcomes and reduced recurrence rates.
Arthroscopic Bankart repair involves reattachment of the detached labrum to the glenoid rim using suture anchors. Advantages of arthroscopic techniques include smaller incisions, less soft tissue trauma, reduced postoperative pain, shorter hospitalization, and earlier rehabilitation compared with open surgical procedures.
Postoperative rehabilitation is considered a critical component of successful treatment. Rehabilitation protocols generally include temporary immobilization followed by progressive range-of-motion exercises, rotator cuff strengthening, scapular stabilization exercises, and gradual return to physical activities. Successful rehabilitation contributes significantly to restoration of shoulder stability and prevention of recurrent dislocation.
Recent literature demonstrates favorable outcomes following arthroscopic Bankart repair, with high patient satisfaction rates and successful return to sports and occupational activities. However, recurrence remains possible, particularly in patients with significant bone loss, inadequate rehabilitation, or premature return to high-risk activities.

Presentation of the clinical case

4.1 Anamnestic and demographic data: The patient was a 28-year-old right-hand-dominant male who presented with recurrent episodes of right shoulder instability following a traumatic anterior shoulder dislocation sustained during recreational swimming.
The initial injury occurred approximately one year prior to definitive surgical treatment. During swimming activity, the patient experienced sudden severe pain in the right shoulder associated with immediate functional impairment and visible deformity. He was transported to the emergency department, where clinical and radiographic evaluation confirmed anterior glenohumeral dislocation.
Closed reduction was successfully performed, followed by temporary immobilization and conservative treatment. Initially, symptom improvement was achieved.
Approximately six months later, the patient experienced a second dislocation episode after a minor fall from bed during sleep. Compared with the initial trauma, this event occurred after significantly lower-energy trauma, suggesting progression toward chronic instability.
A third dislocation occurred several months later while the patient was removing a T-shirt, involving simple overhead arm movement without significant external trauma. Following this episode, the patient sought specialized orthopedic evaluation because of increasing instability, fear of recurrent dislocation, and limitation in daily activities.
The patient denied previous shoulder injuries before the initial traumatic event. No history of connective tissue disorders or generalized ligamentous laxity was reported.

4.2 Physical Examination : Orthopedic examination revealed mild asymmetry of the right shoulder compared with the contralateral side. Tenderness was present over the anterior glenohumeral region.
Range of motion was mildly limited because of pain and apprehension, particularly during abduction and external rotation. The anterior apprehension test was positive, reproducing the sensation of instability. Relocation testing relieved symptoms, supporting the diagnosis of anterior instability.

No neurological deficits were identified. Distal neurovascular examination was normal, including intact peripheral pulses and preserved motor and sensory function of the affected extremity.

4.3 Imaging and diagnosing: Plain radiographs confirmed anterior glenohumeral dislocation. The humeral head demonstrated anterior displacement relative to the glenoid cavity, consistent with subcoracoid anterior dislocation.
Because of recurrent instability episodes, magnetic resonance imaging (MRI) of the shoulder was performed for detailed soft tissue evaluation. MRI demonstrated an anteroinferior labral tear consistent with a Bankart lesion, together with capsular insufficiency contributing to recurrent instability.
Based on the patient's clinical presentation, recurrent low-energy dislocations, physical examination findings, and MRI results, the diagnosis of chronic recurrent anterior shoulder instability associated with Bankart lesion was established.

Surgical technique

Because of recurrent instability episodes and failure of conservative treatment, arthroscopic stabilization was recommended.
The procedure was performed under general anesthesia with the patient positioned in the beach-chair position. Standard posterior and anterior arthroscopic portals were established to allow visualization and instrumentation of the glenohumeral joint.
Diagnostic arthroscopy confirmed detachment of the anteroinferior glenoid labrum consistent with a Bankart lesion. Capsular laxity and instability of the anterior inferior glenohumeral ligament complex were also identified.
The glenoid rim was prepared using arthroscopic instruments to promote healing. Suture anchors were inserted into the anterior glenoid rim, and the detached labrum was mobilized and reattached to restore capsulolabral stability. Adequate tensioning of the repaired structures was achieved arthroscopically.
At the conclusion of the procedure, shoulder stability was reassessed and found to be satisfactory. The patient tolerated the procedure well without intraoperative complications.

Postoperative rehabilitation

Following surgery, the shoulder was immobilized using a sling for approximately four weeks in order to protect the repair and allow soft tissue healing.
Passive range-of-motion exercises were initiated gradually according to the rehabilitation protocol. Progressive physiotherapy focused on restoration of shoulder mobility, strengthening of the rotator cuff musculature, scapular stabilization, and gradual functional recovery.
Strengthening exercises were introduced progressively during the rehabilitation period. Particular attention was directed toward avoiding excessive external rotation and abduction during the early postoperative phase to minimize stress on the repair.
The patient demonstrated excellent compliance with physiotherapy and rehabilitation instructions throughout recovery.

Clinical course and follow-up

The postoperative course was favorable, with progressive improvement in pain, shoulder mobility, and functional stability.

At follow-up evaluation 18 months after surgery, no recurrent instability episodes had occurred. The patient reported absence of pain during daily activities and complete restoration of confidence during overhead arm movements.
Functional outcome assessment demonstrated substantial postoperative improvement.

Functional Score	Preoperative	Postoperative
DASH Score	54	6
Constant-Murley Score	48	92
WOSI Score	1120	120

The patient successfully returned to recreational sports activities and physical exercise without recurrence of instability.

Discussion

The present case demonstrates the typical progression from primary traumatic anterior shoulder dislocation to chronic recurrent instability in a young active adult. Young male patients represent the highest-risk group for recurrent instability following first-time anterior dislocation, particularly when initial treatment is conservative.
A notable aspect of this case is the progressive reduction in the amount of trauma necessary to produce redislocation. While the initial episode occurred during swimming activity, subsequent dislocations developed after minimal trauma, including a minor fall from bed and simple overhead arm movement while removing clothing. Such low-energy redislocations strongly suggest advanced capsulolabral insufficiency and chronic instability.
The role of MRI was particularly important in this patient. Although plain radiographs confirmed the presence of anterior dislocation, MRI provided detailed assessment of soft tissue structures and confirmed the presence of a Bankart lesion. Identification of labral pathology is essential in recurrent instability because soft tissue injuries frequently determine treatment strategy and prognosis.
Conservative treatment following first-time anterior shoulder dislocation remains widely used, especially in patients with lower physical demands. However, recurrence rates among young active males remain high. Repeated instability episodes may lead to progressive soft tissue damage, glenoid bone loss, development of Hill-Sachs lesions, and increasing functional limitation.
Arthroscopic Bankart repair has become one of the preferred surgical techniques for recurrent anterior instability because it allows restoration of capsulolabral anatomy using minimally invasive methods. Compared with open surgical procedures, arthroscopic stabilization offers reduced soft tissue trauma, decreased postoperative pain, shorter hospitalization, and faster rehabilitation while maintaining excellent functional outcomes.
Another important factor contributing to successful recovery in this case was structured postoperative rehabilitation. Physiotherapy plays a critical role in restoring range of motion, muscular strength, proprioception, and dynamic shoulder stability. Patient compliance with rehabilitation protocols significantly influences final functional outcomes and recurrence prevention.
The excellent postoperative recovery observed in this patient is consistent with contemporary literature reporting favorable outcomes following arthroscopic Bankart repair in young active individuals. The absence of recurrent instability at 18-month follow-up and the successful return to physical activity demonstrate the effectiveness of surgical stabilization combined with appropriate rehabilitation.

Despite the favorable outcome, recurrent instability remains a recognized complication after arthroscopic stabilization, particularly in patients with substantial glenoid bone loss, hyperlaxity, or premature return to contact sports. Long-term follow-up therefore remains important.

This case underscores the importance of early recognition of recurrent instability, appropriate imaging evaluation, and timely surgical intervention in high-risk patients with recurrent anterior shoulder dislocation.

Conclusion

Anterior shoulder dislocation in young active individuals carries a significant risk of recurrent instability, particularly when associated with Bankart lesions and treated conservatively after the initial episode.

This case demonstrates the progression from primary traumatic dislocation to chronic recurrent instability characterized by repeated low-energy redislocations and functional impairment. MRI evaluation played a critical role in identifying the underlying capsulolabral injury and guiding definitive treatment.

Arthroscopic Bankart repair combined with structured postoperative rehabilitation resulted in excellent functional recovery, restoration of shoulder stability, and successful return to physical activities without recurrence.

Early recognition of instability progression and timely surgical stabilization may prevent chronic shoulder dysfunction and improve long-term outcomes in young active patients with recurrent anterior shoulder instability.

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FAPI-BASED RADIOPHARMACEUTICALS IN MODERN THERANOSTICS: FROM DIAGNOSTIC IMAGING TO TARGETED RADIONUCLIDE THERAPY

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Abstract

Fibroblast activation protein inhibitor (FAPI)-based radiopharmaceuticals have emerged as one of the most promising innovations in contemporary nuclear medicine and precision oncology. Fibroblast activation protein (FAP), overexpressed in cancer-associated fibroblasts (CAFs) within the tumor microenvironment of many epithelial malignancies, has become an important molecular target for both diagnostic imaging and targeted radionuclide therapy. In recent years, FAPI radiopharmaceuticals have demonstrated outstanding diagnostic performance characterized by rapid tumor uptake, low physiological accumulation in healthy tissues, and excellent tumor-to-background contrast in positron emission tomography/computed tomography (PET/CT) imaging. Furthermore, therapeutic radionuclides such as Lutetium-177, and Actinium-225 have enabled the development of FAPI-based radionuclide therapy, expanding the role of FAPI compounds from diagnostic imaging to therapeutic oncology. This review discusses the biological basis of FAP targeting, the development and radiochemistry of FAPI radiopharmaceuticals and their current clinical applications in diagnostic imaging and targeted radionuclide therapy. Among other aspects, we aimed to highlight the major limitations, current challenges, and future perspectives of FAPI theranostics in precision medicine.

Keywords: FAPI, fibroblast activation protein, theranostics, PET/CT imaging, targeted radionuclide therapy, radiopharmaceuticals.

Introduction

Theranostics has become one of the most rapidly developing concepts in modern radiopharmacy andnuclear medicine, combining molecular imaging and targeted therapy into a unified personalized treatment strategy. Among the emerging theranostic agents, fibroblast activation protein inhibitor (FAPI)-based radiopharmaceuticals have attracted significant scientific and clinical interest because of their ability to target fibroblast activation protein (FAP), a membrane-bound serine protease highly expressed on cancer-associated fibroblasts (CAFs) within the tumor microenvironment of many epithelial malignancies (Siegmund SC et al., 2025). Unlike conventional radiopharmaceuticals that primarily target tumor cell metabolism, FAPI radiopharmaceuticals focus on the tumor stroma, which plays a critical role in tumor growth, invasion, angiogenesis, metastasis, and resistance to therapy (Huang X et al., 2026). Targeting tumor stroma via FAPI represents a promising theranostic approach. Radiopharmaceuticals labeled with diagnostic (99mTc) or therapeutic (177Lu) isotopes enhance imaging specificity and enable targeted therapy (Rustemi-Ahmeti H et al., 2026).
Radiolabeled FAPI compounds, particularly those labeled with Gallium-68 and Fluorine-18, have shown excellent pharmacokinetic characteristics, including rapid tumor uptake, fast blood clearance, and high tumor-to-background ratios, making them highly suitable for PET/CT imaging (Kratochwil C et al., 2019). Clinical studies have demonstrated promising results across multiple malignancies, including pancreatic, breast, lung, colorectal, ovarian, gastric, and head and neck cancers. Moreover, the replacement of diagnostic radionuclides with therapeutic isotopes such as Lutetium-177 and Actinium-225 has enabled the development of

FAPI-based targeted radionuclide therapy, establishing FAPI compounds as important agents in modern theranostics (Wu X et al., 2025). Freeze-dried formulations improve stability, handling, and reproducibility, which are essential for preclinical and clinical translation (Rustemi-Ahmeti H et al., 2026). This technique is widely used in the pharmaceutical industry for the stabilization of vaccines, biologics and other heat sensitive drugs. The process helps to maintain the structural integrity and biological activity of the product, making it ideal for long term storage (Rustemi-Ahmeti H et al., 2025)

Despite the substantial progress achieved in recent years, several important challenges remain unresolved, including optimization of tumor retention time, standardization of dosimetry protocols, radionuclide selection, long-term toxicity evaluation, and validation through large prospective clinical trials (Hicks RJ, 2025). Therefore, continued research is essential to fully establish the clinical role of FAPI-based radiopharmaceuticals in precision oncology.

Biological Background of Fibroblast Activation Protein

Fibroblast activation protein (FAP) is a type II transmembrane glycoprotein belonging to the dipeptidyl peptidase family. It exhibits both dipeptidyl peptidase and endopeptidase activity and plays a significant role in extracellular matrix remodeling, tissue repair, fibrosis, wound healing, and tumor progression. Under normal physiological conditions, FAP expression is generally absent or very limited in healthy adult tissues. However, FAP becomes highly expressed in activated fibroblasts associated with chronic inflammation, fibrosis, and malignant tumors (Watabe T et al., 2020).

Cancer-associated fibroblasts represent one of the dominant cellular components of the tumor microenvironment and contribute significantly to tumor development and progression. CAFs promote angiogenesis, immune suppression, tumor cell proliferation, invasion, and metastasis through the secretion of cytokines, growth factors, extracellular matrix proteins, and signaling molecules. Elevated FAP expression has been reported in multiple malignancies, including pancreatic adenocarcinoma, breast carcinoma, colorectal cancer, ovarian cancer, hepatocellular carcinoma, and sarcomas (Loktev A et al., 2019).

The selective overexpression of FAP in tumor-associated fibroblasts while remaining minimally expressed in healthy tissues makes FAP an ideal molecular target for theranostic applications. Targeting the tumor microenvironment rather than only malignant cells represents an important paradigm shift in oncology and may improve diagnostic sensitivity and therapeutic efficacy.

Development of FAPI-Based Radiopharmaceuticals

The development of FAPI-based radiopharmaceuticals represents a major advancement in targeted molecular imaging and radionuclide therapy. Early FAP inhibitors demonstrated insufficient affinity and suboptimal pharmacokinetic properties, limiting their clinical utility. However, the development of quinoline-based FAPI compounds significantly improved tumor targeting, biodistribution, and clinical applicability (Loktev A et al., 2019).

Several FAPI compounds have been developed over recent years, including FAPI-02, FAPI-04, FAPI-21, FAPI-46, and FAP-2286. Among these compounds, FAPI-04 and FAPI-46 demonstrated particularly favorable pharmacokinetic characteristics, including rapid tumor uptake and improved tumor retention time. Chelators such as DOTA and NOTA are commonly incorporated into FAPI molecules to facilitate stable radiolabeling with both diagnostic and therapeutic radionuclides (Czuczejko J et al., 2026).

Gallium-68 remains one of the most frequently used radionuclides for FAPI PET imaging because of its favorable decay properties and accessibility through generator systems. Fluorine-

18-labeled FAPI radiopharmaceuticals have also attracted increasing interest because of their longer half-life and suitability for centralized production and large-scale distribution. In therapeutic applications, radionuclides such as Lutetium-177 and Actinium-225 are increasingly utilized because of their cytotoxic beta- and alpha-particle emissions (Ballal S et al., 2021).
Optimization of molecular structure, linker design, and radionuclide selection remains essential for improving tumor retention and maximizing therapeutic efficacy. Current research focuses on developing next-generation FAPI radiopharmaceuticals with improved pharmacodynamics and prolonged intratumoral retention.

Diagnostic Imaging Applications

4.1 FAPI PET/CT Imaging: FAPI PET/CT imaging has emerged as one of the most promising diagnostic applications in modern oncologic imaging. Gallium-68-labeled FAPI radiopharmaceuticals have demonstrated remarkable diagnostic performance across a wide range of malignancies due to their high tumor uptake and low physiological accumulation in normal tissues (Giesel FL et al., 2019).
Compared with conventional 18F-FDG PET/CT imaging, FAPI PET imaging offers several important advantages. Physiological uptake in the brain, liver, oral cavity, and gastrointestinal tract is generally low, allowing improved lesion detection in these regions. In addition, FAPI imaging does not require prolonged fasting or blood glucose monitoring before image acquisition, thereby simplifying imaging protocols and improving patient convenience (Kratochwil C et al., 2019).
Fluorine-18-labeled FAPI radiopharmaceuticals are increasingly being investigated because they may provide improved spatial resolution and logistical advantages associated with centralized cyclotron production. Clinical studies suggest that FAPI PET imaging may improve diagnostic sensitivity, especially in tumors characterized by extensive stromal desmoplasia.

4.2 Clinical Applications in Oncology
Pancreatic Cancer
Pancreatic ductal adenocarcinoma exhibits intense stromal fibrosis and abundant FAP expression, making it an excellent target for FAPI imaging. FAPI PET/CT has demonstrated superior tumor delineation and improved lesion contrast in pancreatic malignancies.
Breast Cancer
FAPI imaging has shown promising diagnostic performance in primary and metastatic breast cancer, especially in invasive lobular carcinoma and metastatic lesions with low FDG avidity.
Lung Cancer
In non-small cell lung cancer, FAPI PET imaging has demonstrated favorable lesion visualization and may improve detection of metastatic disease.
Colorectal Cancer
FAPI PET imaging has demonstrated high sensitivity in detecting recurrent and metastatic colorectal cancer, particularly peritoneal metastases.
Additional Malignancies
Promising results have also been reported in ovarian cancer, gastric cancer, cholangiocarcinoma, hepatocellular carcinoma, sarcomas, and head and neck tumors.

FAPI-Based Targeted Radionuclide Therapy

The integration of diagnostic imaging and targeted radionuclide therapy within a single molecular platform represents the core principle of theranostics. In FAPI theranostics, diagnostic radionuclides are used for tumor visualization and patient selection, while therapeutic radionuclides deliver cytotoxic radiation directly to the tumor microenvironment.
Lutetium-177-labeled FAPI radiopharmaceuticals are currently among the most extensively investigated therapeutic compounds because of their favorable beta-particle emission and simultaneous imaging capability. FAPI compounds labeled with alpha-emitting radionuclides such as Actinium-225 offer highly potent localized cytotoxicity with minimal surrounding tissue damage (Wu X et al., 2025).
FAPI radionuclide therapy primarily targets cancer-associated fibroblasts and stromal components, disrupting the supportive tumor microenvironment essential for malignant progression. Preliminary clinical studies have demonstrated encouraging therapeutic responses, pain palliation, and symptom improvement in patients with advanced and treatment-resistant malignancies (Ballal S et al., 2021).
Although initial results are promising, most currently available data originate from small early-phase clinical studies. Large multicenter prospective trials remain necessary to establish standardized treatment protocols and evaluate long-term therapeutic efficacy and safety.

Safety, Toxicity, and Dosimetry

Radiation dosimetry represents an essential component of targeted radionuclide therapy because it directly influences treatment efficacy and toxicity. Current evidence suggests that FAPI-based radiopharmaceuticals generally demonstrate favorable safety profiles with relatively limited severe adverse effects (Hicks RJ, 2025).
The kidneys, bone marrow, liver, and salivary glands represent potential organs at risk depending on the selected radionuclide and radiopharmaceutical characteristics. Reported adverse effects include mild hematologic toxicity, fatigue, nausea, and transient discomfort, although severe toxicity appears relatively uncommon in currently available studies.
One of the primary limitations of therapeutic FAPI radiopharmaceuticals remains relatively short tumor retention time, which may reduce the delivered radiation dose to tumors and limit therapeutic effectiveness. Consequently, significant research efforts are directed toward improving molecular design, increasing tumor retention, and optimizing dosimetry strategies.
Long-term toxicity data remain limited because most FAPI therapeutic applications are still in early clinical development. Future prospective studies will be essential for determining long-term safety and establishing standardized dosimetry protocols.

Challenges and Limitations

Despite their considerable promise, FAPI-based radiopharmaceuticals face several important challenges and limitations. One of the major concerns involves heterogeneous FAP expression between different tumor types and even within individual tumors. Furthermore, increased FAP expression may also occur in inflammatory and fibrotic diseases, potentially reducing imaging specificity.
Another major limitation relates to rapid radiopharmaceutical washout and insufficient tumor retention observed with some FAPI compounds. Optimization of linker systems, chelator design, and radionuclide selection remains critical for improving therapeutic efficacy.

Standardization of imaging protocols, dosimetry methods, and therapeutic regimens remains incomplete. In addition, most available clinical data are derived from small retrospective or early-phase studies, emphasizing the need for larger prospective multicenter investigations.
Economic considerations, production logistics, regulatory approval, and radiopharmaceuticals availability may also influence the widespread clinical implementation of FAPI theranostics.

Future Perspectives

The future of FAPI-based theranostics appears highly promising. Development of next-generation FAPI radiopharmaceuticals with prolonged tumor retention and improved pharmacokinetic characteristics remains a major research focus. Novel compounds incorporating albumin-binding motifs and alternative linker systems may significantly enhance therapeutic efficacy.
Combination therapies involving immunotherapy, chemotherapy, targeted therapy, and external beam radiotherapy may further improve clinical outcomes. Artificial intelligence and quantitative imaging techniques may also contribute to improved lesion characterization, treatment planning, and therapy monitoring.
Beyond oncology, FAPI imaging may also have potential applications in fibrotic and inflammatory diseases, including cardiac fibrosis, pulmonary fibrosis, liver cirrhosis, rheumatoid arthritis, and inflammatory bowel disease.
As precision medicine continues to evolve, FAPI-based radiopharmaceuticals are expected to become increasingly important tools in individualized cancer diagnosis and therapy.

Conclusion

FAPI-based radiopharmaceuticals represent one of the most significant recent advancements in nuclear medicine and precision oncology. Their ability to target cancer-associated fibroblasts within the tumor microenvironment provides unique opportunities for both diagnostic imaging and targeted radionuclide therapy. FAPI PET/CT imaging has demonstrated excellent diagnostic performance across multiple malignancies, while therapeutic FAPI compounds have shown encouraging preliminary clinical outcomes in advanced cancers.
Although several important challenges remain unresolved, including tumor retention optimization, dosimetry standardization, and long-term safety evaluation, ongoing scientific research continues to expand the clinical potential of FAPI theranostics. Future developments in molecular design, radionuclide selection, and combination treatment strategies are expected to further strengthen the role of FAPI-based radiopharmaceuticals in personalized oncology and precision medicine.

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CONTEMPORARY MANAGEMENT OF WOUNDS IN THE EMERGENCY DEPARTMENT: CLINICAL APPROACH AND EFFECTIVE MANAGEMENT

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Abstract

Background: Traumatic wounds are among the most frequent reasons for presentation to emergency departments and require rapid assessment, standardized treatment, and multidisciplinary management to prevent infectious complications and functional sequelae (Prevaldi et al., 2016; Singer & Hollander, 2020).
Aim: To analyze the contemporary management of traumatic wounds, evaluate the incidence of complications according to wound type and degree of contamination, and assess the role of debridement, irrigation, and antibiotic prophylaxis in a clinical series at the Clinical Hospital of Tetovo.
Materials and methods: A retrospective-descriptive study including 96 patients treated at the Emergency Department of the Clinical Hospital of Tetovo from January to May 2026. Age, sex, wound type (lacerated, contused, *scissum*, with skin loss, gunshot), anatomical location, contamination level, treatment modality, and postoperative complications were analyzed.
Results: Male patients predominated (70.8%), with a mean age of 39.4 ± 16.2 years. Lacerated wounds accounted for 38.5% of cases, and most wounds were dirty (58.3%) or contaminated (27.1%). Surgical debridement and irrigation with sterile normal saline were performed according to contemporary protocols (Goh et al., 2024; Reeder, 2024). Complications were recorded in 13.5% of cases, with local infection in 9.4%, mainly in wounds with skin loss and gunshot wounds.
Conclusion: Modern wound management in the emergency setting requires early assessment, accurate classification, adequate cleansing and closure technique, and systematic follow-up. A multidisciplinary approach and contemporary protocols improve clinical outcomes and reduce morbidity (Clare & Baxley, 2023; Prevaldi et al., 2016).

Keywords: traumatic wounds, emergency, debridement, irrigation, infection, gunshot wounds, contemporary management.

Introduction

Traumatic wounds are among the most frequent pathologies encountered in emergency departments and constitute a significant clinical challenge due to the high risk of infection, neurovascular injury, and long-term functional sequelae (Singer & Hollander, 2020; Trott, 2019). According to the World Health Organization, trauma associated with open wounds represents a substantial epidemiological burden, particularly in the active age groups of the population (World Health Organization, 2021). Effective and evidence-based management of these lesions contributes to reducing morbidity, shortening hospital stay, and improving aesthetic and functional outcomes.
Contemporary wound management is based on four fundamental principles: rapid clinical assessment, hemorrhage control, adequate wound cleansing with surgical debridement when necessary, and appropriate tissue closure (Reeder, 2024; Lammers, 2014). Current literature emphasizes the importance of controlled-pressure irrigation and removal of devitalized tissue

as key elements in preventing post-traumatic infections (Prevaldi et al., 2016; MSD Manual Professional Edition, 2025). The study by Anglen (2005) demonstrated that irrigation with an adequate volume of normal saline is perhaps the single most important intervention in reducing the bacterial load of a wound.

The classification of traumatic wounds according to mechanism of injury and degree of contamination has direct clinical relevance. According to the classification established by the U.S. National Research Council and widely accepted, wounds are divided into clean, clean-contaminated, contaminated, and dirty/infected (Berríos-Torres et al., 2017). Dirty wounds are characterized by the presence of necrotic tissue, foreign material, or exposure to environments with a high microbial load, significantly increasing the incidence of septic complications (Clinical Tree, 2024). Furthermore, *scissum* (incised), lacerated, contused, and skin-loss wounds present different challenges in management, ranging from simple primary closure to the need for advanced reconstructive procedures.

In modern emergency practice, advanced irrigation methods at 5–8 psi pressure, atraumatic suturing techniques with monofilament materials, evidence-based antibiotic therapy, and tetanus prophylaxis based on immunization status are applied (Centers for Disease Control and Prevention [CDC], 2020; American Heart Association, 2024). The choice of closure — primary, delayed primary, or secondary — depends on the time elapsed since injury, level of contamination, and anatomical location (Forsch, 2008). Studies have shown that primary closure of clean wounds within 6–8 hours of injury is associated with a lower incidence of infection compared with delayed closure (Quinn et al., 2014).

Complex wounds, particularly gunshot (ballistic) wounds, require a multidisciplinary approach due to multiple soft tissue injuries, possible fractures, and lesions of deep vascular and nerve structures (Clare & Baxley, 2023). The kinetic energy of the projectile causes both temporary and permanent cavitation, resulting in a wide zone of devitalized tissue, even when the entry and exit wounds appear clinically minimal (Bartlett, 2003). For this reason, careful exploration and wound-characteristic-oriented debridement are essential.

The Clinical Hospital of Tetovo, as a referral center for the northeastern region of the Republic of North Macedonia, regularly faces a wide spectrum of traumatic wounds, ranging from minor domestic lacerations to complex ballistic lesions. Systematic analysis of these cases enables the improvement of internal protocols and their alignment with contemporary international guidelines.

Aim of the Study

The general aim of this study is to analyze the contemporary management of traumatic wounds in a real clinical context, based on the experience of the Emergency Department of the Clinical Hospital of Tetovo. More specifically, the study aims to:

Analyze the demographic and clinical characteristics of patients presenting with traumatic wounds.

Evaluate the distribution of wounds by type, anatomical location, and degree of contamination.

Assess the incidence of postoperative complications in relation to wound type and classification.

Highlight the role of surgical debridement, normal saline irrigation, and rational use of prophylactic antibiotics.

Analyze the clinical outcomes in patients with complex wounds, including gunshot wounds.

Compare the study findings with current international literature and provide practical recommendations to improve local protocols.

Materials and Methods

3.1. Study design and population: The study was designed as a retrospective-descriptive study and includes 96 patients treated at the Emergency Department of the Clinical Hospital of Tetovo during the period January – May 2026. Data were extracted from official medical records, anamnesis sheets, and operative protocols, fully respecting the principles of personal data protection and patient confidentiality, in accordance with the Declaration of Helsinki (World Medical Association, 2013).
3.2. Inclusion and exclusion criteria: The study included patients of all age groups who presented with traumatic wounds requiring surgical or conservative treatment in the emergency setting.
Inclusion criteria:
Lacerated wounds;
Contused wounds;
Wounds *scissum* (incised wounds caused by sharp objects);
Wounds with loss of skin substance;
Contaminated and dirty wounds;
Gunshot (ballistic) wounds.
Exclusion criteria:
Patients with superficial wounds not requiring surgical intervention;
Patients with incomplete clinical data or no post-procedural follow-up;
Chronic non-traumatic wounds (diabetic ulcers, vascular wounds, etc.).

3.3. Variables analyzed: For each patient, the following variables were recorded and analyzed: age and sex; mechanism of trauma; anatomical location; morphological type of wound; degree of contamination (clean, contaminated, dirty); time of presentation from the moment of trauma; type of treatment (debridement, primary suturing, delayed closure, secondary healing); antibiotic regimen used; tetanus prophylaxis; and postoperative complications (local infection, dehiscence, marginal necrosis).

3.4. Treatment protocol: All patients underwent a systematic examination including physical assessment, hemostasis control, and distal neurovascular evaluation of the affected extremity (Reeder, 2024). Wound cleansing was performed with intensive irrigation using sterile normal saline (NaCl 0.9%) at volumes of 50–100 mL per cm of wound length, in accordance with literature recommendations (MSD Manual Professional Edition, 2025; Anglen, 2005). In dirty wounds and those with necrotic tissue, careful surgical debridement was performed using a scalpel, preserving viable tissue and removing foreign bodies.
Primary closure was applied in clean wounds and some contaminated wounds after adequate debridement, within the recommended time window (typically ≤ 6–8 hours for trunk and extremities, up to 12–24 hours for the face and head, due to good vascularization) (Quinn et al., 2014; Forsch, 2008). In wounds with severe contamination, delayed primary closure or secondary healing was preferred. Prophylactic antibiotic therapy was used in contaminated and dirty wounds and in all gunshot wounds, with a combination of first-generation cephalosporin and metronidazole as the most frequent regimen (Goh et al., 2024). Tetanus prophylaxis was administered according to the patient's immunization status and wound characteristics (CDC, 2020).

3.5. Statistical analysis: Data were entered and analyzed using Microsoft Excel 2019 and descriptive statistics. Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were expressed as frequencies and percentages. Comparisons

between groups were performed using the chi-square test for categorical variables, with a p-value < 0.05 set as the threshold for statistical significance.

Results

4.1. Demographic characteristics: Of the 96 patients included in the study, 68 (70.8%) were male and 28 (29.2%) were female, with a male-to-female ratio of 2.4:1. The mean age was 39.4 ± 16.2 years, ranging from 4 to 78 years. The most affected age group was 21–40 years (47.9% of cases), confirming the findings of the literature that identify the active population as the most exposed to trauma (World Health Organization, 2021).

4.2. Distribution by wound type: The most frequent type of wound was lacerated, followed by contused wounds and those with skin loss. Although less frequent, gunshot wounds presented the most complex clinical challenges (Table 1).

Table 1. Distribution of patients by wound type (n = 96)

Type of wound	Number (n)	Percentage (%)
Lacerated wounds	37	38.5
Contused wounds	21	21.9
Scissum wounds	14	14.6
Wounds with skin loss	18	18.7
Gunshot wounds	6	6.3
Total	96	100

4.3. Classification by degree of contamination: Most wounds were dirty, reflecting delayed presentation and exposure of the trauma site to contaminated environments (Table 2).

Table 2. Classification of wounds by degree of contamination

Classification	Number (n)	Percentage (%)
Clean	14	14.6
Contaminated	26	27.1
Dirty	56	58.3

4.4. Anatomical location: The most frequent location of wounds was the upper extremities — 40 patients (41.7%), followed by the lower extremities with 33 patients (34.4%), the head and face with 15 patients (15.6%), and the trunk with 8 patients (8.3%). The predominance of the extremities is consistent with the data reported by Singer and Hollander (2020) in a systematic review of laceration management.

4.5. Treatment applied: Surgical debridement was performed in 61 patients (63.5%), and primary suturing in 52 cases (54.2%). In 19 patients (19.8%), delayed primary closure was applied due to severe contamination or presentation outside the optimal time window for primary closure. In 25 patients (26.0%), secondary healing was chosen, mainly in wounds with

substantial skin loss. Prophylactic antibiotics were administered to 74 patients (77.1%), with a combination of first-generation cephalosporin (cefazolin/cephalexin) and metronidazole as the most frequent regimen, especially in dirty wounds and gunshot wounds. Tetanus prophylaxis was administered according to immunization status.

4.6. Complications: Complications were recorded in 13 cases (13.5%), with local infection as the most frequent complication (Table 3). No patient developed systemic sepsis or life-threatening complications during the follow-up period.

Table 3. Recorded postoperative complications

Complication	Number (n)	Percentage (%)
Local infection	9	9.4
Wound dehiscence	2	2.1
Marginal necrosis	2	2.1
Total	13	13.5

The highest incidence of infection was observed in dirty wounds (12.5%) and in wounds with skin substance loss and gunshot wounds. All patients with local infection were successfully treated with culture-guided antibiotic therapy, additional drainage, and dressing changes, without the need for major reoperation.

Discussion

The management of traumatic wounds in the emergency setting remains an essential component of surgical and emergency practice. The results of this study demonstrate a predominance of lacerated and contused wounds, in line with international literature reporting similar frequencies in emergency departments (Singer & Hollander, 2020; Trott, 2019). The male predominance (70.8%) and the active-population mean age (39.4 years) are also consistent with other epidemiological studies, explained by the greater exposure of young men to high-risk activities (industrial, sports, motor vehicle, interpersonal violence).

Most of the wounds in our study (58.3%) were dirty, which is associated with delayed presentation to the emergency department, exposure to contaminated environments, and the presence of devitalized tissue. Modern studies emphasize that aggressive debridement and adequate irrigation are the most important factors in reducing the bacterial load and preventing infection (Anglen, 2005; Prevaldi et al., 2016). The prospective multicenter FLOW (Fluid Lavage of Open Wounds) trial demonstrated that normal saline alone is preferable to soap solutions in open traumatic wounds of long bones, and that low pressure is the default choice (Bhandari et al., 2015). Our data are in line with these recommendations: 0.9% NaCl irrigation was used as the standard in all cases.

The total complication rate in our study (13.5%) and the local infection rate (9.4%) are within the acceptable range reported in the literature for open traumatic wounds, where the figures typically vary from 5% to 15% depending on initial contamination and location (Hollander & Singer, 1999). A higher incidence was observed in wounds with skin substance loss and in gunshot wounds, consistent with existing data showing that ballistic wounds and those with

extensive tissue damage have a substantially higher risk of septic complications (Clare & Baxley, 2023; Bartlett, 2003).

The rational use of prophylactic antibiotics remains a debated topic. In this study, 77.1% of patients received antibiotics, a percentage that may be perceived as high compared with recent recommendations. However, this reflects the high prevalence of dirty and contaminated wounds in our cohort. Current literature suggests that careful irrigation and good debridement have a greater impact than the antibiotic itself in preventing infection of simple lacerated wounds (Cummings & Del Beccaro, 1995; Quinn et al., 2014). Antibiotic prophylaxis is more justified in deep contaminated wounds, wounds of the hands and feet, wounds with bone or tendon exposure, and gunshot wounds (Goh et al., 2024).

Gunshot wounds in our study accounted for 6.3% of cases, a percentage that reflects a non-negligible incidence of civilian ballistic trauma in the region. Their treatment requires careful exploration of neurovascular injuries, rapid hemorrhage control, wound-characteristic-oriented debridement, and sometimes reconstructive intervention (Clare & Baxley, 2023). Modern practice has abandoned routine aggressive debridement in low-energy wounds and favors conservative treatment with prophylactic antibiotics in selected cases (Bartlett, 2003). Multidisciplinary management — involving the general surgeon, orthopedist, vascular surgeon, and plastic surgeon — is decisive for long-term functional outcome.

Tetanus prophylaxis, administered according to the patient's immunization status and wound characteristics, is an indispensable component of traumatic wound management (CDC, 2020). In our study, this element was systematically applied, and no case of tetanus was recorded during the follow-up period.

This study has several limitations that must be acknowledged. First, the retrospective design limits the control of confounding variables and depends on the quality of existing documentation. Second, the five-month period of data collection and the sample size (n = 96) may not fully reflect seasonal and long-term variations. Third, long-term follow-up of patients, especially regarding aesthetic and functional outcomes of head and extremity wounds, was not fully accomplished. Prospective studies with larger samples and extended follow-up will be necessary to confirm our results and refine internal protocols.

Despite these limitations, the findings are consistent with existing literature and provide a realistic picture of the current practice of traumatic wound management at a regional referral center. The systematic adoption of contemporary protocols, continuous staff training, and a multidisciplinary approach are key to further improving clinical outcomes.

Conclusion

Traumatic wounds represent a significant challenge in emergency departments and require a standardized, evidence-based approach. The results of this study at the Clinical Hospital of Tetovo support the following conclusions:

Lacerated and contused wounds are the most frequent types of traumatic wounds in emergency practice, mainly in males of active age.

Dirty wounds, which constitute the majority of cases, have the highest incidence of infectious complications.

Surgical debridement and intensive irrigation with normal saline remain the principal and most effective components of treatment.

Prophylactic antibiotic therapy should be used selectively, tailored to wound type, location, and degree of contamination.

Multidisciplinary management and systematic tetanus prophylaxis improve the prognosis in complex wounds, including gunshot wounds.

The systematic application of contemporary protocols in the treatment of traumatic wounds reduces complications, improves healing, shortens hospital stay, and contributes to more efficient and safer patient care. The experience of the Clinical Hospital of Tetovo confirms that the application of fundamental principles — rapid assessment, adequate irrigation, careful debridement, contamination-based closure, and systematic follow-up — yields clinical results comparable to those reported in advanced international centers.

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COMPARATIVE ANALYSIS OF LAPAROSCOPIC VERSUS OPEN CHOLECYSTECTOMY IN PATIENTS WITH CHOLECYSTOLITHIASIS: A RETROSPECTIVE STUDY FROM THE CLINICAL HOSPITAL OF TETOVA

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Abstract

Background: Cholecystolithiasis is one of the most common gastrointestinal disorders requiring surgical intervention worldwide. Since its introduction in the late 1980s, laparoscopic cholecystectomy (LC) has progressively replaced the conventional open approach (OC) as the standard treatment for symptomatic gallstone disease, although the open technique remains relevant in selected clinical situations.
Aim: To analyze the demographic profile, comorbidity burden, and perioperative outcomes of patients operated for cholecystolithiasis at the Clinical Hospital of Tetova, and to compare postoperative complications and length of hospitalization between LC and OC.
Materials and Methods: A retrospective observational study was carried out at the Department of Surgery of the Clinical Hospital of Tetova, in collaboration with the Faculty of Medical Sciences, University of Tetova. Sixty-four consecutive adult patients operated for symptomatic cholecystolithiasis were included. Demographic data, comorbidities, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification, surgical technique, postoperative complications, and length of hospital stay were extracted and analyzed.
Results: The cohort comprised 48 women (75%) and 16 men (25%), aged 23 to 72 years. Forty-six patients (71.9%) underwent LC and 18 (28.1%) underwent OC. Arterial hypertension was present in 48 patients (75%) and diabetes mellitus in 32 (50%). Approximately 70% of patients had a BMI between 28 and 30 kg/m². ASA classification revealed 44 patients (68.75%) in class I, 16 (25%) in class II, and 4 (6.25%) in class III. Postoperative complications—wound infection, wound bleeding, and prolonged postoperative pain—were more frequent among patients operated by the open technique. Length of hospital stay was substantially shorter in the laparoscopic group.
Conclusion: Laparoscopic cholecystectomy was associated with fewer postoperative complications and shorter hospitalization compared with the open approach, supporting its role as the preferred method for symptomatic cholecystolithiasis. Careful preoperative evaluation of comorbidities and ASA status remains essential for optimal outcomes.

Keywords: cholecystolithiasis; laparoscopic cholecystectomy; open cholecystectomy; postoperative complications; ASA classification; Tetova.

Introduction

Cholecystolithiasis, defined as the presence of stones within the gallbladder, represents one of the most prevalent disorders of the digestive tract in both industrialized and developing countries (Stinton & Shaffer, 2012). Epidemiological data indicate that gallstone disease affects approximately 10–20% of the adult population in Western societies, with even higher prevalence among populations characterized by metabolic risk factors such as obesity, diabetes mellitus, and arterial hypertension (Lammert et al., 2016; Shaffer, 2006). Cholesterol gallstones, the predominant type in Western countries, are closely linked to the metabolic syndrome, female sex, advancing age, multiparity, rapid weight loss, and certain genetic predispositions (Diehl, 1991; Lammert et al., 2016).
Although a substantial proportion of individuals harboring gallstones remain asymptomatic throughout their lifetime, an estimated 10–25% will eventually develop biliary symptoms or complications including biliary colic, acute cholecystitis, choledocholithiasis, ascending cholangitis, or biliary pancreatitis (Festi et al., 2010; Halldestam et al., 2004). Once symptoms

develop, surgical removal of the gallbladder—cholecystectomy—is regarded as the definitive treatment and remains the most frequently performed elective abdominal operation worldwide (Russo et al., 2004; Strasberg, 2008).

Cholecystectomy was first performed as an open procedure by Carl Langenbuch in 1882, and this approach remained the surgical standard for more than a century. The advent of minimally invasive surgery, with the first laparoscopic cholecystectomy performed by Erich Mühe in Germany in 1985 and subsequently popularized by Mouret, Dubois, and Perissat in France, revolutionized the management of gallstone disease (Reynolds, 2001). Within only a few years of its introduction, the laparoscopic technique had been widely adopted, and by the early 1990s it was already being described as the new "gold standard" for the elective treatment of symptomatic cholecystolithiasis (Soper et al., 1992).

A large body of comparative evidence has demonstrated that laparoscopic cholecystectomy (LC), when performed in appropriately selected patients, is associated with reduced postoperative pain, shorter hospital stay, faster return to daily activities, lower wound-related complication rates, and improved cosmetic outcomes when compared with open cholecystectomy (OC) (Keus et al., 2010; McMahon et al., 1994; Trondsen et al., 1993). A systematic review and pooled analysis covering thirty years of laparoscopic cholecystectomy further confirmed sustained improvements in safety and reductions in length of hospitalization (Pucher et al., 2018). Nonetheless, the open technique retains an important role in specific clinical scenarios, including severe acute cholecystitis with extensive inflammation, suspected gallbladder malignancy, complex anatomical conditions, and conversion from laparoscopy because of bleeding, dense adhesions, or unclear anatomy (Bingener-Casey et al., 2002; Coccolini et al., 2015). Reported conversion rates from laparoscopic to open surgery vary between 2% and 15%, depending on patient factors, disease severity, and surgical experience (Bingener-Casey et al., 2002).

In parallel with the diffusion of minimally invasive techniques, the overall frequency of cholecystectomy has continued to rise (Tsui et al., 2013). Despite the dominance of LC, postoperative complications—including wound infection, hemorrhage, biliary leakage, bile duct injury, and prolonged ileus—continue to occur at non-negligible rates, underscoring the importance of meticulous preoperative evaluation and careful patient selection (Khan et al., 2007; Shea et al., 1996; Z'graggen et al., 1998). The American Society of Anesthesiologists (ASA) physical status classification and the systematic assessment of comorbidities such as obesity, diabetes mellitus, and arterial hypertension remain key elements for stratifying surgical risk (Agrawal & Sood, 2015; Dolan et al., 2009).

In the Republic of North Macedonia, and particularly within the Polog region, the Clinical Hospital of Tetova serves as the principal regional referral center for surgical pathology, including biliary tract disease. Both laparoscopic and open cholecystectomy are routinely performed in this institution. However, local data describing the demographic profile, risk burden, and perioperative outcomes of patients undergoing cholecystectomy in this region remain scarce. Generating such evidence is of practical relevance for guiding surgical decision-making, optimizing perioperative management, and benchmarking local practice against international standards.

Aim of the study

The aim of the present study was to analyze the demographic and clinical characteristics, comorbidity profile, and perioperative outcomes of patients operated for symptomatic cholecystolithiasis at the Clinical Hospital of Tetova, and to compare the postoperative course—particularly the frequency of complications and the length of hospitalization—between patients managed by laparoscopic cholecystectomy and those managed by the

conventional open technique. A secondary objective was to characterize the distribution of anesthesiologic risk according to the ASA classification and to assess the prevalence of relevant metabolic comorbidities (arterial hypertension, diabetes mellitus, and increased BMI) in this surgical population.

Materials and methods

3.1 Study design and setting: A retrospective observational study was conducted at the Department of Surgery of the Clinical Hospital of Tetova, Republic of North Macedonia, in collaboration with the Faculty of Medical Sciences of the University of Tetova. The medical records of consecutive adult patients who underwent cholecystectomy for symptomatic cholecystolithiasis at the institution were reviewed. The study was carried out in accordance with the principles of the Declaration of Helsinki, and patient confidentiality was preserved throughout.

3.2 Study population: A total of 64 patients were included. Inclusion criteria were: (i) age ≥ 18 years; (ii) clinical, biochemical, and ultrasonographic confirmation of cholecystolithiasis; (iii) elective or urgent cholecystectomy performed at the institution; and (iv) availability of complete clinical and surgical records. Patients with confirmed or suspected gallbladder malignancy, isolated common bile duct stones treated endoscopically without subsequent cholecystectomy, or incomplete medical records were excluded.

3.3 Variables and data collection: For each patient, the following data were extracted from the institutional records: age, sex, body mass index (BMI), preoperative comorbidities (arterial hypertension and diabetes mellitus), anesthetic risk according to the ASA physical status classification, type of surgical procedure (LC versus OC), intra- and postoperative complications, and length of hospital stay. Postoperative complications recorded included wound infection, hemorrhage from the surgical wound, and persistent or prolonged postoperative pain.

3.4 Surgical procedures: Laparoscopic cholecystectomy was performed using a standard four-port technique under general anesthesia, with carbon dioxide pneumoperitoneum, careful dissection of Calot's triangle to obtain the critical view of safety, and clipping of the cystic artery and cystic duct prior to gallbladder removal, in accordance with internationally accepted standards (Litwin & Cahan, 2008; Yamashita et al., 2013). Open cholecystectomy was performed through a right subcostal (Kocher) incision following standard anatomical dissection. The decision regarding the surgical approach was based on clinical presentation, intraoperative findings, anatomical considerations, available equipment, and surgeon judgment.

3.5 Outcome measures and statistical analysis: The primary outcomes were the frequency of postoperative complications and the length of postoperative hospital stay. Secondary outcomes included the distribution of comorbidities, BMI categories, and ASA classification across the surgical groups. Continuous variables are presented as range (minimum–maximum), while categorical variables are presented as absolute frequencies and percentages. Comparisons between LC and OC groups were performed in a descriptive manner, given the size of the cohort.

Results

4.1 Demographic characteristics: The study included 64 patients operated for symptomatic cholecystolithiasis. Of these, 48 (75%) were female and 16 (25%) were male, yielding a female-to-male ratio of 3:1. The age of patients ranged from 23 to 72 years, with the majority of cases concentrated in the fourth to sixth decade of life. The clear female predominance observed in this cohort is consistent with the well-established epidemiological pattern of gallstone disease, in which women are affected approximately two to three times more frequently than men (Shaffer, 2006; Stinton & Shaffer, 2012).

4.2 Surgical approach: Forty-six patients (71.9%) were operated using the laparoscopic approach, while 18 (28.1%) underwent the conventional open technique. This distribution reflects the institutional preference for minimally invasive management whenever feasible, with the open approach reserved for selected cases characterized by complex local anatomy, severe inflammation, or other technical contraindications.

4.3 Comorbidity profile and BMI: The comorbidity burden of the cohort was substantial. Arterial hypertension was present in 48 patients (75%) and diabetes mellitus in 32 (50%); a considerable proportion of patients had both conditions concurrently. Approximately 70% of patients presented with a BMI in the range of 28–30 kg/m², corresponding to overweight or early obesity, while the remainder had values either within the normal range or above 30 kg/m². This metabolic profile is consistent with the recognized association between gallstone disease and the metabolic syndrome (Lammert et al., 2016; Shaffer, 2006).

4.4 ASA classification: Preoperative anesthetic risk evaluation according to the ASA physical status classification revealed that 44 patients (68.75%) were classified as ASA I, 16 (25%) as ASA II, and 4 (6.25%) as ASA III. None of the patients were classified as ASA IV or higher. The summary of demographic and clinical characteristics is presented in Table 1.

Table 1. Demographic and clinical characteristics of the study population (n = 64).

Variable	n	%
Sex – Female	48	75.0
Sex – Male	16	25.0
Age range (years)	23–72	—
Laparoscopic cholecystectomy	46	71.9
Open cholecystectomy	18	28.1
Arterial hypertension	48	75.0
Diabetes mellitus	32	50.0
BMI 28–30 kg/m² (approx.)	≈45	≈70
ASA I	44	68.75

Variable	n	%
ASA II	16	25.0
ASA III	4	6.25

4.5 Postoperative complications: The frequency of postoperative complications was clearly higher among patients who underwent the open procedure. Wound infection, hemorrhage from the surgical wound, and persistent postoperative pain were the predominant complications observed in the OC group. In contrast, the LC group exhibited a substantially lower complication burden, in line with the findings of large comparative studies and meta-analyses (Coccolini et al., 2015; Keus et al., 2010; Shea et al., 1996). No major bile duct injury, postoperative mortality, or readmission for complications was observed in this cohort. The distribution of postoperative complications by surgical technique is summarized in Table 2.

Table 2. Postoperative complications by surgical technique.

Complication	Laparoscopic (n = 46)	Open (n = 18)
Wound infection	Low frequency	Higher frequency
Wound hemorrhage	Rare	More frequent
Prolonged postoperative pain	Less frequent	More frequent
Length of hospital stay	Shorter	Longer

4.6 Length of hospital stay: Length of postoperative hospitalization was notably shorter in patients who underwent laparoscopic cholecystectomy compared with those treated by the open approach. This finding is in agreement with the broader international literature, which consistently reports shorter hospital stays after LC, even in patients with significant comorbidities (Ahmad et al., 2008; Keus et al., 2010; Pucher et al., 2018).

Discussion

The present study analyzed 64 patients operated for symptomatic cholecystolithiasis at the Clinical Hospital of Tetova, comparing the perioperative outcomes of laparoscopic and open cholecystectomy. The principal findings can be summarized as follows: a clear female predominance, a high prevalence of metabolic comorbidities (arterial hypertension, diabetes mellitus, and increased BMI), a predominantly low-to-intermediate ASA risk profile, a higher rate of wound-related complications and persistent pain in the open group, and substantially shorter hospitalization in the laparoscopic group. These observations are largely consistent with international evidence and reinforce the role of LC as the preferred surgical approach for symptomatic gallstone disease.

The female-to-male ratio of 3:1 observed in this cohort is in agreement with the well-documented sex predisposition to gallstone disease. Stinton and Shaffer (2012) reported that women are approximately twice as likely as men to develop cholelithiasis, with the difference being largest during the reproductive years and decreasing in older age groups. Estrogens increase biliary cholesterol secretion while progesterone reduces gallbladder motility, and pregnancy further accentuates these effects (Lammert et al., 2016). Our findings support the continued relevance of these risk patterns in the population of the Polog region.

The age distribution, ranging from 23 to 72 years, with most patients in the fourth to sixth decade, is in keeping with the natural history of cholelithiasis, in which the prevalence of gallstones increases steadily with age (Diehl, 1991; Shaffer, 2006). The relatively young lower bound of the age range observed in our cohort highlights that gallstone disease is by no means restricted to elderly patients, and that surgical referral pathways must accommodate younger adults presenting with biliary symptoms.

The high prevalence of metabolic comorbidities deserves particular attention. Arterial hypertension was present in three quarters of the cohort and diabetes mellitus in half, while approximately 70% of patients had a BMI in the overweight to early obese range. These figures are consistent with the well-established association between gallstone disease and components of the metabolic syndrome (Lammert et al., 2016; Shaffer, 2006). Obesity, in particular, increases biliary cholesterol saturation and promotes gallbladder hypomotility, while insulin resistance contributes to lithogenic bile composition (Lammert et al., 2016). The clustering of these risk factors in our patients underscores the importance of comprehensive perioperative evaluation and multidisciplinary management, especially in regions where the prevalence of metabolic disease is rising.

Despite the high prevalence of comorbidities, the majority of patients in our cohort were classified as ASA I or II, with only a small minority (6.25%) classified as ASA III. This relatively favorable risk profile is comparable to that reported in other observational series of elective cholecystectomy (Agrawal & Sood, 2015; Dolan et al., 2009). It is important to note that ASA classification is one of the most consistent predictors of postoperative morbidity and mortality after cholecystectomy, with higher classes associated with longer hospital stay, greater rates of complications, and higher conversion rates from laparoscopic to open surgery (Agrawal & Sood, 2015; Bingener-Casey et al., 2002; Dolan et al., 2009).

Approximately 71.9% of our patients underwent laparoscopic cholecystectomy, a figure broadly aligned with international trends, which show that LC has become the dominant approach in elective biliary surgery (Tsui et al., 2013). The remaining 28.1% were managed by the open technique, generally because of severe local inflammation, complex anatomy, or technical considerations. This proportion is somewhat higher than that reported in some Western series, in which open cholecystectomy is now performed in fewer than 10–15% of cases (Pucher et al., 2018; Tsui et al., 2013), and may reflect both case selection and resource availability in the regional setting. Bingener-Casey et al. (2002) similarly reported conversion and primary open rates that varied considerably according to patient comorbidities, acute presentation, and surgeon experience.

The higher frequency of wound infection, wound hemorrhage, and persistent postoperative pain in our open group corresponds closely to the patterns described in randomized trials and meta-analyses comparing the two approaches. McMahon et al. (1994) and Trondsen et al. (1993) demonstrated significantly lower rates of wound complications and postoperative pain in laparoscopic patients in early randomized comparisons. Subsequent Cochrane reviews and updated meta-analyses have consistently shown that LC is associated with fewer wound-related complications, less postoperative pain, faster mobilization, and earlier discharge from hospital (Keus et al., 2010; Pucher et al., 2018). Coccolini et al. (2015), in their meta-analysis comparing LC and OC in acute cholecystitis, also reported significantly lower morbidity and shorter hospital stay in the laparoscopic arm, even in this more challenging clinical setting.

The substantial reduction in length of hospital stay observed in the laparoscopic group is one of the most clinically and economically meaningful advantages of the minimally invasive approach. Multiple studies and pooled analyses have shown that LC enables earlier resumption of oral intake, lower analgesic requirements, and faster mobilization, leading to discharge within 24–48 hours in selected cases and even to ambulatory or day-case management in carefully chosen patients (Ahmad et al., 2008; Pucher et al., 2018). These benefits translate into

lower healthcare costs and improved patient satisfaction, while preserving—and in many series improving—safety outcomes (Pucher et al., 2018).

Although our cohort did not record major bile duct injuries or postoperative mortality, it should be emphasized that LC is not without specific risks. Bile duct injury, although uncommon, remains a feared complication and has been reported with somewhat higher frequency after LC than after OC in some early series (Khan et al., 2007; Shea et al., 1996; Z'graggen et al., 1998). Adherence to standardized technical principles, in particular the routine achievement of the critical view of safety, is widely recommended to minimize this risk (Litwin & Cahan, 2008; Yamashita et al., 2013). Strasberg (2008) further emphasized the importance of timely surgical intervention in acute calculous cholecystitis, ideally within the first week of symptom onset, to reduce both operative difficulty and the risk of conversion.

It is also important to acknowledge that not all patients experience complete symptom relief after cholecystectomy. Berger et al. (2003) reported that abdominal symptoms persist in a proportion of patients postoperatively, particularly when symptoms preoperatively were less specifically biliary in character. Careful selection of surgical candidates, with proper correlation of clinical, biochemical, and imaging findings, is therefore essential to optimize outcomes.

Our study has several limitations. First, the retrospective design and single-center nature of the analysis restrict the generalizability of the findings. Second, the relatively small sample size (n = 64) and the absence of formal inferential statistical testing limit the strength of the comparisons between LC and OC. Third, allocation to surgical approach was not randomized but determined by clinical judgment, which may have introduced selection bias, with more complex cases preferentially allocated to the open technique. Despite these limitations, the present study provides locally relevant data on a representative cohort of patients operated for cholecystolithiasis at a regional tertiary hospital and confirms patterns described in larger international series. Future prospective, multicenter studies with standardized definitions of complications and longer follow-up are warranted to refine outcome estimates and to evaluate long-term symptomatic and functional results.

Conclusion

In this retrospective single-center study of 64 patients operated for symptomatic cholecystolithiasis at the Clinical Hospital of Tetova, in collaboration with the Faculty of Medical Sciences of the University of Tetova, laparoscopic cholecystectomy was the predominant surgical approach (71.9%) and was associated with fewer wound-related complications, less prolonged postoperative pain, and substantially shorter hospitalization compared with the open technique. The cohort was characterized by a marked female predominance, a high prevalence of metabolic comorbidities (arterial hypertension in 75%, diabetes mellitus in 50%, and BMI in the overweight range in approximately 70% of patients), and a predominantly low-to-intermediate anesthesiologic risk profile. These results reinforce the position of laparoscopic cholecystectomy as the preferred treatment for symptomatic cholecystolithiasis and emphasize the importance of comprehensive preoperative evaluation, including ASA classification and detailed assessment of metabolic comorbidities, in order to optimize patient selection, perioperative management, and surgical outcomes in regional clinical practice.

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GEOMETRY AND ORDER: ON THE NEED FOR A THEORETICAL FRAMEWORK FOR THE ANALYSIS OF THE PLANS OF THE HOUSES OF CULTURE IN MACEDONIA

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Abstract

This theoretical article proposes a framework for the analysis of the plans of the Houses of Culture in Macedonia, with a particular focus on the relationship between geometric form, functional organisation and architectural order. Rather than treating the plan as a purely technical document or a passive reflection of the programme, this theoretical article reads it as a structure of thought, in which geometry operates as the organising mechanism of space, movement and hierarchy. The discussion draws on a theoretical synthesis of the principal authors of architectural analysis and plan morphology Francis D. K. Ching, Simon Unwin, Roger H. Clark and Michael Pause, Robin Evans, Christopher Alexander, Julienne Hanson and Nuran Saliu who all approach the plan as a geometric, spatial and meaningful structure, moving from form and order to the vocabulary of forms and the logical construct. The aim is not to present case studies, but to build a transferable analytical model that can be applied to the Houses of Culture in Macedonia. The argument is that the geometry of the plan is neither neutral nor merely compositional: it determines how the building is oriented, how functions are distributed, how movement is generated, how clarity or fragmentation is produced, and how the public character of the building is shaped. The analysis is therefore developed in layers geometric contour, axes and organising centre, functional zoning, spatial hierarchy and circulation, and the relationship between form and architectural meaning. Only through such a multi-layered reading can the plan be understood as the place where geometric form is translated into a functional and spatial system, and where the Houses of Culture articulate a specific public order within socialist modernism.

Keywords: Houses of Culture; geometry of the plan; architectural order; planimetric analysis; modernism; Macedonia.

Introduction

In the former Yugoslavia, during the period of socialist modernism, the Houses of Culture were created as part of a wide public infrastructure, in which the institution of the "house of culture" became the basic unit for the development of the cultural network and for the architectural materialisation of the goals of socialist culture. Houses of Culture appeared almost immediately after the Second World War, as an institutional response to rapid urbanisation and to the need for collective infrastructure in the new industrial cities. They had a dual function:on the one hand, the transformation of "the working person" from a passive consumer into an active subject of culture and the consolidation of the social, political and cultural life of the local community around a shared core (Dimić, 1988; Varga, 1976).

Architectural modernism in Macedonia is closely tied to the shaping of public space and to the construction of a new urban identity, especially during the period of accelerated urbanisation and industrialisation that followed the war. Architecture did not function only as a functional solution, it operated as an active instrument of socialist modernisation. Public buildings simultaneously articulated the idea of cultural democratisation, decentralisation and the social cohesion of the new urban communities. (Saidi et al., 2024) Macedonian architects also aimed to encode national elements in their buildings, producing a tension between modernist universalism and local identity. A tension that would mark the entire architectural production of the socialist period in the region.(Elezi & Saliu, 2014; Saidi et al., 2021)The modernist architectural language clear volumes, rational-functional plans and a legible constructive logic was gradually translated into regional interpretations, in which local materials and façade

articulations grounded modernism in a specific territorial identity (Kulić, Mrduljaš & Thaler, 2012; Stierli & Kulić, 2018). According to Saidi Qazimi (2025), modern architecture aspires to a more rational, functional and universal language, moving away from traditional and symbolic forms; this approach reduces the role of ornament and can introduce a distance between the building and the way users understand and experience it.

Houses of Culture should be understood not simply as service buildings, but as part of the broader modernist project of producing a public sphere and a contemporary urban identity. In most historical readings, these objects are discussed mainly from the standpoint of institutional function, urban history or stylistic categorisation. This theoritical article shifts the focus to the plan. The basic argument is that the plan of the House of Culture must be understood as the place where geometry, function and architectural order are most clearly intertwined. The central question of the study is therefore: how is geometric form converted into a functional and spatial system? To address this question, the paper does not present case studies, but builds a theoretical foundation and an analytical matrix that can be applied to the corpus of Houses of Culture in Macedonia. This matrix draws on the understanding of form, organisation, circulation and order in Ching (2014) and Unwin (2020), on the diagrammatic analysis of Clark and Pause (2012), on the active role of geometry in Evans (1995), on the concept of pattern language in Alexander, Ishikawa and Silverstein (1977), on the configurational reading of the plan in Hanson (1998), and on the morphological approach of Saliu (2018) to the "vocabulary of forms" and the logical construct of the plan. Recent developments in the field of artificial intelligence have demonstrated that the architectural plan can be read and generated as a logical structure of geometric forms and spatial relationships (Saliu & Elezi, 2025a; 2025b), further confirming the need for clear analytical frameworks for reading the plan as proposed in this article.

The Geometry of the Plan as a Theoretical Problem

For Robin Evans, geometry in architecture is not a neutral basis for form, but an active agent moving between thought, imagination, drawing and construction (Evans, 1995). It is precisely this idea that turns the architectural plan into something more than a technical notation: it becomes the trace of a conceptual and operational process. When Evans suggests that architects do not produce geometry but rather consume it, he implies that geometry operates as the medium through which form becomes thinkable, drawable and buildable. For the analysis of the Houses of Culture, this means that the form of the plan should not be read only as a figure, but as an instrument that organises the relationships between the entrance, the foyer, the auditorium, the stage, the backstage, the secondary spaces and the user's experience.

Following the same line of thought, Francis D. K. Ching approaches architecture through the inseparable relationship between form, space and order (Ching, 2014). In his work, the organisation of space, the elements and relations of circulation, and proportion and scale are presented as the fundamental components of architectural reading. The geometry of the plan, cannot be reduced to its outer contour it must also be sought in the way spaces are organised, how they are connected, and how they orient movement. Simon Unwin extends this understanding by treating architecture as a "universal language of place-making", in which the themes of spatial organisation include axis, grid, datum, transition, hierarchy and the heart the central or gravitational space of the building (Unwin, 2020). For the Houses of Culture, this approach is particularly relevant, since these buildings are typically articulated around a public core and around a distribution system that is either explicit or mediated. According to Ramani-Halili et al. (2025), geometry is a fundamental language of architecture, shaping spatial organization, structural order, and visual expression.

The geometry of the plan must be understood as an operational order. It is not merely the "appearance" of the plan, but the logic by which the plan generates clarity, orientation, separation or interweaving. The first questions are not simply whether the plan is rectangular, linear or compact. The more important questions are: is there a clearly defined entrance axis? Is there an organising centre? Is the auditorium dominant, and how does it relate to the foyer? Does the plan generate a centred, radial, sequential or fragmented order? At this level, geometry becomes a form of the language of architectural thinking.

From Form to Function and Movement

Christopher Alexander shifts the focus from form as a closed object to form as a system of repeatable solutions. In A Pattern Language, "patterns" are defined as units of a language that respond to design problems and that can be combined to produce a variety of coherent solutions (Alexander, Ishikawa, & Silverstein, 1977). For the Houses of Culture, this approach is useful because it allows the plan to be read not as a unique and inexplicable composition, but as a configuration of recognisable patterns: the entrance as a point of transition, the foyer as a distributing space, the auditorium as the dominant core, the backstage as a controlled zone, and the clubs or galleries as semi-public areas. Geometry is not only a formal abstraction; it is the way in which patterns become legible and combine into a whole.

Julienne Hanson, in Decoding Homes and Houses, deepens this reading by understanding the plan as a "pattern of organised space" (Hanson, 1998). Although her book focuses on the dwelling, her thesis is directly transferable to public buildings, the plan is not merely an aggregation of rooms, but a configuration of relationships. Hanson shows that space carries social and symbolic information, and that this can be read through relations of visibility and permeability. In the case of the Houses of Culture, this means that the geometry of the plan can show not only how functions are placed, but also who has access where, which spaces are more exposed, which are deeper, and where institutional control begins. The relationship between the public and the backstage, between the foyer and the auditorium, or between the administration and the main body of the building thus becomes a question that is at once geometric and social. These spaces are organised hierarchically, and the transition from one to another is characterised by a threshold; according to Limani (2025), such transitional elements generate distinct spatial experiences, articulating the boundary between public and private through the same logic of hierarchy and accessibility that governs the architectural plan.

This logic is reinforced by Clark and Pause, who propose architectural analysis through a diagrammatic vocabulary: geometry, massing, plan-section, circulation, part-to-whole unity, hierarchy, symmetry and use relationships (Clark & Pause, 2012). Their value for this article lies in the fact that the plan can be divided into analytical layers that can be compared with one another, rather than only described in text. A parallel approach is found in Saliu's doctoral dissertation (Saliu, 2018), in which built form is translated into a "logical construct" and architectural complexes are read through a "vocabulary of forms", based on contours, basic units and morphological relationships. Saliu develops this approach in the context of hospitals, the underlying principle has direct value public buildings as Houses of Culture: the plan can be reduced to geometric elements and fundamental relations without losing its architectural intelligence.

For Saliu, the plan is not seen merely as a final drawing, but as a logical structure that can be decomposed into basic forms and rules of combination. The significance of his work lies in the way it reads the plan: as a composition of contour, principal units and the morphological relations between them. This reading converges directly with Ching's order, with Unwin's themes of place-making, with Clark and Pause's analytical diagrams, with Evans's active geometry, with Alexander's patterns and with Hanson's configurational space. Saliu offers a

methodological bridge between the descriptive vocabulary of these authors and an operational framework for reading the plan, one that can be transferred from the hospital to the Houses of Culture, where the same question reappears: how do basic geometric units organise themselves into a public order?

The Proposed Framework for Analysing the Plans

Based on this theoretical framework, a clear reading model can be built for the plans of the Houses of Culture in Macedonia. The first step is the identification of the principal geometric principle. This means determining whether the plan is compact, linear, central, axial, fragmented or hybrid. At this stage, the analysis is concerned with the basic contour, with the relationship between the main blocks, and with the way in which the body of the auditorium is connected to the entrance, the foyer and the secondary segments. The aim is not the formal naming of the figure, but the understanding of its logic, is the building organised around a central mass, does it develop sequentially, is it divided into functional wings; or is it composed of volumes linked by transitional spaces?

The second step is the reading of the axis, the centre and the datum. Here the question is where the order of the plan begins and what holds it together. In the Houses of Culture, this is often *the entrance–foyer–auditorium relationship*. If this sequence is direct, the plan produces clarity and a high degree of orientation. If it is mediated by turns, splits or lateral distributions, it can generate a more complex experience sometimes more ceremonial, sometimes more fragmented. The dominance of a central foyer, of an auditorium placed at the core of the building, or of a strong frontal axis are indicators of geometric order and of the public character of the object. In Unwin (2020), these elements are linked to axis, datum, transition and hierarchy; in Ching (2014), to the organisation of space and to the relations of circulation.

The third step is functional zoning. It is precisely here that the formula:

"geometry → organises the plan → distributes functions → generates movement → produces order → conveys architectural meaning"

becomes operative. In the Houses of Culture, the plan typically contains at least five fields: the public zone of the entrance and the foyer; the zone of the auditorium and the stage; the backstage and the technical spaces; the administration; and the secondary cultural functions, such as clubs, galleries or multi-purpose rooms. The analysis must observe not only where these fields are placed, but also how the geometry distributes them: are they grouped around a core, divided into linear strips, placed symmetrically around the auditorium, or do they form two parallel systems public and serving? At this point, the correspondence between form and function becomes a direct evaluation criterion.

The fourth step is the analysis of the dominant space and of the user's movement. Every successful plan of a Houses of Culture has a gravitational space: sometimes the auditorium, sometimes the foyer, sometimes the mediation between them. The decisive question is whether this dominant space is only the largest, or whether it is also the one that organises the others. This is linked to hierarchy, but also to the user's experience: how the public enters, where it stops, where it disperses, how legible the passage to the auditorium is, and how separate the movements of staff, performers and technicians are. Hanson (1998) is particularly valuable here for understanding depth, accessibility and control, while Clark and Pause (2012) offer a diagrammatic representation of circulation and of part-to-whole relationships.

The fifth step is the interpretation of what the geometry produces. This is the phase in which analysis moves from description to meaning. An axial and centred geometry can produce monumentality, ceremoniality and high legibility. A compact geometry can produce functional efficiency and institutional concentration. A fragmented geometry can produce a plurality of uses, but also disorientation. A clear foyer positioned as a node can create a genuine internal

public space; a plan in which the auditorium dominates absolutely can reduce the experience of the building to the logic of the performance. The analysis of the plan does not stop at "how it is made", but reaches "what it does". It is at this point that architectural order appears as the result of the interaction between geometry, function and experience.

The Evaluation Matrix

The analytical model outlined above can be made operational through the evaluation matrix shown in Figure 1. The matrix translates the five steps into a comparative instrument with guiding questions, indicators, theoretical references and a numerical score from 1 to 5 for each layer. The points are intended to support comparative readings across the analysed Houses of Culture, while the qualitative columns preserve the architectural specificity of each case. The matrix is therefore not a substitute for analysis, but a structured device that allows the reader to move systematically from geometric form to architectural order.

Figure 1. Evaluation Matrix — Planimetric Analysis of the Palaces of Culture

Five-layer analytical framework: from geometric form to architectural order

Analytical layer	Guiding questions	Indicators	Theoretical references	Characteristic diagram	Score (1–5)
I. Geometric figure	Is the plan compact, linear, centralised or hybrid? How does the hall relate to the entrance and foyer? What logic governs the form?	Basic contour Principal mass Hall–entrance link Dominant formal principle	Ching (2014) Evans (1995) Saliu (2018)	 *Ching (2014)*	
II. Axes and centre	Where does the order of the plan begin? Is there a legible entry axis? Is there an organising centre? How does the datum operate?	Frontal axis Central foyer Entrance–hall sequence Spatial hierarchy	Unwin (2020) Ching (2014) Evans (1995)	 *Evans (1997), Fig. 10* *Amesbury House, Webb, 1661*	
III. Functional zoning	How are the five principal fields distributed? Are they grouped or separated? Public-to-backstage ratio? Do form and function correspond?	Entrance / foyer zone Auditorium and stage Backstage / technical Administration / secondary	Alexander et al. (1977) Hanson (1998) Saliu (2018)	 *Saliu (2018), Fig. 4.19*	
IV. Movement and hierarchy	How does the public enter? Are flows separated (public/staff)? Which space dominates? How deep is the institutional control?	Depth of accessibility Public / staff separation Gravitational space Circulation diagram	Hanson (1998) Clark & Pause (2012)	 *Hanson (1998)*	
V. Architectural meaning	What does the geometry produce? Monumentality or efficiency? Genuine public space? Clarity or fragmentation?	Public order Institutional character Spatial meaning Form → functional system	Evans (1995) Unwin (2020) Clark & Pause (2012)	 *Clark & Pause (2012)*	
Total					/ 25

Geometric form → organises the plan → distributes functions → generates movement → produces order → conveys architectural meaning

Source: Framework proposed by the authors, based on Ching (2014), Evans (1995), Unwin (2020), Alexander et al. (1977), Hanson (1998), Clark & Pause (2012), Saliu (2018).

Figure 1. Evaluation matrix for the analysis of the plans of the Houses of Culture (a five-layer analytical framework, from geometric form to architectural order).

Each layer of the matrix is accompanied by a characteristic diagram of the corresponding author, illustrating the analytical logic on which that layer rests. The first layer the geometric figure is grounded in Ching's spatial organisations (Ching, 2014): centralised, linear, radial, clustered and grid organisation, which represent the basic principles by which the plan of a House of Culture can be classified as compact, linear or hybrid. The second layer axes and centre is illustrated by the plan of Amesbury House by John Webb (1661), as cited by Evans (1997) in "Figures, Doors and Passages" (Fig. 10): a plan with directly interconnected rooms and no intermediate corridor, in which the organising centre and the axes of circulation are legible as the spatial structure of the building itself. The third layer functional zoning is supported by Figure 4.19 of Saliu's dissertation (Saliu, 2018), where the planar cuboids A, B, C, D and E with orientation arrows show how simple states are organised in order to distribute functions within the architectural form. The fourth layer movement and hierarchy is illustrated by Hanson's justified graph (Hanson, 1998): plan, spatial graph and justified graph with depth from 0 to 5, which measure accessibility, visibility and the institutional control of spaces. The

fifth layer architectural meaning closes with the full analytical panel of Clark and Pause (2012), in which structure, geometry, parti, circulation, hierarchy and part-to-whole relationships are overlaid on the same plan, moving the reading from the description of the form to the interpretation of order and architectural meaning.

Conclusions

The Houses of Culture in Macedonia should be read as public objects in which the plan is the principal carrier of architectural order. Within the brief history of socialist modernism in the region, these buildings were part of a wider cultural infrastructure and of a project for the education of the population and for the active participation of the citizen. Their contribution cannot be fully understood without entering the geometry of their plans. Only there does it become visible how form organises function, how functional distribution generates movement, and how movement, in turn, produces hierarchy, orientation, clarity or fragmentation.
This article has proposed a theoretical foundation for such a reading. By synthesising Evans (1995), Ching (2014), Unwin (2020), Alexander, Ishikawa and Silverstein (1977), Hanson (1998), Clark and Pause (2012) and the morphological approach of Saliu (2018), it argues that the plan must be analysed in layers: as a geometric figure, as a system of axes and centres, as a functional organisation, as a scenario of movement and as a structure of meaning. The plan is not only a division of spaces, but a document of architectural thought. Future research on the Houses of Culture in Macedonia should move from typological or stylistic description towards comparative planimetric analysis, in which the fundamental question remains the one that has guided the present study: what does the geometry of the plan produce, and how is it converted into a public architectural order?

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EVALUATION OF BRUCELLOSIS SURVEILLANCE IN NORTH MACEDONIA USING A ONE HEALTH APPROACH

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Abstract

Brucellosis is an important zoonotic disease that continues to represent a public health and socio-economic concern in North Macedonia despite a substantial decline in incidence over recent decades. This study aimed to evaluate the human brucellosis surveillance system in North Macedonia and assess its performance according to standard surveillance attributes. The evaluation was conducted through a review of the National Program for Prevention and Control of Brucellosis, national surveillance reports, legislation, and epidemiological data from 1980 to 2023. Surveillance system attributes assessed included data quality, sensitivity, predictive value positive, representativeness, timeliness, stability, flexibility, and usefulness. The surveillance system is based on mandatory passive reporting with laboratory confirmation and coordination between the Institute of Public Health and the Food and Veterinary Agency under a One Health approach. Human brucellosis incidence declined markedly following implementation of livestock vaccination programs, reaching only six reported human cases in 2023. The system demonstrated strengths including national coverage, legal support, standardized case definitions, and integration with veterinary surveillance. However, important limitations were identified, including reliance on paper-based reporting, lack of integrated electronic databases, incomplete reporting indicators, and possible under-reporting in rural areas. Limited epidemiological staffing in some regional centers for public health may also affect surveillance performance. The surveillance system remains effective and useful for monitoring and control of brucellosis, but modernization is needed to sustain elimination efforts. Strengthening electronic integration, improving timeliness and completeness of reporting, maintaining livestock vaccination, and increasing epidemiological capacity are essential to ensure continued control and prevention of brucellosis in North Macedonia.

Keywords: Brucellosis, Surveillance system, One Health, Zoonotic disease

Introduction

Brucellosis is a zoonotic bacterial infection of major public health and socio-economic concern. In North Macedonia, the disease was first recorded in epidemic form in 1980 in Bitola municipality and peaked in 1992 with 922 cases across 22 municipalities. Since the introduction of livestock vaccination in 2008, incidence in humans has declined markedly. In 2023, only 6 cases were reported (0.3 per 100,000), compared to annual averages of more than 270 in the 1980–2000s period. Despite this decline, brucellosis remains a priority zoonosis due to its chronic health effects, hospitalisation burden, and risk of recurrence.

Table 1. Reported brucellosis cases and incidence in North Macedonia, 2012–2023

Year	Cases	Incidence (per 100,000 population)
2012	82	4.0
2013	20	1.0
2014	18	0.9
2015	15	0.7
2016	16	0.8
2017	10	0.5
2018	7	0.3
2019	9	0.45
2020	7	0.34
2021	6	0.29

2022	4	0.19
2023	6	0.3

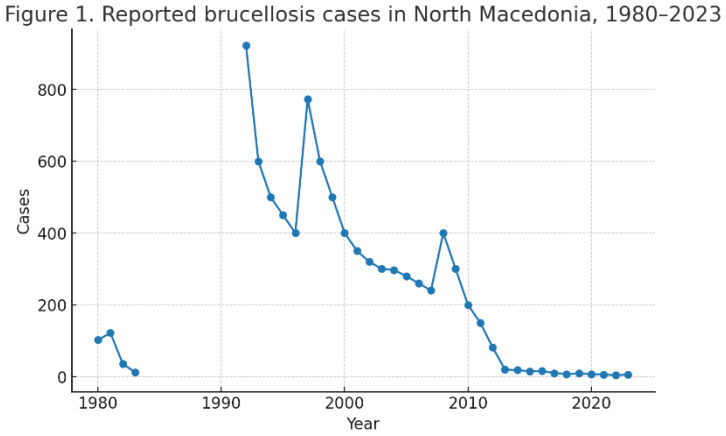


Figure 1. Reported brucellosis cases in North Macedonia, 1980–2023

North Macedonia has implemented a National Programme for Prevention and Control of Brucellosis, integrating veterinary and human health actions. This programme for 2025 outlines objectives, measures, and indicators to sustain low incidence. Evaluation of the surveillance system is critical to assess its capacity to detect, monitor, and respond to brucellosis, in alignment with ECDC guidance and MediPIET standards.
Objectives of this evaluation:
- To describe the surveillance system for brucellosis in North Macedonia.
- To assess its performance according to standard attributes (data quality, sensitivity, predictive value positive, representativeness, timeliness, stability).
- To provide recommendations to strengthen the system.

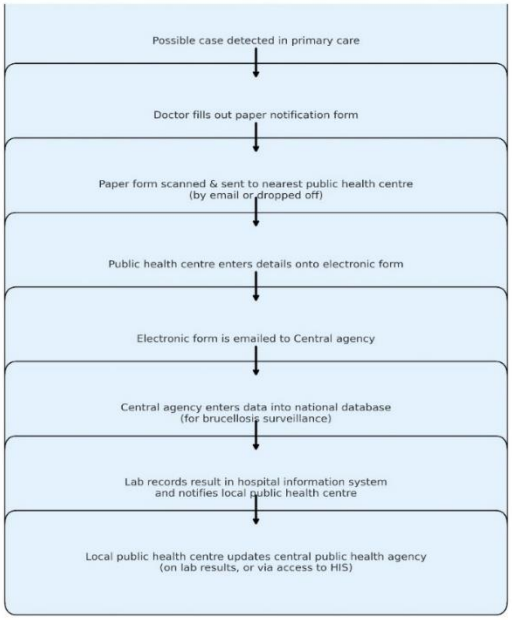
Methods

2.1 Description of the surveillance system: The evaluation was based on review of the 2025 National Brucellosis Programme, IPH surveillance reports, and relevant legislation. Stakeholders include the Ministry of Health, Institute of Public Health (IPH), 10 regional Centres for Public Health (CPH), local epidemiological units, and the Food and Veterinary Agency (AHV).
Population under surveillance: the entire population of North Macedonia, with focus on rural and livestock-exposed groups. Case definitions follow the national communicable disease regulations and WHO/ECDC standards. The surveillance system is primarily passive with stimulated and active elements during outbreaks.
Data flow: cases are detected and reported by clinicians to regional CPH epidemiologists, entered into the national database managed by IPH, and shared with the Ministry of Health and AHV. Feedback is provided quarterly and annually in aggregated reports.

2.2 Analysis of the surveillance system: Attributes assessed: Data quality, Sensitivity, Predictive Value Positive (PVP), Representativeness, Timeliness, Stability. Methods included document review, analysis of surveillance data (1980–2023 trends, 2012–2021 incidence), and comparison with programme indicators.

Results

3.1 Description of the surveillance system: Objectives: To prevent and control brucellosis in humans, reduce incidence, avoid complications, achieve microbiological confirmation of all suspected cases, and improve awareness among health workers and the population.



Case definitions: Standard case definitions for acute, recurrent, and reinfection cases are applied. All cases must be notified to the epidemiological service of the local CPH.
System type: The system is based on passive surveillance with mandatory case reporting, complemented by active outbreak investigations when clusters are suspected. No formal statistical outbreak detection algorithms are applied; instead, outbreaks are identified through routine review of case reports and temporal/geographic clustering, as case numbers are generally low and focus remains on detecting sporadic cases quickly.
Data structure: Individual case reports, including epidemiological questionnaires, are first completed on paper by healthcare providers and sent to the regional Centres for Public Health, which forward them to the Institute of Public Health (IPH). At IPH, data are entered into the national surveillance database for brucellosis, which is currently not linked with the national electronic health record system ("Moj Termin"). Laboratory data are recorded separately at IPH and CPH laboratories and then matched manually with case reports before analysis. Laboratory confirmation is performed using Brucelacapt, a serum agglutination test for detecting anti-Brucella antibodies, and the BAB test (Buffered Acidified Antigen test), a rapid slide agglutination screening test. Positive screening results are confirmed with Brucelacapt before cases are classified.
Indicators: Indicators include incidence, coverage of awareness activities, and laboratory confirmation rates. Distinguishing new infections from recrudescence or reinfections is not routinely performed, as only serological methods (BAB and Brucelacapt) are used for confirmation. Molecular typing is not part of routine surveillance; therefore, cases are classified based on clinical and epidemiological information and timing of onset, rather than definitive laboratory differentiation.
Feedback: CPHs submit quarterly reports to IPH; IPH provides quarterly and annual reports to MoH and AHV. Annual summary reports include epidemiological commentary and recommendations.

Actions: Surveillance data guide awareness campaigns, risk communication, and coordination with the Food and Veterinary Agency (AHV) under a One Health approach. Human surveillance data are shared with AHV, which uses this information—together with its own animal surveillance data—to target livestock vaccination and implement control measures in affected areas. Non-human cases are recorded in AHV's animal health database by farm and location, and these data inform culling, movement restrictions, and intensified animal vaccination to reduce the risk of human infection.

3.2 Analysis of system attributes: Simplicity: The surveillance system uses standardized case definitions and a uniform notification form completed by physicians within 24h. Data remain case-level from the healthcare facility through the CPHs to the IPH, but IPH analyses are reported in aggregate. The process is simple, but reliance on paper forms and multiple reporting levels can slow transmission.
Flexibility: The system can adopt new diagnostics and case definitions, but lacks an integrated electronic platform. Currently:
Physicians: paper forms.
CPHs: receive, scan, and re-enter data into an electronic template.
IPH: transfers these to the national surveillance database.
Labs: record results in hospital systems and notify CPHs, which update the IPH.
Thus, reporting is case-based at all stages, but methods vary (paper, email, manual electronic entry), reducing efficiency.
Acceptability: The system is broadly accepted by clinicians and public health staff, as evidenced by continuous national reporting since 1980. No staff interviews were conducted, so this assessment is inferred; future work should include structured interviews with reporting staff (with sampling method, core questions, and interview guide provided as an appendix). Under-reporting in rural areas is plausible: 79.5% of patients reported village residence, and in 2020–2022 livestock infection in Poloshki and Northeastern regions remained ~5% while few human cases were reported. This discordance suggests potential gaps in case detection, particularly in rural areas, which are further explored under representativeness.
Data quality: Data quality is generally good, given the long history of mandatory notification and standardized reporting since 1980. However, limitations were noted: the reporting form lacks sufficient epidemiological and clinical details, preventing more detailed analysis, and there is no systematic linkage with clinical records or the national e-health database, which reduces completeness.
Sensitivity: The declining number of reported brucellosis cases over the past decade suggests a real reduction in disease incidence. Between 2010 and 2023, annual notifications decreased from 168 to just 6 cases. However, the possibility of under-detection of mild or chronic cases cannot be excluded, given the limitations in notification completeness and laboratory confirmation.
To illustrate these trends, Figure 2 shows the annual case numbers for 2010–2023, alongside the 3-year moving average percentage change. The graph confirms a sustained decline, although small increases were observed in the most recent years (2022–2023), which may reflect localized outbreaks or improved detection. Seasonal peaks are also documented in the national study (highest incidence in April, May, July, and September), indicating that presentation of data as monthly aggregates could further highlight seasonal transmission dynamics.

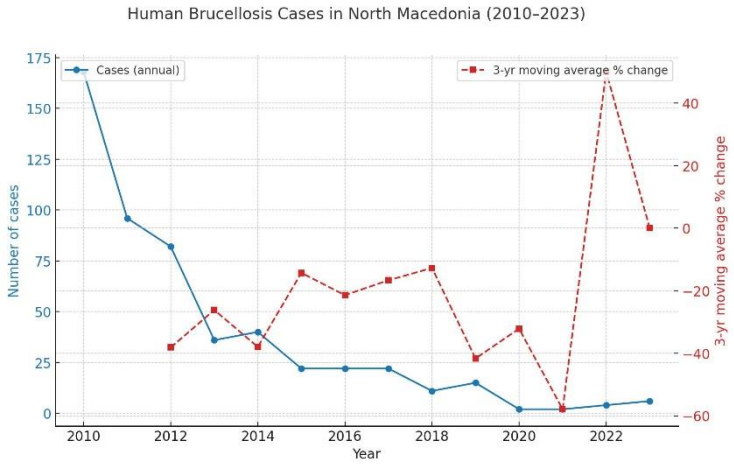


Figure 2. Number of cases during the period 2010-2023

The seasonal index shows marked peaks in April, May, July, and September, coinciding with periods of intensive livestock handling and consumption of fresh dairy products. The lowest activity is observed in March, October, and November. These consistent seasonal patterns suggest that the surveillance system is sensitive enough to capture temporal fluctuations, even if mild or chronic cases may be under-detected. (Figure 3).

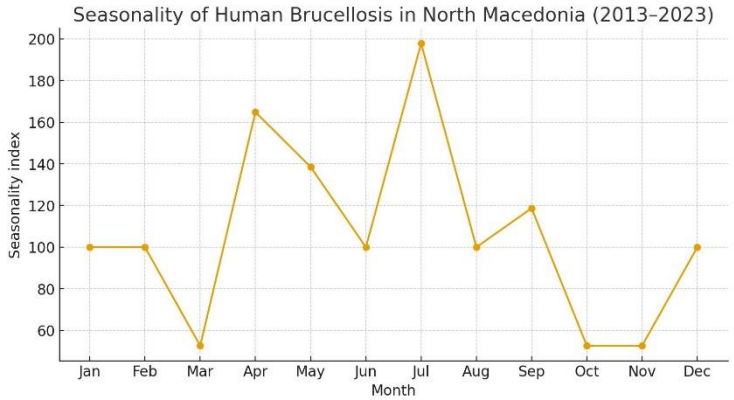


Figure 3. Seasonality of human brucellosis in North Macedonia (2013–2023).

Positive Predictive Value: For the six documented outbreaks (2007–2010), all 74 notified cases were laboratory confirmed, giving a PPV of 100% for outbreak notifications. For routine surveillance notifications, PPV cannot be calculated from the published study because counts of false positive notifications are not reported. This gap highlights a limitation of the current system.

Representativeness: National coverage of human brucellosis surveillance is ensured. However, comparison with veterinary surveillance indicates possible rural under-reporting. For example, in 2020–2022, livestock brucellosis prevalence was around 5% in Poloshki and Northeastern regions, while human notifications were very low. This discordance suggests that rural surveillance may be less representative than urban surveillance.

Table 2. Human brucellosis cases and livestock prevalence by selected region, North Macedonia

Region	Region type	Human cases (1980–2023), n	Livestock herd prevalence (2020–2022)
Polog	Rural	1,236	~5%
Northeastern	Rural	563	~5%
Southeastern	Rural	4,009	Lower
Skopje	Urban	1,596	Very low

Human case counts represent cumulative notifications from 1980–2023. Livestock prevalence refers to farm-level data reported by the Food and Veterinary Agency for 2020–2022.

Cumulative surveillance data from 1980 to 2023 show marked regional variation in the burden of human brucellosis. The highest number of reported human cases was recorded in the Southeastern region (n = 4,009), while the lowest was recorded in the Northeastern region (n = 563). Despite this, livestock brucellosis prevalence of approximately 5% at farm level persisted in the Polog and Northeastern regions during 2020–2022, while recent human notifications remained very low. This discordance suggests potential under-detection of human cases in rural regions, affecting the representativeness of the surveillance system.

Timeliness: Quarterly reporting is adequate for long-term trend monitoring but not optimal for rapid outbreak detection. In surveillance evaluation, timeliness also refers to the delay between symptom onset and notification, onset and laboratory confirmation, and notification to database entry. The national study does not report these data, so calculation of median delays by year or region was not possible. This represents a limitation of the current system. Future analyses should use case-based data to quantify these delays, as they are critical for early outbreak detection.

Cost: The national study does not provide data on actual expenditures of the brucellosis surveillance system, so the true cost could not be assessed. Instead, the approximate 2025 programme budget was reported as 1,000,000 MKD (≈ 16,000 EUR), split between the Institute of Public Health (363,000 MKD) and the Centres for Public Health (637,000 MKD), primarily for laboratory testing and training activities. While cost and budget are not the same, the budget illustrates the resources allocated to sustain surveillance of a disease that may be close to elimination. This highlights a key challenge: maintaining adequate funding for the last few cases, when surveillance becomes more resource-intensive despite declining incidence.

Usefulness: The surveillance system is useful for decision-making and prevention, particularly through its One Health approach. Human case notifications are coordinated with veterinary surveillance, allowing rapid tracing to livestock sources, targeted herd-level interventions, and identification of rural areas where animal infection persists but human cases may be under-reported. This integration strengthens both human and animal disease control, especially important in the elimination phase.

Stability: The surveillance system is supported by a legal mandate and established institutional structure, which ensures continuity. A major challenge, however, is the limited number of epidemiologists at regional Centres for Public Health. As shown in the table 3, staffing varies considerably, ranging from only 1 epidemiologist in Strumica and Ohrid to 4 in Skopje and Shtip. Such uneven distribution may weaken regional capacity for case detection and reporting, and could partly explain lower notification numbers in some areas. Ensuring adequate epidemiological staffing across all regions is critical to maintain system stability, particularly in the context of elimination efforts.

Table 3. Number of epidemiologists by Centre for Public Health, North Macedonia

CPH	Number of epidemiologists
Shtip	4
Kumanovo	3
Ohrid	1
Kocani	2
Skopje	4
Tetovo	3
Bitola	3
Prilep	3
Strumica	1
Veles	2

Discussion

The surveillance system for brucellosis in North Macedonia largely meets its objectives of monitoring incidence and supporting prevention. Its strengths include a strong legal framework, established under the Law on Protection of the Population from Infectious Diseases (Official Gazette no. 37/2016, with amendments), which mandates 24-hour notification of suspected cases. The system benefits from national coverage, routine laboratory confirmation, and integration with veterinary services through the Food and Veterinary Agency. The declining trend in reported cases reflects the effectiveness of livestock vaccination programmes, which have been in place since the early 2000s. To illustrate this impact more clearly, vaccination campaigns should be marked on the time-series graph of human cases (2010–2023).

Nevertheless, important challenges remain:

1. Shortage of epidemiologists in regional and local Centres for Public Health (e.g. only 1 in Strumica and Ohrid, compared to 4 in Skopje and Shtip), which may weaken capacity for timely case detection and reporting.
2. Timeliness and completeness of data reporting, as the national study does not provide onset, notification, or laboratory confirmation dates, preventing calculation of median delays.
3. Absence of a fully integrated electronic information system linking the Ministry of Health, Institute of Public Health, Centres for Public Health, and the Food and Veterinary Agency. At present, case notifications and laboratory data are stored separately. Without a common patient episode identifier, linkage can only be done probabilistically, which reduces accuracy and limits evaluation of key attributes such as positive predictive value and timeliness.

Limitations of this evaluation include reliance on programme and report data rather than case-level validation, and the absence of detailed quantitative indicators (e.g. notification delays, routine PPV). To address these gaps, obtaining case-level national data for the last 10 years (including dates of symptom onset, notification, and laboratory results) is essential. Such data would allow calculation of sensitivity, timeliness, and PPV, as well as more detailed analyses by region and by rural versus urban classification. Linkage between human and animal surveillance data is currently descriptive rather than case-based, limiting the ability to quantify transmission pathways.

Conclusions and Recommendations

The brucellosis surveillance system in North Macedonia is effective and useful but needs strengthening in certain areas.

Key recommendations:

Develop an integrated electronic One Health information system linking human and veterinary surveillance. At present, case notifications and laboratory data are stored separately without a shared identifier. Integration would allow case-level linkage, reduce duplication, and improve analysis of sensitivity, timeliness, and positive predictive value.

Address human resource shortages in epidemiology. The national study highlights limited staffing as a weakness, with current CPH epidemiologist numbers ranging from only 1 in Strumica and Ohrid to 4 in Skopje and Shtip. Ensuring at least a minimal baseline (e.g. ≥2 per regional CPH, more in Skopje due to population size) would improve stability and local response capacity. These suggested figures are indicative and based on the observed gaps in the existing distribution, not on a formal workforce standard.

Improve timeliness and completeness of data reporting through digitalisation and staff training. At present, quarterly reporting is adequate for monitoring trends but insufficient for outbreak detection, and no systematic data are available on notification delays. A digital platform with mandatory entry of onset and notification dates would allow measurement of median delays and strengthen outbreak response.

Continue animal vaccination campaigns to maintain low incidence. Livestock vaccination, in place since the early 2000s, coincides with the steep decline in human brucellosis cases, as shown in the time-series analysis. This measure remains critical to sustain elimination.

Strengthen health education for rural populations and high-risk occupational groups (farmers, shepherds, abattoir workers), where the majority (≈80%) of human cases originate. Targeted education campaigns should focus on safe animal handling and dairy product consumption.

Ensure sustainable funding for laboratory testing and training activities. The 2025 budget of 1,000,000 MKD (≈16,000 EUR), split between IPH and CPHs, demonstrates continued investment but also highlights the challenge of sustaining resources in the elimination phase, when surveillance becomes more costly relative to the few remaining cases.

Conclusion

Brucellosis surveillance in North Macedonia has contributed to a marked decline in human cases, supported by livestock vaccination and integration with veterinary services. The system is legally grounded and nationally implemented, but faces challenges of limited epidemiology staffing, incomplete and delayed reporting, and lack of electronic integration. Sustaining high-quality surveillance in the elimination phase requires continued vaccination, improved digital data systems, and investment in human resources, education, and laboratories. These measures will ensure that the last sporadic cases are detected and controlled, safeguarding both public health and livestock production.

Abbreviations

AHV – Food and Veterinary Agency
CPH – Centre for Public Health
ECDC – European Centre for Disease Prevention and Control
IPH – Institute of Public Health
PVP – Predictive Value Positive
WHO – World Health Organization

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INTEGRATING ARTIFICIAL INTELLIGENCE AND BLOCKCHAIN TECHNOLOGY INTO SMART MOBILE APPLICATIONS

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Abstract

The rapid development of contemporary technologies tends to digitalize all services across various public and private institutions, where most services are also provided on mobile devices due to their great practical usability by people in everyday life. The integration of Blockchain Technology (BT) and Artificial Intelligence (AI) into mobile devices and mobile programming enables, among other things, the creation of intelligent, autonomous, independent systems that, in automated form, are able to not only process data in real time, but also predict and make decisions in an intelligent way while preserving privacy and offering complete security and transparency. Through this paper, we attempt to explain the importance of the practical integration of these two technologies, with particular emphasis on the role of Edge AI in mobile devices and programming, security and privacy, and practical code frameworks and sequences used to create decentralized mobile applications. Through BT and AI, and the creation of hybrid architectures, the trust, transparency and integrity of mobile applications are increased, and validation is automated by creating intelligent autonomous mobile ecosystems. Even though technological developments tend to focus on improving privacy and security issues, there are many weaknesses and challenges directly related to practical implementations. However, the combination of BT, Edge AI and federated learning is seen as a mechanism for improving security and privacy, reducing dependence on cloud servers and focusing data processing locally. The findings show that despite challenges related to scalability, resource constraints, and costs, continuous developments in these contemporary technologies and hybrid infrastructures accelerate the creation of secure and intelligent systems on mobile devices.

Keywords: Blockchain Technology, Artificial Intelligence, Edge AI, mobile applications, hybrid architectures, privacy and security.

Introduction

The integration of Artificial Intelligence (AI) and Blockchain Technology (BT) are key components in the development of modern intelligent systems, including mobile applications, transforming the way people interact with technologies while providing more secure, transparent and intelligent services in the implementation of certain processes. Most mobile applications, in addition to the static and traditional functions they implement, today, thanks to Machine Learning (ML) techniques, are able to learn from user data, and thus analyze their behavior and make intelligent decisions in real time, or even provide suggestions and recommendations for future actions. Mobile Artificial Intelligence (Mobile AI) is a term that refers to the integration of artificial intelligence algorithms into mobile devices for the purpose of local data processing on mobile devices, with the aim of increasing security, privacy, reducing latency and various cyberattacks. Mobile AI is increasingly becoming a key component of mobile computing, integrating contemporary technologies such as ML, edge intelligence, and mobile computing with the aim of automating processes and increasing the performance of mobile applications, but above all, the main focus is on user privacy (Slyusar et al., 2024). Facial recognition, the implementation of intelligent chatbots, the personalization of activities in mobile applications, increased performance and efficiency in resource management, and above all, process automation and intelligent decision-making are just some of the modern technological evolutions (Li et al., 2025). The integration of Neural Processing Units (NPU) has enabled the development of the on-device AI concept, where ML algorithms are executed on the mobile device itself, without the need for cloud computing, although with certain limitations in terms of memory and other resources, yet with numerous advantages in terms of privacy, data security, process execution latency and increased performance in general

(Kwon & Kang, 2024). The main goal of modern mobile applications is to provide real-time services in line with dynamic changes, content personalization, assistance for easier process implementation, detection of various security threats, and even prediction of user behavior and automatic recommendations for future actions, in order to meet the needs and preferences of different users (Usman et al., 2025).

The latest implementations in mobile applications are towards the use of Large Language Models (LLM), and Generative AI, with the aim of natural language understanding, real-time responses, AI assistance for support and process automation, with the aim of maintaining performance and optimizing resources, but above all, facilitating many user processes (Dubiel et al., 2024). Facial recognition technology, intelligent document scanning, Augmented reality (AR) and Virtual Reality (VR) filters in mobile device cameras, medical diagnostic applications, various virtual games, use Convolutional Neural Networks (CNNs) models. Supervised learning is among the ML techniques used in mobile applications for the purpose of data classification and prediction, and experience personalization, where it practically finds implementations in facial recognition, voice, spam, and predictive keyboard (Ashok & Katarya, 2025). Deep Learning, on the other hand, is an advanced technique that is finding wide application in many fields, including mobile devices, which is mainly based on the combination of Computer Vision and Natural Language Processing techniques for the purpose of biometric authentication, image recognition, and virtual and augmented implementation in mobile programming (Kwon & Kang, 2024). Reinforcement learning, where applications learn through user interaction and optimize behavior based on the feedback they receive, is also widely implemented in some mobile applications. It is mainly used in battery optimization, creating adaptive user interfaces, gaming, and efficient resource management (Pan et al., 2020). And finally, Blockchain technology through smart contracts offers automation of processes on mobile devices, enabling the elimination of third parties, and in this way increasing security, reliability and the risk of possible data misuse (Rustemi et al., 2024). Blockchain technology through decentralization, transparency, immutability, offers higher security and reliability among users, but at the same time is seen as the only hope that guarantees self-sovereign identity, high security mechanisms through advanced cryptographic algorithms and decentralized storage (Rustemi et al., 2025). Through Figure 1, we have presented a taxonomy, where we summarize the main concepts of implementing blockchain technology and artificial intelligence in mobile applications.

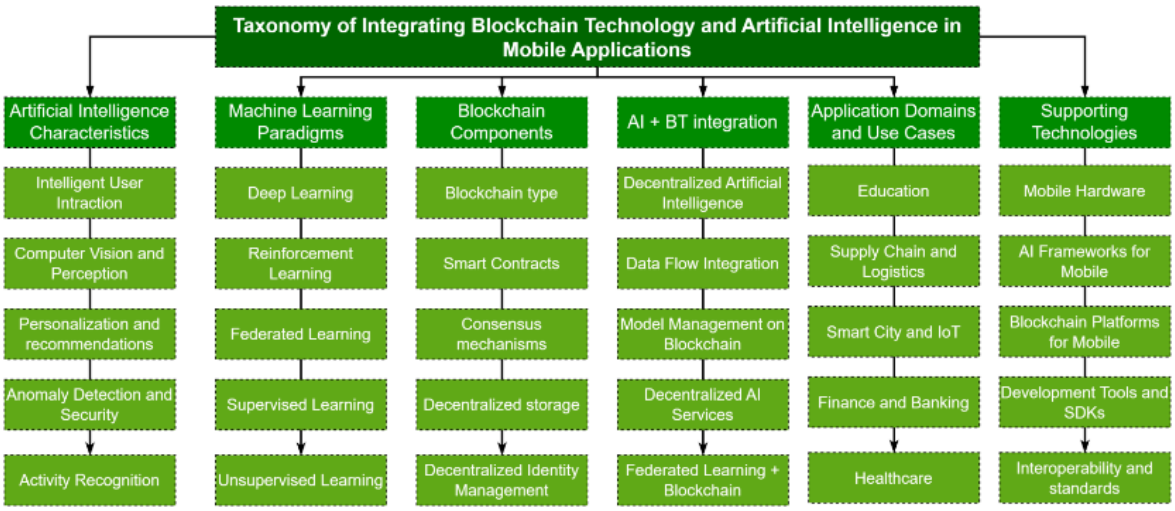


Figure 1. Taxonomy of Blockchain and AI implementation in mobile applications

Edge Computing in Mobile AI

Edge Computing is a new paradigm that aims to process data on mobile devices or edge servers, instead of sending data to cloud servers. This offers the possibility for ML algorithms, among others, to be executed directly on smartphones, wearable devices, reducing latency, traffic and dependence on the internet. The Edge AI architecture in mobile applications consists of three main layers, the mobile device layer, which includes mobile devices that collect data in real time, the edge layer, which includes servers or gateways that perform more complex processes, and the cloud layer for handling larger models and longer data storage (Ale et al., 2024). Edge AI plays an important role because, without relying on cloud services, it enables immediate response to many features of mobile devices such as face recognition, AI assistants, healthcare monitoring, and more. Above all, the use of edge AI enables energy and performance optimization compared to cloud architectures (Na & Lee, 2024). Many coherent techniques are used for maximum resource optimization, due to memory, processor and energy limitations, therefore quantization, pruning, knowledge distillation, and lightweight neural networks are some techniques that offer optimization of these resources. Among the modern frameworks used for efficient execution of ML models on smartphones and edge devices are TensorFlow Lite, Core ML, and ONNX Runtime Mobile, which, among other things, enable optimization of hardware resources and faster inference (Grzesik & Mrozek, 2024). Edge AI today finds application in many areas, including real-time patient monitoring in medicine, intelligent diagnostics, biometric signal analysis, local traffic analysis, object detection in autonomous vehicles, and many others (Ale et al., 2024). Also in mobile financial applications, it is used for detecting various attacks, as well as for predictive analytics and recommendations in various intelligent systems (Grzesik & Mrozek, 2024). Despite the great importance of Edge AI in mobile applications, many important technical challenges remain, such as battery and other hardware resource limitations, which are critical factors in the execution of deep learning algorithms. Also, the security of AI nodes and models from various attacks, as well as the heterogeneity of mobile devices create difficulties in standardizing practical implementations, where, among other things, work is being done on the integration of blockchain technology with Edge AI with the sole purpose of increasing security and reliability, but on the other hand, blockchain is facing practical challenges, which complicates the practical integration of these two technologies (Shaheen et al., 2024).

Privacy and security analysis from the integration of blockchain and AI in mobile applications

The integration of BT and AI in the creation of mobile applications, in addition to bringing new opportunities towards the creation of autonomous, secure and reliable systems, also brings complex challenges in terms of security and privacy. AI is primarily used for intelligent analysis and decision-making, and BT for immutable storage, smart contract execution and integrity verification. This integration enables the development of mobile applications that ensure transparency, trustworthiness and auditability of AI processes (Deval et al., 2024).
Mobile systems are exposed to various security threats due to the nature of transparency and the use of ML models, with one of the main problems being the manipulation of AI models through adversarial attacks, where attackers attempt to trick ML algorithms into entering incorrect inputs, which will result in incorrect results. There are also opportunities when attackers attempt to extract parameters or inference logic, where through abstraction attacks they attempt to compromise intellectual property and system security (Gill et al., 2025). One of the vulnerabilities in mobile applications is data poisoning attacks, where manipulated data is injected with the aim of degrading performance, which is particularly problematic in

federated learning (Rudin; 2019). One of the other important challenges in Mobile AI is privacy, as intelligent mobile applications process personal data, and in most cases, we as users, without carefully reading the terms and conditions of various applications, give confirmation for the use of personal data, which can also be misused by malicious people.
Although on-device AI and edge AI have been developed to overcome the problems of transferring data to cloud servers, where there is a risk of unauthorized access and data leakage, they are still facing limitations in hardware resources for processing ML algorithms and storing data in larger capacity (Kwon & Kang, 2024). On the other hand, on-device AI also faces various privacy risks, due to various attacks that attempt to alter data from the outputs of ML models, which is especially critical in fields where personal information is exposed, such as medicine, finance, etc. (Gill et al., 2025). BT is seen as a hope for improving security and privacy in Mobile AI applications, especially in terms of verifying information without the need for a central authority, but through smart contracts. So BT finds use for secure AI model verification, where the hash values of AI models or even the results are stored on the blockchain to guarantee the integrity and authenticity of the same. Through Figure 2, we have presented an example of a smart contract that implements immutable AI verification, trusted timestamping, decentralized storage, and auditability of results.



```
pragma solidity ^0.8.0;
contract AIIntegrity {
    struct Prediction {
        string hashValue;
        uint256 timestamp;
    }
    Prediction[] public records;
    function storeResult(
        string memory _hash
    ) public {
records.push(
            Prediction(
                _hash,
                block.timestamp
            ) ); }
    function verifyResult(
        uint index
    )
        public
        view
        returns(
            string memory,
            uint256 )
    {
        return (
            records[index].hashValue,
            records[index].timestamp
        );  } }
```

Figure 2. Blockchain Smart Contract for AI Verification

AI-blockchain integration, although improving security and privacy, creates trade-offs that directly impact various technical issues, such as energy consumption, latency, computational overhead, and others. Blockchain technology, although it is known for increasing the reliability and immutability of data, in practice it has problems with scalability and management of mutable data, or in other words, updating data, because each action represents a transaction in itself, which generates a unique hash value. Edge AI, on the other hand, although it has benefits in terms of local inference by increasing security, has challenges in terms of various attacks on the models used. Smart contracts, although they offer automatic validation and access control by increasing privacy, still have challenges in various vulnerabilities, and each execution of a smart contract has its own cost, and the same cannot be changed during execution (Valdez-Solis et al., 2026).

Practical implementations of Blockchain and AI on mobile devices

The practical integration of blockchain technology and artificial intelligence is in the early stages, namely in the conceptual modeling stages, due to the many practical challenges that these two technologies are facing separately. However, the efforts and implementations of some features in current systems are only practically implemented, making users familiar with these technologies and gaining trust above all (Rustemi & Dalipi, 2026). Recently, there has

been an increasing trend towards hybrid architectures, taking the best elements of each technology and adapting them into an architecture that is appropriate for the environment in which they are implemented. Similarly, in mobile applications, edge-cloud-blockchain architectures are being implemented, with the aim of analyzing as much data as possible locally and storing hash values and metadata on the blockchain (Ale et al., 2024). Through Figure 3 we have presented a code sequence of the practical implementation of EdgeAI through TensorFlow Lite, which enables, among other things, efficient execution of ML models, directly on mobile devices with the aim of optimizing battery usage and minimal latency, respectively, local inference of the AI model on the mobile device. Through the variable *input_data*, input data such as biometric information, image tensors, and others are received, while *prediction* represents the predicted result after analyzing the ML model.

```python
import tensorflow as tf

interpreter = tf.lite.Interpreter(
    model_path="avni_model.tflite"
)

interpreter.allocate_tensors()

input_details = interpreter.get_input_details()
output_details = interpreter.get_output_details()

interpreter.set_tensor(
    input_details[0]['index'],
    input_data
)

interpreter.invoke()

prediction = interpreter.get_tensor(
    output_details[0]['index']
)

print(prediction)
```

Figure 3. ML execution code sequence in TensorFlow Lite

As usual, for communication between mobile applications and the blockchain network, React Native is used together with the Web3.js API, which among other things enables the creation of decentralized mobile applications. React Native is known among other things as one of the frameworks that offer cross-platform mobile development, and is very easily integrated with blockchain and AI infrastructure. This code sequence through Figure 4 represents the communication between mobile applications and smart contracts on the blockchain via Web3 API and the storage of AI results in a decentralized manner. This approach is used to reduce the risk of manipulation and provide a more reliable intelligent ecosystem with blockchain verification mechanisms.

```
import web3 js;
define contractAdress;
define contractABI;
contract= new web3.eth.contract ( contractABI, contractAddress)
define function AIResult (hash) {
accounts=await web3.eth.getAccount();
}
await contract.methods.storeResult(hash: from accounts;)
```

Figure 4. Code sequence in pseudocode form in React Native (mobile device - blockchain communication)

The use of decentralized identity systems and Self-Sovereign Identity (SSI) is also an important aspect of integrating AI and BT into mobile devices, where users control their digital identity without the need for centralized authorities and traditional databases. It is mainly applied in

face recognition, anomaly detection, while blockchain stores credentials and provides reliable authentication, directly affecting the privacy and control of personal data (Spomy et al., 2022).

Conclusion

The integration of AI and BT in mobile applications represents one of the innovative and transformative directions of mobile computing, which among other things enables the development of more secure, autonomous and more capable mobile intelligent systems to perform activities in real time. In this paper, the main concepts of Mobile AI, the role of Edge AI in mobile devices, data security and privacy issues in the integration of AI and BT in mobile devices, and even practical implementations of AI and BT integration in mobile devices and the most used frameworks for this purpose were analyzed in brief points. The implementation of Edge AI and on-device ML through TensorFlow Lite undoubtedly reduces latency and dependence on cloud servers, while blockchain guarantees transparency, integrity and automatic verification of results. The implementation of React Native, Web3 API, and Solidity smart contracts are practical examples of developing decentralized mobile applications with intelligent mechanisms for validation and authentication.

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SURGICAL MANAGEMENT OF FOURNIER'S GANGRENE: CLINICAL EXPERIENCE WITH FOUR CASES TREATED AT THE SURGERY CLINIC OF THE CLINICAL HOSPITAL OF TETOVO

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Abstract

Introduction: Fournier's gangrene is a progressive necrotizing fasciitis of the perineal, genital, and perianal region, with high mortality potential if it is not promptly diagnosed and treated. It is characterized by the rapid spread of polymicrobial infection along the fascia, causing vascular thrombosis and necrosis of the soft tissues.
Aim: To present the clinical experience of the Surgery Clinic of the Clinical Hospital of Tetovo in the diagnosis, antibiotic treatment, surgical treatment, and reconstruction of large abdominal wall defects in four patients with Fournier's gangrene.
Materials and methods: This is a retrospective study including four male patients aged 38 to 62 years, treated over several years. Data were collected from operative protocols, clinical records, and laboratory and microbiological analyses.
Results: Two patients on admission presented with skin necrosis in the inguinal region extending to the scrotum, while the other two patients initially presented with subcutaneous purulent collections in the lower abdominal wall, which rapidly evolved into skin necrosis. All patients underwent extensive necrectomy, which left a large abdominal wall defect without skin coverage. Laboratory analyses showed marked leukocytosis, elevated CRP values, and disturbances of several other biochemical parameters. Microbiology identified polymicrobial infection with *MRSA, Escherichia coli, Pseudomonas aeruginosa,* and *Enterococcus spp.* Patients were treated with antibiogram-guided antibiotic therapy, regular dressing changes, VAC therapy, and definitive reconstruction with split-thickness skin autografting. Hospital stay ranged from 10 days to three weeks; all four patients were discharged healed.
Conclusion: Rapid diagnosis, early and aggressive surgical debridement, broad-spectrum antibiotic therapy guided by the antibiogram, negative pressure therapy (VAC), and careful reconstruction of defects with skin autografting are the pillars of success in the management of Fournier's gangrene. Our small but homogeneous experience confirms the value of this algorithm.

Keywords: Fournier's gangrene, necrotizing fasciitis, surgical debridement, MRSA, VAC therapy, skin grafting.

Introduction

Fournier's gangrene (FG) is a specific form of necrotizing fasciitis affecting the skin, subcutaneous tissue, and fascia of the perineal, genital, and perianal region, and very often extending toward the lower abdominal wall, the thighs, or the gluteal area [1–3]. Although the first description of an idiopathic gangrenous process of the genital organs is attributed to Baurienne in 1764, it was the French dermatologist Jean Alfred Fournier who, in 1883, reported five cases of healthy young men with sudden gangrene of the scrotum, thereby making widely known the disease that bears his name [2,3,12]. It is now known that the disease occurs mainly in men over 50 years of age and is associated with a high mortality rate, which in the literature ranges from 20% to over 40%, although certain series report extreme values [1,3,17,19].
The pathogenesis of FG is complex and multifactorial [3,4]. The process is usually initiated by an exogenous or endogenous portal of entry — perianal fistula, perirectal abscesses, urogenital infections, perineal trauma, urological or proctological surgery, urethral catheterization, small scrotal wounds, or injections in the gluteal region [2–4]. Aerobic and anaerobic microorganisms act synergistically: aerobes consume oxygen and create a hypoxic environment, while anaerobes produce heparinase, collagenase, hyaluronidase, and other enzymes that destroy connective tissue [3,6]. The direct consequence is an obliterative endarteritis with thrombosis of the subcutaneous arterioles, which leads to ischemia and

necrosis of the overlying skin. The infection spreads with characteristic rapidity along the fascial planes: Colles' fascia in the perineum, the dartos fascia in the scrotum and penis, and Scarpa's fascia in the lower abdominal wall — a fact that also explains the rapid extension of the process toward the abdomen, as was likewise observed in our patients [3,4,9].

Well-known risk factors include diabetes mellitus (present in 40–60% of cases according to various series), chronic alcohol abuse, obesity, malnutrition, immunosuppressive diseases, malignant neoplasms, end-stage renal disease, HIV infection, parenteral drug use, prolonged corticosteroid therapy, and advanced age [2–4,11,13]. In women, Fournier's gangrene is rarer but more severe, and is often associated with Bartholin's abscesses, infected episiotomies, or gynecological interventions [1,3].

The clinical picture in the early stages can be misleading: local pain disproportionate to objective findings, mild edema, erythema, and a sensation of perineal heaviness [4,5]. Within 24–48 hours, hemorrhagic blisters, subcutaneous crepitation, foul-smelling discharge, dark discoloration of the skin, and the appearance of systemic signs may develop — high temperature, tachycardia, hypotension, and confusion [3,5]. The diagnosis is clinical, but it is supported by laboratory examinations (leukocytosis, neutrophilia, elevated CRP, elevated procalcitonin, hypoalbuminemia, electrolyte disturbances, elevated creatinine, hyperglycemia, coagulopathy, metabolic acidosis) and by imaging methods (ultrasound, computed tomography — CT), which are particularly useful for assessing the extent of the process beneath the skin surface and for identifying gas within the tissues [4,5,11].

Several scoring systems have been proposed for prognostic quantification, the best known being the Fournier's Gangrene Severity Index (FGSI), developed by Laor and colleagues in 1995, which combines the deviations of nine physiological and biochemical parameters (temperature, heart rate, respiratory rate, sodium, potassium, creatinine, hematocrit, leukocytes, and bicarbonate) [7]. An FGSI value above 9 is associated with a high risk of mortality [7,8,13]. Subsequent variants have also been proposed — UFGSI (Uludag) and sFGSI (simplified) — as well as more general instruments such as LRINEC and FGMI [8,14].

Treatment rests on four inseparable pillars: (1) aggressive hemodynamic resuscitation, (2) immediate and extensive debridement of all non-viable tissue — which often requires several repeated interventions, (3) empirical antibiotic therapy with a very broad spectrum that covers gram-positive cocci, gram-negative bacteria, and anaerobes, followed by de-escalation based on the antibiogram, and (4) management of the residual wound, and definitive reconstruction with skin grafting or local and distant flaps [3,4,9–12,15]. Adjuvant treatment with hyperbaric oxygen is debatable but may have value in centers where it is available [11,12]. Fecal diversion with protective colostomy is reserved for cases with active perianal contamination [11,19].

Aim of the study: The aim of this paper is to document the experience of the Surgery Clinic of the Clinical Hospital of Tetovo with four patients treated over several years, focusing on the clinical presentation, the laboratory and microbiological findings, the antibiotic susceptibility profile, the course of treatment, and the final outcomes, and also to discuss these findings in the context of the current literature.

Materials and methods

This is a retrospective, observational, descriptive study including four male patients diagnosed with Fournier's gangrene who were treated at the Surgery Clinic of the Clinical Hospital of Tetovo over several years. The inclusion criteria were a clinical diagnosis confirmed by intraoperative findings (necrosis of the subcutaneous tissue and fascia, characteristic discharge, and tissue planes that slid easily under finger pressure) and the existence of complete medical documentation.

The data collected included: demographic data (age, sex), comorbidities, mode and site of presentation, results of routine laboratory analyses (leukocytes, hemoglobin, hematocrit, platelets, CRP, glycemia, urea, creatinine, transaminases, electrolytes, albumin, coagulogram), antibiogram findings from wound swabs taken at the time of admission, surgical interventions, antibiotic regimens, length of hospital stay, method of wound closure, and final clinical outcome.
Treatment was carried out according to a standardized institutional algorithm: resuscitation with crystalloid solutions, correction of metabolic disturbances, immediate initiation of empirical broad-spectrum antibiotic therapy (usually a combination of a carbapenem or third-generation cephalosporin with an anti-anaerobic agent and a glycopeptide against resistant gram-positive cocci), prompt debridement in the operating theatre with removal of all suspicious tissue, swab collection for culture and antibiogram, daily wound assessments, repeated debridements as needed.

Results

3.1. Demographic characteristics and clinical presentation
All four patients were male, with a mean age of approximately 50 years and a range from 38 to 62 years. The disease presented in two different clinical patterns. The first pattern, observed in two patients, was characterized by extensive skin necrosis already at the time of admission, located in the inguinal region and extending continuously from above downward to the skin of the scrotum. Both of these patients had systemic signs of severe infection: temperature above 38.5°C, tachycardia, severe perineal and inguinal pain, surrounding erythema, a sensation of crepitation on palpation, and fetid discharge from the necrotic area.
The second pattern, observed in the other two patients, had an unusual presentation: the patients were initially referred with purulent collections (subcutaneous abscesses) in the lower abdominal wall, without visible necrosis of the overlying skin at the time of admission. After incision, drainage, and clinical assessment during the first 24–72 hours, the very rapid evolution toward skin necrosis caused the diagnosis to be redefined as Fournier's gangrene with extension to the abdominal wall. This dynamic confirms the spread of the infection along Scarpa's fascia — a well-known anatomical route that connects the perineum with the lower abdominal wall [3,9].
In all four patients, an extensive necrectomy was performed with removal of all non-viable tissue. After the first debridement, a considerable defect of the abdominal wall remained, devoid of skin, involving a large surface area and requiring secondary coverage. In two of the patients, one or two additional debridements were required during the following days because of further areas of necrosis, while in the other two patients a single radical debridement was sufficient.

Table 1. Clinical characteristics of the four patients

Patient	Age	Initial clinical presentation	Number of debridements	Microbiology
P1	38 years	Inguinal skin necrosis extending to the scrotum	1	*MRSA* + *E. coli*
P2	47 years	Inguinal skin necrosis extending to the scrotum	2	*MRSA* + *E. coli*

Patient	Age	Initial clinical presentation	Number of debridements	Microbiology
P3	55 years	Subcutaneous abscesses of the lower abdominal wall with progression to necrosis	2	*MRSA + E. coli + Pseudomonas aeruginosa*
P4	62 years	Subcutaneous abscesses of the lower abdominal wall with progression to necrosis	1	*MRSA + Enterococcus spp. + Pseudomonas aeruginosa*

3.2. Laboratory findings: All four patients presented with marked leukocytosis, with values ranging from approximately 16,000 to over 24,000 leukocytes/μL, accompanied by neutrophilia and a left shift of the leukocyte differential. C-reactive protein (CRP) values were greatly elevated, reaching 180–320 mg/L, which is consistent with the systemic inflammatory response expected in an infection of this severity. In addition, other laboratory disturbances reflecting the seriousness of the condition were observed:
hypoalbuminemia (values from 22 to 30 g/L), a sign of marked catabolism and capillary leakage;
hyperglycemia (values above 9–14 mmol/L), mainly in the two patients with previously diagnosed diabetes mellitus;
moderate elevation of urea and creatinine as a result of hypovolemia and the prerenal component of kidney injury;
electrolyte disturbances — hyponatremia (130–134 mmol/L) and hypokalemia in two cases;
moderate elevation of hepatic transaminases;
mild hyperbilirubinemia;
a tendency toward metabolic acidosis, with serum lactate elevation above 2.5 mmol/L in two patients;
mild coagulogram disturbances (prolonged INR, decreased platelets) which partly reflected the septic state.
After resolution of the infectious focus by debridement and after the initiation of targeted antibiotic therapy, the inflammatory parameters began to fall progressively. Leukocyte values normalized typically within 7–10 days, while CRP took 10–14 days to reach near-normal values. Serum albumin recovered more slowly and often required enteral and parenteral nutritional support.

3.3. Microbiological findings: Immediately after admission and during the first debridement, swabs were taken from the necrotic tissue and the wound discharge for aerobic culture and — when technically possible — anaerobic culture. All four cultures yielded polymicrobial growth, a fact that fully corresponds to the synergistic nature of Fournier's gangrene [6]. The pathogens isolated were: methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli, Pseudomonas aeruginosa*, and *Enterococcus spp.* The combinations of pathogens for each patient were as follows:
Patient 1 and Patient 2: *MRSA + Escherichia coli;*
Patient 3: *MRSA + Escherichia coli + Pseudomonas aeruginosa;*
Patient 4: *MRSA + Enterococcus spp. + Pseudomonas aeruginosa.*

The notable observation in our microbiological context is the constant presence of MRSA in all four cases — a phenomenon that reflects a global epidemiological trend of increased MRSA colonization and infection in surgical patients [16,18]. The presence of *Pseudomonas* in two patients is consistent with the nature of the contaminating nosocomial environment and with an increased risk factor due to weakened immunity [6]. None of the cultures identified pure anaerobes, but this may reflect the technical difficulties of transporting and cultivating anaerobes, and does not exclude their participation, which is well known in the pathogenesis of FG [3,6].

3.4. Antibiotic susceptibility profile

The antibiogram was performed in accordance with the institutional standards and current guidelines (EUCAST/CLSI). The susceptibility profile of the pathogens isolated in our patients, combined with typical data from the current literature [15,16,20,21], is summarized in Table 2.

Table 2. Antibiotic susceptibility and resistance profile for the isolated pathogens (combination of our data and current literature)

Bacterium	Antibiotics with susceptibility (effective)	Antibiotics with resistance (ineffective)
MRSA	Vancomycin, teicoplanin, linezolid, daptomycin, clindamycin (when the strain is not iMLSB), tigecycline, trimethoprim-sulfamethoxazole, doxycycline, ceftaroline (5th-generation cephalosporin), rifampicin (only in combination).	All penicillins and antistaphylococcal penicillins (oxacillin, methicillin, cloxacillin), aminopenicillins with/without inhibitor (amoxicillin-clavulanate), most cephalosporins of generations I–IV (cefazolin, cefuroxime, cefotaxime, ceftriaxone, cefepime), carbapenems (imipenem, meropenem, ertapenem) — according to the classical laboratory definition. *Note: in our patients the antibiogram for MRSA showed susceptibility to meropenem and to ceftriaxone, a finding that is significant only in vitro and that must be interpreted with clinical caution.*
E. coli	Carbapenems (meropenem, imipenem, ertapenem), aminoglycosides (amikacin, gentamicin), ciprofloxacin, ceftriaxone, cefepime, piperacillin-tazobactam, fosfomycin, nitrofurantoin (only for urinary infections), tigecycline.	Ampicillin (frequent resistance), amoxicillin-clavulanate (variable resistance), cotrimoxazole (in ESBL-positive strains), generation I–II cephalosporins in many nosocomial strains. Strains producing extended-spectrum β-lactamases (ESBL) are resistant to all generation III–IV cephalosporins.
P. aeruginosa	Ceftazidime, cefepime, piperacillin-tazobactam, antipseudomonal carbapenems (meropenem, imipenem, doripenem — not ertapenem), aminoglycosides (amikacin,	All aminopenicillins, non-pseudomonal cephalosporins (cefazolin, cefuroxime, ceftriaxone, cefotaxime), ertapenem, cotrimoxazole,

Bacterium	Antibiotics with susceptibility (effective)	Antibiotics with resistance (ineffective)
	tobramycin, gentamicin), ciprofloxacin, levofloxacin, aztreonam, polymyxins (colistin, polymyxin B), ceftolozane-tazobactam.	tigecycline, macrolides, lincosamides.
Enterococcus spp.	Ampicillin (first choice for susceptible strains, especially *E. faecalis*), vancomycin, teicoplanin, linezolid, daptomycin, tigecycline, nitrofurantoin (for UTI), fosfomycin (for UTI). For endocarditis, combinations of ampicillin or vancomycin with an aminoglycoside are used.	All cephalosporins (intrinsic/innate resistance), oxacillin and antistaphylococcal penicillins, clindamycin (intrinsic resistance), aminoglycosides as monotherapy, cotrimoxazole (in vivo). VRE strains (*E. faecium*) are resistant even to vancomycin.

Note: The above table presents susceptibility according to the typical profiles of susceptible strains. The actual profile varies from case to case and should always be guided by the individual antibiogram of each patient. It must be particularly emphasized that Enterococcus spp. have intrinsic (innate) resistance to all cephalosporins; these should never be used as monotherapy for enterococci, regardless of any in vitro value.

3.5. Treatment and clinical course: In all four patients, treatment was initiated immediately according to the institutional algorithm. The empirical antibiotic therapy included a combination covering aerobes and anaerobes — usually meropenem or piperacillin-tazobactam, plus vancomycin (for MRSA coverage pending the antibiogram), plus clindamycin or metronidazole for additional anaerobic coverage [15,16]. After the antibiogram results were obtained, therapy was de-escalated and individually adapted: vancomycin was retained for MRSA in all cases, while for the gram-negative pathogens meropenem, ciprofloxacin, or ceftazidime (in the cases with *Pseudomonas*) were used.

Hemodynamic resuscitation was performed with crystalloid solutions and, as needed, colloids; electrolyte and acid-base correction was performed according to laboratory values; nutritional support was provided mainly via the enteral route with protein and vitamin supplements. Analgesia was administered according to the WHO scale, with a combination of paracetamol, non-steroidal anti-inflammatory drugs, and weak opioids when necessary. Thromboembolic prophylaxis with low-molecular-weight heparin was given after stabilization of hemostasis. We also maintained strict glycemic control with intravenous insulin in the acute phase.

Wounds were inspected and dressed twice daily during the initial phase. After the formation of a good granulation bed — usually achieved within 7–14 days — the phase of definitive closure was initiated.

Definitive treatment of the large defects of the abdominal wall and the inguino-scrotal area was performed with split-thickness skin autografting (according to the classical Thiersch–Ollier technique), harvested with a dermatome from the anterolateral region of the thigh [9,12]. The skin strips were processed using the meshing technique (1:1.5) in order to increase the coverage area and to allow drainage of any collections beneath the graft. In two patients, in addition to the skin autografting, the scrotal defects were resolved by advancement of the remaining scrotal skin and by bringing the testicles into a medial position. No patient required large local flaps or distant musculocutaneous flaps.

The length of hospital stay ranged from 10 days (in the youngest patient, with more limited spread) to three weeks (in the older patients with larger defects requiring longer wound bed preparation). All four patients were discharged in good general condition, with skin grafts adherent over more than 90% of the area at the first postoperative checks. No deaths, no major complications (resistant sepsis, multi-organ failure, massive hemorrhage), and no recurrence of the disease were recorded during the period of regular postoperative follow-up.

Discussion

Our experience with four patients confirms several fundamental principles of the management of Fournier's gangrene that have been established by the international literature of the last three decades, but also raises some questions that deserve more detailed discussion. The age of our patients (38–62 years) is slightly lower than the mean age reported in large European and American series (usually 50–60 years), but it is within the usual range [1,3,19]. All patients were male, which corresponds to the well-known male-to-female ratio of approximately 10:1 [1,3].

Part of the literature classifies FG according to the portal of entry: urogenital, anorectal, cutaneous (perineal or abdominal), and idiopathic [2–4]. In our patients, the two cases with an initial presentation of purulent collections in the lower abdominal wall suggest a cutaneous or subcutaneous portal of entry (perhaps a folliculitis, a subcutaneous abscess of the lower abdomen, or a local infection from the rupture of an infected atheroma) which then evolved very rapidly toward fascial and skin necrosis. This atypical presentation is a well-known diagnostic pitfall — the fact that the skin overlying the infection initially appears almost normal often leads to underestimation of the real severity and delays complete surgical intervention [4,5]. The practical lesson for the cautious surgeon: any open abscess of the lower abdominal wall in a patient with risk factors should be evaluated closely during the first 48–72 hours, with a low threshold for extended debridement if there are signs of fascial spread.

The microbiological profile in our patients confirms the polymicrobial nature of FG, which is reported in over 70–80% of cases in the literature [6]. The combination of gram-positive microbes (MRSA, *Enterococcus*) with gram-negative ones (*E. coli*, *Pseudomonas*) and — most likely — anaerobes that were not isolated for technical reasons, constitutes the classical synergy that sustains the necrotizing process [3,6]. The finding of MRSA in all four cases deserves attention. Some European series report a continuous increase in MRSA colonization in soft tissue infections, especially in units with high hospital traffic and extensive use of broad-spectrum antibiotics [16,18]. The practical importance is that in any case suspicious for FG, empirical antibiotic therapy must include an agent against MRSA (vancomycin, linezolid, or daptomycin) from the very first hour [15,16].

With regard to *Pseudomonas*, its presence brings its own considerations. This bacterium is classically resistant to most narrow-spectrum β-lactams and requires specific antipseudomonal antibiotics: ceftazidime, cefepime, piperacillin-tazobactam, antipseudomonal carbapenems (not ertapenem), aminoglycosides (amikacin, tobramycin), ciprofloxacin, aztreonam, and — for highly resistant strains — polymyxins (colistin), ceftolozane-tazobactam, or ceftazidime-avibactam [15]. In our patients, the antibiogram for *Pseudomonas* showed susceptibility to ceftazidime, ciprofloxacin, piperacillin-tazobactam, and amikacin, a fact that allowed a successful de-escalation.

A technical point that should be emphasized is the intrinsic resistance of *Enterococcus* to cephalosporins [20,21]. Despite any susceptibility that may be reported in vitro, cephalosporins do not reach clinically effective concentrations to kill enterococci, because this bacterial genus possesses penicillin-binding proteins (PBPs) with low affinity for β-lactams, as well as alternative pathways for peptidoglycan biosynthesis [21]. As a consequence, even if the

antibiogram suggests susceptibility to a cephalosporin, clinicians should disregard this finding and choose ampicillin (when the strain is susceptible), vancomycin, linezolid, or daptomycin [20,21]. In Patient 4, therapy was directed toward vancomycin (which covered both MRSA and *Enterococcus*) plus an antipseudomonal agent.

Surgical treatment remains the main pillar of healing. The literature is unanimous: the time between admission and the first debridement is an independent prognostic factor — delays beyond 24 hours double mortality in some series [3,11,19]. In our patients, debridement was performed within the first hours after the diagnosis was established. The size of the defect after debridement, although large, is not an indicator of poor prognosis if the antibiotic coverage is appropriate and if a strategy for secondary coverage is planned from the outset.

With regard to definitive reconstruction, split-thickness skin autografting remains the most common and most practical solution for large defects of the abdominal wall and the inguinal area [9,12]. Local flaps (medial thigh, inguinal flap, gracilis flap) and perforator flaps are valuable alternatives in centers with plastic surgery expertise, especially when defects are very large or when important organs are exposed (testicle, penis, sacrum) [9]. In our series, although extensive, the spread of the defect in the abdominal wall did not reach dimensions that would require complex flaps, and skin grafting provided satisfactory cosmetic and functional results.

Several adjuncts have been widely discussed in the literature. Hyperbaric oxygen, although not available in every center (including our institution), has shown potential benefits in anaerobic strains and in wounds with marked ischemia; however, current evidence is not sufficient to recommend it as a standard [11,12]. Fecal diversion with protective colostomy is reserved for cases with active perianal contamination or with damaged sphincters — conditions that were not observed in our patients [11,19].

The summary of findings and the limitations of this study should be honestly stated. The small number of cases (n=4) and the retrospective nature do not allow advanced statistical analyses, but they at least offer a clear picture of clinical practice in a regional center. The positive results (absence of mortality, reasonable length of hospital stay, effective wound closure) suggest that a unified algorithm — rapid diagnosis, radical debridement, antibiogram-guided antibiotic therapy,

Conclusion

Fournier's gangrene remains a surgical emergency that requires immediate and coordinated action. Our experience with four patients treated at the Surgery Clinic of the Clinical Hospital of Tetovo confirms that a structured algorithm — based on rapid clinical diagnosis, aggressive hemodynamic resuscitation, radical and early surgical debridement with repetition as needed, broad-spectrum empirical antibiotic therapy followed by antibiogram-guided de-escalation, and definitive reconstruction with split-thickness skin autografting — provides good clinical results even in a regional hospital [3,9,10,15].

The polymicrobial profile with predominance of MRSA in all four cases emphasizes the importance of empirical coverage against MRSA from the start of treatment, and raises the need for continuous epidemiological surveillance of antimicrobial resistance in our hospitals [16,18]. The atypical presentation of two patients with purulent collections in the abdominal wall, which evolved rapidly toward necrosis, reminds surgeons that any deep infection of the abdominal wall in a patient with risk factors should be evaluated with a high suspicion for an extended necrotizing fascial process [4,5].

Future studies with larger numbers of patients, the systematic inclusion of anaerobic pathogens, the systematic evaluation of prognostic indices (FGSI, UFGSI, LRINEC), and long-term functional follow-up of these patients would help to further refine local algorithms [7,8,13,14].

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CHRONIC DERMATOPHYTIC INFECTION OF THE FACE AND HANDS: A CLINICAL REVIEW OF TINEA FACIEI AND TINEA MANUUM

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Abstract

Background: Tinea faciei and tinea manuum are superficial dermatophyte infections affecting the glabrous skin of the face and the hands, respectively. Although they are well-recognized clinical entities, both are frequently misdiagnosed because their morphology may mimic eczema, lupus erythematosus, rosacea, contact dermatitis, and other inflammatory dermatoses. Persistence of lesions beyond several weeks of topical antifungal therapy in immunocompetent adults is increasingly reported and represents a relevant clinical challenge.
Case Presentation: A 40-year-old immunocompetent male presented with a two-month history of erythematous, scaly lesions on the cheeks, forehead, and dorsal aspects of both hands. Initial empirical therapy with topical miconazole for three months produced no clinically significant improvement. Direct microscopy of skin scrapings with 20% potassium hydroxide (KOH) revealed septate fungal hyphae, confirming a diagnosis of concomitant tinea faciei and tinea manuum. Systemic therapy was initiated with oral fluconazole 150 mg once weekly for eight weeks, with concurrent skin care advice and hygienic measures. Marked clinical improvement was observed within four weeks, and complete resolution of the lesions was achieved at the end of the treatment course. No adverse effects were reported, and no recurrence was observed during follow-up.
Discussion: Failure of topical antifungal therapy in adult dermatophytosis of the face and hands is multifactorial and may reflect inadequate drug penetration in hyperkeratotic lesions, poor adherence, large affected surface area, prior use of topical corticosteroids, and the emergence of less susceptible dermatophyte strains. In such circumstances, systemic azole therapy, particularly weekly fluconazole, has been shown to be both effective and well tolerated, providing a reasonable second-line option when first-line topical regimens fail.
Conclusion: This case underlines the importance of mycological confirmation of facial and hand dermatoses that fail to respond to topical therapy, and the role of weekly oral fluconazole as an effective treatment option for chronic, topically-resistant tinea faciei and tinea manuum in immunocompetent adults.

Keywords: tinea faciei; tinea manuum; dermatophytosis; fluconazole; topical antifungal failure; KOH examination; case report.

Introduction

Dermatophytoses are superficial fungal infections of keratinized tissues caused by a group of closely related filamentous fungi belonging to the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. They constitute one of the most prevalent infectious conditions worldwide, with an estimated 20–25% of the general population affected by superficial mycoses at some point in life (Havlickova, Czaika, & Friedrich, 2008). Among the various clinical presentations, tinea faciei and tinea manuum represent two regional variants whose clinical importance is often underestimated, because their atypical morphology frequently leads to delayed or incorrect diagnosis (Lin, Szepietowski, & Schwartz, 2004).
Tinea faciei is a dermatophyte infection limited to the glabrous skin of the face, sparing bearded areas in adult males (which are instead affected by tinea barbae). It can occur at any age but has historically been described more often in children and women (Romano, Ghilardi, & Massai, 2005; Atzori, Aste, Aste, & Pau, 2012). Recent studies, however, suggest that tinea faciei is increasingly observed in immunocompetent adults, with a wide spectrum of clinical presentations ranging from typical annular plaques with raised scaly borders to atypical, erythematous, or eczematoid lesions without a clearly defined edge (Noguchi, Jinnin, Miyata, Hiruma, & Ihn, 2014; Borges, Brasileiro, Galhardas, & Apetato, 2018). Because of these atypical features, tinea faciei has been described as the most frequently misdiagnosed

cutaneous mycotic infection, with reported misdiagnosis rates approaching 70% in some series (Lin et al., 2004; Khiewplueang et al., 2024).

Tinea manuum, on the other hand, is a dermatophytosis of the palmar or dorsal surface of the hand. It frequently coexists with tinea pedis in the so-called "two feet–one hand syndrome", in which both feet are affected by chronic, often hyperkeratotic plantar tinea and one (more rarely both) hand becomes secondarily involved (Daniel, Gupta, Daniel, & Daniel, 1997; Mizumoto, 2021; Suphatsathienkul et al., 2025). The most commonly isolated pathogens are anthropophilic species, particularly *Trichophyton rubrum*, followed by *Trichophyton mentagrophytes* complex and, less frequently, zoophilic species such as *Microsporum canis* (Veraldi & Esposito, 2019; Zhan et al., 2013; Suphatsathienkul et al., 2025). Tinea manuum is more common in adolescent and adult males, and certain occupations involving repeated skin contact with humid environments, animals, or other infected individuals (e.g., masseurs, barbers, cattlemen, masons, mechanics, veterinarians) have been identified as risk factors (Veraldi & Esposito, 2019).

From a clinical standpoint, both entities share the typical features of dermatophyte infection of glabrous skin: erythema, scaling, mild to moderate pruritus, and centrifugal extension of the lesions, often with a more inflammatory peripheral border. However, in tinea faciei the morphology is frequently modified by the complex anatomy and high vascularization of the face, by exposure to ultraviolet light, and by the inappropriate use of topical corticosteroids and calcineurin inhibitors, all of which may produce so-called "tinea incognito" (Hainer, 2003; Ansar, Farshchian, Nazeri, & Ghiasian, 2011). In tinea manuum, the dominant clinical pattern is a chronic, dry, hyperkeratotic scaling of the palms with accentuation of skin markings, often unilateral and only mildly symptomatic, which explains the frequently long delay before patients seek medical attention (Suphatsathienkul et al., 2025).

The diagnosis of these conditions is essentially based on a high index of clinical suspicion, supported by direct microscopic examination of skin scrapings using 20% potassium hydroxide (KOH), and confirmed when possible by fungal culture on Sabouraud dextrose agar (Drake et al., 1996; Hainer, 2003). The treatment relies primarily on topical antifungal agents (azoles, allylamines, ciclopirox), reserving systemic therapy for extensive, recalcitrant, or recurrent disease, in cases with hair follicle involvement, or when topical therapy has failed despite adequate adherence (El-Gohary et al., 2014; Gupta & Cooper, 2008). Among oral antifungals, terbinafine, itraconazole, and fluconazole are the agents most frequently used in clinical practice, each with specific pharmacokinetic and tolerability profiles (Faergemann & Mörk, 1999; Gupta & Cooper, 2008).

Despite the availability of several effective therapeutic options, the management of chronic, topically-resistant dermatophytosis of the face and hands in immunocompetent adults can be problematic. Treatment failure rates of topical regimens are not negligible, and recent reports from various geographical regions have highlighted an increasing prevalence of chronic, relapsing, and treatment-resistant tinea, including in the head, neck and hand region (Sahoo & Mahajan, 2016; Khiewplueang et al., 2024). In this context, oral fluconazole, used as a once-weekly pulse regimen, represents an attractive therapeutic alternative because of its long tissue half-life, favorable safety profile, ease of administration, and low cost (Suchil et al., 1992; Faergemann & Mörk, 1999).

Aim of the Study

The present article has two complementary objectives. First, it aims to provide a focused clinical review of tinea faciei and tinea manuum, summarizing current evidence on their epidemiology, microbiology, clinical presentation, diagnostic workup, and therapeutic options, with particular attention to the management of chronic, topically-resistant disease in

immunocompetent adults. Second, it reports the case of a 40-year-old immunocompetent male with simultaneous tinea faciei and tinea manuum that failed to respond to a three-month course of topical miconazole and was successfully treated with weekly oral fluconazole. The intended contribution of the report is to underline the relevance of mycological confirmation of facial and hand dermatoses that do not respond to first-line topical antifungals, and to discuss, in the light of available literature, the role of systemic azole therapy as a second-line option for persistent dermatophyte infections of the face and hands.

Case Report

3.1. Patient and clinical history: A 40-year-old male presented to the dermatology outpatient clinic with a two-month history of erythematous, scaly lesions involving the face and the dorsal surface of both hands. The patient had no significant past medical history, was not taking any chronic medication, denied known allergies, and reported no comorbidities such as diabetes mellitus, immunodeficiency, or atopic disease. He had not previously been hospitalized and had no history of skin disease prior to the current episode.

The lesions had appeared insidiously, initially as small, slightly erythematous, scaly patches on the cheeks and on the dorsa of the hands. Over the following weeks they had progressively enlarged and became more confluent, accompanied by mild pruritus and a sensation of cutaneous tightness. The patient reported that the hand lesions caused a degree of functional discomfort, particularly when performing manual tasks involving frequent washing or contact with detergents. He denied any recent close contact with persons with similar lesions, contact with pets or farm animals, recent travel, or new occupational exposures. There was no history of facial trauma, prior topical corticosteroid application, or self-medication with herbal preparations.

3.2. Physical examination: On dermatological examination, the patient presented well-demarcated, erythematous, scaly patches on both cheeks and on the forehead. The facial lesions were relatively flat, with mildly elevated borders and centrally less inflammatory areas. On the dorsal aspects of both hands, several erythematous, slightly raised plaques with peripheral scaling were observed; the lesions extended towards the wrists but spared the palms and the interdigital spaces. There were no vesicles, pustules, fissures, or signs of secondary bacterial infection. The scalp, trunk, lower limbs, nails, and genital region were unremarkable. There was no regional lymphadenopathy. The general physical examination was within normal limits.

3.3. Diagnostic workup: A clinical differential diagnosis was considered, including seborrheic dermatitis, contact dermatitis, discoid lupus erythematosus, rosacea, and superficial dermatophytosis. To confirm the etiology, skin scrapings were obtained from the active borders of two facial lesions and from one hand lesion. Direct microscopic examination of the scrapings prepared with 20% potassium hydroxide (KOH) revealed numerous septate, branching hyphae compatible with a dermatophyte infection. Routine laboratory investigations, including complete blood count, fasting glucose, hepatic transaminases, and serum creatinine, were within normal limits. Based on the clinical morphology and the positive direct mycological examination, a diagnosis of concomitant tinea faciei and tinea manuum was established.

3.4. Initial treatment and clinical course: Prior to dermatological referral, the patient had been treated empirically with topical miconazole 2% cream applied twice daily for approximately three months, with strict adherence as confirmed during a structured medication interview. Despite this prolonged topical regimen, the lesions persisted and showed only minimal subjective improvement, with no objective reduction in extent or scaling. There was no clinical

evidence of contact sensitization, and the patient had not used topical corticosteroids on the affected areas.

3.5. Systemic therapy and outcome: In view of the persistence of the lesions despite an adequate course of topical therapy, the absence of contraindications, and the relatively wide cutaneous involvement, systemic antifungal therapy was initiated. The patient was started on oral fluconazole 150 mg once weekly, for a planned duration of eight weeks. He was instructed to continue careful skin hygiene, to avoid sharing personal items such as towels and razors, to keep the affected areas dry, and to refrain from any topical corticosteroids.
At the one-month follow-up, the patient reported a clear subjective improvement, with marked reduction in erythema, scaling, and pruritus on both the face and hands. By the end of the eight-week treatment course, the facial and hand lesions had almost completely resolved, with only mild post-inflammatory hyperpigmentation visible on the dorsa of the hands. The patient tolerated fluconazole well; no adverse effects, gastrointestinal symptoms, or laboratory abnormalities were reported. At a follow-up visit three months after the end of treatment, no clinical recurrence was observed and the patient remained asymptomatic.

Discussion

The clinical course described in this report illustrates several aspects that have been progressively recognized as relevant in the modern epidemiology of dermatophytoses: the simultaneous involvement of two anatomical sites (face and hands) in an immunocompetent adult, the failure of an adequate course of topical azole therapy, and the favorable response to a relatively short, well-tolerated, weekly oral fluconazole regimen. Each of these aspects is worth discussing in the light of current literature.

4.1. Epidemiology of tinea faciei and tinea manuum: Although superficial dermatophyte infections are common worldwide, regional differences in epidemiology and in the spectrum of causative species are well established (Havlickova et al., 2008; Ameen, 2010). *Trichophyton rubrum* remains the predominant anthropophilic dermatophyte in most parts of the world and is the most frequent agent of tinea corporis, tinea pedis, tinea manuum, and onychomycosis in adults (Havlickova et al., 2008; Suphatsathienkul et al., 2025). Tinea faciei has historically been considered uncommon, with the literature emphasizing its predominance in pediatric populations, particularly when caused by zoophilic species such as *Microsporum canis* (Atzori et al., 2012; Del Boz, Crespo, & De Troya, 2012). However, several recent series have shown that tinea faciei is increasingly diagnosed in adults, with *T. rubrum* and *T. mentagrophytes* being among the most frequent isolates (Romano et al., 2005; Noguchi et al., 2014; Borges et al., 2018; Khiewplueang et al., 2024).
Tinea manuum is comparatively less studied than tinea pedis. In a recent five-year retrospective study of 107 patients, dermatophytes accounted for approximately 86% of culture-positive cases, with *T. rubrum* being responsible for more than half of these (Suphatsathienkul et al., 2025). The same study confirmed that tinea manuum predominantly affects adult males, with a male-to-female ratio reflecting both biological and occupational factors, and reported that itching and palmar scaling were the most common symptoms and signs, respectively (Suphatsathienkul et al., 2025). The Italian series by Veraldi and Esposito (2019) similarly highlighted the relevance of occupational exposure: in their cohort of 18 patients with mycologically confirmed tinea manuum, masseurs were the most frequently affected occupational category, followed by barbers, masons, and cattlemen, with *T. rubrum* and *M. canis* as the main isolated species. The patient described in our case, while not declaring a high-

risk occupation, did report frequent manual activities that may have contributed to the chronicity of hand involvement.

4.2. Clinical presentation and diagnostic challenges: Tinea faciei is renowned for its protean clinical presentation. Lin and colleagues (2004), in a seminal review entitled "Tinea faciei, an often deceptive facial eruption", emphasized that the disease is often misdiagnosed and that, in many cases, the diagnosis is established only after a long delay during which patients are treated for other dermatoses. In a histopathological case report, Meymandi, Wiseman, and Crawford (2003) described tinea faciei mimicking cutaneous lupus erythematosus, illustrating how the absence of typical annular, raised, scaly borders can mislead even experienced clinicians. Other authors have reported tinea faciei mimicking seborrheic dermatitis, contact dermatitis, rosacea, polymorphous light eruption, granuloma faciale, and dermatomyositis (Romano et al., 2005; Atzori et al., 2012; Borges et al., 2018). Most recently, an association has been suggested between prolonged use of facial masks during the COVID-19 pandemic and an increased incidence of tinea faciei, the so-called "mask tinea" (Khiewplueang et al., 2024).
Tinea manuum can also pose diagnostic difficulties. The classic palmar hyperkeratotic form, with chronic, dry, fine scaling and accentuation of skin creases, is frequently confused with chronic hand eczema, irritant contact dermatitis, palmar psoriasis, or hyperkeratotic eczema (Drake et al., 1996; Suphatsathienkul et al., 2025). The unilateral distribution and the simultaneous involvement of both feet ("two feet–one hand syndrome") are important clinical clues that should always raise suspicion of a dermatophyte etiology (Daniel et al., 1997; Mizumoto, 2021). On the dorsum of the hand, by contrast, the presentation tends to resemble tinea corporis, with annular or polycyclic, erythematous, scaly plaques with active borders, as observed in the present case.
In both entities, KOH examination of skin scrapings remains the cornerstone of microbiological confirmation, given its rapidity, low cost, and good sensitivity in experienced hands (Hainer, 2003; Drake et al., 1996). Fungal culture on Sabouraud dextrose agar is recommended whenever feasible, in order to identify the species and to support epidemiological surveillance, although in routine clinical practice the diagnosis is often established on the basis of typical morphology and a positive direct examination (Khiewplueang et al., 2024; Suphatsathienkul et al., 2025). In the present case, the absence of fungal culture is a limitation, but the presence of typical septate hyphae on direct examination, combined with the clinical picture and the favorable response to antifungal therapy, supports the diagnosis.

4.3. Tinea incognito and the role of prior topical therapy: The concept of tinea incognito refers to dermatophyte infections whose typical clinical features have been altered by the use of topical or systemic immunomodulatory agents, particularly corticosteroids and calcineurin inhibitors (Ansar et al., 2011). Although the patient described here did not report use of topical corticosteroids, three months of topical antifungal therapy without effect can itself modify the lesion morphology and complicate clinical diagnosis. Furthermore, partial treatment may select for less susceptible fungal populations, although robust epidemiological data on this phenomenon in tinea faciei and tinea manuum are still limited. In any case, the literature consistently recommends that any chronic facial or hand dermatosis that fails to respond to appropriate first-line therapy should prompt mycological investigation before adopting a different therapeutic strategy (Lin et al., 2004; Hainer, 2003).
4.4. Why does topical therapy fail?: Several factors may explain the failure of topical antifungal monotherapy in chronic tinea faciei and tinea manuum. First, the affected surface area, although limited in absolute terms, can be functionally extensive when multiple anatomical sites are involved simultaneously, as in our patient, making consistent and adequate application of topical therapy more difficult (Drake et al., 1996; Sahoo & Mahajan, 2016). Second,

hyperkeratotic lesions, particularly on the hands, may impair drug penetration through the stratum corneum (Suphatsathienkul et al., 2025). Third, repeated cleansing of the face and hands removes the topical agent and reduces effective contact time. Fourth, a Cochrane systematic review by El-Gohary and colleagues (2014) showed that, despite generally good efficacy, topical antifungals can yield variable cure rates depending on the molecule, formulation, and treatment duration, and treatment failures are not infrequent in routine clinical practice. Finally, recent global trends suggest an increasing proportion of chronic, relapsing, and partially resistant dermatophyte infections, particularly in regions where over-the-counter steroid–antifungal combinations are widely used (Sahoo & Mahajan, 2016).

4.5. Rationale for oral fluconazole: Oral antifungal therapy has been a recognized option for dermatophytoses since the introduction of griseofulvin, but the development of newer azoles and allylamines has substantially expanded the therapeutic armamentarium (Gupta & Cooper, 2008; Faergemann & Mörk, 1999). For tinea corporis and related variants such as tinea faciei, tinea cruris, and tinea manuum, three oral agents are most commonly used: terbinafine, itraconazole, and fluconazole. Each has distinct pharmacological characteristics and a specific risk-benefit profile (Drake et al., 1996; Faergemann & Mörk, 1999).

Fluconazole is a triazole antifungal that inhibits fungal lanosterol 14-α-demethylase, leading to depletion of ergosterol in the fungal cell membrane. It has a long half-life, good oral bioavailability, low protein binding, and prolonged retention in the stratum corneum, properties that make it particularly suitable for once-weekly pulse regimens (Suchil et al., 1992; Faergemann & Mörk, 1999). Suchil and colleagues (1992) reported that once-weekly fluconazole 150 mg was effective in the treatment of tinea corporis, tinea cruris, and cutaneous candidiasis, with high mycological cure rates and good tolerability. A subsequent review by Faergemann and Mörk (1999) summarized the evidence supporting the use of fluconazole 50–100 mg daily or 150 mg once weekly for 2–4 weeks in tinea corporis and tinea cruris. More recent literature has confirmed that, although fluconazole is not necessarily considered a first-line option for typical, uncomplicated tinea corporis or tinea pedis—where terbinafine often offers slightly higher cure rates—it remains a valuable therapeutic option in chronic, resistant, or relapsing disease, especially when good adherence to a daily regimen cannot be guaranteed or when other oral agents are contraindicated (Gupta & Cooper, 2008).

In the present case, the choice of weekly fluconazole 150 mg for eight weeks was based on three considerations. First, the patient had failed an adequate trial of topical therapy, justifying escalation to systemic therapy (Drake et al., 1996; El-Gohary et al., 2014). Second, the simultaneous involvement of two anatomical regions, including the face, made a regimen that achieves rapid systemic distribution and high cutaneous concentrations particularly attractive (Faergemann & Mörk, 1999). Third, the simplicity of a weekly regimen offered an obvious advantage in terms of adherence over a daily or twice-daily oral regimen, which is particularly relevant in working-age patients. The favorable clinical course observed, with marked improvement at four weeks and complete resolution at eight weeks, is consistent with previous reports of weekly fluconazole regimens in dermatophytoses of the glabrous skin (Suchil et al., 1992; Faergemann & Mörk, 1999).

4.6. Safety considerations: Fluconazole is generally well tolerated, with a low overall incidence of clinically relevant adverse effects when used at the doses and durations applied in dermatophytoses (Faergemann & Mörk, 1999; Gupta & Cooper, 2008). The most common adverse effects include mild gastrointestinal symptoms, headache, and rash. Hepatic enzyme abnormalities and, more rarely, hepatotoxicity have been reported, particularly with longer treatment courses, higher doses, or in patients with significant hepatic comorbidity. Drug–drug interactions are another important consideration, since fluconazole inhibits cytochrome P450

isoenzymes (notably CYP2C9, CYP2C19, and CYP3A4) and may therefore alter the metabolism of warfarin, certain statins, sulfonylureas, calcium channel blockers, and several other drugs. In our patient, who was not on any chronic medication, the safety profile was favorable, and no clinical or biochemical adverse effects were observed. Nevertheless, baseline and follow-up monitoring of liver function tests is generally advisable when prolonged courses of azole therapy are employed (Gupta & Cooper, 2008).

4.7. Practical lessons from the case: From a practical standpoint, the present case illustrates several lessons that align with consolidated literature. First, the simultaneous occurrence of facial and hand dermatosis in an immunocompetent adult should always include dermatophytosis in the differential diagnosis, even in the absence of obvious epidemiological risk factors (Lin et al., 2004; Suphatsathienkul et al., 2025). Second, mycological confirmation, particularly by KOH examination, is rapid, inexpensive, and indispensable when topical therapy fails (Hainer, 2003; Drake et al., 1996). Third, prolonged courses of topical antifungals without clinical improvement should not be perpetuated indefinitely; rather, they should prompt diagnostic re-evaluation and, where appropriate, escalation to systemic therapy (El-Gohary et al., 2014). Fourth, weekly oral fluconazole 150 mg is a reasonable, well-tolerated, and adherence-friendly option for adults with chronic, topically-resistant tinea faciei and tinea manuum (Suchil et al., 1992; Faergemann & Mörk, 1999). Finally, hygienic and behavioral measures, including avoidance of sharing of personal items, treatment of any concomitant tinea pedis or onychomycosis, and management of predisposing factors (such as occlusion or hyperhidrosis), are an essential component of management aimed at preventing recurrence (Drake et al., 1996; Mizumoto, 2021).

4.8. Limitations: This report is subject to the inherent limitations of a single-patient case description. Fungal culture and species identification were not performed, and antifungal susceptibility testing was not available, so it is not possible to identify the specific causative species or to comment definitively on its susceptibility profile. Furthermore, the relatively short follow-up after the end of treatment does not allow firm conclusions to be drawn regarding long-term recurrence rates. Despite these limitations, the case is clinically informative because it documents a real-world scenario in which weekly oral fluconazole was effective and well tolerated in a chronic, topically-resistant dermatophytosis of the face and hands.

Conclusion

Tinea faciei and tinea manuum are dermatophyte infections that, despite being well characterized, are still frequently misdiagnosed or undertreated, particularly in immunocompetent adults. Atypical morphology, prior empirical topical therapy, and prolonged use of antifungal creams without microbiological confirmation can all delay correct diagnosis and effective treatment. The case described here, of a 40-year-old male with concomitant tinea faciei and tinea manuum unresponsive to a three-month course of topical miconazole and successfully treated with eight weeks of weekly oral fluconazole 150 mg, supports the role of systemic azole therapy as a second-line option in chronic, topically-resistant disease. The case also reinforces the importance of mycological confirmation, particularly by KOH examination, before initiating prolonged or escalated treatment regimens. Further prospective studies and well-designed randomized trials would be useful to better define the optimal dose, duration, and place of weekly oral fluconazole in the therapeutic algorithm of chronic dermatophytosis of the face and hands, particularly in light of the increasing global prevalence of resistant and recalcitrant tinea infections.

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CONTEMPORARY APPROACHES IN THE MANAGEMENT OF VARICOCELE: SURGICAL AND MINIMALLY INVASIVE TECHNIQUES

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Abstract

Varicocele is one of the most common and correctable causes of male infertility, as well as an important source of chronic testicular discomfort. Contemporary management encompasses open surgical techniques, laparoscopic varicocelectomy, microsurgical approaches, and minimally invasive radiological procedures such as percutaneous embolization. The present retrospective study evaluates the outcomes of patients treated for varicocele at Tetovo Clinical Hospital over a three-year period. Fifteen patients aged 16–48 years were included. Ten of them underwent laparoscopic varicocelectomy, while five were treated with open surgery. The parameters analyzed included age distribution, length of hospital stay, postoperative pain, and early postoperative complications. The laparoscopic approach resulted in a shorter hospital stay, reduced pain, and faster recovery compared with open surgery. Patients treated with open techniques more frequently experienced postoperative discomfort and prolonged convalescence. Current literature data support minimally invasive techniques as safe and effective alternatives, associated with lower morbidity and improved clinical outcomes. This study confirms that laparoscopic varicocelectomy represents an effective treatment modality with favorable clinical results in carefully selected patients.

Keywords: varicocele, laparoscopic varicocelectomy, open surgery, minimally invasive surgery, male infertility, postoperative pain.

Introduction

Varicocele is defined as the abnormal dilation and tortuosity of the pampiniform venous plexus within the spermatic cord and is recognized as one of the most prevalent disorders of the male reproductive system (Agarwal et al., 2016). Its prevalence in the general male population is estimated at approximately 15%, while in men with primary infertility the figures rise to 35–40%, and up to 75–81% in those with secondary infertility (Alsaikhan et al., 2016; Gorelick & Goldstein, 1993). The anatomical predominance of varicocele on the left side is related to the right-angle venous drainage of the left spermatic vein into the renal vein, the greater length of this vein, and the absence or insufficiency of competent venous valves (Sharlip et al., 2002; Wishahi, 1991). Bilateral involvement, although less frequent, is documented in a considerable number of cases when high-sensitivity Doppler scanning is employed (Gat et al., 2004).

The pathophysiology of varicocele is complex and multifactorial. The principal mechanisms of testicular damage include increased scrotal temperature, oxidative stress, hypoxia induced by venous stasis, reflux of renal and adrenal metabolites, and disruption of the hypothalamic–pituitary–gonadal axis (Cho et al., 2016; Hassanin et al., 2018). These processes lead to sperm DNA fragmentation, injury to Leydig cells, and progressive reduction of testicular volume, particularly in adolescents with high-grade varicocele (Diamond et al., 2007). The accumulation of reactive oxygen species (ROS) is considered one of the chief molecular causes of varicocele-associated infertility, as it reduces sperm motility and compromises membrane integrity (Agarwal et al., 2014).

Clinically, patients may present with a variety of complaints: a sensation of heaviness in the scrotum, chronic pain that worsens after prolonged standing or physical exertion, testicular atrophy, or, more commonly, infertility identified during evaluation of the couple (Baazeem et al., 2011; Owen et al., 2017). Diagnosis is usually established through physical examination in the standing and supine positions, with and without the Valsalva maneuver, and is confirmed

by color Doppler ultrasonography, which is regarded as the principal imaging modality for determining the grade and the presence of venous reflux (Pauroso et al., 2011).
Over the last decades, therapeutic approaches have evolved markedly. Classical open techniques, such as the Palomo procedure (high retroperitoneal ligation) and the Ivanissevich procedure (inguinal ligation), have been complemented and frequently replaced by subinguinal microsurgical methods and minimally invasive techniques such as laparoscopy and radiological percutaneous embolization (Çayan et al., 2009; Goldstein et al., 1992; Marmar & Kim, 1994). Laparoscopic varicocelectomy and embolization currently represent preferred options in many centers because of reduced postoperative pain, improved visualization of anatomical structures, shorter hospital stay, and faster return to daily activities (Kim et al., 2013; Iaccarino & Venetucci, 2012).
Despite the wide adoption of minimally invasive approaches, scientific debate remains open regarding the optimal technique. Comparative studies have reported variable results in terms of recurrence rates, postoperative hydrocele formation, improvement in semen parameters, and achieved pregnancy rates (Practice Committee of the American Society for Reproductive Medicine, 2014; Çayan et al., 2009). For this reason, ongoing evaluation of surgical outcomes within the local context remains essential for optimizing patient management.
The present paper presents the experience of the Department of Urology at Tetovo Clinical Hospital in the management of varicocele through laparoscopic and open techniques over a three-year period and discusses the results in the light of contemporary literature.

Aim of the study

The primary aim of this study was to assess current surgical approaches in the management of varicocele and to compare postoperative outcomes between laparoscopic and open varicocelectomy.
The specific objectives were:
To assess postoperative pain in both groups;
To compare the length of hospital stay;
To evaluate early postoperative recovery;
To analyze perioperative and early postoperative complications;
To compare clinical outcomes between the minimally invasive and the open approach;
To place the clinical findings within the context of current international literature.

Materials and methods

This is an observational, retrospective study based on a cohort of 15 patients diagnosed with varicocele and treated surgically at the Department of Urology of Tetovo Clinical Hospital during the period 2023–2026. Data were collected from operative protocols, admission records, ultrasonography reports, and postoperative follow-up visits.

3.1 Study population: The study population comprised male patients aged 16–48 years. All patients underwent a standard clinical assessment, including history-taking, physical examination of the scrotum in the standing and supine positions with the Valsalva maneuver, and color Doppler ultrasonography. Surgical indications included symptomatic varicocele, the presence of chronic scrotal pain refractory to conservative treatment, infertility associated with abnormalities in semen analysis parameters, or a progressive reduction in testicular volume relative to the contralateral side (according to a criterion of >20% volume difference). Clinical classification was performed according to the Dubin–Amelar system (Dubin & Amelar, 1971),

with the inclusion of patients with grade II and grade III varicocele. Patients with subclinical varicocele were excluded from the study.

3.2 Surgical techniques: Of the 15 patients included in the study:
10 patients (66.7%) underwent laparoscopic varicocelectomy;
5 patients (33.3%) were treated with open surgery.

3.3 Laparoscopic technique: The laparoscopic procedure was performed under general anesthesia, with the patient placed in a slight Trendelenburg position. A standard transperitoneal three-port approach was used: a 10-mm umbilical port for the camera and two auxiliary 5-mm ports in the lower abdominal quadrant. After inspection of the operative field, the internal spermatic vein was identified above the level of the internal inguinal ring. The peritoneum was incised, and the veins were carefully dissected, isolated, and ligated with metallic clips or with intracorporeal suture, with an attempt to preserve the testicular artery and lymphatic vessels whenever this was technically feasible (Donovan & Winfield, 1992). This modality afforded magnified visualization of anatomical structures and minimal trauma to the surrounding tissues.

3.4 Open surgical technique: Open operations were performed through an inguinal or subinguinal incision according to the Ivanissevich modification. After opening the external oblique fascia, the spermatic cord was identified, the dilated veins of the pampiniform plexus were exposed, and ligations were performed with non-absorbable suture. The vas deferens and the testicular artery were preserved with care (Ivanissevich, 1960). The wound was closed in anatomical layers using standard technique.

3.5 Parameters evaluated: The following variables were analyzed systematically:
Patient age and distribution by age group;
Type of surgical procedure and operative duration;
Intensity of postoperative pain assessed using the Numerical Rating Scale (NRS 0–10);
Length of hospital stay (in days);
Early postoperative complications (bleeding, wound infection, hydrocele, recurrence);
Time to return to usual activities (in days).

3.6 Statistical analysis: Data were processed using descriptive statistical analysis. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between the two groups were carried out at a descriptive level, given the small sample size. The data were processed using Microsoft Excel and the SPSS statistical package, version 25.0.

Results

During the study period, a total of 15 patients with a diagnosis of varicocele were operated on. The mean age of the patients was 29.4 years (range 16–48 years). Most patients (n = 11; 73.3%) were within the 20–35 year age group, which corresponds to the age range most frequently affected by varicocele-related reproductive problems (Hassanin et al., 2018). All fifteen patients had left-sided varicocele, while bilateral involvement was documented in two cases — a finding consistent with the literature, which reports a clear left-sided predominance (Sharlip et al., 2002).

4.1 Distribution by surgical technique: The distribution of patients by surgical treatment modality was as follows: laparoscopic varicocelectomy — 10 patients (66.7%); open surgery — 5 patients (33.3%). Table 1 presents the baseline characteristics of the two groups.

Table 1. Baseline characteristics of the study groups.

Characteristic	Laparoscopic group (n=10)	Open group (n=5)
Mean age (years)	28.6 ± 7.2	31.0 ± 9.4
Left-sided varicocele (n)	9	4
Bilateral varicocele (n)	1	1
Grade II (Dubin–Amelar)	4	2
Grade III (Dubin–Amelar)	6	3
Indication: infertility (n)	6	2
Indication: scrotal pain (n)	4	3

4.2 Length of hospital stay: Patients treated by the laparoscopic approach had a markedly shorter hospital stay. The majority were discharged within the first 24 postoperative hours, while patients operated on with the open technique required more prolonged clinical observation. The mean length of stay was approximately 1 day in the laparoscopic group and 2–3 days in the open surgery group. These results are in line with data reported in other comparative studies that have shown clear benefits of minimally invasive approaches with respect to length of stay (Tan et al., 1995; Watanabe et al., 2005).

4.3 Postoperative pain: Postoperative pain was more pronounced and more frequent in patients treated with open surgery. Patients in the laparoscopic group reported mild and transient discomfort, with earlier mobilization and a reduced need for opioid analgesics. Mean NRS values during the first 24 hours were 2.4 in the laparoscopic group, compared with 5.2 in the open surgery group. These results corroborate the findings of Kim et al. (2013) and Al-Said et al. (2008), who likewise reported reduced pain following minimally invasive approaches.

4.4 Recovery and complications: Patients treated with the laparoscopic technique resumed their usual activities earlier than those in the open surgery group (an average of 7 days versus 14 days). No serious intraoperative complications were observed in either group. Mild postoperative edema and transient discomfort were documented in a small number of patients, mainly in the group operated on with the open technique. No significant wound infections or hydrocele formation were recorded during the early follow-up period (1–3 months postoperatively). No patient presented clinical recurrence of varicocele during early follow-up.

Table 2. Comparison of postoperative outcomes between the two groups.

Parameter	Laparoscopic (n=10)	Open (n=5)
Hospital stay (days, mean)	1.0	2.6
Pain NRS at 24 h (mean)	2.4	5.2
Return to activity (days)	7	14
Major complications (n)	0	0
Edema / minor complications (n)	1	2

Parameter	Laparoscopic (n=10)	Open (n=5)
Early recurrence (n)	0	0

Discussion

Varicocele continues to be one of the most important causes of correctable male infertility and a meaningful source of chronic scrotal symptoms (World Health Organization, 1992). Technological advances in minimally invasive surgery have profoundly transformed therapeutic approaches, modifying the postoperative morbidity profile and enhancing the patient experience (Agarwal et al., 2016).

The findings of the present study indicate clear advantages of laparoscopic varicocelectomy compared with open surgery, particularly with respect to postoperative recovery and patient comfort. The reduction of postoperative pain and the shortening of hospital stay were the most evident benefits in the laparoscopic group. These findings are consistent with previous studies reporting reduced morbidity and accelerated recovery following minimally invasive approaches (Çayan et al., 2009; Kim et al., 2013).

Laparoscopic varicocelectomy provides excellent visualization of the spermatic vessels at the retroperitoneal level, facilitating precise ligation while minimizing trauma to the surrounding tissues (Donovan & Winfield, 1992). The magnified operative field afforded by laparoscopic optics contributes to reducing postoperative discomfort and allows earlier patient mobilization. Similar advantages have been highlighted in comparative analyses by Al-Said et al. (2008) and Tan et al. (1995), who demonstrated faster postoperative recovery following minimally invasive approaches. In bilateral cases in particular, the laparoscopic approach provides the possibility of simultaneous treatment of both sides through the same ports, obviating the need for two separate open incisions (Watanabe et al., 2005).

Open surgical techniques, although older, remain effective and continue to be widely used, especially in centers where laparoscopic resources or specialized expertise may be limited. Nevertheless, open surgery is generally associated with greater postoperative pain, longer convalescence, and a higher risk of wound-related complications (Baazeem et al., 2011). In our study, patients treated with the open technique experienced more pronounced postoperative discomfort and a longer hospital stay than those treated laparoscopically, confirming the trends reported in the literature.

Subinguinal microsurgical varicocelectomy, introduced and popularized by Goldstein et al. (1992) and Marmar and Kim (1994), is often regarded as the gold standard of surgical treatment because of its very low rates of recurrence (1–2%) and of postoperative hydrocele formation (<1%) (Hopps et al., 2003). The use of the operating microscope allows the systematic identification and preservation of the testicular artery, lymphatic vessels, and vas deferens, thereby minimizing long-term complications. However, this technique requires a long learning curve, specialized equipment, and a longer operative time. The laparoscopic approach, by contrast, remains an attractive alternative because of its relative technical simplicity, the possibility of bilateral treatment, and favorable cosmetic outcomes (Ficarra et al., 2006).

Percutaneous radiological embolization constitutes another minimally invasive modality, performed by interventional radiologists under fluoroscopy, with a technical success rate of 85–95% and clear benefits in terms of recovery time (Iaccarino & Venetucci, 2012). However, this technique may not be available in all centers and has limitations in cases of complex venous anatomy.

With regard to improvement in semen parameters and pregnancy rates, the meta-analysis by Marmar et al. (2007) reported that surgical correction of clinical varicocele in men with oligospermia increases the chances of spontaneous pregnancy compared with conservative

management. Esteves et al. (2016) likewise showed that varicocelectomy can increase success rates among couples undergoing assisted reproductive techniques, including intracytoplasmic sperm injection (ICSI). Although our study did not systematically assess these long-term outcomes, the symptomatic improvement and the safety profile observed support surgical treatment in carefully selected patients.

The present study has several limitations that should be acknowledged. First, the small sample size (n = 15) and the retrospective nature of the design limit the generalizability of the results. Second, postoperative semen analysis parameters and long-term reproductive outcomes were not systematically evaluated. Third, the absence of a microsurgical treatment group did not allow a direct comparison with the current gold standard. Despite these limitations, the study reflects a real clinical experience in a regional urological center and supports the global trend toward minimally invasive management of varicocele.

Future studies with larger patient samples, prospective designs, and long-term follow-up of reproductive parameters are needed in order to refine optimal treatment strategies and to tailor the choice of technique to each patient's clinical profile.

Conclusions

Contemporary approaches in the management of varicocele are increasingly oriented toward minimally invasive techniques, owing to the reduced postoperative morbidity and the faster recovery they offer.

In this study, laparoscopic varicocelectomy demonstrated several clear advantages over open surgery, including:

Shorter length of hospital stay;

Reduced postoperative pain;

Faster postoperative recovery;

Greater patient comfort;

Absence of major intraoperative complications.

Open surgical repair remains an effective and safe therapeutic option, particularly in settings with limited technological resources; however, postoperative discomfort was more frequent and more pronounced in this group of patients.

The results support laparoscopic varicocelectomy as a safe and effective approach to the surgical management of varicocele. Careful patient selection, adequate surgical expertise, and appropriate equipment are essential for achieving optimal clinical outcomes. Placing the findings in the context of contemporary literature confirms that the global trend toward minimally invasive approaches is also reflected in our regional practice, providing tangible benefits for male patients with varicocele.

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CONTINUITY OF PROBABILITY MEASURES AND ITS ROLE IN STATISTICAL MODELING

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Abstract

This paper examines the notion of continuity in probability measures and its essential function in statistical modelling. In measure-theoretic probability, continuity properties—namely continuity from below and continuity from above—are crucial for examining the asymptotic behavior of sequences of events and random variables. These characteristics guarantee that probability measures exhibit uniformity under monotone limits, establishing a robust foundation for numerous conclusions in probability and statistics. This study establishes the relationship between the continuity of probability measures and fundamental principles in stochastic convergence, such as convergence in probability and almost sure convergence. The paper specifically illustrates the application of continuity arguments to validate the convergence of sequences of random variables, which is fundamental to statistical inference. The role of continuity is also looked at in the context of statistical modelling, with a focus on distribution functions and their right-continuity, as well as on asymptotic results like the Law of Large Numbers. By using specific examples, the paper shows how theoretical continuity properties can be used in real life to make models and estimates in statistics. The findings underscore that the continuity of probability measures is not merely a theoretical construct, but a fundamental principle that underpins the stability and reliability of statistical models. This work offers a cohesive viewpoint that links abstract probability theory to its contemporary applications in statistical analysis.

Keywords: Probability measure, continuity, stochastic convergence, statistical modeling, Law of Large Numbers, distribution function

Introduction

A robust mathematical foundation for modeling uncertainty and random phenomena is provided by probability theory (Billingsley, 1999; Durrett, 2019). It is fundamentally based on the concept of a probability measure defined on a σ-algebra of events (Kallenberg, 2002). Nevertheless, despite its solid measure-theoretic basis, probability theory lacks a natural topological structure (Salinetti & Wets, 1987). This absence makes the study of limiting behavior—essential for both theoretical developments and practical applications in probability and statistics—more challenging.

A central aspect of modern probability theory is the analysis of sequences of random variables and probability measures (Billingsley, 1999). In this context, concepts of convergence, including convergence in probability, almost sure convergence, and convergence in distribution, play a crucial role (Durrett, 2019). These notions are fundamental for understanding asymptotic behavior, particularly in statistical inference, where estimators are expected to converge to underlying population parameters. In particular, weak convergence of probability measures has emerged as a key tool for analyzing such limiting processes in metric spaces (Billingsley, 1999).

To address the lack of an intrinsic topological structure, continuity properties of probability measures are introduced and studied (Kallenberg, 2002). These properties, such as continuity from below and continuity from above, ensure that probability measures behave consistently under monotone sequences of events (Durrett, 2019). Such continuity conditions provide an essential link between measure-theoretic and topological perspectives, enabling a deeper understanding of convergence phenomena (Salinetti & Wets, 1987).

Recent approaches have further explored this relationship by representing probability measures through upper semicontinuous functions, often referred to as semicontinuous measures (Salinetti & Wets, 1987). This perspective allows convergence to be studied using tools such as hypo-convergence, which captures the global behavior of functions rather than relying solely on pointwise behavior. These developments highlight that continuity is not merely a technical condition, but a fundamental principle governing the stability and coherence of probabilistic models.

The importance of continuity becomes particularly evident in statistical modeling. Distribution functions, which describe the probabilistic behavior of random variables, possess intrinsic continuity properties that are essential for defining and analyzing convergence in distribution (Billingsley, 1999). Moreover, classical results such as the Law of Large Numbers illustrate how sequences of random variables converge to deterministic quantities, emphasizing the role of continuity in ensuring reliable statistical inference (Durrett, 2019).

This study examines the notion of continuity of probability measures and its role in statistical modeling. It aims to establish the connection between continuity properties and various forms of stochastic convergence, while also demonstrating how these theoretical principles support practical modeling and estimation techniques in statistics. Through this unified perspective, the work seeks to bridge abstract probability theory with its applications in modern statistical analysis.

Preliminaries

The foundation of probability theory is the concept of a probability space, which provides the formal framework for modeling random phenomena (Kallenberg, 2002). A probability space is defined as a triple (Ω, F, P), where Ω is the sample space of all possible outcomes, F is a $\sigma - algebra$ of events, and P is a probability measure that assigns values in $[0,1]$ to events in F (Billingsley, 1999). This structure enables a rigorous mathematical analysis of uncertainty and forms the basis for describing random variables and their distributions.

A random variable is defined as a measurable function from the sample space into the real numbers, allowing numerical values to be assigned to random outcomes (Durrett, 2019). Through random variables, it becomes possible to study probabilistic phenomena using analytical methods. One of the key concepts associated with random variables is the distribution function, defined by

$$F(x) = P(X \leq x),$$

which describes the probability distribution of a random variable. Distribution functions possess important continuity properties, most notably right-continuity, which plays a crucial role in statistical modeling and the study of convergence (Billingsley, 1999).

The concept of convergence of random variables is central in probability theory. Several modes of convergence are commonly used, each capturing a different aspect of limiting behavior. Convergence in probability is defined by the condition that, for every $\varepsilon > 0$, the probability $P(|X_n - x| > \varepsilon)$ tends to zero as $n \to \infty$ (Durrett, 2019). Almost sure convergence is a stronger notion, requiring that the sequence converges pointwise with probability one. In contrast, convergence in distribution is defined in terms of the convergence of distribution functions and is particularly important in statistical applications (Billingsley, 1999).

Weak convergence of probability measures is closely related to convergence in distribution and provides a general framework for analyzing limiting behavior in metric spaces. It allows sequences of probability measures to be studied through their action on bounded continuous functions, making it a fundamental tool in modern probability theory (Billingsley, 1999). This

concept plays a crucial role in connecting probability theory with statistical modeling, especially in the study of asymptotic properties of estimators.
The concepts introduced in this section provide the mathematical foundation for the study of continuity properties of probability measures. In particular, the interaction between distribution functions, convergence, and probability measures offers the necessary framework for understanding how continuity influences the behavior of probabilistic models and their applications in statistics.

Continuity of Probability Measures

In order to comprehend how probabilities behave under limiting operations, continuity features of probability measures are essential. These characteristics explain how probability measures interact with event sequences in measure-theoretic probability, especially when those sequences are monotone. Establishing rigorous linkages between probability theory and conceptions of convergence requires these continuous qualities (Billingsley, 1999; Durrett, 2019).
Continuity from below and continuity from above are two essential types of continuity for probability measurements. These findings guarantee that probabilities exhibit consistent behaviour when applied to growing or decreasing event sequences.

3.1 Continuity from Above: Let $\{A_n\}_{n=1}^{\infty}$ be an increasing sequence of events such that

$$A_1 \subseteq A_2 \subseteq A_3 \subseteq \cdots,$$

and define

$$A = \bigcup_{n=1}^{\infty} A_n.$$

Then, the probability measure satisfies

$$P = \bigcup_{n=1}^{\infty} A_n = \lim_{n\to\infty} P(A_n)$$

This property is known as continuity from below (Billingsley, 1999). It ensures that when events expand progressively, their probabilities converge to the probability of their union.

3.2 Continuity from Above: Let $\{A_n\}_{n=1}^{\infty}$ be an decreasing sequence of events such that

$$A_1 \supseteq A_2 \supseteq A_3 \supseteq \cdots,$$

and define

$$A = \bigcap_{n=1}^{\infty} A_n$$

$If\ P(A_1) < \infty, then$

$$P(\bigcap_{n=1}^{\infty} A_n) = \lim_{n\to\infty} P(A_n)$$

This property, known as continuity from above, guarantees that probabilities behave consistently under decreasing sequences of events (Durrett, 2019).

3.3 Interpretation and Importance
These continuity characteristics serve as a link between limit operations and probability theory. In many fields of probability and statistics, they guarantee that probability measures are compatible with the limiting behavior of sequences of occurrences.

Specifically, these findings are commonly used in:
proving convergence theorems
analyzing distribution functions
establishing properties of random variables
Moreover, continuity of probability measures is closely related to the concept of σ-additivity, which is one of the defining properties of probability measures (Kallenberg, 2002).

3.4 Example
Consider the probability space (Ω, F, P), where $\Omega = [0,1]$ and P is the uniform distribution. Define a sequence of events

$$A_n = \left[0, 1 - \frac{1}{n}\right].$$

Then, the sequence $\{A_n\}$ is increasing, and

$$\bigcup_{n=1}^{\infty} A_n = [0,1).$$

We compute:

$$P(A_n) = 1 - \frac{1}{n}$$
$$\lim_{n\to\infty} P(A_n) = 1$$

And

$$P\left(\bigcup_{n=1}^{\infty} A_n\right) = P\big([0,1)\big) = 1$$

This example illustrates continuity from below, showing that the probability of the union equals the limit of the probabilities.

3.5 Connection to Convergence
The previously stated ideas of convergence are intimately related to the continuity of probability measures. For instance, sequences of occurrences of the form are frequently taken into consideration while analyzing convergence in probability.

$$A_n = \{|X_n - X| > \varepsilon\}$$

whose probabilities tend to zero as n → ∞. The behavior of such sequences relies on the continuity properties of the underlying probability measure.
Additionally, continuity is crucial for weak convergence and convergence in distribution, where the behavior of probability measures on sets or functions is used to analyze their limits (Billingsley, 1999).

Stochastic Convergence

One of the key ideas in contemporary probability theory and statistical analysis is stochastic convergence. It explains how random variable sequences behave as the number of observations or experiments rises. The study of asymptotic features of probabilistic and statistical models relies heavily on several modes of convergence, which capture distinct elements of limiting behavior (Durrett, 2019; Billingsley, 1999).
The continuous qualities of probability measures are strongly related to the study of stochastic convergence. Convergence results frequently depend on probability measures' capacity to maintain limiting operations on random variables and event sequences. As a result, continuity provides convergence theory with a crucial theoretical basis.

4.1 Convergence in Probability

One of the most commonly used forms of stochastic convergence is convergence in probability. A sequence of random variables $\{X_n\}$ is said to converge in probability to a random variable X if, for every $\varepsilon > 0$,

$$P(|X_n - X| > \varepsilon) \to 0 \; as \; n \to \infty$$

his definition means that the probability of observing a significant difference between X_n and X becomes arbitrarily small as n increases (Durrett, 2019).

Convergence in probability is widely used in statistics, particularly in the study of estimators. An estimator is considered consistent if it converges in probability to the parameter it estimates.

4.2 Almost Sure Convergence

A stronger notion of stochastic convergence is almost sure convergence. A sequence $\{X_n\}$ converges almost surely to X if

$$P\left(\lim_{n\to\infty} X_n = X\right) = 1$$

For almost all outcomes in the sample space, this type of convergence requires pointwise convergence (Billingsley, 1999). Convergence in probability is implied by almost certain convergence, albeit this isn't always the case.

Because it offers a more robust assurance about the long-term behaviour of random variables, almost sure convergence is crucial to probability theory.

4.3 Convergence in Distribution

The different forms of stochastic convergence are closely related. In particular, the following implications hold:

$$X_n \xrightarrow{a.s.} X \Rightarrow X_n \xrightarrow{P} X \Rightarrow X_n \xrightarrow{d} X \Rightarrow$$

These relationships demonstrate the hierarchical structure of convergence concepts in probability theory (Durrett, 2019).

The opposite implications, however, typically do not apply. For instance, unless certain requirements are met, convergence in distribution does not always imply convergence in probability.

4.5 Example

Consider the sequence of random variables

$$X_n = \frac{1}{n}$$

For every $\varepsilon > 0$,

$$P(|X_n - 0| > \varepsilon) = 0$$

for sufficiently large n. Therefore,

$$X_n \xrightarrow{P} 0.$$

Since the sequence converges pointwise for all outcomes, it also converges almost surely to zero.

This example illustrates how stochastic convergence describes the limiting behavior of sequences of random variables.

4.6 Role in Statistical Analysis

Numerous statistical techniques and asymptotic findings are theoretically based on stochastic convergence. Convergence principles underpin ideas like estimator consistency, asymptotic normalcy, and convergence of empirical distributions.

Specifically, convergence in distribution is crucial for asymptotic approximations and hypothesis testing, but convergence in probability is key to estimation theory. These convergence results are guaranteed to stay mathematically rigorous and well-defined by the continuity properties of probability measures.
Additionally, significant probabilistic conclusions like the Central Limit Theorem and the Law of Large Numbers, which are essential to contemporary statistical modelling, are intimately linked to stochastic convergence (Billingsley, 1999).

Role of Continuity in Statistical Modeling

In statistical modelling and inference, continuity features of probability measures are crucial. Models are built under the presumption that sequences of random variables or estimators show stable limiting behavior in many statistical applications. The consistency of probabilistic structures under limiting operations is guaranteed by the continuity of probability measures, which makes statistical methods theoretically sound and mathematically dependable (Billingsley, 1999; Durrett, 2019).

5.1 Distribution Functions and Continuity
Because they explain the probabilistic behaviour of random variables, distribution functions are essential tools in statistical modelling. The distribution function for a random variable X is given by

$$F(x) = P(X \leq x).$$

An important property of distribution functions is right-continuity, meaning that

$$\lim_{h \to 0^+} (x + h) = F(x).$$

Small changes in the variable won't result in erratic variations in probability values thanks to this continuity quality. Therefore, continuity enables distribution functions to behave consistently under convergence and provide stability in probabilistic models (Billingsley, 1999).
Right-continuity is particularly important in convergence in distribution, where the limiting behavior of random variables is analyzed through the convergence of their distribution functions.

5.2 Law of Large Numbers
The Law of Large Numbers is one of the most significant uses of stochastic convergence in statistics. According to this theorem, the sample mean approaches the predicted value as the sample size grows under suitable circumstances.
If $X_1, X_2, \ldots, X_n$are independent and identically distributed random variables with expected value $\mathbb{E}[X]$, then

$$\overline{X_n} = \frac{1}{n}\sum_{i=1}^{n} X_i \to \mathbb{E}[X]$$

This finding shows how statistical estimation is theoretically justified by stochastic convergence. As the sample size increases, probabilistic behaviour is guaranteed to remain constant by the continuity features of probability measures (Durrett, 2019).
Because it explains why averages derived from data tend to match underlying population features, the Law of Large Numbers serves as the basis for many statistical processes.

5.3 Estimation and Consistency

Estimators are used to approximate unknown population parameters in statistical inference. Consistency, or the estimator's ability to converge to the correct parameter value as the sample size grows, is a desired characteristic of an estimator.

Formally, an estimator $\hat{\theta}_n$ is consistent for a parameter θ if

$$\hat{\theta}_n \xrightarrow{P} \theta$$

Since this definition is predicated on probability convergence, it directly depends on the continuity characteristics of probability measures. With more samples, consistency guarantees that statistical estimating techniques grow more reliable (Billingsley, 1999).

The concept of consistency is essential in many statistical models, including regression analysis, parameter estimation, and machine learning algorithms.

5.4 Continuity and Statistical Stability

The stability and dependability of statistical models are greatly enhanced by the continuity of probability measures. Statistical processes frequently require approximations, limiting arguments, or asymptotic conclusions in real-world applications. Unstable probabilistic behavior could result from minor changes in data or model parameters in the absence of continuity qualities.

Continuity ensures that probabilistic models retain coherent asymptotic behavior and react smoothly to limiting procedures. Given the frequent use of huge datasets and asymptotic approximations in contemporary statistical research, this stability is particularly crucial.

Furthermore, a number of traditional statistical conclusions, such as the Central Limit Theorem and the weak convergence of empirical distributions, depend heavily on continuity features (Durrett, 2019).

5.5 Example

Consider a sequence of independent Bernoulli random variables $X_1, X_2, \dots, X_n$, where

$$P(X_i = 1) = p, \qquad P(X_i = 0) = 1 - p$$

The sample mean is given by

$$\bar{X}_n = \frac{1}{n}\sum_{i=1}^{n} X_i$$

By the Law of Large Numbers,

$$\bar{X}_n \xrightarrow{P} p.$$

This example illustrates how convergence principles and continuity properties justify statistical estimation. As the sample size increases, the sample proportion approaches the true population probability p, demonstrating the stability and reliability of statistical inference.

Conclusions

This paper explored the continuity of probability measures and its importance in statistical modeling. The study showed that continuity properties, especially continuity from below and continuity from above, are essential for understanding how probabilities behave under limiting operations. These properties provide a solid mathematical foundation for analyzing sequences of events and random variables in probability theory.

The paper also examined different forms of stochastic convergence, including convergence in probability, almost sure convergence, and convergence in distribution. These concepts are closely connected to continuity and help explain how random variables behave as the number

of observations increases. In this way, continuity plays a key role in establishing many important results in probability and statistics.

In addition, the study highlighted the importance of continuity in statistical modeling and inference. Concepts such as distribution functions, weak convergence, and estimator consistency all rely on continuity properties to ensure stable and reliable statistical behavior. Classical results such as the Law of Large Numbers further demonstrate how convergence principles support statistical estimation and asymptotic analysis.

Through theoretical explanations and practical examples, this work demonstrated that continuity of probability measures is not simply a technical concept in measure-theoretic probability. Rather, it is a fundamental idea that connects probability theory, stochastic convergence, and statistical modeling. Understanding these relationships provides deeper insight into the mathematical structure of modern statistical analysis and its applications.

Future research may extend these ideas to more advanced areas such as stochastic processes, empirical process theory, and modern machine learning methods.

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THE IMPACT OF USING ARTIFICIAL INTELLIGENCE AS A SUPPLEMENTARY TOOL IN CONTEMPORARY CHEMISTRY TEACHING: AN EXPERIMENTAL STUDY.

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Abstract

This paper addresses the impact of the use of artificial intelligence as a supportive tool in contemporary chemistry teaching, with a particular focus on the understanding of ionic and covalent chemical bonds. This research aims to evaluate whether the integration of artificial intelligence into the learning process can influence the improvement of students' learning, compared to traditional teaching methods without the support of artificial intelligence. The study was carried out as an experimental research with two comparable groups of students, selected after a preliminary test (pre-test). In the first group, teaching was conducted through a traditional approach with contemporary visual and explanatory methods, whereas in the second group, in addition to the same explanation, students were given the opportunity to use artificial intelligence as a supportive tool for self-learning and clarification of concepts. After the completion of the learning process, a final test (post-test) was conducted for both groups, with the aim of assessing the level of understanding. This research aims to contribute to discussions on the use of artificial intelligence in education, highlighting its potential as a tool that can increase engagement, conceptual understanding, and the independence of students in the process of learning chemistry.

Keywords: chemistry education, artificial intelligence, student achievement, ionic and covalent bonding.

Introduction

In recent decades, the development of digital technology has significantly influenced the teaching and learning process at all educational levels. The digital revolution has brought important changes in many spheres of human life, including the field of education (Priyadi *et al*., 2025).

In particular, artificial intelligence (AI) has emerged as one of the most transformative technologies in contemporary education. Due to its potential in the educational process, artificial intelligence, including ChatGPT, has attracted great interest from researchers in the field of education (Erümit & Sarıalioğlu, 2025).

Various sectors, including education, are undergoing significant transformations as a result of the rapid advancement of artificial intelligence. AI plays an important role in both general and higher education, influencing students' academic development through the opportunities and challenges it offers (Vieriu & Petrea, 2025). In the field of education, artificial intelligence has introduced new approaches and solutions for teaching and learning, which are being applied and tested in different educational contexts (Pedro *et al*., 2019).

Artificial intelligence can contribute to the continuous improvement of the learning environment by fostering students' motivation, initiative, and creativity (Huang, Saleh & Liu, 2021).

Understanding and mastering fundamental scientific concepts and principles, including those of chemistry, represents a challenge for many students. Numerous studies have identified significant difficulties in learning and have highlighted the main factors influencing these difficulties (Treagust, Duit & Nieswandt, 2018).

Due to its abstract nature, chemistry is often perceived as a challenging subject for students. In this regard, it can greatly benefit from the use of artificial intelligence tools. These tools enable interactive simulations, virtual laboratories, and personalized learning approaches, making the

learning process more engaging and more accessible, especially for students who face difficulties with traditional teaching methods (Mandina & Kusakara, 2025).
Artificial intelligence has great potential to facilitate the understanding of complex topics in chemistry and to improve the learning process, becoming an important component in contemporary educational research. In this context, tools such as ChatGPT have shown the ability to explain and solve chemistry problems, helping to strengthen conceptual understanding and improve the learning process among students (Daher, Diab & Rayan, 2023).
Teaching chemistry in relation to real-life situations and problems is considered an effective way to increase students' motivation and interest in this subject. The use of practical examples enables students to understand the interdisciplinary nature of chemistry and its relevance in everyday life, making the learning process more meaningful and closer to their experiences (Mandler *et al*., 2012).
The integration of artificial intelligence into natural science subjects such as chemistry, biology, and physics contributes to the development of students' skills, encourages collaboration during learning, and creates a more accessible and effective environment for research and learning (Bauyrzhan & Zhylysbayeva, 2025).
This study aims to analyze the impact of artificial intelligence as a complementary tool in contemporary chemistry teaching, with a particular focus on improving students' understanding of ionic and covalent chemical bonds. Through an experimental design, the study evaluates whether the integration of AI in the learning process has a positive effect on students' achievement compared to traditional teaching methods.

Methodology

2.1. Participants / Sample: The research was conducted at the secondary school "Kiril Pejçinoviq" in Tetovo, with first-year students aged 14–15. Initially, four classes (A, B, C, and D) were included in the study and were administered a pre-test to assess their initial knowledge of chemical bonding.

2.2 Research method: This study was designed as a comparative experimental research. Based on the pre-test results, classes A and B were selected as comparable groups for the experiment. Class A was assigned as the experimental group, while Class B served as the control group, in order to evaluate the impact of artificial intelligence on the teaching and learning process.

2.3. Teaching Unit: The instructional unit covered in this study was "Ionic and Covalent Chemical Bonds." The aim of this unit was to develop students' conceptual understanding of the main types of chemical bonds and the differences between them.

2.4. Procedure: The teaching process was conducted during a 45-minute lesson in both groups. In both classes, contemporary teaching methods were used, including a PowerPoint presentation and verbal explanation by the teacher.
In the experimental group (Class A), in addition to traditional teaching methods, artificial intelligence (ChatGPT) was used as a supplementary tool for concept clarification and self-learning for approximately 10-15 minutes of the lesson.
In the control group (Class B), artificial intelligence was not used. After the lesson, both groups completed a post-test lasting 10 minutes to evaluate their acquired knowledge.

2.5. Research tools: The tools used in this study included a pre-test and a post-test, which were used to assess students' initial knowledge and learning outcomes after the teaching process.

The tests included questions related to ionic and covalent chemical bonds and were used to analyze changes in students' understanding after the completion of the lesson.

Table 1: Comparison of pre-test and post-test

Section	Pre-test (General Chemistry)	Post-test (Ionic & Covalent Bonds)
Part I – Multiple Choice	Atomic number, acids, bases, electron configuration, basic chemistry concepts	Ionic bond formation, covalent compounds, properties of ionic compounds
Q1	What does atomic number represent?	In an ionic bond there is: transfer of electrons
Q2	Identify an acid	Identify a covalent compound
Q3	Formation of ionic bond	Properties of ionic compounds
Q4	Identify a base	—
Q5	Unit of substance amount	—
Q6	Formation of covalent bond	—
Section	Pre-test	Post-test
Part II – Short Answer / Classification	Atom particles, electron configuration of oxygen, acid-base reaction products	Classification of substances as ionic or covalent
Q7	Parts of an atom	Classify $MgCl_2$, H_2O, SO_2, KI
Q8	Electronic configuration of oxygen	—
Q9	Product of acid-base reaction	—
Section	Pre-test	Post-test
Part III – Problem Solving / Reasoning	Mole calculation (CO_2)	Conceptual explanation of ionic bond and comparison
Q10	Calculate moles in CO_2	Why NaCl is ionic
—	—	Differences between ionic and covalent bonds

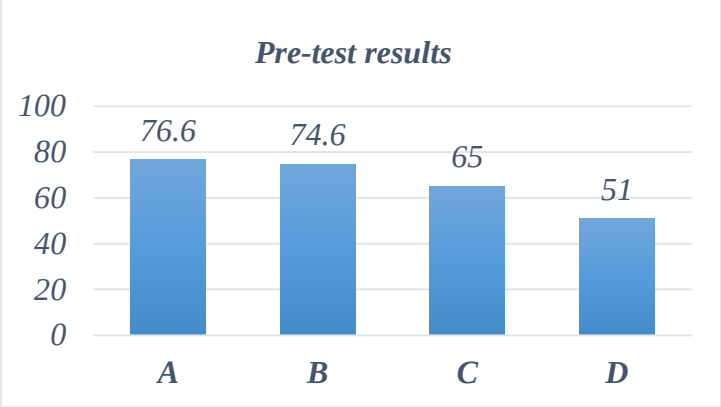
Results

To assess the initial level of students' knowledge on ionic and covalent chemical bonds, a pre-test was first conducted in four classes (A, B, C, and D). The results showed that Classes A and B had the most similar initial levels of knowledge; therefore, they were selected for the experimental study.

Table 2. Pre-test results

Class	Number of students	Total points	Average score	Percentage (%)
A	14	161	11.5	76.6%
B	20	224	11.2	74.6%
C	20	196	9.8	65%
D	25	192	7.68	51%

Based on the pre-test results, Classes A and B were considered the most comparable groups for conducting the experiment.



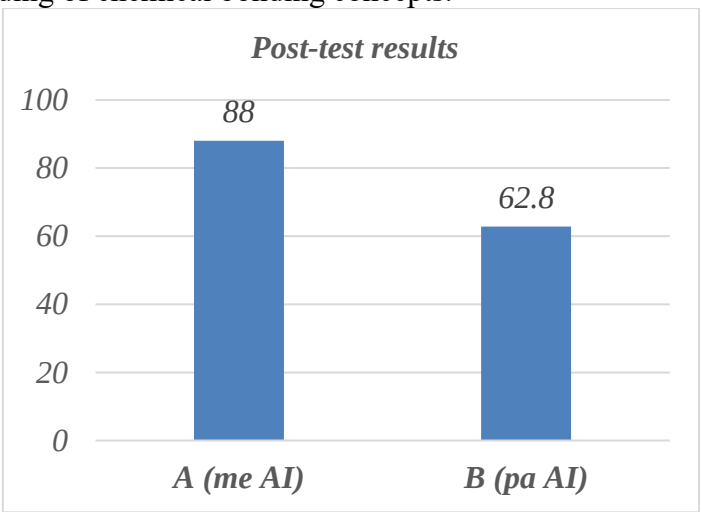
Graph 1. Comparison of pre-test results among Classes A, B, C, and D.

After the teaching process was completed, a post-test was conducted for both groups. In both classes, the same contemporary teaching method was used, supported by a PowerPoint presentation and verbal explanation by the teacher. In Class A, students were given approximately 10 minutes to use ChatGPT as a supportive tool for self-learning and clarification of concepts, while Class B continued only with the traditional teaching method. After the lesson was completed, both groups took a post-test to evaluate the knowledge acquired.

Table 3. Post-test results

Class	Teaching method	Number of students	Total points	Average score	Percentage (%)
A	Teaching + AI + post-test	15	198	13.2	88%
B	Teaching + post-test	26	245	9.42	62.8%

The post-test results show that Class A, in which artificial intelligence was used as a supportive teaching tool, achieved significantly higher results compared to Class B. The average score in Class A was 13.2 points (88%), while in Class B it was 9.42 points (62.8%).
The comparison between pre-test and post-test results shows a noticeable improvement in the experimental group, suggesting that the use of artificial intelligence had a positive impact on students' understanding of chemical bonding concepts.



Graph 2. Comparison of post-test results between Class A and Class B.

Discussion

The results of this study show that the use of artificial intelligence as a complementary tool in chemistry teaching has a positive impact on students' understanding of chemical concepts.

Students who used AI achieved higher post-test results compared to those who were taught using only traditional methods.

ChatGPT in chemistry education, when used under proper guidance and supervision, offers significant opportunities for innovation and supports more interactive, adaptive, and technology-based learning (Priyadi *et al*., 2025). However, its use still faces challenges, particularly regarding the potential dependency of students on artificial intelligence and the accuracy of the information provided (Priyadi *et al*., 2025).

In a previous study, it was reported that ChatGPT, when tested on solving 30 chemistry problems, successfully solved 13 of them (43.33%) without showing conceptual difficulties. These results suggest that ChatGPT can serve as a supportive tool for students in solving chemistry problems and improving the learning process. In this context, its integration into chemistry teaching is recommended as support for student learning (Bauyrzhan & Zhylysbayeva, 2025).

During the implementation of the research, it was observed that although both groups (class A and class B) completed the post-test within the same time duration of 10–15 minutes, students in class A, who used artificial intelligence as a supporting learning tool, completed the test faster compared to students in class B. This may indicate that the use of AI contributed to better understanding and greater efficiency in problem-solving.

Furthermore, during the research process, it was observed that students in the experimental group (class A), when instructed to use artificial intelligence as a learning aid, did not show confusion or hesitation in its use. They immediately engaged in the learning process and explored the content with ease, demonstrating a high level of acceptance and interest in the use of AI in education.

In the post-test, a significant difference was observed between the experimental group and the control group regarding questions involving examples of ionic and covalent bonds that had not been explicitly covered during the lesson. In the experimental group (with the use of artificial intelligence), 2 out of 15 students (13.3%) provided incorrect answers, while 13 students (86.7%) answered correctly. In the control group (without the use of artificial intelligence), 10 out of 26 students (38.5%) gave incorrect answers, while 16 students (61.5%) answered correctly.

A considerable performance gap was observed, expressed as a **25.2 percentage-point difference** in favor of the experimental group. This indicates that students exposed to artificial intelligence demonstrated a higher ability to transfer knowledge to new problem-solving contexts.

In this regard, the findings suggest that the use of artificial intelligence had a positive impact on the development of conceptual understanding and problem-solving skills for tasks not directly covered in classroom instruction, making the learning process more flexible and more oriented toward the practical application of knowledge.

Overall, the findings of this study support the idea that artificial intelligence should be used as a complementary tool in chemistry teaching, contributing to improved learning outcomes and the modernization of the educational process.

Conclusions

This study demonstrates that the integration of artificial intelligence as a supplementary tool in chemistry education can significantly enhance students' understanding of chemical concepts, particularly ionic and covalent bonding. The experimental results indicate that students who had access to AI-supported learning achieved higher performance compared to those who followed traditional instructional methods only. This suggests that AI can serve as an effective

bridge between abstract chemical concepts and students' comprehension by offering immediate explanations, interactive support, and personalized learning experiences.

Beyond improved academic achievement, the findings imply broader educational benefits. Artificial intelligence has the potential to transform the learning environment into a more dynamic and student-centered process, where learners are encouraged to explore, question, and learn independently. However, this does not reduce the importance of the teacher; rather, it highlights the teacher's role as a guide who ensures the correct and responsible use of technology in education.

In the future, the use of artificial intelligence in science education is expected to expand further, especially through more advanced adaptive systems and virtual learning environments. Therefore, educators and institutions should consider integrating such tools in a balanced way, combining traditional teaching methods with modern digital technologies. Overall, this study supports the idea that AI should not replace teaching, but rather complement it to improve the quality and effectiveness of education.

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STATISTICAL AND MULTIVARIATE ANALYSIS OF DIETARY HABITS AND LIFESTYLE BEHAVIORS IN RELATION TO BODY WEIGHT

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Abstract

Dietary habits and lifestyle behaviors are important factors associated with body weight and metabolic health. Nut and seed consumption, cooking oil preference, sleep duration, and meal frequency may influence nutritional status and body-weight-related outcomes.

This cross-sectional study presents a statistical analysis of dietary habits based on questionnaire responses collected from 22 participants. Descriptive statistics, Bayesian correlation, Bayesian regression, crosstab analysis, and Multiple Correspondence Analysis (MCA) were applied to investigate relationships among body weight, age, nut and seed consumption, bread intake, cooking oil usage, and lifestyle variables.

The results showed an average body weight of 96.14 kg and an average age of 50.14 years among participants. Most participants reported irregular meal frequency, short sleep duration, and predominant use of sunflower oil. Bayesian analyses did not identify a reliable association between age and body weight or between meal frequency and body weight. MCA suggested that body weight, bread consumption, nut and seed intake, and cooking oil preference contributed most strongly to the latent variability structure of the dataset.

The findings provide exploratory insight into dietary and lifestyle behaviors associated with body weight and may support future nutritional and public health investigations using larger population samples.

Keywords: dietary habits, lifestyle, Bayesian analysis, cross-sectional study, nutrition, Multiple Correspondence Analysis

Introduction

Dietary patterns, sleep duration, and socio-economic conditions are recognized correlates of body weight regulation and metabolic disease. Nutritional behaviors such as nut and seed consumption, bread intake, meal frequency, and cooking oil preference may influence obesity risk, insulin resistance, and long-term cardiometabolic health (Campos and Egea 2025). In recent years, increased attention has been directed toward the role of healthy dietary fats and lifestyle habits in preventing obesity and type 2 diabetes.

Nuts and seeds are rich in unsaturated fatty acids, dietary fiber, antioxidants, vitamins, and minerals, and their regular consumption has been associated with improved lipid metabolism and lower obesity prevalence. Sabaté and Ang (2009) reported that frequent nut consumption may contribute to lower body weight and reduced risk of metabolic disorders. Similarly, systematic reviews suggest that nut-enriched diets generally do not promote weight gain and may support satiety regulation and metabolic balance (Nishi et al. 2021).

Lifestyle-related variables such as short sleep duration and irregular meal patterns have also been associated with increased BMI and impaired metabolic homeostasis. Sleep deprivation may alter appetite-regulating hormones and increase energy intake, while irregular eating behavior may contribute to unhealthy dietary patterns (Campos and Egea 2025). However, the strength and direction of these associations often vary depending on sample characteristics, population structure, and statistical methodology.

From a computational and statistical perspective, nutritional datasets frequently contain both continuous and categorical variables with potentially complex interactions. Classical

descriptive statistics are commonly used to summarize distributions and identify dominant dietary patterns, while Bayesian statistical methods provide probabilistic estimation of associations under uncertainty, particularly in small samples. Bayesian correlation and Bayesian regression approaches allow estimation of posterior parameter distributions and credible intervals instead of relying exclusively on frequentist significance testing.
In addition, exploratory multivariate techniques such as Multiple Correspondence Analysis (MCA) enable dimensionality reduction and visualization of latent relationships among categorical variables. MCA transforms categorical data into multidimensional geometric structures using inertia decomposition and eigenvalue analysis, allowing identification of variables contributing most strongly to the overall variance structure of the dataset (Balakrishna et al. 2022).
Therefore, the aim of this study was to evaluate dietary habits related to nut and seed consumption, bread intake, cooking oil preference, and lifestyle behaviors in relation to body weight using descriptive statistics, Bayesian computational analyses, and exploratory multivariate methods in a cross-sectional sample of adult participants.

Materials and Methods

2.1 Study Design and Sample: This study represents a cross-sectional secondary statistical analysis of questionnaire-based nutritional and lifestyle data collected from a convenience sample of 22 participants (N = 22). The analysis aimed to investigate associations between body weight, dietary habits, and selected lifestyle-related variables using both classical and Bayesian statistical approaches.

2.2 Data Source and Preparation: The dataset was imported from an Excel worksheet (Book1.xlsx, Sheet1) into IBM SPSS Statistics software for preprocessing and statistical analysis. The active dataset was subsequently stored as *data.sav*. User-defined missing values were treated as missing during all analyses.
Because several questionnaire responses contained slight textual inconsistencies (e.g., variations in category formatting), SPSS treated some responses as separate categorical levels during frequency and multivariate analyses.

2.3 Variables: The study included both continuous and categorical variables. Continuous variables: Age (years), Body weight (kg), height (m), BMI (kg/m^2). Categorical variables: Religion Employment status Socio-economic condition (income categories) Sleep duration Diabetes diagnosis (yes/no) Meal frequency Frequency of nut consumption Amount of nut consumption Frequency of seed consumption Daily bread intake Bread type Primary cooking oil used for cooking

2.4 Statistical Analysis: Descriptive and inferential statistical analyses were performed using IBM SPSS Statistics.

2.4.1 Descriptive Statistics and Frequency Analysis: Continuous variables were summarized using:
arithmetic mean $\tilde{x}$
standard deviation (SD),
minimum values,
maximum values.

The arithmetic mean was calculated according to: $\tilde{x} = \Sigma_{i=1}^{n} x_i$ (1), while the standard deviation was calculated as: $S = \sqrt{\frac{\Sigma_{i=1}^{n}(x_i - \tilde{x})^2}{n-1}}$ (2).

Categorical variables were analyzed using frequency distributions and percentage representation .

$P(\theta|D) = \frac{P(D|\theta)P(\theta)}{P(D)}$ (3)

where:

$P(\theta|D)$ represents the posterior distribution,

$P(D|\theta)$ represents the likelihood,

$P(\theta)$ represents the prior distribution,

$P(D)$ represents the marginal likelihood.

Posterior means, posterior modes, variances, and 95% credible intervals were reported.

2.4.2 Bayesian Regression Analysis

Bayesian regression analysis was conducted to examine the relationship between body weight and meal frequency categories. The linear regression model can be expressed as:

$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$ (4)

where:

y_i - dependent variable (the outcome for observation *i*)

x_i – independent variable (the predictor for observation *i*)

β_0 - intercept (the value of y when x=0)

β_1 - regression coefficient (the change in y for a one-unit increase in x)

ε_i- error term (the unexplained variation for observation *i*)

Reference priors were applied and posterior parameter estimation was obtained through Bayesian inference. ANOVA summaries generated by SPSS were additionally reported.

2.4.3 Crosstab Analysis: Crosstabulations were performed descriptively to evaluate distributions between:

body weight and seed-consumption frequency,

body weight and daily bread intake,

body weight and employment status,

body weight and sleep duration,

body weight and meal frequency.

Due to sparse cell frequencies and numerous single-observation categories, inferential interpretation of contingency associations was limited.

2.4.4 Nonparametric Analysis

Nonparametric tests including one-sample, related-sample, and independent-sample procedures were performed primarily for diagnostic and exploratory purposes because the small sample size and sparse categorical structure reduced the robustness of classical parametric assumptions.

2.4.5 Multiple Correspondence Analysis (MCA)

Multiple Correspondence Analysis (MCA) was applied to investigate latent multidimensional relationships among categorical dietary and lifestyle variables. Variable-principal normalization was used with two extracted dimensions and a maximum of 100 iterations. Convergence was successfully achieved.

MCA decomposes categorical variance using inertia-based dimensional representation:

$I = \sum \frac{(f_{ij} - f_i f_j)^2}{f_i f_j}$ (5),

where:

f_{ij} – represent observed joint frequencies,

$f_i f_j$ – represents expected frequencies under indepedence

SPSS automatically discretized string variables using ranking-based transformation procedures.

All statistical analyses used two-sided inference procedures, while Bayesian analyses reported 95% credible intervals. Given the relatively small sample size and sparse contingency tables, all findings were interpreted cautiously and considered exploratory rather than confirmatory.

Results

3.1. Sample Characteristics: A total of 22 participants were included in the statistical analysis (N = 22). The average age of participants was 50.14 years (SD = 12.40), with values ranging from 29 to 68 years. The average body weight was 96.14 kg (SD = 26.55), with a minimum value of 60 kg and a maximum value of 191 kg. These descriptive indicators suggest that the analyzed sample consisted predominantly of middle-aged individuals with relatively elevated body weight values.

Table 1. Descriptive statistics of continuous variables

Variable	N	Minimum	Maximum	Mean	SD
Age (years)	22	29	68	50.14	12.40
Body weight (kg)	22	60	191	96.14	26.55
BMI (kg/m^2)	22	22.6	58.95	41.86	10.56

The arithmetic mean was calculated using equation $\bar{x} = \frac{\sum x}{N}$ (6), while the standard deviation was estimated using equation $S = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n-1}}$ (7), where xi represents individual observations and n is the sample size.

3.2. Distribution of Categorical Variables: The categorical analysis demonstrated that the majority of participants identified as Orthodox Christian (68.2%), followed by Muslim participants (27.3%). According to employment status, office-based work was the most represented occupational category (40.9%), while unemployed individuals and pensioners each represented 22.7% of the sample.

Regarding socio-economic condition, the most frequent income category was 300 € (27.3%), followed by 500 € and above 500 € (22.7% each). Most participants reported sleeping between 5–6 hours per night (45.5%), while 22.7% reported sleeping 7–8 hours.

Half of the participants (50%) reported having diabetes mellitus. Meal frequency analysis showed that irregular meal consumption dominated within the sample (54.5%), whereas only 22.7% reported regular meal frequency.

Dietary indicators demonstrated that nut consumption was most commonly reported as 1–2 times weekly (36.4%), while seed consumption was frequently occasional or irregular. White bread (40.9%) and integral bread (36.4%) represented the dominant bread categories. Sunflower oil was the predominant cooking oil, used by 72.7% of participants.

Table 2. Distribution of main categorical variables

Variable	Dominant category	Percentage (%)
Religion	Orthodox Christian	68.2
Employment status	Office work	40.9
Sleep duration	5–6 h	45.5

Diabetes diagnosis	Yes	50.0
Meal frequency	Irregular	54.5
Bread type	White bread	40.9
Cooking oil	Sunflower oil	72.7

The categorical frequency distributions indicate relatively heterogeneous nutritional and lifestyle patterns within the analyzed sample.

3.3. Descriptive and Diagnostic Statistical Testing: One-sample t-tests were performed for the continuous variables age and body weight. As expected, both variables produced statistically significant results ($p < 0.001$), primarily because the hypothesized test value was fixed at zero. Consequently, these analyses were considered diagnostic rather than substantively informative for nutritional interpretation.

The t-statistic is defined with equation:

$t = \frac{\bar{x} - \mu_0}{s/\sqrt{n}}$ (8),

where:

$\bar{x}$ – the sample mean

μ_0 – the hipothesiyed population mean

s – the sample standard deviation

n – the sample size

In addition, one-sample chi-square goodness-of-fit tests were performed to evaluate whether categorical responses were uniformly distributed across categories. Significant deviations from equal category distribution were observed for religion ($p = 0.001$), sleep duration ($p = 0.006$), daily nut-consumption amount ($p = 0.013$), seed-consumption frequency ($p = 0.045$), bread type ($p = 0.002$), and cooking oil preference ($p < 0.001$). These findings indicate the presence of dominant behavioral and dietary patterns within the analyzed sample. Due to the relatively small sample size and sparse categorical frequencies, the chi-square results should be interpreted cautiously.

The chi-square goodness-of-fit statistic is defined with equation :

$x^2 = \sum \frac{(O_i - E_i)^2}{E_i}$ (9),

where:

O_i- observed frequency in category i

E_i – expected frequency in category i

$\sum$ - sum over all categories

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The categories of Пациенти occur with equal probabilities.	One-Sample Chi-Square Test	1,000[1]	Retain the null hypothesis.
2	The categories of религија occur with equal probabilities.	One-Sample Chi-Square Test	,001[1]	Reject the null hypothesis.
3	The categories of работно место occur with equal probabilities.	One-Sample Chi-Square Test	,327[1]	Retain the null hypothesis.
4	The categories of социо-економски услови occur with equal probabilities.	One-Sample Chi-Square Test	,802[1]	Retain the null hypothesis.
5	The categories of времетрајно на спиење occur with equal probabilities.	One-Sample Chi-Square Test	,006[1]	Reject the null hypothesis.
6	The categories defined by дали е дијагностициран со дијабет = не and да occur with probabilities 0,5 and 0,5.	One-Sample Binomial Test	1,000[1,1]	Retain the null hypothesis.
7	The categories of Фрекфенција на оброци occur with equal probabilities.	One-Sample Chi-Square Test	,108[1]	Retain the null hypothesis.
8	The categories of колку често консумирате јаткасти плодови occur with equal probabilities.	One-Sample Chi-Square Test	,054[1]	Retain the null hypothesis.
9	The categories of Колку консумирате дневно occur with equal probabilities.	One-Sample Chi-Square Test	,013[1]	Reject the null hypothesis.
10	The categories of Колку често консумирате семиња occur with equal probabilities.	One-Sample Chi-Square Test	,045[1]	Reject the null hypothesis.
11	The categories of Колку парчиња леб јадете дневно occur with equal probabilities.	One-Sample Chi-Square Test	,074[1]	Retain the null hypothesis.
12	The categories of Каков леб користите occur with equal probabilities.	One-Sample Chi-Square Test	,002[1]	Reject the null hypothesis.
13	The categories of Кое масло пренственото користете за готвење occur with equal probabilities.	One-Sample Chi-Square Test	,000[1]	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is ,05.

[1] Exact significance is displayed for this test.

[1] Lilliefors Corrected

[2] This is a lower bound of the true significance.

Figure 1. Summary of one-sample chi-square goodness-of-fit tests for categorical variables.

3.4. Associations Between Variables

3.4.1. Bayesian Correlation Between Age and Body Weight

Bayesian correlation analysis was applied to evaluate the probabilistic relationship between age and body weight. The posterior mean correlation coefficient was approximately:

$r \approx -0.304$

with a 95% credible interval ranging from −0.648 to 0.059. The posterior mode was approximately −0.344. Since the credible interval crosses zero, the Bayesian evidence is insufficient to support a reliable association between age and body weight within this sample.

Table 3. Bayesian correlation between age and body weight

Parameter	Value
Posterior mean	−0.304
Posterior mode	−0.344
95% credible interval	[−0.648 ; 0.059]

Bayesian inference was estimated according to Bayes' theorem equation:

$$P(A|B)=\frac{P(B|A)P(A)}{P(B)} \quad (10),$$

P(A|B) - posterior probability

P(B | A) – likelihood

P(A) - prior probability

P(B) - *evidence* (marginal probability)

3.4.2. Bayesian Regression: Body Weight vs. Meal Frequency: Bayesian regression analysis was conducted to investigate whether meal frequency predicts body weight. The obtained model was not statistically significant:
F=1.246,p=0.310
indicating that meal frequency was not a reliable predictor of body weight in this sample. Posterior intervals for meal-frequency categories were broad and overlapped zero, reflecting substantial uncertainty associated with the small sample size.

Table 4. Bayesian regression analysis

Parameter	Value
F statistic	1.246
p-value	0.310

The regression model is represented with equation :
$Y = a + bX$ (11),
where X is the explanatory variable and Y is the dependent variable. The slope of the line is b, and a is the intercept (the value of y when x = 0).

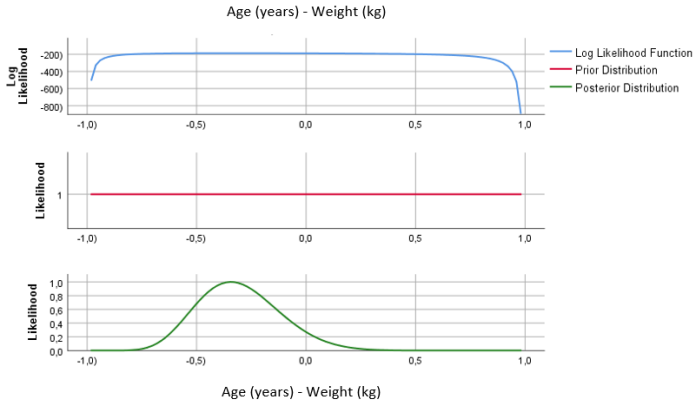


Figure 2. Bayesian posterior distribution and likelihood estimation for the relationship between age and body weight.

The posterior distribution demonstrated a weak negative tendency between age and body weight, although the posterior credible interval crossed zero, indicating insufficient Bayesian evidence for a reliable linear association.

3.4.3. Crosstab Analysis
Descriptive crosstab analyses were performed between body weight and:
seed consumption frequency,
bread-slice intake,
employment status,
sleep duration,
meal frequency.
The contingency tables contained numerous sparse cells with single observations and zero frequencies, limiting the reliability of classical inferential χ^2 association testing. Consequently, the crosstab results were interpreted descriptively rather than inferentially.
The distributions suggest heterogeneous behavioral and nutritional patterns across body-weight categories without clearly defined clustering tendencies.

3.5. Multiple Correspondence Analysis (MCA)
Multiple Correspondence Analysis (MCA) was applied as an exploratory multivariate method for identifying latent relationships among categorical variables. Convergence was achieved

after 36 iterations using variable-principal normalization. The first two dimensions produced eigenvalues of approximately 7.57 and 7.49, respectively, accounting for approximately 54% of the variance per dimension.

Table 5. MCA dimensional structure

Dimension	Eigenvalue	Explained variance (%)
Dimension 1	7.57	54.07
Dimension 2	7.49	53.47

MCA decomposes categorical variance through inertia estimation with equation:

$$I = \sum i \sum j \frac{(pij - ricj)2}{ricj}$$

where:

I - total inertia (total variance explained in MCA)

P_{ij} - joint proportion of category i and category j

R_i - marginal proportion (row mass) for category i

C_j - marginal proportion (column mass) for category j

$\sum$ - summation over all categories (rows and columns)

Discrimination measures indicated that age, body weight, daily bread consumption, nut frequency, and cooking oil usage contributed most strongly to the latent variance structure of the dataset. Given the relatively small sample size and ranking-based discretization of categorical variables in SPSS, MCA findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

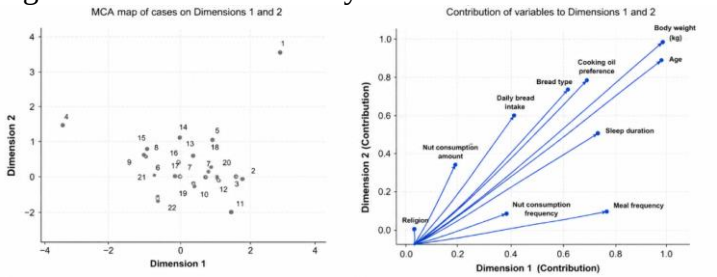


Figure 3. Multiple Correspondence Analysis (MCA) results showing participant distribution and variable contribution across the first two dimensions.

The MCA results presented in Figure 3 provide a multidimensional representation of both participant distribution and variable contribution within the analyzed nutritional and lifestyle dataset. The left panel illustrates the object-point map of participants projected onto the first two MCA dimensions, while the right panel presents the discrimination measures showing the contribution strength of individual variables to the latent multidimensional structure.

In the left panel, each numbered point represents an individual participant positioned according to the similarity of categorical dietary and lifestyle characteristics. Participants located closer to each other exhibit more similar response patterns, whereas participants positioned farther apart demonstrate greater heterogeneity in nutritional and behavioral profiles. Most participants are clustered around the central region of the multidimensional space, indicating moderate similarity among dietary habits and lifestyle behaviors within the sample. However, several observations, particularly cases 1 and 4, appear relatively distant from the primary cluster, suggesting more atypical participant profiles compared to the remaining sample population. These isolated cases may reflect differences in body weight, sleep duration, bread consumption, cooking oil preference, or other analyzed lifestyle variables.

The right panel presents the discrimination measures for the first two MCA dimensions. The length and direction of each vector indicate the relative contribution of variables to the explained multidimensional variance. Variables positioned farther from the origin demonstrate stronger discriminatory contribution to the latent structure of the dataset. The strongest contributions were observed for body weight and age, indicating that these variables

contributed most substantially to the separation of participants across the MCA dimensions. Cooking oil preference, bread type, daily bread intake, and sleep duration also demonstrated relatively strong contributions, suggesting that these nutritional and lifestyle characteristics play an important role in defining variability within the analyzed sample. In contrast, variables such as religion, nut-consumption frequency, and meal frequency exhibited weaker contributions, as reflected by their shorter vectors and closer proximity to the origin.

Overall, the MCA findings suggest that anthropometric characteristics together with selected dietary and lifestyle variables contribute substantially to the multidimensional variability of the analyzed population. Although the observed clustering tendencies are exploratory and limited by the relatively small sample size, the analysis provides useful insight into the latent structure of nutritional and behavioral patterns within the dataset.

Discussion

The present study explored dietary habits and lifestyle-related variables in relation to body weight using descriptive statistics, Bayesian inference, and exploratory multivariate analysis. The findings demonstrated that irregular meal frequency, short sleep duration, predominant sunflower oil consumption, and frequent white-bread intake were common characteristics within the analyzed sample. Although Bayesian analyses did not identify statistically reliable associations between age, meal frequency, and body weight, the multivariate MCA results suggested that anthropometric characteristics together with selected dietary variables contributed substantially to the latent variability structure of the dataset.

The observed predominance of sunflower oil and white-bread consumption reflects dietary behaviors commonly reported in transitional and middle-income populations, where refined carbohydrates and vegetable oils remain highly represented in everyday nutrition. Similar nutritional tendencies have been discussed in studies investigating obesity-related dietary patterns and metabolic health (Campos and Egea 2025). In addition, irregular meal frequency and short sleep duration observed in the present sample are consistent with previous findings suggesting that lifestyle-related behaviors may influence metabolic regulation and appetite control. Similar observations regarding obesity-related nutritional behaviors and mathematical analysis of obesity predictors were reported by Knights et al. (2024), where statistical and machine learning methods identified BMI and dietary variables as important contributors to obesity-related outcomes.

The Bayesian correlation analysis demonstrated only a weak negative tendency between age and body weight, with posterior credible intervals crossing zero. This finding indicates substantial uncertainty in the estimated relationship and suggests that age alone may not sufficiently explain body-weight variability within the analyzed sample. The broad credible intervals likely reflect the relatively small sample size and heterogeneous participant characteristics. Bayesian approaches are particularly useful in small exploratory datasets because they allow probabilistic interpretation of parameter uncertainty rather than relying exclusively on classical significance testing. Similar applications of mathematical and machine learning approaches in metabolic-disease prediction were presented by Mazlami and Antonska Knights (2025), where logistic regression and statistical modeling successfully identified important predictors of type 2 diabetes mellitus.

The MCA results provided additional insight into the multidimensional structure of the dataset. Body weight and age demonstrated the strongest discriminatory contribution to the first two MCA dimensions, followed by cooking oil preference, bread type, and sleep duration. These findings suggest that anthropometric and nutritional characteristics jointly contribute to latent behavioral structure within the analyzed population. Similar applications of exploratory multivariate approaches in nutritional epidemiology have shown that dietary variables

frequently cluster together and may reflect broader lifestyle patterns rather than isolated nutritional effects (Balakrishna et al. 2022). Furthermore, Markovikj and Knights (2022) demonstrated that optimization approaches in nutritional modeling may support more sustainable dietary planning and healthier nutritional structures.

The present findings are partially consistent with previous studies reporting beneficial effects of nuts and seeds on metabolic health and body-weight regulation. Nuts and seeds are rich in unsaturated fatty acids, antioxidants, dietary fiber, and micronutrients, which may contribute to improved satiety and lipid metabolism (Sabaté and Ang 2009). Systematic reviews further indicate that moderate nut consumption generally does not promote weight gain and may support long-term metabolic balance (Nishi et al. 2021). However, in the present study, nut-consumption frequency demonstrated relatively limited discriminatory contribution within the MCA analysis, potentially due to the small sample size and heterogeneous consumption patterns among participants.

The observed variability in body weight and dietary habits may additionally reflect differences in dietary adherence and behavioral responses among individuals. Similar findings were reported by Markovikj, Knights, and Gajdoš Kljusurić (2023), who demonstrated variability in body-weight reduction efficiency among overweight and obese adults following ketogenic dietary interventions. Their results further support the importance of individualized nutritional approaches and continuous monitoring of dietary behavior.

From a methodological perspective, the integration of Bayesian statistics, chi-square testing, and multivariate exploratory methods demonstrates the growing importance of computational approaches in nutritional and biomedical research. Experimental and statistical design methodologies similar to those used in the present study were discussed by Antoska Knights and Millaku (2023), emphasizing the applicability of mathematical and statistical frameworks in complex health-related datasets.

Several limitations should be considered when interpreting the findings. First, the study included a relatively small convenience sample, limiting statistical power and generalizability. Second, several categorical variables contained sparse frequencies and minor textual inconsistencies in questionnaire responses, which increased category fragmentation during SPSS processing. Third, the cross-sectional design does not permit causal interpretation of relationships between dietary habits and body weight. Consequently, the findings should be considered exploratory and hypothesis-generating rather than confirmatory.

Despite these limitations, the study demonstrates the applicability of Bayesian statistics and exploratory multivariate techniques such as MCA in nutritional and lifestyle research. The integration of descriptive statistics, Bayesian inference, chi-square testing, and multidimensional analysis provides a computational framework for investigating complex behavioral datasets containing both continuous and categorical variables. Future studies should include larger and more balanced population samples, standardized questionnaire structures, and additional nutritional biomarkers to improve statistical robustness and biological interpretation.

Conclusions

The present study investigated dietary and lifestyle behaviors in relation to body weight using descriptive statistics, Bayesian computational analysis, and Multiple Correspondence Analysis (MCA). The results demonstrated that irregular meal frequency, short sleep duration, sunflower-oil consumption, and white-bread intake were common characteristics within the analyzed sample. Bayesian analyses did not identify reliable associations between age, meal frequency, and body weight, while MCA indicated that body weight, bread consumption, and

cooking-oil preference contributed most strongly to the latent variability structure of the dataset.

Despite the relatively small sample size, the study demonstrates the applicability of Bayesian statistics and exploratory multivariate methods in nutritional and lifestyle research. The integration of mathematical and statistical approaches provides a useful computational framework for investigating complex behavioral datasets containing both continuous and categorical variables. Future studies should include larger population samples and additional nutritional and metabolic indicators to improve statistical robustness and predictive interpretation.

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EDUCATION IN SUSTAINABLE URBAN PLANNING AND DESIGN AS A PREREQUISITE FOR INFORMED CIVIC AGENCY IN URBAN DECISION-MAKING IN NORTH MACEDONIA

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Abstract

Legal and urban policy frameworks worldwide, including in North Macedonia, recognise citizen participation as an important component of planning processes and regulate it through mandatory mechanisms for civic involvement in the planning of settlements. However, the existence of participatory mechanisms raises a fundamental question: to what extent are citizens equipped with the knowledge necessary to engage meaningfully in urban development processes? Legislation may ensure access to participation, but it does not ensure the capacity to interpret spatial proposals, evaluate trade-offs, and assess the long-term implications of urban transformation. Without such competencies, participation risks becoming symbolic rather than substantive.

UNESCO also emphasises active citizen participation in the development of cities and human settlements, while stressing that meaningful participation requires education. Through its Education for Sustainable Development frameworks, also promoted in North Macedonia, UNESCO seeks to equip citizens with the knowledge, skills, values, and critical understanding needed to contribute positively to sustainable development. However, the role of basic urban planning and urban design literacy in supporting informed civic participation in urban development processes remains insufficiently emphasised.

Drawing on urban theory, this research argues that urban planning and urban design play a central role in shaping sustainable urban environments. Principles such as density, mobility, walkability, connectivity, mixed-use diversity, permeability, adaptability, and the quality of the public realm directly influence environmental performance, social inclusion, accessibility, and urban resilience. Therefore, sustainability education frameworks should also integrate basic education on urban planning policies and urban design principles. In this way, it will generate informed civic participation in urban decision-making and a multidimensional approach to sustainable urban development.

Keywords: urban planning, urban design, civic inclusion, civic education, sustainable development

Introduction

Urban planning and design discourse has increasingly positioned citizen participation as a central component of democratic and sustainable urban development. International frameworks and planning theory emphasise that inclusive decision-making processes can enhance legitimacy, responsiveness, and long-term urban resilience (Healey, 1997; Innes & Booher, 2004; Alexander, 1977, 2002–2005; Carmona, 2001). In parallel, national legislations, including those of North Macedonia, have incorporated formal mechanisms to involve citizens in the planning process. Yet, citizens are typically involved at later stages of the planning process, and their contributions remain largely consultative, with limited influence on final decisions. However, the existence of participatory mechanisms raises a fundamental question: to what extent are citizens equipped with knowledge for engaging meaningfully in urban planning and design processes? While legislation ensures access, it does not ensure understanding. The capacity to interpret spatial proposals, evaluate trade-offs, and assess long-term impacts requires specific knowledge and competencies. Without these, participation risks becoming symbolic rather than substantive, aligning with what Arnstein (1969) described as tokenistic participation, where citizens are heard but lack real influence over outcomes. This reveals a critical gap between formal inclusion and actual capacity for participation.

On the other hand, UNESCO also emphasises the importance of active citizen participation in the proper development of cities and human settlements. However, it argues that meaningful participation requires education and public awareness, as citizens need adequate knowledge and critical understanding of environmental, social, economic, and spatial processes in order to effectively engage in sustainable development. Through its Education for Sustainable Development (ESD) framework, UNESCO promotes the development of knowledge, skills, values, and participatory capacities necessary for more sustainable and inclusive urban environments. Similar initiatives related to sustainability education and civic participation have also been promoted in North Macedonia through collaborations between UNESCO, national institutions, and international organisations. (Polenakovikj, 2024) However, they do not explicitly address urban planning and design as a distinct and necessary domain of knowledge, despite the fact that cities represent an important spatial context in which sustainability is materialised.

Urban planning and urban design constitute the operational interface through which sustainability principles are translated into the built environment. Urban planning primarily addresses the strategic organisation of land use, density, mobility, infrastructure, and the distribution of urban functions, while urban design focuses on the physical and experiential qualities of urban space, including walkability, connectivity, permeability, mixed-use diversity, adaptability, legibility, and the quality of the public realm. Together, these principles directly influence ecological performance, social inclusion, accessibility, economic vitality, and long-term urban resilience. From this perspective, sustainable development depends not only on environmental policies and technological systems, but also on the spatial organisation and everyday experience of the city (Carmona, 2021; Bentley et al., 1985; Homes and Communities Agency, 2013; English Partnerships et al., 2007; Ferati et al., 2019; Saidi et al., 2024; Saidi Qazimi, 2025). Without an understanding of these processes, citizens remain unable to meaningfully engage with the decisions that structure their urban environments.

Therefore, this research argues that sustainability education frameworks should integrate basic education on spatial, urban planning, and urban design principles that support healthy and sustainable environments. Such education should be introduced progressively across different stages of learning, from early awareness of the built and natural environment in preschool and primary education, to more critical engagement with mobility, land use, public space, density, infrastructure, and urban decision-making in secondary, higher, and adult education. In the case of North Macedonia, the existing Education for Sustainable Development (ESD) framework and climate education initiatives already aim to integrate sustainability across educational levels and teacher training. (Polenakovikj, 2024) However, they do not yet define sustainable urban planning and urban design literacy as a concrete educational domain. Without this spatial and regulatory literacy, citizens may become environmentally aware, yet remain unable to understand, evaluate, and participate meaningfully in the planning decisions that shape the sustainable development of their settlements.

Legal Framework and the Limits of Effective Participation

The legal framework of urban planning in North Macedonia reflects a long-standing recognition of public participation. Public engagement was first introduced through the Law on Urban Planning (Закон за урбанистичко планирање, 1958), which dedicated Articles 10, 11, and 12 to public inspection and the collection of citizens' comments and proposals over a consultation period of 30 to 60 days. These mechanisms were later redefined by the Law on Regional, Spatial and Urban Planning (Закон за регионално, просторно и урбанистичко планирање, 1965), which provided for public inspection during the adoption of regional and urban plans, while leaving the procedure to municipal assemblies. The Law on Spatial and

Urban Planning (Закон за просторно и урбанистичко планирање, 1973) made public inspection compulsory at all phases of spatial and urban planning, although the implementation procedures remained under the authority of local assemblies. The Law on the System of Spatial and Urban Planning (Закон за системот на просторното и урбанистичкото планирање, 1985) introduced councils and mandatory public debates as mechanisms of social influence in spatial and urban planning. Later, the Law on Spatial and Urban Planning (Закон за просторно и урбанистичко планирање, 1996) allowed public surveys and expert debates, enabling citizens to participate through written remarks, although this participation remained time-limited and predominantly advisory. Participation was further expanded through the Law on Spatial and Urban Planning (Закон за просторно и урбанистичко планирање, 2005), which introduced municipal participatory bodies, mandatory public presentations and surveys, and transparent reports with written responses to submitted remarks. The Law on Spatial and Urban Planning (Закон за просторно и урбанистичко планирање, 2014) further detailed public survey and public presentation procedures through the e-urbanism system, including written and electronic submissions and mandatory responses to submitted survey sheets. The current Law on Urban Planning (Закон за урбанистичко планирање, 2020) formalises participation through public surveys lasting between 30 and 90 days, public presentations of proposed plans, and participatory bodies composed of representatives from local government, civic associations, urban and local communities, experts, and activists.

Although participation is legally embedded, official mechanisms are often perceived as procedural formalities rather than instruments of meaningful engagement, since they are standardised, time-bound, and primarily oriented toward statutory compliance rather than genuine dialogue. In addition, these mechanisms are usually activated in the later stages of the planning process, when the main spatial parameters and planning agendas have already been defined. This limits citizens' ability to influence the formulation of planning priorities from the outset and confines participation largely to commenting on already developed proposals (Dokuzova et al., 2026).

These limitations are not only procedural but also educational and interpretive. A recent study conducted in North Macedonia, specifically in Skopje, shows that public participation tends to be fragmented, uneven, and reactive, clustering around controversial plans rather than reflecting sustained and systematic civic engagement. The same study found that, when citizens were asked to observe and represent their immediate urban environments, their interpretations were often rooted in localised everyday experience, while wider spatial relations and systemic urban structures remained less apparent. This does not mean that citizens lack valuable knowledge; rather, it shows that lived experience does not automatically translate into planning-relevant input. Without accessible visualisation tools, a shared spatial vocabulary, and basic planning knowledge, citizens often rely on descriptive narratives rather than analytical reasoning, making it difficult for their observations to enter formal planning discourse. (Dokuzova et al., 2026)

Such findings correspond with broader debates in planning theory. Participation is often institutionalised procedurally but lacks substantive impact when citizens are heard without being able to influence outcomes (Arnstein, 1969; Hordijk et al., 2015). As Forester (1989) argues, planning processes are shaped by the management of information, knowledge, trust, and power; therefore, meaningful participation requires more than formal access. Similarly, communicative planning theory emphasises dialogue, mutual learning, and the construction of shared understanding among stakeholders (Healey, 1997). This position is theoretically supported by Habermas's theory of communicative action, in which rational communication and public justification are central to reaching understanding and coordinating collective action (Habermas, 1984).

Christopher Alexander's (2002–2005) understanding of design as a gradual and generative process further strengthens this critique. He rejects mechanical, top-down design methods and instead argues for adaptive processes in which environments are shaped step by step, through decisions that respond to the existing spatial and social structure of a place. Such an approach implies that inhabitants should not be consulted only after plans have been completed. Their knowledge of everyday routines, needs, and spatial experience should inform the project while decisions are still being developed. Participation, therefore, is not a late-stage procedure for reacting to fixed proposals, but part of the generative process through which coherent and life-supporting environments are formed. Thus, effective participation requires both earlier inclusion in the planning process and the development of citizens' capacity to understand, evaluate, and communicate spatial issues in ways that can meaningfully inform urban decision-making.

Education as a Precondition for Informed Civic Agency

The limitations of civic participatory planning cannot be understood solely as institutional shortcomings; they must also be examined as a consequence of insufficient civic capacity. While legal frameworks provide mechanisms for inclusion, they do not equip citizens with the knowledge required to engage meaningfully with complex planning processes. In this sense, participation is not simply a matter of access but of competence. The ability to interpret spatial information, evaluate planning proposals, and engage in reasoned deliberation depends on forms of knowledge that are neither intuitive nor universally distributed. Therefore, one of the main ways to develop citizens' capacity for informed evaluation and meaningful participation is through education.

This perspective aligns with the broader principles of UNESCO's Education for Sustainable Development (ESD), which emphasises that sustainable societies require citizens to be educated in the principles of sustainable development so that they can understand complex environmental, social, and economic interdependencies, make responsible decisions, use resources sustainably, and contribute to more just, inclusive, and climate-resilient societies. UNESCO has played a central role in promoting ESD and, for the period 2020–2030, introduced the framework Education for Sustainable Development: Towards achieving the Sustainable Development Goals. This framework seeks to integrate ESD and the 17 Sustainable Development Goals into education systems worldwide. It focuses on developing the knowledge, skills, values, and attitudes that learners, as future citizens and active members of society, need to contribute to sustainable development. Its implementation roadmap identifies five priority action areas: advancing policy, transforming learning environments, strengthening the capacities of educators, empowering youth, and accelerating local-level action. (Anon., 2022; Polenakovikj, 2024)

However, although UNESCO strongly emphasises the need to educate citizens in the principles of sustainable development, its framework does not sufficiently foreground education in the basic principles of urban planning and urban design. This is a relevant gap, because urban planning and urban design shape many dimensions of sustainable development in cities and settlements, including land use, mobility, density, public space, environmental quality, social inclusion, and everyday urban life. If citizens are not educated in these spatial and planning-related issues, sustainability education remains partial. At the same time, the legal right granted to citizens to participate in planning processes remains limited in practice, since they may lack the knowledge required to understand, evaluate, and influence decisions that direct the sustainable development of their settlements. Without an understanding of these processes, citizens are unable to connect abstract sustainability concepts with the concrete realities of urban development.

In the context of North Macedonia, the integration of Education for Sustainable Development (ESD) and Climate Change Education (CCE) into the education system is considered particularly important for preparing future generations to respond to challenges such as uncontrolled urbanisation, air pollution, waste management, the lack of green spaces, and climate change. Education should not only raise individual awareness but also influence how cities, infrastructure, and public policies are planned and developed. According to the 2024 Action Plan, North Macedonia aims to integrate ESD and CCE across all levels of education and teacher training, in line with UNESCO principles. Its main priorities include the integration of ESD and CCE into curricula, the development of educators' capacities, and investment in educational infrastructure. (Polenakovikj, 2024) These curricula would become more complete if they also integrated education on urban planning processes and on the principles through which healthy and sustainable cities and settlements are planned, designed, and developed.

In the education system of North Macedonia, particularly at the primary and secondary levels, ESD topics are mainly focused on environmental protection, biodiversity, pollution, energy, and waste management. (Polenakovikj, 2024) However, more concrete content related to sustainable urban development remains insufficiently developed. This includes topics such as urban planning, public transport, rational land use, sustainable consumption, ecological construction, and the relationship between urbanisation and climate change. Issues related to active citizenship and social responsibility are also not addressed in sufficient depth. As a result, students may develop general environmental awareness, but still lack a clear understanding of urban challenges and of the role that individuals and communities can play in shaping more sustainable cities.

This gap is important because urban planning represents the link between sustainability principles and concrete decisions concerning land use, infrastructure, mobility, public space, and the built environment. Without the basic ability to interpret plans and understand urban processes, civic participation often remains limited to short-term concerns or individual interests. Citizens may evaluate urban conditions mainly through personal experiences, everyday inconveniences, or immediate needs, but such evaluations do not necessarily address the broader structural and global processes that shape the city and its sustainability, such as climate change, resource consumption, mobility systems, social inequality, land-use pressures, or long-term environmental resilience (Dokuzova et al., 2026). For this reason, such competencies should begin to develop from early education and continue through formal and non-formal learning.

Workshops, digital platforms, and community-based learning environments can help citizens connect everyday spatial experience with professional planning discourse. However, the most important step is to embed these issues within formal education by preparing teachers and integrating spatial literacy, urban sustainability, and civic participation into school curricula. This would allow citizens to gradually develop basic knowledge about urban processes from an early age, rather than engaging with planning only when specific local problems directly affect them. Spatial education could also take place through the way children experience, use, and interpret their school environment. In this sense, the schoolyard can also function as a pedagogical space for learning, social interaction, play, contact with nature, and the gradual development of environmental and spatial awareness (Dehari et al., 2022). In this context, gradual education becomes a precondition for meaningful participation, enabling citizens to move from fragmented reaction toward more informed and proactive civic engagement in sustainable urban decision-making.

Well-informed citizens can contribute not only to decisions concerning sustainable urban development in general, but also to more specific issues that directly affect everyday urban life and experience. For example, when abandoned buildings or neglected sites appear within the city, citizens can recognise their potential and question the absence of sustainable strategies for

their management and reuse (Ibraimi & Radevski, 2025; Ibraimi, 2022). They can also critically respond to decisions driven primarily by short-term economic interests or private investment priorities, rather than by long-term sustainability goals that include the community and correspond to its needs (Ibraimi et al., 2025). Similarly, informed citizens can defend their rights when built and unbuilt public spaces fail to accommodate all users equally, which contradicts the social dimension of sustainable urban planning (Ibraimi & Merxhani, 2023). They can also raise their voice when the physical and experiential qualities of cultural heritage need to be protected or cultivated, whether in relation to individual buildings (Saidi et al., 2021) or to the collective memory of characteristic traditional urban elements (Limani, 2023, 2025).

Several developed Western countries have already integrated aspects of spatial awareness, urban development, and civic education into broader educational and public-learning frameworks. Germany offers one of the most developed examples of institutionalised civic education in Europe. The Federal Agency for Civic Education (Bundeszentrale für politische Bildung / bpb), established in 1952, has as its central mission the strengthening of democratic awareness and political education. Through publications, seminars, educational materials, digital platforms, and public programmes, it supports citizens' ability to understand political and social processes. Its work also addresses themes related to democracy, participation, society, and public life, making it a relevant example of how civic education can intersect with spatial and urban issues without necessarily being organised as a separate urban planning subject (Bundeszentrale für politische Bildung, 2003, 2011).

Denmark provides another illustrative example. The Danish Folkeskole is structured around national aims that prepare pupils for participation, responsibility, rights, and duties in a democratic society, while also developing their understanding of the relationship between human beings and the environment. Within this educational framework, spatial and environmental knowledge can be introduced through subjects such as geography, social studies, biology, and other curriculum areas concerned with society, environment, resources, and everyday life. This shows that urban and environmental awareness can begin in compulsory education, without treating urban planning as an exclusively professional field (Danish Ministry of Children and Education).

The Netherlands is also relevant as a comparative context because of its long tradition of integrated spatial planning and consensus-oriented public decision-making, often associated with the "polder model." Dutch planning culture has been linked to cooperation, negotiation, democratic self-rule, and consensus-building in economic, environmental, and spatial governance. This does not mean that citizens automatically possess planning expertise, but it suggests that public participation becomes stronger when it is supported by long-term institutional cultures of dialogue, public debate, and spatial decision-making. The Dutch case, therefore, illustrates that citizens' urban awareness is not accidental but shaped through sustained educational, cultural, and institutional practices. (Schreuder, 2001)

The following section briefly elaborates on how urban planning and urban design influence sustainable development, and why this research insists that citizens should be better informed about these principles. If citizens are expected to participate in the planning of their cities and settlements, their participation should be supported by an understanding of how planning and design decisions shape environmental quality, social inclusion, mobility, public space, and the long-term sustainability of urban life.

Urban Planning and Design as a Determinant of Sustainable Urban Environments

Urban planning and urban design play a fundamental role in shaping sustainable urban environments because they determine how settlements are organised, used, and transformed over time. Through decisions concerning land use, density, urban growth, mobility,

infrastructure, public space, and the relationship between built and natural systems, planning and design influence ecological performance, social inclusion, economic activity, and cultural continuity. At the environmental level, these decisions affect energy consumption, emissions, land transformation, resource efficiency, and the preservation of natural systems. Compact and well-connected urban structures can reduce transport-related energy use and limit the conversion of agricultural and natural land, while dispersed development tends to increase infrastructure costs, car dependency, emissions, and environmental degradation. In this sense, sustainable development is not shaped only by technological innovation, environmental regulation, or individual behaviour, but also by the spatial and physical structure of settlements themselves. (Næss, 2001; Larco & Knudson, 2024)

Urban planning and urban design influence sustainable development across multiple spatial scales, from the region and city to the neighbourhood, street, block, and parcel. Each scale contributes differently to ecological performance, social well-being, economic vitality, and long-term adaptability. Sustainability is therefore not produced through a single intervention, but through the coordination of planning and design decisions across interconnected levels. At the regional and city scale, planning decisions determine the direction of urban growth, the protection of natural and agricultural land, the location of major infrastructure, and the relationship between settlements, transport systems, and ecological networks. These decisions influence land consumption, emissions, commuting distances, access to services, and the long-term resilience of urban systems. Compact and well-connected urban growth can reduce pressure on agricultural land and natural habitats, while fragmented and dispersed development tends to increase infrastructure costs, car dependency, and environmental degradation. (Næss, 2001; Larco & Knudson, 2024; Carmona, 2001)

At the neighbourhood scale, decisions concerning density, land-use mix, public facilities, green spaces, schools, local services, and mobility networks shape the quality of the environment, everyday accessibility, social inclusion, and health outcomes. A well-planned neighbourhood can reduce dependence on private vehicles by placing daily needs within walking or cycling distance, thereby helping to lower traffic-related air pollution and emissions. It can also support residents' physical and mental well-being through safe pedestrian routes, accessible green spaces, active public spaces, and opportunities for social interaction. Thus, neighbourhood planning becomes a direct determinant of both environmental quality and everyday well-being. (Næss, 2001; Larco & Knudson, 2024; Carmona, 2001)

At the street and block scale, urban design shapes the quality of the environment and the everyday well-being of residents through the way movement, safety, public life, and environmental comfort are organised. Street connectivity, pedestrian comfort, shade, active frontages, traffic calming, stormwater management, and ecological continuity influence whether streets operate only as traffic corridors or become livable public spaces. Well-designed streets and blocks can reduce exposure to traffic stress, improve walkability, moderate heat, support safer movement, and create conditions for social interaction. At this scale, sustainability becomes directly experienced through walkability, microclimate, safety, social activity, and the capacity of streets and blocks to support multiple forms of use. (Næss, 2001; Larco & Knudson, 2024; Carmona, 2001)

At the parcel and building interface, design decisions shape the quality of the environment indoors as well as outdoors and residents' everyday well-being through the way buildings meet the street and relate to the surrounding public space. Building orientation, setbacks, ground-floor use, vegetation, surface permeability, entrances, edges, and the transition between private and public space influence energy performance in indoor spaces as well as outdoor ones, environmental comfort, privacy, safety, and opportunities for social interaction. This scale is important because it mediates between individual buildings and the wider urban environment. A building can either activate the street, provide shade, support pedestrian comfort, and create

a clear relationship between public and private space, or it can contribute to inactive edges, poor microclimatic conditions, social isolation, and fragmented urban experience. In this way, even small-scale design decisions affect how sustainable, comfortable, and socially responsive an urban environment becomes over time. (Carmona, 2001; Gehl, 2011; Larco & Knudson, 2024; Goxha et al., 2024).

Environmental policies and green technologies often define the desired outcomes of sustainable development, including reduced emissions, resource efficiency, ecological protection, and healthier environments. Urban planning and urban design translate these outcomes into spatial conditions through the form, configuration, and interrelation of primary urban elements, such as buildings, parcels, blocks, streets, and open spaces. Through these spatial arrangements, planning and design shape movement, accessibility, public life, ecological continuity, environmental comfort, and everyday urban use, making urban form a central mechanism through which sustainable development is generated.

The discussion above presented only a brief overview of how the built environment, together with urban planning and urban design strategies, can influence sustainable development and the creation of healthy environments for living. Several influential works in urban literature have attempted to synthesise the principles through which the planning and design of cities shape urban quality of life in ecological, economic, social, cultural, psychological, and temporal terms. One of the most comprehensive frameworks is offered in the work of Matthew Carmona (2001), where urban environments are understood through multiple interrelated dimensions: morphological, functional, social, visual, perceptual, and temporal. This perspective shows that urban sustainability depends not only on environmental performance, but also on how urban form supports accessibility, public life, identity, safety, adaptability, and long-term change.

A similar user-oriented logic is developed in Responsive Environments (Bentley et al., 1985), which explains how urban design can increase people's choices through permeability, variety, legibility, robustness, visual appropriateness, richness, and personalisation. These principles suggest that well-designed environments are those that people can move through, understand, use in different ways, adapt over time, and develop attachment to. The book "A Pattern Language: Towns, Buildings, Construction" (Alexander et al., 1977) adds another important layer by translating everyday spatial experience into recurring patterns of human use, showing how settlements, neighbourhoods, streets, buildings, thresholds, and rooms can be shaped to support social life, comfort, belonging, and everyday well-being. Taken together, these works demonstrate that the built environment has a direct role in shaping both the sustainability and the lived quality of urban settlements.

However, such works often remain selectively used by professionals and require considerable theoretical and practical commitment to be understood and applied by non-professionals. In contrast, the *Urban Design Compendium 1&2* represents an attempt to simplify and operationalise key principles of urban planning and urban design in a more accessible form. It translates complex urban design knowledge into practical guidance related to character, continuity and enclosure, public realm quality, ease of movement, legibility, adaptability, diversity, density, mixed use, streets, public spaces, safety, and resource efficiency. In this sense, it is not merely a professional manual, but a bridge between specialised urban knowledge and broader public understanding of how the built environment can be improved.

This is important because urban literature already contains substantial evidence and practical knowledge on how spatial planning and urban design can contribute to more sustainable and higher-quality environments. Many of these principles are also present, at least implicitly, in planning laws and regulations, where notions such as the humanisation of space, spatial harmony, protection of local character, environmental quality, and public interest are often mentioned as criteria that should guide planning decisions. However, these principles are

frequently formulated in broad and abstract terms, without clearly explaining the spatial mechanisms through which they should be achieved. As a result, they may remain declarative, weakly interpreted, or easily neglected in practice. The challenge, therefore, is not only the absence of knowledge but also its accessibility, simplification, operationalisation, and contextual adaptation.

While some principles of sustainable urban planning and design have broad relevance, others must be critically examined and adapted to the physical, social, cultural, and institutional conditions of specific settlements. For North Macedonia, this means that existing urban design knowledge should not be adopted mechanically. It should be analysed, contextualised, and translated into clear educational content and practical mechanisms that can be integrated across different levels of schooling. The aim is for these principles to become internalised knowledge, not only for citizens as a basis for informed public evaluation, but also for future professionals who will participate in planning, designing, regulating, and managing the built environment. In this way, education can help transform abstract planning values, such as spatial harmony, humanisation of space, protection of local character, and environmental quality, into more concrete capacities for understanding and shaping sustainable urban environments.

Conclusion

This research addresses the importance of educating citizens on the basic principles of urban planning and urban design, so that the legal and institutional right granted to them to participate in urban decision-making can become informed, meaningful, and effective. While legal and policy frameworks increasingly recognise citizens as participants in the planning and development of settlements, the mere existence of participatory mechanisms does not guarantee substantive engagement. A central concern raised in this paper is whether citizens are sufficiently equipped to understand spatial proposals, evaluate urban plans, identify trade-offs, and provide relevant input that can contribute to the sustainable development of their cities.



Fig. 1: Word cloud of key concepts

The discussion has shown that meaningful participation depends not only on legal access, but also on knowledge and interpretive capacity. UNESCO's Education for Sustainable Development frameworks attempt to strengthen citizens' ability to contribute to sustainable development by promoting knowledge, skills, values, and critical understanding. However, these frameworks tend to address sustainability in broad environmental, social, and economic terms, while the role of urban planning and urban design as key determinants of sustainable urban environments remains insufficiently emphasised.

By briefly demonstrating how planning and design decisions shape land use, density, mobility, public space, infrastructure, ecological systems, environmental quality, social inclusion, health, and everyday urban life, this research argues that sustainability education should also include basic urban planning and urban design literacy. Citizens cannot meaningfully evaluate or

influence the development of their settlements if they do not understand how the physical structure of the city is produced and how it affects sustainability.

The main contribution of this paper is therefore to argue for the integration of sustainable urban planning and urban design principles into education frameworks for sustainable development. These principles should be analysed, simplified, contextually adapted, and introduced across different levels of education, so that they become part of citizens' and future professionals' basic knowledge. In this way, participation can move beyond formal consultation and become a more informed civic capacity. If citizens are expected to contribute to the sustainable development of their settlements, they must also be educated in the essential spatial and design principles through which such development is actually shaped.

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SAFETY MONITORING OF IRON SUPPLEMENTATION IN PREGNANCY: INSIGHTS FROM A CROSS-SECTIONAL STUDY

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Abstract

Iron deficiency anemia is one of the most common conditions during pregnancy and is typically managed with iron supplementation. However, iron supplements may be associated with adverse reactions that affect tolerance and treatment adherence. This study aimed to evaluate the safety of iron supplements in pregnant women with anemia by analyzing adverse reactions and factors associated with their occurrence. A cross-sectional study was conducted among 105 pregnant women with anemia who were using iron supplements. Data were collected through an anonymous self-administered questionnaire consisting of four sections: demographic and obstetric data, use of iron supplements, adverse reactions, and potential influencing factors. The intensity of adverse reactions was assessed using a 5-point Likert scale. The most frequently reported adverse reactions were nausea and constipation. Most reactions were classified as moderate in intensity. No statistically significant associations were found between the pharmaceutical form of iron and reaction intensity. Taking iron with food showed a tendency toward better tolerance, while reaction intensity varied by trimester, with lower levels observed in the third trimester. Iron supplementation during pregnancy is commonly associated with gastrointestinal adverse reactions of moderate intensity. Monitoring adverse reactions and providing appropriate clinical counselling are essential to improve tolerance and ensure the safe management of anemia during pregnancy.

Keywords: adverse reactions, drug safety, pregnancy, anemia, iron supplementation

Introduction

Pregnancy represents a unique physiological period characterized by profound hormonal, metabolic, and hematological changes that support fetal growth and prepare the maternal body for childbirth. These changes include significant adaptations in the cardiovascular, hematopoietic, and immune systems, which ensure sufficient oxygen and nutrient transfer to the fetus (Cunningham et al., 2018). Plasma volume increases by about 40–50%, accompanied by a smaller increase in erythrocyte mass, resulting in physiological hemodilution. This adaptation leads to a relative decrease in haemoglobin concentration, which may contribute to the development of anemia in pregnant women (Pavord et al., 2019). According to the World Health Organisation, anemia is diagnosed when haemoglobin levels are less than 11 g/dL (WHO, 2021). Iron deficiency is the most common cause, although other factors such as folic acid and vitamin B12 deficiency, chronic infections, and inflammatory diseases can contribute to its development (Milman, 2015).

Given the high global prevalence of anemia and the increased physiological demand for iron during pregnancy, iron supplementation remains an essential component of prenatal care. The World Health Organization recommends routine iron and folic acid supplementation for pregnant women to prevent and treat anemia (WHO, 2016). Iron supplementation can be administered in various forms, including oral preparations and intravenous therapy in cases of intolerance to oral treatment or severe anemia. Oral iron therapy is considered the first-line treatment due to its effectiveness, low cost, and favourable safety profile (Pavord et al., 2019). Although iron supplementation is essential for the management of anemia during pregnancy, its use may be associated with adverse reactions that can affect tolerability and patient adherence. These reactions may lead to treatment discontinuation or irregular use of therapy, thereby reducing the effectiveness of anemia correction (Tolkien et al., 2015). In rare cases,

excessive iron intake during pregnancy may lead to toxicity, which is associated with increased oxidative stress, gastrointestinal mucosal damage, and metabolic disturbances. High iron levels may also interfere with the absorption of other micronutrients and interact with certain medications, potentially affecting their therapeutic effectiveness (Ru et al., 2024; Kalman et al., 2025).

Monitoring adverse reactions to iron supplementation is essential to ensure an optimal balance between therapeutic benefits and potential risks. This includes identification and reporting of adverse reactions, evaluation of haematological indices, assessment of individual tolerability, identification of risk factors for intolerance, and evaluation of possible drug interactions (Pavord et al., 2019). In the context of pharmacovigilance, active monitoring of adverse reactions contributes to improving clinical practice and increasing patient safety, especially in vulnerable populations such as pregnant women (EMA, 2020). Therefore, this study aims to evaluate the safety of iron supplements in pregnant women with anemia by analyzing adverse reactions and the factors influencing their occurrence.

Material and methods

This is a descriptive, cross-sectional study conducted in Tetovo, an urban city in the western part of the Republic of North Macedonia, from June 2025 to January 2026. The study population consisted of pregnant women diagnosed with anemia who used iron supplements during pregnancy. Convenience sampling was used, with participants recruited voluntarily. A self-administered questionnaire was used to collect data. The questionnaire consisted of 20 items organized into four sections: a) demographic and obstetric characteristics; b) use of iron supplements and the mode of administration; c) adverse reactions of iron supplements; and d) potential factors influencing the occurrence and intensity of adverse reactions. A 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) was used to evaluate adverse reactions and factors influencing them

Data were coded and analyzed using IBM SPSS Statistics. Categorical variables were presented as frequencies and percentages, while Likert-scale responses were treated as ordinal variables and summarized using mean and standard deviation. Associations between influencing factors and adverse reactions were assessed using Spearman's correlation coefficient. Statistical significance was defined at $p < 0.05$.

The study was conducted in accordance with ethical principles for scientific research. Participation was voluntary, and anonymity and confidentiality of data were ensured. All data were used exclusively for academic purposes.

Results

A total of 105 pregnant women diagnosed with anemia who used iron supplements during pregnancy were included in the study.

Demographic and obstetric characteristics of study participants

Based on the data presented in Table 1, the most represented age group was 20–29 years (55.2%), followed by the 30–39 years age group (32.4%) among the study participants.

Table 1. Demographic and obstetric characteristics of study participants

Variables	Percentage
Age	
≤20	12.4
21–30	55.2
31–40	32.4

Gestational age	
I trimester	6.7
II trimester	79.0
III trimester	14.3
Number of pregnancies	
First pregnancy	55.2
Second pregnancy	36.2
More than two pregnancies	8.6

Most of the participants were in the second trimester of pregnancy (79.0%), while a smaller percentage were in the first and third trimesters. This distribution reflects the higher frequency of prenatal check-ups and anemia diagnosis during the second trimester, a period in which iron requirements increase and supplementation begins more often.

Regarding the number of pregnancies, more than half of the participants (55.2%) were in their first pregnancy, and only 8.6% had had more than two pregnancies. This distribution indicates that the sample is dominated by primigravidas, who may have more limited experience with supplementation during pregnancy and potentially higher susceptibility to adverse reactions.

Use of iron supplements and the mode of administration

The use of iron supplements was analyzed in terms of formulation, duration of use, and route of administration as factors that may influence the occurrence of adverse reactions. These variables are particularly important for evaluating the safety and tolerability of iron therapy during pregnancy.

Tablets were the most commonly used form of iron supplementation (42.9%), followed by syrup (34.3%) and capsules (22.9%). The dominance of the tablet form may be related to standard clinical recommendations and their wide availability. Regarding the duration of use, the majority of participants (61.0%) reported using iron supplements for 1–3 months, while 24.8% reported use for less than one month and 14.3% for more than three months (Table 2).

Table 2. Formulation of iron supplements and duration of use

Variables	**Frequency**	**%**
Supplement formulation		
Tablets	45	42.9
Syrup	36	34.3
Capsules	24	22.9
Duration of use		
<1 month	26	24.8
1–3 months	64	61.0
>3 months	15	14.3

The use of iron supplements was mainly based on a doctor's recommendation (58.1%), while 21.9% of participants started supplementation on the advice of a pharmacist and 20.0% on their own initiative. These data highlight the key role of health professionals in guiding the safe and rational use of supplements during pregnancy.

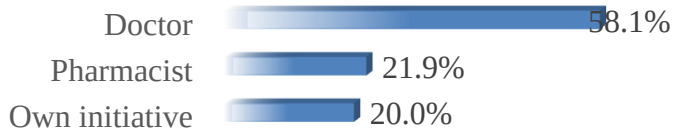


Figure 1. Source of recommendation for iron supplementation

More than half of the participants (61.0%) reported taking iron supplements with food, while 39.0% reported taking them on an empty stomach. Regarding the consumption of tea or coffee at the time of iron intake, 53.3% of participants reported consuming these beverages, 37.1% did not, and 9.5% were unsure (Table 3). These practices may influence iron absorption and, potentially, the effectiveness and tolerability of the treatment.

Table 3. Mode of iron supplementation and factors influencing absorption

Variables	Frequency	%
Mode of iron intake		
With food	41	61.0
On an empty stomach	64	39.0
Consumption of tea or coffee during iron intake		
Yes	39	37.1
No	56	53.3
Not sure	10	9.5

Prevalence and severity of adverse reactions

The prevalence of adverse reactions was determined based on the proportion of participants reporting high-intensity symptoms (Likert ≥ 4). Nausea (69.5%) and constipation (57.6%) were the most commonly reported reactions, while fewer participants reported abdominal pain (27.6%) and changes in stool colour (9.5%) (Figure 2). These findings indicate that gastrointestinal adverse reactions represent the most common form of intolerance to iron supplements in the studied population, affecting the daily activities of 48.6% of participants.

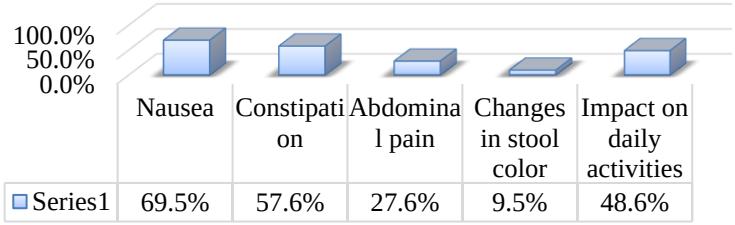


Figure 2. Prevalence of adverse reactions

The majority of participants reported a moderate intensity of adverse reactions (79.0%), while a smaller proportion reported high intensity (9.5%). This distribution suggests that adverse reactions are relatively common but are generally of moderate severity (Table 4).

Table 4. Classification of the intensity of adverse reactions among study participants

Variable	Frequency	%
Intensity of adverse reactions		
Mild (<3.0)	12	11.4
Moderate (3.1–4.0)	83	79.0
High (>4.1)	10	9.5

The intensity of adverse reactions was assessed using a reaction index, calculated as the mean of responses to five items (nausea, constipation, abdominal pain, changes in stool colour, and impact on daily activities), with higher values indicating greater intensity. The mean reaction

index was 3.58 ± 0.33, with a median of 3.60, indicating an overall moderate intensity of adverse reactions in the studied population.

Factors influencing the intensity of adverse reactions

Mode of iron intake (with food vs. on an empty stomach)

Participants who took iron with food (n = 64) had a mean reaction index of 3.55, whereas those who took it on an empty stomach (n = 41) had a mean of 3.60. The difference was not statistically significant ($p = 0.087$).

Pharmaceutical formulation of iron supplements

No statistically significant differences in the intensity of adverse reactions were observed between different pharmaceutical formulations of iron supplements ($p = 0.628$).

Trimester of pregnancy

Differences between trimesters were statistically significant ($p < 0.001$). Higher intensity of adverse reactions was observed during the first and second trimesters, whereas lower values were reported in the third trimester.

Discussion

This study evaluated the safety and tolerability of iron supplementation in pregnant women with anemia, by analyzing the frequency, intensity and factors influencing the occurrence of adverse reactions. The findings indicate that gastrointestinal adverse reactions are common and usually moderate in intensity, while the trimester of pregnancy may affect iron tolerance. In this study, the most frequently reported reactions were nausea and constipation, followed by abdominal pain and a change in stool colour. These results are consistent with the existing literature demonstrating that oral iron supplementation is frequently associated with gastrointestinal intolerance. A systematic review by Tolkien et al. (2015) reported that constipation, nausea and abdominal pain are among the most common adverse reactions often affecting treatment adherence. Similarly, Pavord et al. (2019) highlight that gastrointestinal intolerance remains a major barrier to the management of iron deficiency anemia during pregnancy. The predominance of gastrointestinal symptoms observed in this study is also in line with research suggesting that unabsorbed iron in the gastrointestinal tract can contribute to symptoms such as nausea, constipation, and abdominal discomfort (Moretti et al., 2015).

The results showed that the majority of participants experienced reactions of moderate intensity (79.0%), while a smaller percentage reported high intensity. This suggests that, although reactions are common, they are usually manageable. Previous studies have reported similar results, showing that most pregnant women tolerate iron supplementation, despite the presence of mild to moderate gastrointestinal effects (Milman, 2015). These findings are further supported by recent evidence from a multi-centre observational clinical study by Liu et al., which emphasized the importance of systematic safety monitoring of oral iron supplementation in pregnant women. Similar to our results, Liu et al. reported that adverse reactions are relatively common but are predominantly mild to moderate in intensity and manageable with appropriate clinical oversight.

The analysis of factors influencing adverse reaction intensity in this study revealed no statistically significant differences related to the mode of iron intake (with food vs. on an empty stomach). Although dietary factors such as food intake and the consumption of tea or coffee are known to influence iron absorption, their effect on adverse reaction intensity may be limited and influenced by substantial interindividual variability (Hurrell & Egli, 2010; Milman, 2015). This variability may explain the absence of statistically significant associations observed in this study. The World Health Organisation recommends that, in case of gastrointestinal

intolerance, iron supplements can be taken with food to improve tolerance, balancing effectiveness and patient comfort (WHO, 2016). No statistically significant differences in the intensity of reactions were observed between tablets, syrup and capsules. This result suggests that the pharmaceutical formulation may not be a determining factor in iron tolerance. The literature supports this finding, indicating that gastrointestinal effects are more related to the dose of elemental iron and individual patient characteristics than to the pharmaceutical form (Milman, 2015; Tolkien et al., 2015). In contrast, statistically significant differences in adverse reaction intensity were observed across pregnancy trimesters, with higher intensity reported during the first and second trimesters. This may be related to higher gastrointestinal sensitivity and hormonal changes in the early stages of pregnancy, which may predispose women to greater intolerance of iron supplementation (Achebe & Gafter-Gvili, 2017). Cunningham et al. have reported that gastrointestinal symptoms are more pronounced in the first trimester due to hormonal changes and increased sensitivity to nausea. This may affect the tolerance of iron supplements during this period.

From a clinical and pharmacovigilance perspective, these findings highlight the importance of active monitoring of adverse reactions during iron supplementation, particularly in vulnerable populations such as pregnant women. As emphasized by both Liu et al. and the World Health Organization, systematic monitoring and patient-centred management strategies are essential for optimizing adherence, minimizing treatment discontinuation, and improving maternal outcomes (WHO, 2016).

Conclusion

Iron supplementation in pregnant women with anemia is commonly associated with gastrointestinal adverse reactions, mainly nausea and constipation, which are generally of moderate intensity and manageable in clinical practice. While pharmaceutical formulation and mode of intake were not significantly associated with reaction intensity, the trimester of pregnancy emerged as an important factor, with higher intensity observed in early pregnancy. Although most adverse reactions were not severe, they may influence treatment adherence. These findings highlight the importance of continuous monitoring, individualised counselling, and patient education to improve tolerability and ensure treatment effectiveness.

In conclusion, iron supplementation remains an important part of managing anemia during pregnancy. At the same time, an individualized and patient-focused approach, together with the active support of healthcare professionals, including pharmacists, plays a key role in improving treatment safety and achieving better clinical outcomes.

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INHALED PHARMACOLOGICAL TREATMENT AND CRITICAL ERRORS IN INHALATION TECHNIQUE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a fairly common disease characterized by airflow limitation in the lungs that is not fully reversible. The main cause in developed countries is exposure to tobacco smoke. The aim of this study is the analysis and evaluation of inhaled pharmacological treatment and critical errors in inhalation technique in patients with chronic obstructive pulmonary disease (COPD). Material and methods: This is a prospective, observational, transversal study carried out in outpatient primary and secondary care patients with COPD in the city of Struga, in the period from 12.07.2024 to 24.09.2024, where a total of 68 patients were evaluated. Results: From the total of 68 patients with COPD included in the study, 39 or 57.4% of them, are female patients. The average age is 57.87±13.34. About 60 % of patients had two or more exacerbations of COPD symptoms. In total, 82.3% of patients used treatment containing inhaled corticosteroids. The largest percentage of patients (45.6%) declared to use metered dose inhalers, despite 22.1% of them using dry powder inhalers. Treatment with ≥1 type of device was initiated in 32.4% of patients in the study. Conclusion: To improve COPD results, all inhalation steps should be followed to eliminate as many (critical) errors as possible. This research aims to contribute to reducing critical errors in inhalation technique and advancing pharmacological inhaler treatment in COPD patients. By increasing the quality of COPD management, the efficiency and effectiveness of disease treatment can be increased.

Keywords: Chronic obstructive pulmonary disease (COPD), inhalation technique, inhaled pharmacological treatment, critical errors.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease caused by exposure to harmful particles or gases (Agarwal et al., 2023). It is a preventable and treatable disease characterized by irreversible or partially reversible narrowing of the airways, leading to restriction of airflow (Celli et al., 2022; Gupta et al., 2013). It is a major public health issue globally, contributing significantly to morbidity and mortality (Mathers & Loncar, 2006). Some of the risk factors that increase the likelihood of COPD include smoking, passive smoking, exposure to dust and fumes, exposure to air pollutants, genetic factors, and socio-economic status (Agustí et al., 2022; Ezzati, 2005; Agarwal et al., 2023). COPD includes Chronic Obstructive Bronchitis and Pulmonary Emphysema (Widysanto & Mathew, 2022; Pahal et al., 2023). Although these two diseases do not initially develop in the same way, they are grouped because they are characterized by respiratory obstruction, or airflow obstruction, in the bronchial passages (Pahal et al., 2023; Widysanto & Mathew, 2022). Clinically, the most common symptoms of chronic bronchitis are chronic cough, excessive sputum production, dyspnea, wheezing, and cyanosis of the lips and fingernails (Widysanto & Mathew, 2022; NHS, 2024). COPD exacerbations are defined as an acute worsening of respiratory symptoms (Ritchie & Wedzicha, 2020). They are classified as mild (treated with short-acting bronchodilators alone), moderate (treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), and severe symptoms (requiring hospitalization or an emergency room visit) (Gupta et al., 2013). Severe exacerbations may also be associated with acute respiratory failure (Ritchie & Wedzicha, 2020). Complications may include acute complications such as acute respiratory failure, pneumothorax, and recurrent and prolonged

lower respiratory tract infections, such as pneumonia, bronchitis, and other bacterial or viral infections, and chronic complications such as cardiopulmonary diseases, osteoporosis, depression and anxiety, sleep disorders, weight loss, and muscle loss (Agarwal et al., 2023).
Pharmacological therapy includes bronchodilators (short-acting and long-acting), antimuscarinics (inhaled), methylxanthines (oral), PDE4 inhibitors, antibiotics, and anti-inflammatory agents (Gupta et al., 2013). The primary goals of inhaled pharmacotherapy are to alleviate symptoms, improve lung function, reduce exacerbation frequency and severity, and enhance overall health status (Jones et al., 2016; van Dijk et al., 2023).
Despite the proven efficacy of inhaled therapies, optimal disease control is often not achieved in clinical practice. One of the major contributing factors is incorrect inhalation technique (Usmani et al., 2018; Sulku et al., 2022). Evidence indicates that a substantial proportion of COPD patients commit critical errors when using inhalation devices, significantly reducing drug deposition in the lower airways and thereby diminishing therapeutic effectiveness (Kocks et al., 2023; Ahn et al., 2019). Common errors include failure to follow these techniques: holding the breath for 10 seconds while inhaling, exhaling slowly through the mouth after inhaling, correctly sealing the lips around the inhaler, shaking the device before use, and breathing slowly and deeply while inhaling (Sulku et al., 2022; Usmani et al., 2018). Factors that influence errors in inhalation technique are age, educational level, lack of information from healthcare workers, and the variety and complexity of inhalation devices (Kocks et al., 2023; Usmani et al., 2018). The persistence of these errors highlights the importance of proper patient education and healthcare professional support to avoid errors in inhalation technique (Ahn et al., 2019; Sulku et al., 2022). Therefore, this study aims to analyze and evaluate pharmacological treatment with inhalers and critical errors in inhalation technique in patients with chronic obstructive pulmonary disease.

Materials and methods

This is a prospective, observational, cross-sectional study conducted in primary and secondary care outpatients with COPD in the city of Struga and its surroundings. The group included in the study are patients diagnosed with COPD in the city of Struga, in the period from 12.07.2024 to 24.09.2024. The instrument that will be used for data collection is a self-administered questionnaire, using trusted online reference databases. This questionnaire provides data on age, gender, current smoking, educational level (primary, secondary, or higher education), and the health status of patients with COPD assessed according to the CAT table and through the number of exacerbations within 12 months. The GOLD A–D categorization of COPD (A (low risk, fewer symptoms), B (low risk, more symptoms), C (high risk, fewer symptoms), and D (high risk, more symptoms)) in the patients included in the study was based on the patient's CAT score and history of exacerbations (GOLD2017).
Pharmacological treatment was categorized into long-acting beta-2-agonists (LABA), long-acting muscarinic antagonists (LAMA), LABA + LAMA, inhaled corticosteroids (ICS), ICS + LABA, ICS + LAMA and ICS + LABA + LAMA. Inhaler device models included were categorized into Dry Powder Inhalers (DPI), Metered Dose Inhalers (MDI or pMDI), Soft Mist Inhalers and more than one device type.
The steps for the correct technique that the patient should follow during inhalation, in the form of a checklist, were determined by consulting the patient information leaflets for each device and previous studies. If a patient's technique deviated from the six defined steps, even in just one of them, it would be judged as a critical error.
The data collected were expressed as frequencies and percentages, and as means and standard deviations (SD) for continuous and categorical variables. The CAT asks questions about eight domains, with a score range of 0 to 5 for each domain, with a total score ranging from 0 to 40.

Higher scores indicate that COPD has a greater impact on the patient's overall health and well-being. Table 1 presents the impact of COPD on the patient's overall health and well-being according to CAT (https://www.healthline.com/health/cat-score-for-copd?utm_source).

Table 1. Impact of COPD on the patient's overall health and well-being according to CAT

CAT results	Impact	Meaning
0-9	Low	You may not experience many symptoms of COPD, or at least not enough to affect your daily activities. Most days are fine, but you cough regularly and get tired easily.
10-20	Medium	COPD symptoms regularly affect your life. You have some good days, but you get short of breath easily and cough up phlegm regularly. You have 1 or 2 flare-ups each year.
21-30	High	Your symptoms regularly prevent you from doing the things you want to do. Regular daily activities like getting dressed are tiring. You don't feel in control of your chest problem.
31-40	Very high	Your symptoms regularly prevent you from doing the things you want to do. Regular daily activities like getting dressed are tiring. You don't feel in control of your chest problem.

Results

A total of 68 patients with chronic obstructive pulmonary disease (COPD) from the city of Struga were included in this study, in the period from 12.07.2024 to 24.09.2024, who voluntarily expressed their willingness to participate in the study. From the data analyzed and presented in
Table 2, it results that out of the total of 68 patients with
COPD included in the study, 39 or 57.4% of them, are female patients. The average age is 57.87±13.34. According to the level of education, 57.4% of the patients declared having completed only primary education. According to the data collected, the majority of COPD patients 49 (72.1%) included in the study were found to have been smokers in the past, despite 25 (36.8%) of them continuing to be current smokers.

Table 2. Sociodemographic charactersitics of the patients in the study

Variable	Frequency	Percentage
Gender		
Male	29	42.6
Female	39	57.4
Age	57.87±13.34	
Educational level		
Primary school	39	57.4
Secondary school	18	26.5
University	11	16.2
Current smoker		
Yes	25	36.8
No	43	63.2
Former smoker		
Yes	49	72.1
No	19	27.9

During the data analysis, it is noted that about 58.0% of patients have had two or more exacerbations of COPD symptoms. In a significant percentage of them (47.1% and 39.7%), COPD have a medium, respectively high impact on the patient's overall health and well-being. Thus, the categorization of COPD according to GOLD A–D in the patients included in the study was based on the patient's CAT score and history of exacerbations (GOLD 2017).

Table 3. Distribution of exacerbation frequency and CAT scores among COPD patients

Variable	Frequency	Percentage
Number of exacerbations		
≤ 1	29	42.6
≥ 2	39	57.4
CAT Score	19.8±7.4	
0-9 (low impact)	4	5.9
10-20 (moderate impact)	32	47.1
21-30 (high impact)	27	39.7
31-40 (very high impact)	5	7.4

Based on the findings of this study, 55.9% of patients were classified as GOLD stage D COPD (≥2 exacerbations and CAT score ≥10), while 38.2% were classified as GOLD stage B COPD (≤1 exacerbation and CAT score ≥10) according to the GOLD A–D classification.

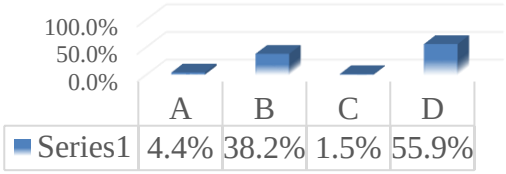


Figure 1. Distribution of patients according to GOLD A–D COPD classification

In our study, a total of 82.3% of patients were using treatment containing inhaled corticosteroids. Dual ICS+LABA treatment (52.9%) was the most common treatment among patients with COPD. The largest proportion of patients (45.6%) reported using metered dose

inhalers compared to 22.1% using dry powder inhalers. Treatment with ≥1 type of device was initiated in 32.4% of patients in the study (Table 4).

Table 4. Distribution of COPD treatment regimens and inhaler device types among study participants

Variable	Percentage (%)
Treatment	
No treatment	10.3%
LABA	1.5%
LAMA	5.9%
ICS	14.7%
ICS + LABA	52.9%
ICS + LAMA	1.5%
ICS + LABA + LAMA	13.2%
Inhaler Type	
Dry powder inhaler	22.1%
Metered-dose inhaler	45.6%
More than one type of device	32.4%

In total, 95.6% of patients included in the study made one or more critical errors while using a currently prescribed inhaler device. A very small percentage, only 4.4% of patients reported "Always" performing all six steps of the inhalation technique, compared to 7.4% of them who did not report "Always" performing any step. Holding the breath for at least 10 seconds after use and exhaling slowly after use were the most common types of critical error identified, contributing to 67.6% of the total critical errors. Exhaling completely before use was the second most common type of critical error identified (66.2%). Shaking the device before use was the only error type with a significantly lower prevalence (22.1%). A significant percentage of COPD patients included in the study (59.0%) considered that healthcare personnel had instructed and taught them on the correct use of an inhaler, despite a small percentage (9.0%) stating the opposite (Table 5).

Table 5. Critical errors in inhalation technique and instructions received from healthcare professionals

Variables	Percentage (%)
Number of Critical Errors	
0	4.4%
1	20.6%
2	23.5%
3	22.1%
4	14.7%
5	7.4%
6	7.4%
Types of critical errors in inhalation technique	
Shakes the device before use	22.1
Exhales completely before use	66.2
Closes lips tightly around the mouthpiece	45.6
Breathes in deeply and slowly through the mouthpiece	54.4
Holds breath for at least 10 seconds	67.6
Breathes out slowly after use	67.6
Healthcare professionals' instructions regarding inhalation technique	
More details	59.0%
Not at all	9.0%
In general	32.0%

Discussion

This study aims to analyze and evaluate pharmacological treatment with inhalers and critical errors in inhalation technique in patients with Chronic Obstructive Pulmonary Disease (COPD). A total of 68 patients with COPD from the city of Struga, in the period from 12.07.2024 to 24.09.2024, voluntarily expressed their willingness to participate in this study. When comparing the findings of the present study with those of a one-year follow-up study conducted in Sweden by Johanna Sulku in 2022, it was observed that 82.3% of the 68 COPD patients included in our study were receiving treatment containing inhaled corticosteroids. Similarly, in the Swedish study, 310 out of 360 patients who completed the one-year follow-up were using inhaled therapy at both study visits. The distribution of COPD patients according to the GOLD A–D classification was 6% in stage A, 56% in stage B, 29% in stage C, and 8% in stage D. Regarding treatment patterns, triple therapy consisting of ICS + LABA + LAMA was the most frequently prescribed regimen (50%). Other therapeutic approaches included as-needed therapy (7%), LABA monotherapy (2%), LAMA monotherapy (16%), LABA + LAMA (6%), ICS monotherapy (3%), ICS + LABA (12%), and ICS + LAMA (4%).

The findings of the present study demonstrated that inhaler misuse and critical inhalation technique errors remain highly prevalent among COPD patients. More than 90% of the patients included in our study made at least one critical error while using their prescribed inhaler device, whereas only 4.4% performed all inhalation steps correctly. The most frequently identified errors were failure to hold the breath for at least 10 seconds after inhalation (67.6%), failure to breathe out slowly after use (67.6%), failure to exhale completely before inhalation (66.2%), and failure to inhale deeply and slowly through the mouthpiece (54.4%). In addition, nearly half of the patients did not close their lips tightly around the mouthpiece (45.6%). These findings indicate substantial deficiencies in inhalation technique that may negatively affect drug delivery and disease control. Similar findings were reported in the multi-country cross-sectional observational PIFotal study conducted by Janwillem Kocks, which included 1,434 COPD patients using dry powder inhalers. In that study, 81.3% of patients made at least one critical inhalation error. Errors related to inhalation manoeuvre, breath holding, and exhalation after inhalation were significantly associated with worse health status and higher CAT scores, while errors involving inhaler preparation and inhalation technique were associated with more severe exacerbations. The authors also demonstrated that an increasing number of inhalation errors was associated with poorer health status and a higher rate of COPD exacerbations. Our findings are consistent with these observations, particularly regarding the high frequency of errors involving exhalation before inhalation, breath holding, and post-inhalation breathing technique. Comparable results were also observed in the prospective cross-sectional case-control study conducted by June Hong Ahn among 189 COPD patients. The study reported that 42.9% of patients made at least one critical inhaler error, with the highest proportion of errors observed among users of pressurized metered-dose inhalers. The authors identified associations between inhaler misuse and frequent exacerbations, while factors such as lower educational level, use of multiple inhaler devices, and inadequate inhalation technique contributed to poorer disease control. In contrast to that study, our results demonstrated an even higher prevalence of inhalation technique errors, suggesting that inhaler misuse remains a major challenge in routine clinical practice.

An important finding of our study was that only 59.0% of patients reported receiving detailed instructions regarding inhaler technique from healthcare professionals, while 9.0% reported not receiving any instructions at all. This finding may partly explain the high prevalence of inhalation errors observed in our population and underscores the importance of repeated patient education and regular reassessment of inhaler technique in clinical practice.

Conclusion

Inhaler therapy is very important in the pharmacological treatment of patients with COPD, providing a variety of medications that can significantly improve respiratory function and quality of life. Therefore, this research attempts to contribute to the reduction of critical errors in inhalation technique and the advancement of pharmacological treatment with inhalers in patients with COPD. By increasing the quality of adequate management of COPD, the efficiency and effectiveness of the treatment of the disease can be increased, and thus the quality of life of millions of individuals worldwide can be significantly improved, considering that COPD is the third leading cause of death in the world.
Therefore, in conclusion, these results will help identify areas where improvements can be made, which will contribute to the advancement of inhaler treatment and improvements in inhalation technique that lead to symptom relief and improved general well-being.

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THE INFLUENCE OF THE TREATMENT OF SnS THIN FILMS WITH ALCOHOLIC SOLUTION, FOLLOWED BY ANNEALING

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Abstract

Tin(II) sulfide (SnS) is a promising semiconductor material for photovoltaic and optoelectronic applications due to its suitable band gap, high absorption coefficient, non-toxicity, and abundance in nature. In this work, SnS thin films were deposited on glass substrates using the chemical bath deposition (CBD) technique. The deposition bath contained $SnCl_2 \cdot 2H_2O$, NH_4F, NH_4OH, and $Na_2S_2O_3$ solutions at pH = 7. After deposition, the films were treated in an alcoholic $SnCl_2$ solution for different immersion times and annealed at 300 °C. Structural properties of the films were investigated using X-ray diffraction (XRD). The analysis confirmed the formation of polycrystalline orthorhombic SnS. Crystallite size was estimated using the Scherrer equation and increased from 34 nm for untreated films to 50 nm after repeated treatment and annealing. The reduction in diffraction peak broadening indicates improved crystallinity and grain growth. Untreated films exhibited p-type conductivity, while longer treatment in $SnCl_2$ solution resulted in conversion to n-type conductivity. The results demonstrate that post-deposition treatment significantly affects the structural and electrical properties of SnS thin films and may improve their suitability for thin-film solar cell applications.

Keywords: Tin(II) sulfide (SnS), chemical bath deposition, thin films, X-ray diffraction, crystallite size, photovoltaic materials.

Introduction

Tin(II) sulfide (SnS) is a semiconductor material belonging to the IV–VI chalcogenide group that has attracted considerable scientific attention due to its potential applications in photovoltaic and optoelectronic devices (Banai et al.2016,Hedge et al.2011,Norton et al.2021). The increasing demand for renewable energy sources necessitates the development of efficient, low-cost, and environmentally friendly materials (Han et al.2026). In this context, SnS represents a promising candidate for the absorber layer in thin-film solar cells because of its high absorption coefficient in the visible spectrum ($>10^4$ cm^{-1}), suitable band gap energy (Eg ≈ 1.1–1.5 eV), and good chemical and thermal stability (Banai et al.2016,Di Mare et al.2017,Norton et al.2021).

Unlike materials such as CdTe and CIGS, SnS does not contain toxic elements and is composed of earth-abundant raw materials, making it suitable for large-scale production. However, the properties of SnS thin films strongly depend on the preparation method and post-deposition treatments; therefore, detailed structural, optical, and electrical characterization is essential for optimizing their applications.

SnS crystallizes in an orthorhombic structure (Herzenbergite phase) with a layered crystal lattice, resulting in anisotropic electrical and optical properties. The material naturally exhibits p-type conductivity due to defects such as sulfur vacancies and tin interstitial atoms, which act as acceptor centers and generate holes as the dominant charge carriers.

The band gap energy of SnS depends on the deposition method, grain size, and the presence of defects. Structural imperfections may create localized energy states within the forbidden band, affecting both the absorption spectrum and electrical conductivity. Therefore, controlling defects and improving the crystal structure are crucial for enhancing material performance.

Chemical Deposition of SnS

Chemical bath deposition (CBD) is a simple, low-cost, and low-temperature technique for obtaining thin films, enabling direct deposition of the material onto the substrate through controlled chemical reactions in solution. This method is particularly suitable for the deposition of chalcogenide semiconductors such as SnS (Dekhil et.al 2023, Sajeesh et al.2010).
In this study, SnS thin films were deposited using the chemical bath deposition method. The composition of the deposition bath was as follows: 30 mL of distilled water, 0.8 g NH_4F, 1.125 g $SnCl_2 \cdot 2H_2O$, 6 mL of 0.25% NH_4OH, and 5 mL of 2 M $Na_2S_2O_3$. Distilled water was added to obtain a total volume of 100 mL(A.Tanusevski.2003).
The deposition of SnS films, described in this paper, was based on the reducing ability of thiosulfate ions by the following reactions(A.Tanusevski.2003):

$$2S_2O_3^{2-} \rightarrow S_4O_6^{2-} + 2e \quad (1)$$

$$2S_2O_3^{2-} + H^+ \rightarrow S + HSO_3^- \quad (2)$$

$$S + 2e \rightarrow S^{2-} \quad (3)$$

$$Sn^{2+} + S^{2-} \rightarrow SnS \quad (4)$$

Ammonium fluoride was used as the complexing agent and also served to control the pH value of the solution. The films were deposited at pH = 7 using a thiosulfate bath as the source of S^{2-} ions.
Microscope glass slides were used as substrates. Prior to deposition, the substrates were cleaned in chromosulfuric acid and rinsed thoroughly with distilled water. The cleaned substrates were then immersed vertically along the walls of the reaction beaker.
During deposition, the color of the solution gradually changed from yellow to yellow-brown and finally to black, indicating the formation of SnS thin films. After 18 hours of deposition, thin films with a thickness of approximately 0.34 μm were deposited on both sides of the glass slides (75 × 25 × 1 mm^3), while additional precipitate accumulated at the bottom of the beaker. For all measurements, the films deposited on the side facing the beaker wall during deposition were used. The layers formed on the opposite side of the slides were removed using a cotton swab soaked in diluted HCl solution. The obtained films exhibited a dark red color and showed p-type semiconductor behavior.
Following deposition, the films were immersed in an alcoholic $SnCl_2$ solution for 1 minute, 2 minutes and 3 minutes, respectively. Subsequently, the films underwent thermal treatment at 300 °C.

Film Treatment

SnS is naturally a p-type semiconductor, mainly due to the presence of defects in the crystal lattice such as sulfur vacancies and tin interstitial atoms (Dahule et al.2022, Norton et al.2021). In order to achieve a transformation from p-type to n-type conductivity, the SnS films were treated with a $SnCl_2$ solution followed by thermal annealing at 300°C.
During this process, some sulfur atoms in the lattice may be substituted by chlorine ions, which act as donor impurities and provide free electrons. The thermal treatment enables the diffusion of chlorine and sulfur ions into the interior of the film and simultaneously contributes to recrystallization, grain growth, and reduction of defect concentration(Pandey et al.2021,Yanagi et al. 2016).
In this study, four samples were characterized:
0 min – as-prepared p-type film
2 min – treated once for 2 minutes, p-type
3 min – treated once for 3 minutes, n-type
2×3 min – treated twice for 3 minutes, n-type

Structural Analysis by XRD and Grain Size Determination

X-ray diffraction (XRD) was used to determine the crystalline phase and degree of crystallinity of the films. The analysis is based on Bragg's law, which relates the wavelength of X-ray radiation to the interplanar spacing in the crystal lattice (Freund et al.2021,Pope C.G 1997). Figure 1, shows the diffraction patterns obtained from the XRD analysis of the investigated samples.

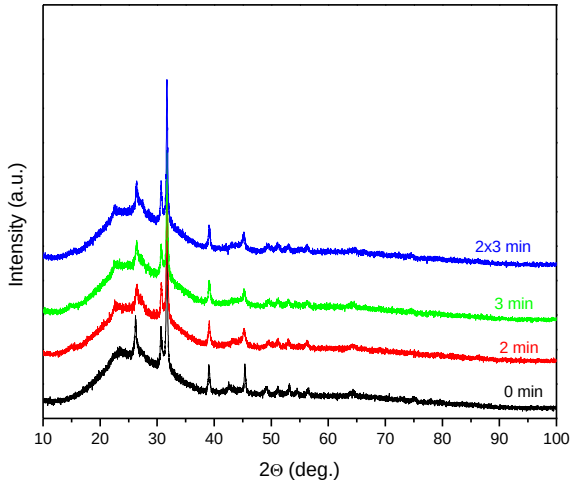


Figure 1. X-ray diffraction analysis (XRD) of the investigated SnS thin films.

The crystallite size was estimated using the Scherrer equation, which relates the broadening of diffraction peaks to grain size (Balaz et al.2013,Howarth et al.2016):

$$D = \frac{K\lambda}{\beta \cos(\theta)} \qquad (5)$$

Where:
λ = 0.154 nm (X-ray wavelength)
β = full width at half maximum (FWHM)
θ = Bragg angle
K = 0.94 (shape factor constant)
A decrease in the full width at half maximum after treatment indicates an increase in grain size and improved crystal ordering.
The grain sizes calculated for the analyzed samples are presented in Table 1.

Table 1. Crystallite size of the analyzed samples determined using the Scherrer equation.

Sample	D (nm)
0 min (p-type)	34
2 min (p-type)	35
3 min (n-type)	41
2×3 min (n-type)	50

From Table 1, it can be observed that treatment of the films in $SnCl_2$ solution followed by heating at 300 °C leads to an increase in grain size. Larger grains imply fewer grain boundaries, resulting in reduced scattering of charge carriers and improved electrical properties.

Discussion

The obtained results demonstrate that post-deposition treatment significantly affects the structural and optical properties of chemically deposited SnS thin films. XRD analysis confirmed the polycrystalline nature of the films and revealed improved crystallinity after treatment with $SnCl_2$ solution and thermal annealing.
The increase in crystallite size from 34 nm for the untreated sample to 50 nm for the twice-treated sample indicates enhanced recrystallization and grain growth during thermal treatment. Larger crystallites reduce the density of grain boundaries, which in turn decreases charge carrier scattering and improves electrical transport properties.
The conversion from p-type to n-type conductivity after longer treatment durations indicates successful incorporation of sulfur or chlorine donor impurities into the SnS lattice.
Overall, the results demonstrate that $SnCl_2$ treatment combined with thermal annealing effectively modifies the structural and optical properties of SnS thin films and improves their suitability for photovoltaic and optoelectronic applications.

Conclusion

SnS thin films were successfully deposited by the chemical bath deposition method using a thiosulfate bath at pH = 7. The deposited films exhibited a polycrystalline orthorhombic structure and p-type semiconductor behavior.
Post-deposition treatment in alcoholic $SnCl_2$ solution followed by thermal annealing at 300 °C significantly influenced the structural and optical properties of the films. XRD analysis showed an increase in crystallite size and improved crystallinity after treatment.
Furthermore, the treatment process enabled the transformation of conductivity from p-type to n-type, indicating successful donor doping through chlorine incorporation. These findings suggest that chemically deposited SnS thin films possess promising structural and optical properties for potential application in thin-film solar cells and other optoelectronic devices.

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SHARP INITIAL COEFFICIENT BOUNDS FOR A GENERALIZED JANOWSKI-TYPE SUBCLASS OF STARLIKE FUNCTIONS DEFINED BY SUBORDINATION

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Abstract

For a function f of the class $\mathcal{A}$ involving an analytic function ϕ using subordination is defined a generalized Janowski-type subclass of normalized analytic functions. For functions belonging to this class, we derive sharp bounds for the initial coefficients $|a_2|$ and $|a_3|$. These bounds are given explicitly in terms of the parameters A and B, as well as the derivatives $\phi'(1)$ and $\phi''(1)$. Several significant special cases are examined, including the classical Janowski starlike class, a square-root–type case, and a case associated with exponential distortion. The sharpness of the obtained results is established by constructing appropriate extremal Schwarz functions

Keywords: univalent functions; differential subordination; coefficient bounds; Janowski functions; Schwarz lemma; starlike functions; sharp estimates.

Introduction and preliminaries

Let $\mathbb{D} = \{z \in \mathbb{C}: |z| < 1\}$ denote the open unit disk , and let $\mathcal{A}$ be the class of a function analytic in $\mathbb{D}$ of the form

$$f(z) = z + \sum_{n=2}^{\infty} a_n z^n \tag{1}$$

A function $f \in \mathcal{A}$ is said to be starlike if

$$Re\left(\frac{zf'(z)}{f(z)}\right) > 0, z \in \mathbb{D}. \tag{2}$$

and the class of all such function is denoted with S^*.

Lemma 1. (Schwarz Lemma)

If $\omega(z) = \sum_{k=1}^{\infty} c_k z^k$ *analytic in* $\mathbb{D}$ *and satisfy the condition* $|\omega(z)| < 1$, *then*

$$|\omega(z)| \le |z|, \qquad (z \in \mathbb{D}) \ \textit{and} \ |c_1| \le 1$$

are obtained. In particular , $|\omega(z_0)| = |z_0|$, *for some* $z_0 \in \mathbb{D} \setminus \{0\}$ *or* $|c_1| = 1$ *if and only if* $\omega(z) = e^{i\theta} z$ *for some* θ $(0 \le \theta < 2\pi)$.

An analytic function $\omega: \mathbb{D} \to \mathbb{C}$ satisfying $\omega(0) = 0$ si called Schwarz function and this function has a Taylor series expansion $\omega(z) = c_1 z + c_2 z^2 + \cdots$, with $|\omega(z)| < 1$ for all $z \in \mathbb{D}$.

The standard estimation for a coefficient of a Schwarz function are

$$|c_1| \le 1 , \qquad |c_2| \le 1 - |c_1|^2, \tag{3}$$

both inequalities are sharp

Special cases:

If $c_1 = 0$, then the estimate reduces to

$$|a_2| \le 1,$$

with equality for

$$\omega(z) = e^{i\theta} z^2.$$

If $|a_1| = 1$, then $w(z) = e^{i\theta} z$ and $a_2 = 0$, which also satisfies the bound sharply.

A standard way to generalize starlike functions is through subordination, because subordination is used in exploring geometric properties of univalent functoin. If p and q are analytic in $\mathbb{D}$, then p is subordinate to q, written as

$$p(z) \prec q(z)$$

If there exists a function $\omega: \mathbb{D} \to \mathbb{D}$, analytic in $\mathbb{D}$, normalized with $\omega(0) = 0$ with $|\omega(z)| < 1, \forall z \in \mathbb{D}$ such that

$$p(z) = q\big(\omega(z)\big), \forall z \in \mathbb{D}.$$

Also the concept of differential subordination play an important role in geometric properties of analytic functions by embedding them into controlled inequalities. It was formalized by Miller and Mocanu and has become a central tool in modern complex analysis.

Definition 1. *Let $\psi: \mathbb{C}^2 \times \mathbb{D} \to \mathbb{C}$ be a given function and let h be analytic function in $\mathbb{D}$. If an analytic function p satisfies*

$$\psi(p(z), zp'(z); z) \prec h(z), \qquad z \in \mathbb{D},$$

then $\boldsymbol{p}$ is said to satisfy a first-order differential subordination.

Janowski functions generalize the classical starlike functions and extend many classical subclasses of univalent functions and by varying of parameters A,B, are obtained different subclasses of univalent functions

The Janowski function is given by

$$J_{A,B}(z) = \frac{1 + A\,z}{1 + B\,z}, -1 \le B < A \le 1. \tag{4}$$

and the Janowski class of starlike functions $S^*(A, B)$ if

$$\frac{zf'(z)}{f(z)} \prec \frac{1 + A\,z}{1 + B\,z}, \qquad z \in \mathbb{D}. \tag{5}$$

Now using this class of a function let us define the class $S^*[A, B; \phi]$.

Let ϕ be analytic in a domain containing 1, with

$$\phi(1) = 1.$$

For $-1 \le B < A \le 1$, we define the class

$$S^*[A, B; \phi] = \left\{ f \in \mathcal{A}: \frac{zf'(z)}{f(z)} \prec \phi\left(\frac{1 + A\,z}{1 + B\,z}\right) \right\} \tag{6}$$

Equivalently , $f \in S^*[A, B, \phi]$ if there exists a Schwarz function

$$\omega(z) = c_1 z + c_2 z^2 + \cdots.$$

such that

$$\frac{zf'(z)}{f(z)} = \phi\left(\frac{1 + A\,\omega(z)}{1 + B\,\omega(z)}\right).$$

For a Schwarz function we use the standard estimates

$$|c_1| \le 1 \;\; and \;\; |c_2| \le 1 - |c_1|^2.$$

This inequality are sharp.

2. Main result

Theorem 1. *Let $f \in S^*[A, B; \phi]$, where*

$$f(z) = z + a_2 a^2 + a_3 z^3 + \cdots.$$

Assume that ϕ is analytic at 1, with $\phi(1) = 1$. Then

$$|a_2| \le |A - B||\phi'(1)| \tag{7}$$

and

(8) $$|a_3| \le \frac{1}{2} max\left\{|(A-B)\phi'(1)|, \left|(A-B)^2\left(\phi'(1)\right)^2 - B(A-B)\phi'(1) + \frac{(A-B)^2}{2}\phi''(1)\right|\right\}.$$

Both estimates are sharp.

Proof

Since $f \in S^*[A,B;\phi]$, there exists a Schwarz function

$$\omega(z) = c_1 z + c_2 z^2 + \cdots$$

such that

$$\frac{zf'(z)}{f(z)} = \phi\left(\frac{1+A\,\omega(z)}{1+B\,\omega(z)}\right).$$

Firs, from Janowski function we have the expansion

$$\frac{1+A\,\omega(z)}{1+B\omega(z)} = 1 + (A-B)\omega(z) - B(A-B)\omega(z)^2 + \cdots$$

and since

$$\omega(z) = c_1 z + c_2 z^2 + \cdots,$$

we obtain

$$\frac{1+A\,\omega(z)}{1+B\,\omega(z)} = 1 + (A-B)c_1 z + [(A-B)c_2 - B(A-B)c_1^2]z^2 + \cdots,$$

now if we expand ϕ around 1

$$\phi(\omega) = 1 + \phi'(1)(\omega-1) + \frac{\phi''(\omega)}{2}(\omega-1)^2 + \cdots.$$

Therefore

$$\phi\left(\frac{1+A\,\omega(z)}{1+B\,\omega(z)}\right) = 1 + (A-B)\phi'(1)c_1 z + \left[(A-B)\phi'(1)c_2 - B(A-B)\phi'(1)c_1^2 + \frac{(A-B)^2}{2}\phi''(1)c_1^2\right]z^2 + \cdots.$$

On the other hand,

$$\frac{zf'(z)}{f(z)} = 1 + a_2 z + (2a_3 - a_2^2)z^2 + \cdots.$$

Comparing coefficients gives

$$a_2 = (A-B)\phi'(1)c_1.$$

Hence

$$|a_2| \le |A-B||\phi'(1)|$$

For the second coefficient ,

$$2a_3 - a_2^2 = (A-B)\phi'(1)c_2 - B(A-B)\phi'(1)c_1^2 + \frac{(A-B)^2}{2}\phi''(1)c_1^2.$$

Since

$$a_2^2 = (A-B)^2\left(\phi'(1)\right)^2 c_1^2,$$

we obtain

$$a_3 = \frac{(A-B)\phi'(1)}{2}c_2 + \frac{1}{2}\left[(A-B)^2\left(\phi'(1)\right)^2 - B(A-B)\phi'(1) + \frac{(A-B)^2}{2}\phi''(1)\right]c_1^2.$$

If we put

$$M = (A-B)\phi'(1), \tag{9}$$

and

$$N = (A-B)^2\left(\phi'(1)\right)^2 - B(A-B)\phi'(1) + \frac{(A-B)^2}{2}\phi''(1), \tag{10}$$

then

$$a_3 = \frac{1}{2}Mc_2 + \frac{1}{2}Nc_1^2.$$

Using the inequality

$$|c_2| \le 1 - |c_1|^2,$$

we obtain

$$|a_3| \le \frac{1}{2}|M|(1-|c_1|^2) + \frac{1}{2}|N||c_1|^2$$

Let

$$x = |c_1|^2, \qquad 0 \le x \le 1.$$

Then

$$|a_3| \le \frac{1}{2}[|M|(1-x) + |N|x]\,.$$

Since the right-hand side is linear in x, its maximum on [0,1] is attained at an endpoint. Hence

$$|a_3| \le \frac{1}{2}\max\{|M|, |N|\}.$$

Thus

$$|a_3| \le \frac{1}{2}\max\left\{|(A-B)\phi'(1)|, \left|(A-B)^2\left(\phi'(1)\right)^2 - B(A-B)\phi'(1) + \frac{(A-B)^2}{2}\phi''(1)\right|\right\}.$$

This proves the desired estimate.

Now let's proof the sharpnes.

For $|a_2|$, equality holds when

$$|c_1| = 1.$$

By Schwarz lemma this happens when

$$\omega(z) = e^{i\theta}z.$$

Now let's construct the extremal function,

$$\frac{zf_\theta'(z)}{f_\theta(z)} = \phi\left(\frac{1+Ae^{i\theta}z}{1+Be^{i\theta}z}\right)$$

Since

$$z\frac{d}{dz}\log\frac{f(z)}{z} = \frac{zf'(z)}{f(z)} - 1$$

we can write

$$\frac{d}{dz}\log\frac{f(z)}{z} = \frac{\phi\left(\frac{1+Ae^{i\theta}z}{1+Be^{i\theta}z}\right) - 1}{z}$$

Integrating from 0 to z

$$\log\frac{f(z)}{z} = \int_0^z \frac{\phi\left(\frac{1+Ae^{i\theta}t}{1+Be^{i\theta}t}\right) - 1}{t}dt$$

or

$$f(z) = z\, e^{\int_0^z \frac{\phi\left(\frac{1+Ae^{i\theta}t}{1+Be^{i\theta}t}\right)-1}{t}dt}$$

For $|a_3|$, the sharpness argument is based on the fact that a_3 depends on the first two Schwarz coefficients of ω.
From

$$|a_3| \le |N|x + |M|(1-x), \;\; x = |c_1|^2, \qquad 0 \le x \le 1.$$

So the problem reduces to maximizing the linear function

$$G(x) = |N|x + |M|(1-x), \;\; 0 \le x \le 1.$$
$$G'(x) = |N| - |M|$$

There are two cases.
Case 1. $|\boldsymbol{N}| > |\boldsymbol{M}|$
$G'(x) > 0$, $G(x)$ is increasing $\Rightarrow |N| - |M| > 0 \Rightarrow |N| > |M|$,, the maximum occurs at $x = 1$,

$$|c_1|^2 = x = 1$$

By the equality case of Schwarz's lemma,

$$\omega(z) = e^{i\theta} z,$$

that is $c_1 = e^{i\theta}$, $c_2 = 0$
Hence

$$a_3 = Ne^{2i\theta}, \Rightarrow |a_3| = |N|$$

Thus,when $|N| > |M|$, equality is obtained by taking

$$\omega(z) = e^{i\theta} z.$$

Case 2. $|\boldsymbol{N}| < |\boldsymbol{M}|$
$G'(x) < 0$, $G(x)$ is decreasing $\Rightarrow |N| - |M| < 0 \Rightarrow |N| < |M|$,, the maximum occurs at $x = 0$, this mean $c_1 = 0$
To get equality in the Schwarz estimate, we take

$$\omega(z) = e^{i\theta} z^2$$

For this choice,

$$c_1 = 0, \qquad c_2 = e^{i\theta}.$$

Hence

$$a_3 = Me^{i\theta} \;\; so \;\; |a_3| = |M|$$

Thus when $|N| < |M|$, equality is obtained by taking

$$\omega(z) = e^{i\theta} z^2.$$

Case 3. |M|=|N|

$$|a_3| \le |N|x + N(1-x) = |N|$$

Therefor

$$|a_3| \le |N| = M$$

both extremal choices work
Thus the bound for $|a_3|$ is sharp.

Corollary 1 (Classical Janowski Starlike Class)
Let $\phi(w) = w$.
Then

$$S^*[A, B; \phi] = S^*[A, B],$$

the usual Janowski starlike class.
If $f \in S^*[A, B]$, then

$$|a_2| \le A - B,$$

and

$$|a_3| \leq \frac{A-B}{2}\max\{\,1, |A-2B|\}.$$

Proof

Since

$$\phi(w) = w,$$

We have

$$\phi'(1) = 1, \qquad \phi''(1) = 0.$$

Substituting these into the main theorem gives

$$|a_2| \leq A - B,$$

Also,

$$N = (A-B)^2 - B(A-B) = (A-B)(A-2B)$$

Therefor

$$|a_3| \leq \frac{1}{2}\max\{\,A-B, |(A-B)(A-2B)|\}.$$

Since $A - B > 0$, we get

$$|a_3| \leq \frac{A-B}{2}\max\{1, |A-2B|\}$$

Corollary 2 (Classical Starlike Functions) Let $A = 1, B = -1,\ \phi(w) = w$. Then

$$S^*[1,-1;\phi] = S^*,$$

the classical class of starlike functions. If

$$f(z) = z + a_2 z^2 + a_3 z^3 + \cdots \in S^*$$

Then

$$|a_2| \leq 2 \ \ and\ |a_3| \leq 3.$$

Proof

From Corollary 1,

$$|a_2| \leq A - B = 1 - (-1) = 2$$

Also

$$A - 2B = 3$$

Thus

$$|a_3| \leq \frac{2}{2}\max\{1,3\} = 3$$

These are the well-known sharp coefficient bounds for the classical starlike class.

Corollary 3. (The case $\boldsymbol{\phi(w) = w^{\mu}}$) .

Let

$$\phi(w) = w^{\mu}, \mu > 0$$

where the principal branch is taken near $w = 1$.

If $f \in S^*[A, B; w^{\mu}]$,

$$|a_2| \leq \mu(A-B),$$

$$|a_3| \leq \frac{\mu(A-B)}{2}\max\left\{1, \left|-B + \frac{(A-B)(3\mu-1)}{2}\right|\right\}.$$

Proof

For

$$\phi(w) = w^{\mu},$$

we have

$$\phi'(1) = \mu, \qquad \phi''(1) = \mu(\mu - 1)$$

Therefor

$$|a_2| \leq \mu(A - B).$$

Morever

$$N = (A - B)^2\mu^2 - B(A - B)\mu + \frac{(A - B)^2}{2}\mu(\mu - 1).$$

Hence

$$N = \mu(A - B)\left[-B + \frac{(A - B)(3\mu - 1)}{2}\right].$$

Therefor

$$|a_3| \leq \frac{1}{2}\max\left\{\mu(A - B), \mu(A - B)\left|-B + \frac{(A - B)(3\mu - 1)}{2}\right|\right\}$$

Thus,

$$|a_3| \leq \frac{\mu(A - B)}{2}\max\left\{1, \left|-B + \frac{(A - B)(3\mu - 1)}{2}\right|\right\}$$

Corollary 4. (Square-Root Subclass)

Let $\phi(w) = \sqrt{w}$. Then $\mu = \frac{1}{2}$ in Corollary 3.

If

$$f \in S^*[A, B; \sqrt{w}],$$

Then

$$|a_2| \leq \frac{A - B}{2},$$

And

$$|a_3| \leq \frac{A - B}{4}\max\left\{1, \left|-B + \frac{A - B}{4}\right|\right\}.$$

In particular, for $A = 1$ and $B = 0$.

$$|a_2| \leq \frac{1}{2}, \qquad |a_3| \leq \frac{1}{4}.$$

Corollary 5: (Exponential-Type Subclass). Let

$$\phi(w) = e^{w-1}.$$

If

$$f \in S^*[A, B; e^{w-1}]$$

Then

$$|a_2| \leq A - B,$$

And

$$|a_3| \leq \frac{A - B}{2}\max\left\{1, \left|-B + \frac{3}{2}(A - B)\right|\right\}.$$

Proof

For

$$\phi(w) = e^{w-1},$$

We have

$$\phi'(1) = 1, \qquad \phi''(1) = 1.$$

Therefor

$$|a_2| \leq A - B.$$

Also,

$$N = (A-B)^2\left[-B + \frac{3}{2}(A-B)\right].$$

Therefor

$$|a_3| \leq \frac{A-B}{2}\max\left\{1, \left|-B + \frac{3}{2}(A-B)\right|\right\}.$$

Corollary 6 (Exponential Case with $\boldsymbol{A = 1, B = -1}$)
Let

$$A = 1, \qquad B = -1, \qquad \phi(w) = e^{w-1}.$$

If

$$f \in S^*[1, -1; e^{w-1}],$$

Then

$$|a_2| \leq 2;$$
$$|a_3| \leq 4$$

Corollary 7. (The case B=0 and the case A=1,B=0)
The case B=0.
Then the class is determined by

$$\frac{zf'(z)}{f(z)} \prec \phi(1 + A\, z)$$

If $f \in S^*[A, 0, \phi]$,
Then

$$|a_2| \leq |A||\phi'(w)|$$

And

$$|a_3| \leq \frac{1}{2}\max\left\{|A\phi'(w)|, \left|A^2\left(\phi'(1)\right)^2 + \frac{A^2}{2}\phi''(w)\right|\right\}$$

The case A=1, B=0.
Then the class is determined by

$$\frac{zf'(z)}{f(z)} \prec \phi(1 + \ z)$$

If $f \in S^*[1,0; \phi]$
Then

$$|a_2| \leq |\phi'(1)|,$$

And

$$|a_3| \leq \frac{1}{2}\max\{|\phi'(1)|, |\left(\phi'(1)\right)^2 + \frac{1}{2}\phi''(1)|\}$$

Below we have presented a table for the bound of $|a_2| and\ |a_3|$ where are given special cases for the function $\phi(w)$ and the parameters $-1 \leq B < A \leq 1$

Example	$\boldsymbol{\phi(w)}$	$\boldsymbol{(A,B)}$	$\boldsymbol{\lvert a_2\rvert, bound}$	$\boldsymbol{\lvert a_3\rvert, bound}$
1	w	$\left(\frac{1}{2},-\frac{1}{2}\right)$	1	$\frac{3}{4}$
2	w	$(1,-1)$	2	3
3	w^2	(1,0)	2	$\frac{5}{2}$
4	$\sqrt{w}$	(1,0)	$\frac{1}{2}$	$\frac{1}{4}$
5	e^{w-1}	(1,0)	1	$\frac{3}{4}$
7	e^{w-1}	$(1,-1)$	2	4
8	w^2	$\left(\frac{1}{2},0\right)$	1	$\frac{5}{8}$
9	$1+\sin(w-1)$	(1,0)	1	$\frac{1}{2}$

Conclusion

In this paper, we considered a generalized Janowski-type subclass of starlike functions defined by the differential subordination

$$\frac{zf'(z)}{f(z)} \prec \phi\left(\frac{1+A\,z}{1+B\,z}\right), -1 \le B < A \le 1, \qquad z \in \mathbb{D}$$

where ϕ is analytic in a neighborhood of 1 and satisfies $\phi(1) = 1$. By using the power-series expansion of the logarithmic derivative, the Janowski function, and the standard coefficient estimates for Schwarz functions, we obtained sharp upper bounds for the initial coefficients $|a_2|$ and $|a_3|$. The main estimates are expressed explicitly in terms of the parameters A, B, and the quantities $\phi'(1)$ and $\phi''(1)$, which shows clearly how the choice of the function ϕ influences the coefficient structure of the class..

The obtained bounds are

$$|a_2| \le |A-B||\phi'(1)|$$

and

$$|a_3| \le \frac{1}{2}\max\left\{|(A-B)\phi'(1)|, \left|(A-B)^2\left(\phi'(1)\right)^2 - B(A-B)\phi'(1) + \frac{(A-B)^2}{2}\phi''(1)\right|\right\}.$$

The sharpness of these estimates are verified by choosing suitable extremal Schwarz functions, particularly

$$\omega(z) = e^{i\theta}z$$

and

$$\omega(z) = e^{i\theta}z^2.$$

Several special cases are also given. In particular, the general theorem reduces to the classical Janowski starlike class when $\phi(w) = w$, and to the classical starlike class when A=1, B=−1.

Also some example are given in a table form for special cases of choice $\phi(w)$ and A and B and the resultin bounds.

The results of this paper may be extended in several directions. One natural continuation is to study the Fekete–Szegö functional for function $S^*[A,B;\phi]$. Another possible direction is the investigation of higher-order coefficients such as $|a_4|$, $|a_5|$, and inverse coefficients. It would also be interesting to study Hankel determinants, logarithmic coefficients, and radius problems for this generalized class.

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ANTHROPOGENIC MOTIVES IN THE FUNCTION OF DEVELOPING ALTERNATIVE FORMS OF TOURISM IN THE SOUTHWEST REGION OF THE REPUBLIC OF NORTH MACEDONIA

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Abstract

The richness of tourist spaces is greater when there is an interrelationship between natural and anthropogenic forms. Unlike natural tourist motives, anthropogenic tourist motives are phenomena and processes in space that attract tourists and originated under the influence of human activity and creativity.
Anthropogenic motives are an extremely important element for the development of alternative forms of tourism. Unlike natural motives, anthropogenic motives primarily satisfy people's cultural needs; these values are important factors for human development and therefore for tourism. Cultural-historical monuments can act independently or as part of other tourist values that characterize a space such as the Southwest region of the Republic of North Macedonia.
The Southwest region is rich in cultural heritage with a total of 278 sites dating from different time periods, representing a large potential for the development of alternative forms of tourism.
Many tourists engage in travel motivated by a desire to satisfy their cultural needs, to learn about the historical and cultural heritage of certain countries or a region, and to experience achievements in various fields of culture, architecture, and art.

Key words: Southwest region, anthropogenic motives, events.

Geo-tourist position and communication

The Southwest region is located in the southwestern part of the Republic of North Macedonia with an exceptionally favorable geographic position and a high concentration of diverse natural and anthropogenic tourist values of global significance.
[5] Today its total area is 3,340 km², with 286 settlements and a total population of 177,398 inhabitants (2021). [3]Transport connectivity is an important precondition for tourism development, because it makes natural rarities and beauties accessible to modern people and links tourism supply with tourism demand.
The Republic of North Macedonia features a well-developed road network with a total length of 14,182 km, including motorways, main, regional and local roads. The main axes of the national road network are the two Pan-European corridors, Corridor 8 (east-west) and Corridor 10 (north-south). Most important is the Skopje–Ohrid route, along which runs much of the present main road M-4 (Skopje–Tetovo–Gostivar–Kichevo). This main road is the most developed tourist direction in North Macedonia and provides the region with strong predispositions for the development of alternative forms of tourism. This highway connects to many important main roads, increasing the tourist value of the Southwest region.

Anthropogenic motives in the function of developing alternative forms of tourism in the Southwest region of the Republic of North Macedonia

Cultural motives are one of the most important pillars for tourism development, transforming local heritage into an attractive tourism product. These values, including material and intangible goods, offer an authentic experience that is becoming increasingly popular among modern tourists.

[3] The Southwest region of North Macedonia is among the richest regions in cultural values with a total of 278 sites, which constitute significant national and even international heritage. Cultural values are inextricably linked to the natural beauties of the region, especially the Ohrid–Struga area, which is under UNESCO protection.
[3] Below are the numbers and types of cultural heritage per municipality in the Southwest region of North Macedonia:
Ohrid: 111 cultural heritage objects — churches, monasteries, a basilica, the Bay of Bones, archaeological sites, fortress/castle, fortress (citadel), mosque, tomb (turbe), tekke (Sufi lodge), museums and the old town;
Struga: 38 objects — churches, mosques, tekke, museums, the city library, archaeological sites, old town;
Vevchani: 35 objects — churches, old houses, archaeological sites;
Debar: 17 objects — churches, mosques, old houses, archaeological sites;
Debarce: 21 objects — churches, old houses, archaeological sites, fortress, memorial fountain, Leshan mill, memorial to fallen fighters of the National Liberation War (WWII), monument to freedom;
Kichevo: 24 objects — churches, old houses, archaeological sites, fortress, monastery, memorial tomb of Hristo Uzunov, Kichevo bazaar, museum, memorial construction;
Makedonski Brod: 12 objects — churches;
Plasnica: 1 object — Church of St. Nikola;
Centar Župa: 19 objects — churches and archaeological sites.
Source: Processed by the author
From the data above, we conclude that the Southwest region is very rich in cultural heritage with a total of 278 objects dating from different periods, representing a great potential for the development of alternative forms of tourism. By valorizing the total number of cultural heritage assets in the region, we can incorporate them to build a rich tourist offer for this type of tourism. This potential leads to spatial transformation and economic development of the Southwest region of the country. Below there are data on some of the most important sites.
Mesheshta has a rich history. The oldest archaeological locality near the village is the site of St. Elijah (Sv. Ilija), where remains from the older Iron Age have been found. At this location there is a small single-nave monastery church dedicated to St. Prophet Elijah.
[14] According to some sources, the old name of Mesheshta was Dabovo. Although there are no specific studies on the origin of the village's modern name, it probably derives from the Turkish word for oak—"meşe." The village name first appears in the Ottoman census of the Ohrid kaza from 1582 as Meshevishte. Types of alternative tourism forms: cultural-recreational, walking, rural, cultural-heritage, weekend-excursion.
[14] Among the cultural-historical landmarks concentrated in this area, greatest attention is drawn to the St. Naum monastery, the church of the Virgin of Zahumska, and the cave church of St. Stephen. Built on a high cliff in the old part of Ohrid, at one of the most beautiful spots on the shore of Lake Ohrid, the Church of St. John at Kaneo dates from the 13th century.
[10] Architecture is very important for studying Ohrid's medieval monuments because it represents a successful combination of Byzantine and Armenian elements.



Figure 1: Church of St. John at Kaneo in Ohrid
Source: www.macedonia-timeless.com

The frescoes have been preserved in the dome and altar area but are considerably damaged; for a long period between the 17th and 19th centuries the church was partially destroyed and abandoned, during which many of the frescoes were destroyed and lost forever.
The founding of this monastery is associated with the name Naum (Haum), a collaborator of Clement—both among the most renowned enlighteners of the Macedonian people. Naum's monastery with the Church of the Holy Archangel, as well as Clement's monastery with the Church of St. Panteleimon in Ohrid, are the first monuments of Slavic church architecture and art in the Southwest region. [4] The monastery and its interior are a quiet place for rest and walking, and together with its surroundings, the whole area captivates with the tranquil beauty of the pearly transparent water of the Black Drim source, one of the cleanest spots on the Ohrid shore.
After 530 years, on the day of the consecration of the renewed monastery, the relics of St. Clement of Ohrid were again transferred to Plaoshnik—the first Slavic bishop from 893 AD and the founder of the Macedonian Orthodox Church – Ohrid Archbishopric. Here stood the Ohrid School of Slavic literacy, spirituality and culture, considered the first Slavic university in the world. This complex is one of the most important archaeological localities in the Southwest region and in the Republic of North Macedonia and is one of the most sacred places.
[14] Ohrid Fortress, the emblem of the Southwest region and the city of Ohrid, represents one of the largest medieval urban fortifications in North Macedonia. With its fortifications and walls it occupies the entire Ohrid ridge. From all sides, except the southern side facing the lake, the hilly part of the town was protected with high walls and towers extending about three kilometers, up to the proximity of Ohrid's harbor.
[12] The present form of the fortress dates from the time of Tsar Samuel, though records show later destructions and repairs by Turks and Byzantines. Under the partly ruined outer layer of the inner walls horizontal layers of bricks in Byzantine format are visible. In the walls of the upper gate many stones with Greek inscriptions are embedded, originating from ancient buildings that abound in the area.
[6] From history a large trace here is Katino Kale. The site dates from prehistoric times and is considered the place from which modern Kichevo originated, thus regarded as the core of the eponymous town. [15] The fortress of Katino Kale dates from the Roman period. Information on Kichevo's existence is available from Byzantine emperor Basil II. Later Katino Kale served as the seat of Turkish authorities and around 1850 lost its role and was abandoned; locals were later allowed to use stones from the fortress to build structures.
[15] Developed tourism forms include: cultural-recreational, weekend, walking, cultural-heritage, weekend-excursion.
[3] The Museum of Western Macedonia is of great importance for this region; it is located in the building of the Main Headquarters of the National Liberation Army of Macedonia during WWII. The museum opened in 1980 and is located on the central square in Kichevo.

The Bay of Bones is located at Gradishte in Lake Ohrid. In 1977 the first underwater archaeological research in Macedonia was conducted at the site Plocha Mićov Grad in the Bay of Bones, along the south shore of the Gradishte peninsula near the village of Peshtani.
At depths of three to five meters numerous wooden piles were found driven into the lakebed and many movable archaeological materials dating to the end of the Bronze Age and the beginning of the Iron Age (roughly 1200 BCE to 700 BCE). It is assumed that this and other similar settlements on Lake Ohrid belong to the period when the first tribal populations began to form. [14] Researchers recorded 6,000 wooden piles during campaign surveys between 1997 and 2005. Measurements indicate the settlement covered approximately 8,500 m². Remains were discovered about ten meters from the shore of the Bay of Bones, on the southern shore of the Gradishte peninsula, extending 155 m (west–east) by 55 m (north–south).
[3] The ancient theater is located at the foothill of the eastern slope of the higher Ohrid ridge, under Samuel's fortress, near one of the main entrances to the fortified town—Gorna Porta—offering unforgettable views of Lake Ohrid and the surrounding mountains.
It was built over two millennia ago, toward the end of the 3rd or beginning of the 2nd century BCE, during the late Hellenistic period, intended for dramatic, musical and poetic performances. The first supposition that there was a theater in the ancient Lichnid (today's Ohrid) came from the Russian art historian Nikodim P. Kondakov at the beginning of the 20th century; first archaeological excavations occurred in 1935. [15] In 1999 a project began to fully reveal and put it into function, and since 2001 the reconstructed open stage of the ancient theater again hosts dramatic performances, music events and various manifestations after twenty centuries.
Other important museums in the Southwest region include: the Natural Science Museum, the "Dr. Nikola Nezlobinski" Museum, the Memorial House of the Miladinov Brothers, the Vangel Kodžoman Memorial Gallery. The ethnological department organizes the event "Review of Folk Costumes," a traditional show of folk dress and folklore.
[16] Ali Pasha Mosque — Ali Pasha Mosque is believed to be among the first mosques built in North Macedonia. This square-shaped mosque is thought to have been built of stone and fired brick at the end of the 15th or beginning of the 16th century. In 1823 a madrasa was established within the mosque complex, though it no longer exists today. Remains of a minaret are on the south side of the mosque; it was destroyed in 1912 and has not been rebuilt. It is believed there was another minaret on the western part raised by Sultan Bayezid II (1481–1512).
[3] The base of Ali Pasha Mosque is square, 15 x 15 meters, above which rises an octagonal tambour and above it another twelve-sided tambour crowned by a shallow dome. The interior transitions are solved with pendentives. All sides of the harem continuously lead to the single point of the dome that symbolizes the unity of Allah. The relatively narrow window openings are characteristic of local masonry, suggesting the builder was likely from Ohrid. The interior features unity of space, simplicity of forms and dominance of volume. The mihrab, set in the southeastern wall, is simple—recessed in the wall without decorative elements and framed with a shallow profiled frame. The minbar is carved from stone and bears the only decorative elements in the interior. On the upper part of the minbar shallow relief rosettes and cypress motifs appear, an ancient and universal funerary symbol, typical of folk motifs from the late 18th and early 19th centuries.



Figure 2: Ali Pasha Mosque in Ohrid
Source: www.ohrid.com.mk

Along the entire length of the mosque's southwest side is the mahfil, which calms the interior volume. The minaret's remains lie on the south side; it was destroyed in 1912 and never rebuilt. Based on its foundation dimensions, it was a minaret whose height and elegance dominated this part of Ohrid's bazaar. It was built of brick and accessed from both the porch and the mahfil in the mosque.

[13] Inchkar Mosque is an Islamic temple located in Debar. According to an inscription above the mosque entrance, written in irregular sulus script in five lines, the mosque was built in the period 1467–68.

Inchkar Mosque was built as a vakıf (endowment) of Mehmed II (1451–1481). It sits in a spacious yard with numerous older graves and richly decorated tombstones. The building is rectangular, measuring 12.70 x 9.38 meters, covered by a hipped roof. The prayer hall (harem) is the preserved part of the authentic building; its old walls and window forms have maintained their original shape and placement.

[3] In the courtyard of the Fatih Sultan Mehmed Mosque is the turbe (tomb) of Shaban-Baba. The turbe is of the open type with an octagonal base. Polygonal columns forming the turbe are connected by vaulted arches. The turbe was built of well-dressed stone blocks, which indicates the importance of the persons buried there. Based on stylistic features it was built toward the 18th or early 19th century, a period when the turbe of Kaplan-pasha in Tirana, with similar stylistic-architectural characteristics, was built.

[17] Juma Mosque or Sultan Bayazid Mosque is an archaeological site in Kichevo representing a medieval object. During earthworks for building a fountain in the mosque courtyard, fragments of ceramic vessels, roof tiles and other building material were found, suggesting a medieval structure was located in its immediate vicinity.

Other known mosques in the Southwest region include: Bajram Mosque, Salahuddin Ayubi Mosque (Labunishta), Tekke Mosque, Inchkar Mosque-Debar, Central Mosque–Veleshta, mosques in Gorna Belica, Dolna Belica, Jablaniça, Juma (Sultan Bayazid) Mosque–Kichevo, Mustafa Çelebi Mosque–Struga, Hajji Durgut's Mosque (the oldest mosque in Ohrid, built in 1466), etc.

[4] In the Southwest region tekkes (Sufi lodges), turbes (tombs) and memorial houses are also well-known attractions for alternative tourism. The most significant are: the memorial house of the father of Mustafa Kemal Atatürk, Ali Riza Efendi (Debar), Hayati Baba Tekke, Çulu Baba Tekke, Sheh Selim Tekke–Kichevo, Helveti Hayat Tekke–Struga, Zeynel Abedin Pasha Tekke–Ohrid, Saat Kula of Suleiman Agha–Ohrid, Turbe of Sinan Çelebi, etc.

Among cultural monuments in the form of old urban architecture and preserved old town complexes and houses are cultural heritage assets preserved despite strong pressures from urbanization and new architecture. Among them the most significant are the Varosh complex

in Ohrid and the Robevci and Uranija houses, and the old part of Struga. From more recent historical monuments and memorials noteworthy are the Monument to the Fallen Fighters of the National Liberation War (WWII) in Ohrid and Struga.

The old bazaars of both Ohrid and Struga are full of shops, small restaurants and confectioneries; they are some of the busiest places in the cities and among the most pleasant spots for walking and shopping. The old bazaar is an ideal part of town for buying souvenirs and Ohrid pearls. Types of alternative tourism: cultural-recreational, weekend, walking, cultural-heritage, lake-related, weekend-excursion, sport-recreational, cultural-event tourism.

Events (manifestations) are part of anthropogenic tourist motives; they represent various ways and forms of public expression and presentation of phenomena and processes with interesting content that can attract visitors on their own, and more often serve as complementary features of the region's tourist offer.

[3] Events present cultural-artistic, sports, economic, religious, entertainment and promotional manifestations, which besides their general significance, have tourist characteristics. [1] Through them, in a lively, dynamic and above all authentic way, the ancient customs and culture of a people or population are displayed.

[2] In this context, events as tourist motives will be considered through the existing ones, while also noting opportunities for new attractive events that would enrich the tourist stay in the region and could, in the foreseeable future, become motives for tourist movements and the development of alternative forms of tourism.

The region is strongly boosted by major international and national events. Cultural events of special significance include: "Struga Poetry Evenings," "Ohrid Summer," "The Balkan Festival of Folk Songs and Dances," "Struga Music Autumn," "Jazz Festival," "May Opera Evenings," "Goce Days," "International Festival of the Film Camera Brothers Manaki," "World Gallery of Caricature," "Review of Folk Costumes," "Ohrid Old Town Meetings" and other locally oriented events.

Struga Poetry Evenings is the largest international poetry event held annually in Struga. First held on 15 July 1961, on the occasion of the publication of the collection of the Miladinov brothers, the idea arose to organize a traditional festival-type event in the town as an annual review of poetic achievements in the Republic of Macedonia.

[17] The event is a fundamental marker of the town as a tourist center and is attended by at least 200 poets from around the world. At the poetry festival among other awards the highest recognition for lifetime poetic achievement—the "Golden Wreath"—and the "Miladinov Brothers" award for the best poetry book in the Macedonian language are presented.

Struga Poetry Evenings experienced rapid growth and quickly became a unique international event of its kind, a bridge between literary meridians of the world. It represents an important forum from which each year the polyphony of the poetic word, its humane messages and its power to ennoble and bring people together resound.

[16] Each year Struga Poetry Evenings is a real festival both for the town and for all poetry lovers. It has become an important cultural event in the world of literature—an event through which one can, as through an open window, see and hear what is happening in poetry, in that "country without borders." By promoting poetry and its values, Struga Poetry Evenings has an invaluable mission in our approaching world.

The name Struga Poetry Evenings is included on all poetic maps of the world. Struga lives in all who have visited and seen it; it will be on the way for those who will see it for the first time. "If somewhere there is a biblical heavenly paradise of ideal beauty, then one of its earthly corners is this town," wrote one of many foreign participants, departing from Struga.

Ohrid Summer is an international music and stage festival held in Ohrid under the patronage of the President of the Republic of North Macedonia. The festival is a member of the European

Festivals Association. The beginning of the "Ohrid Summer" festival dates from 4 August 1961. [14] A major development was its joining the European Festivals Union in 1994. Later, in 2001, a new stage space was introduced—the Ancient Theater. Since then the festival's opening traditionally takes place at this location on 12 July, and its closing on 20 August.
One of the most famous events in Vevchani is the Vevchani Carnival. Written sources testify that the carnival is at least 1,460 years old, but archaeological finds indicate it has existed for at least 2,200 years. Today the carnival is an interesting and unusual mingling of pagan and Christian customs. Traditionally participants try to avoid introducing modern carnival elements, but in recent years, organized by the Municipality and the Ministry of Culture, order has been introduced into this otherwise timelessly chaotic event.
[11] Vevchani Carnival is essentially a masked custom called "St. Vasili" (Vasilica). It is celebrated on 13 and 14 January each year and is dedicated to St. Basil the Great. On that day the Orthodox New Year is welcomed and the old year is sent away. It is originally a pagan custom that has been preserved here to the present day. Participants are called "vasilichari" — masked individuals and groups of all ages organized by neighborhood. Since 1993 the carnival has been a member of the Association of European Carnival Cities.



Figure 3: Vevchani Carnival
Sources: www.cac.org.mk / www.sdk.mk

Conclusion

Protection of cultural wealth implies care and maintenance of selected or designated spaces, which due to their cultural and spiritual values are specifically analyzed and assessed spatially and temporally. Man, as part of nature and as the main factor in its transformation processes, strives through his activities to exploit natural and cultural resources for tourism development.
The Southwestern region is rich in cultural heritage with a total of 278 capacities/sites, dating from different time periods and representing a great potential for the development of alternative forms of tourism; thanks to these assets the region attracts a large number of tourists. In recent years the number of tourists in the Southwestern region has been steadily increasing: in 2022 there were a total of 378,226 tourists; in 2023 there were 451,598 tourists, of whom 244,254 were foreign tourists — for the first time surpassing the number of

domestic tourists. In 2025 the number of tourists reached 539,096 with 222,251 domestic tourists and 316,845 foreign tourists.

Any country, region or area that strives for balanced development of alternative forms of tourism simultaneously pays great attention to preserving natural and cultural values, and through this development they can be incorporated to build a rich tourism offer.

Thanks to the rich potential of the Southwestern region, it represents a special area of interest and value, not only nationally but also internationally.

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PLACENTAL INSUFFICIENCY AND FETAL GROWTH RESTRICTION

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Abstract

Compromise of placental function causes an unfavorable pregnancy and, in most cases, results in fetal growth restriction. The aim of this research was to find an ultrasound parameter that can determine a placental insufficiency and prevent FGR. It was a cohort prospective study that includes 573 pregnant women between 20-24 gestational week. 523 had no ultrasound changes and comprise the control group, and 50 of them had changes in doppler values and/or placental volume, so they comprise the research goup. All pregnant women were monitored during pregnancy for fetal biometry, pulse doppler of both uterine arteries, placental volume, and in delivery for bodily measurement of the newborn. Pregnant women with FGR had significantly higher mean values of the pulsatility index (PI) in the right uterine artery compared with pregnant women in the control group. The obtained results showed that 90% of pregnant women with FGR and 59.2% of pregnant women in the control group had an elevated resistance index (RI) in the right uterine artery. In the left uterine artery, the resistance index was elevated in 78% of women with FGR and in 67.7% of the control group. In the FGR group, significantly higher mean values of the resistance index were measured in both uterine arteries compared with the control group. Compared with the control group, a placental volume below the reference value was significantly more frequent in pregnant women with FGR. The largest mean placental volume was measured in pregnant women from the control group, whereas pregnant women with FGR had a lower mean placental volume.

Keywords: uterine arteries, placenta, fetal growth restriction

Introduction

The placenta is a temporary, very specific organ during pregnancy that carries out physiological growth and processes essential for fetal development. The growth and function of placenta is well regulated for maximal effective exchange of nutrients and metabolic products between maternal and fetal blood circulations. In normal pregnancy, fetoplacental circulation is increased proportionally with the gestational week of pregnancy, thus enabling the physiological intrauterine growth of the fetus.(1) Placental insufficiency arises from disruptions in the maternal–fetal interface that impair the delivery of oxygen and nutrients. Central to this process is a failure in early gestational placentation, characterized by inadequate trophoblast invasion and incomplete spiral artery remodeling.(2) This condition shows a persistence of high-resistance, low-flow uterine arteries, ultimately resulting in reduction of uteroplacental perfusion.

Feto-placental insufficiency is responsible for oxygen decrease and low transport of nutritions to the fetus, so it suffers and stagnates in intrauterine growth, thus increases the possibility of some other complications during pregnancy and during delivery. Using high frequency ultrasound waves is a possibility of measuring the blood circulation in certain organ.(3) In pregnancies with high blood pressure, preeclampsia, intrauterine growth retardation and other adverse outcomes, the circulatory impendance of a. uterine is increased, that is high resistant index or appearance of early diastole notch. Also, it can appear high an impendance of a. umbilicalis, if the obliteration of placental circulation is up to 60%.(4)

Placental insufficiency occurs in approximately 8% to 15% of all pregnancies, worldwide. It is a leading cause of fetal growth restriction (FGR) and some other complications during fetal development and stillbirth.

The most common reasons for placental insufficiency are: gestational diabetes, high blood pressure, maternal heart diseases, blood clothing conditions, preeclampsia, maternal age, using of certain medications, smoking, drinking alcohol, etc.
Placental insufficiency arises from disruptions in the maternal–fetal interface that impair the delivery of oxygen and nutrients. Central to this process is a failure in early gestational placentation, characterized by inadequate trophoblast invasion and incomplete spiral artery remodeling.(5)
This condition shows a persistence of high-resistance, low-flow uterine arteries, ultimately resulting in reduction of uteroplacental perfusion.
Fetal growth restriction is a condition of failure of a fetus to reach its predetermined growth potential. FGR antenatal diagnosis requires a detailed assessment of maternal risk factors, including reproductive history, chronic diseases, maternal risk factors, and serial ultrasounds among women identified as at risk. *(6)* It should be noted that a large proportion of SGA infants are not actually growth restricted but are either constitutionally small or small due to physiologic reasons, such as congenital malformations. FGR affects an estimated 3–5% of pregnancies. Placental insufficiency, as measured by structural abnormalities and histologic findings, is the most frequent cause of FGR, but fetal factors, including chromosomal abnormalities and congenital infections, and maternal risk factors also contribute to FGR.(7)

Objective: Assess ultrasound doppler and placental imaging findings to determine placental insufficiency and to prevent FGR and/or improve pregnancy outcome.

Methods

This research is realized at the Special Hospital for Obstetrics and Gynecology during the period of time from 01.01.2023 – 31.12.2024. It is a cohort prospective study that includes 573 pregnant women who came for a routine check up at our hospital during 20-24 gestational week of pregnancy. Previosly, to all participants was explained the aim of the study and their contribution so all of them assigned an volunteer's agreement for participation in it
Incusion criteria: singltone pregnancy, age of mother up to 18, gestational age 20-24 weeks, exclude anomalies during ultrasound check up.
Exclusion criteria: twins or multiple pregnancy, fetus mortus in utero, anomaly findings, preegsistential hypertension of mother, other chronic diseases of mother, use of Aspirin during pregnancy.
All of them underwent ultrasound for fetal biometry, volume of placenta and color doppler values of both uterine arteries. From overall number of pregnant women, 523 had no ultrasound changes and comprise the control group, and 50 of them had ultrasound changes in doppler values and/or placental volume, so they comprise the research goup. All pregnant women were monitored during pregnancy termination for fetal weight and heigh of the newborn.
It was used ultrasound machine Voluson E8 Expert with 4D convex probe RM6C, GE Healthcare.
Fetal biometry included: biparietal diameter, abdominal circumference, femur length, exclusion of fetal anomalies and placental volume (cm3) measuring by Merwins calculator as standard Apple tool. By pulse doppler were finded the values of pulsatile index (PI) and resistant index (RI) of both uterine arteries.

Table Figures and Equations

Overall number of participants N=573

FGR
N=50

CG
N=523

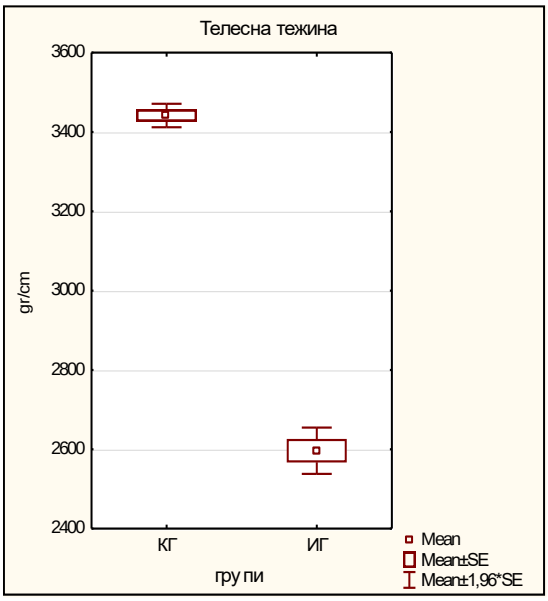


Fig. 1 Graphic depiction of body weight in CG and RG

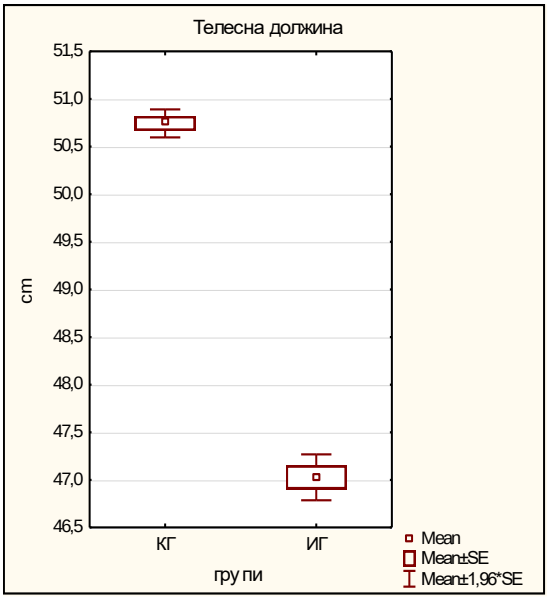


Fig. 2 Graphic depiction of body heigh in CG and RG

Newborn from mothers with FGR newborns had significant smaller fetal bodily measurment (fetal height and weight) comparing to newborns with favorable outcome. (2596.5 ± 364.4 *vs* 3441.5 ± 344.6 gr/cm, и, 47.0 ± 1.5 vs 50.7 ± 1.7 *cm*; p<0.0001).

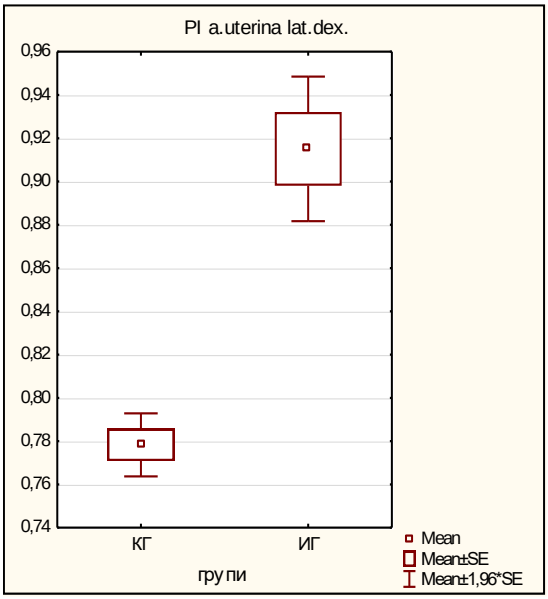


Fig. 3 Graphic depiction of PI PI a. uterine lat. sin. in CG and RG

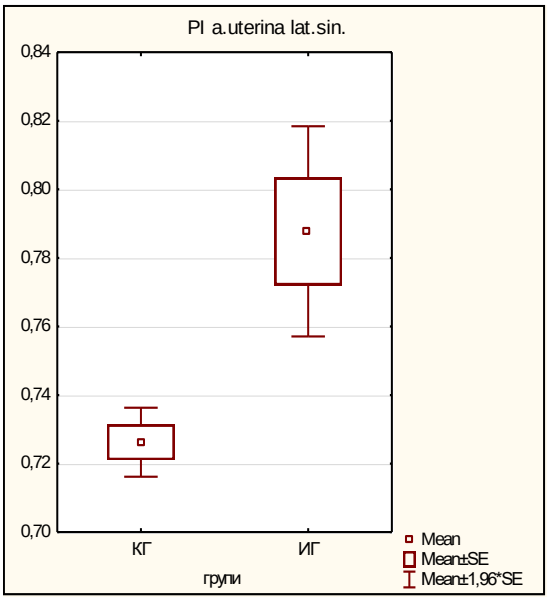


Fig. 4 Graphic depiction of PI a. uterine lat. sin. in CG and RG

The pulsatility index of both uterine arteries differed between the study and control group. The mean PI of the right artery was 0.92 ± 0.2 in pregnant women with an adverse pregnancy outcome, and 0.78 ± 0.2 in pregnant women with a favorable outcome, with the difference of 0.14 confirmed as statistically significant. The mean pulsatility index of the left uterine artery was 0.79 ± 0.2 in pregnant women with an adverse pregnancy outcome, and 0.73 ± 0.1 in pregnant women with a favorable outcome, with the difference of 0.06 confirmed as statistically significant at p = 0.000002. (Figures 3 and 4)

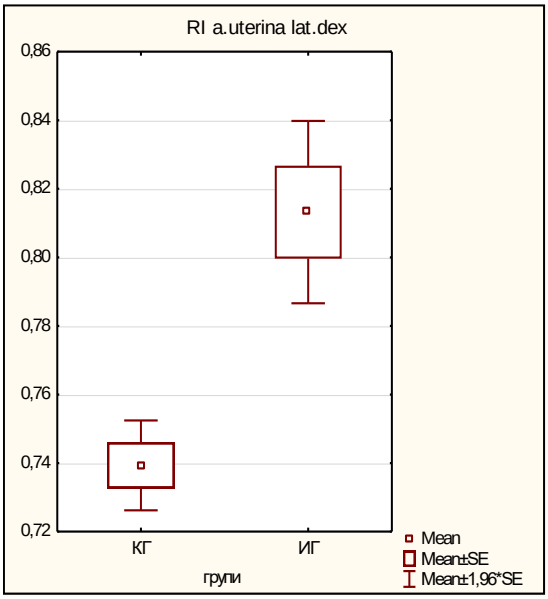


Fig. 5 Graphic depiction of RI a. uterine lat. dex. in CG and RG

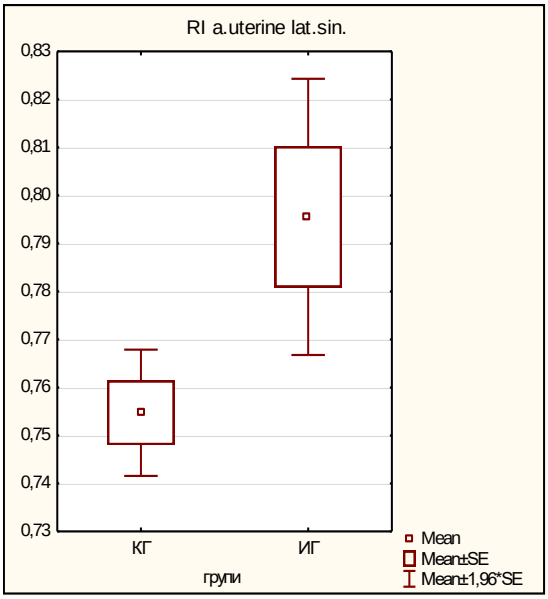


Fig. 6 Graphic depiction of RI a. uterine lat. sin. in CG and RG

Pregnant women with adverse and favorable pregnancy outcomes had different resistance indices in both uterine arteries. The RI of the right uterine artery had a mean value of 0.81 ± 1.2 in the study group (SG) and 0.74 ± 0.15 in the control group (CG), and the difference of 0.07 was confirmed as statistically significant at $p < 0.0001$. The RI of the left uterine artery had a mean value of 0.79 ± 0.2 in the SG and 0.75 ± 0.15 in the CG, and the difference of 0.04 was confirmed as statistically significant at $p = 0.0059$. (Figures 5 and 6)

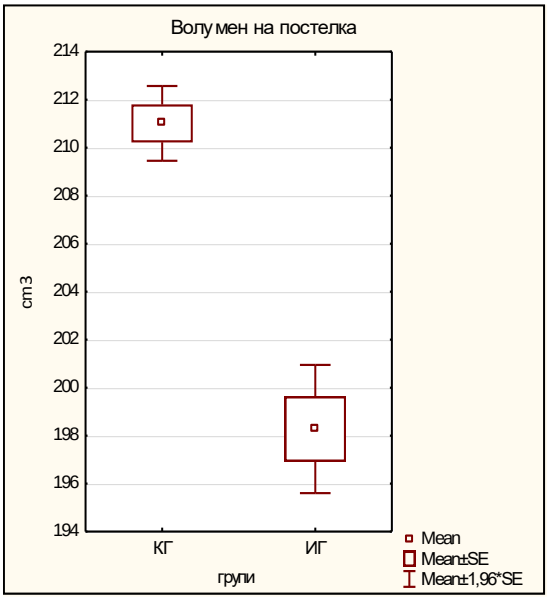


Fig. 7 Graphic depiction of placental volume in CG and RG

In the study group (SG), the mean placental volume measured was 202.3 ± 49.1, while in the control group (CG), the mean volume was 211.0 ± 18.2. The difference in mean placental volumes between the two groups, amounting to 8.7, was confirmed as statistically significant at p = 0.00085. A significantly smaller placental volume was measured in pregnant women with FGR. (Figure 7)

Results

Table 1 Resistent index in both uterine arteries

Variable	Calculated parameter	Groups	
		FGR	KG
RI a.uterina lat. dex	mean ±SD	0.86± 0.16	0.74± 015
	min - max	0.61–1.21	0.37–1.19
	p-level	t=5.48 ***p=0.0000sig	
RI a.uterina lat.sin.	mean ±SD	0.83 ± 0.2	0.75±0.15
	min - max	0.55– 1.16	0.47–1.96
	p-level	t=3.44 ***p=0.0006sig	

t(Student t-test) ***p<0.0001

In the FGR group, significantly higher mean values of the resistance index were measured in both uterine arteries compared with the control group (CG): 0.88 ± 0.15 vs. 0.74 ± 0.15, p < 0.0001 for the right uterine artery, and 0.75 ± 0.15, p = 0.0009 and 0.75 ± 0.15, p = 0.0006 for the left uterine artery.

Table 2. Depiction of placental volume in FGR group in relation to control group

Варијабла/ Variable	калкулиран параметар/ calculated parameter	Групи / Groups	
		IUGR	КГ / CG
Волумен на постелка Placental volume /(cm^3)	mean ±SD	194.83±14.1	211.01±18.2
	min - max	172 – 212	120 – 290
	p-level	t=6.12 ***p=0.0000sig	

t(Student t-test) ****p<0.0001

Pregnant women with fetal growth restriction (FGR) had a low mean placental volume (194.83 ± 14.1). According to the results of the statistical analysis, the differences tested between the examined groups and the control group were statistically significant for the comparison between the FGR group and the control group (CG) ($p < 0.0001$) (Table 2).

Conclusions

Pregnant women with fetal growth restriction (FGR) had significantly higher mean values of the pulsatility index (PI) in the right uterine artery compared with pregnant women in the control group (mean values: 0.90 ± 0.15 and 0.78 ± 0.2 in the FGR and CG groups, respectively).

The obtained results showed that 90% of pregnant women with fetal growth restriction and 59.2% of pregnant women in the control group had an elevated resistance index in the right uterine artery. In the left uterine artery, the resistance index was elevated in 78% of women with intrauterine growth restriction and in 67.7% of the control group.

In the FGR group, significantly higher mean values of the resistance index were measured in both uterine arteries compared with the control group (0.86 ± 0.16 vs. 0.74 ± 0.15, respectively, in the right uterine artery, and 0.83 ± 0.2 vs. 0.75 ± 0.15, respectively, in the left uterine artery). The FGR group had a similar mean resistance index to the control group in both uterine arteries. Compared with the control group, a placental volume below the reference value was significantly more frequent in pregnant women with fetal growth restriction (100% vs. 73.6%). The largest mean placental volume was measured in pregnant women from the control group (211.01 ± 18.2), whereas pregnant women with fetal growth restriction had a lower mean placental volume (194.83 ± 14.1).

Nomenclature

FGR fetal growth restriction
CG control group
RG research group

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FROM UNILATERAL LIMB WEAKNESS TO GAIT INSTABILITY AND INVOLUNTARY MOVEMENTS – A UNIQUE CASE OF HEMIPLEGIC VARIANT OF AMYOTROPHIC LATERAL SCLEROSIS

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Abstract

Motor neuron disease comprises progressive neurodegenerative disorders affecting upper and lower motor neurons. Mills' syndrome, the hemiplegic variant of amyotrophic lateral sclerosis, is a rare phenotype characterized by unilateral spastic hemiparesis without sensory deficits. We report a 50-year-old woman with a two-year history of progressive left-sided motor impairment, initially presenting with lower back pain followed by stiffness and weakness, leading to severe gait impairment. Neurological examination revealed spastic hemiparesis, hyperreflexia, and preserved sensory function. Magnetic resonance imaging and cerebrospinal fluid analysis were normal. Electromyography demonstrated widespread chronic neurogenic changes, while other investigations excluded alternative diagnoses. These findings support the diagnosis of the hemiplegic variant of ALS (Mills' syndrome).

Keywords: Amyotrophic lateral sclerosis, Mills Syndrome, magnetic resonance imaging.

Introduction

Motor neuron disease encompasses a spectrum of progressive neurodegenerative disorders involving upper motor neurons (UMNs) in the motor cortex and lower motor neurons (LMNs) in the brainstem and spinal cord [1,2]. Amyotrophic lateral sclerosis (ALS) is the most common form, typically characterized by a combination of UMN and LMN signs in multiple body regions [1,3]. Mills' syndrome, also referred to as the hemiplegic variant of ALS, represents a rare and atypical phenotype marked by slowly progressive unilateral spastic hemiparesis, often ascending or descending in distribution, without sensory deficits [4,5]. Because of its asymmetric presentation and relatively slow progression, it frequently poses a diagnostic challenge and requires extensive exclusion of structural, inflammatory, infectious, metabolic, and neoplastic causes [2,6].

We present a case illustrating the clinical and electrophysiological features of this rare ALS variant.

Case Presentation

A 50-year-old woman presented with a two-year history of progressive motor impairment. The onset was marked by lower back pain associated with sweating and fever. Shortly thereafter, she developed pain in the left leg, followed within days by stiffness and progressive weakness. Walking became increasingly difficult, eventually progressing to near inability to ambulate independently. Initial treatment with analgesics and corticosteroids did not result in clinical improvement. Over the subsequent six months, her condition deteriorated significantly. She developed severe difficulty climbing and descending stairs, impaired balance, frequent falls, clumsiness, and involuntary movements of the left arm. Fine motor control of the left hand became impaired. The patient denied paresthesias or sensory disturbances and maintained full urinary continence throughout the disease course. She reported intermittent muscle twitching around the left knee and left shoulder, as well as a sensation of tightness in the left scapular region.

Neurological assessment revealed:
Spastic weakness in the left upper and lower limbs
Spastic hypertonia in the left leg
Exaggerated patellar and Achilles reflexes
Positive Babinski sign on the left
Foot clonus on the left
Pseudoathetosis of the left hand
Spastic-paretic gait with circumduction of the left leg
All sensory modalities were intact. Cognitive function was preserved. The clinical course of the disease is summarized in Table 1.

Table 1. Timeline of Disease Progression

Time	Clinical events
Onset	Lower back pain associated with sweating and fever
Few days later	Pain in the left leg followed by stiffness and progressive weakness
Following months	Progressive difficulty walking
6 months	Impaired balance, frequent falls, difficulty climbing and descending stairs
Later course	Involuntary movements of the left arm and impaired fine motor control
At presentation	Severe gait impairment and spastic hemiparesis

Investigations

Laboratory Studies:
Routine biochemical analyses, tumor markers, thyroid hormone levels, virusologic serology, antinuclear antibodies and paraneoplastic antibodies testing were within reference ranges.
Lumbar puncture with cytochemical, virological, and immunological cerebro-spinal fluid (CSF) analysis yielded normal results.
Neuroimaging:
Magnetic resonance imaging (MRI) of the cervical and thoracolumbar spine demonstrated disc herniations at the C6/C7 and T7/T8 levels without evidence of myelopathy.
MRI of the brain with intravenous contrast was normal.
To exclude lumbosacral plexopathy of compressive or infiltrative origin, computed tomography (CT) of the abdomen and pelvis was performed and revealed no abnormalities.
A blood analysis revealed paraproteinemia.

Electrophysiological Studies:
Initial EMG suggested chronic radicular lesions of moderate severity involving C4–C7 and L4–L5–S1 roots bilaterally. A repeat EMG demonstrated widespread chronic neurogenic changes:
Left m. extensor digitorum brevis**:** rare fibrillations and severe chronic neurogenic lesion with rare remaining motor units
Right side**:** pronounced denervation activity at rest with severe chronic neurogenic changes
Bilateral m. tibialis anterior**:** frequent fibrillations and positive sharp waves; repetitive high-frequency discharges on the left
Bilateral m. vastus medialis**:** denervation activity and high-frequency discharges; occasional fasciculations on the right

Left arm muscles**:** increased insertional activity with rare fibrillations; moderate-to-severe chronic lesion in m. abductor pollicis brevis
Trunk muscles**:** increased insertional activity, otherwise unremarkable
These findings indicated widespread chronic neurogenic changes of varying severity.
Motor evoked potentials showed reduced amplitudes in the left median, ulnar, peroneal, and tibial nerves, and in the right tibial nerve. F-wave latency was prolonged in the left peroneal nerve. Sensory nerve conduction parameters were within physiological limits.
Genetic testing for spinocerebellar ataxias was negative.

Table 2. Summary of Clinical and Diagnostic Findings

Category	Findings
Motor	Progressive unilateral spastic hemiparesis
Reflexes	Hyperreflexia, Babinski sign, clonus
Sensory	Intact
MRI	No myelopathy
CSF	Normal
EMG	Widespread chronic denervation
Other findings	Paraproteinemia

Differential Diagnosis

Given the unilateral presentation and spastic features, the patient was initially evaluated for:
Cervical or thoracic myelopathy
Radiculopathy
Lumbosacral plexopathy
Inflammatory or infectious myelitis
Paraneoplastic syndromes
Spinocerebellar ataxias
Neuroimaging excluded compressive or structural myelopathy. CSF analysis showed no inflammatory or infectious process. Genetic testing ruled out spinocerebellar ataxias. Sensory nerve conduction studies were normal, arguing against peripheral neuropathy or plexopathy.
The progressive course, absence of sensory deficits, and combination of UMN signs with EMG-confirmed chronic denervation ultimately supported a motor neuron disease.
The differential diagnosis and reasons for exclusion are summarized in Table 3.

Table 3. Differential Diagnosis and Exclusion Criteria

Condition	Reason for Consideration	Reason for Exclusion
Cervical/thoracic myelopathy	Spastic weakness and gait impairment	No spinal cord compression on MRI
Radiculopathy	Initial pain and disc herniation	Symptoms extend beyond single root distribution
Lumbosacral plexopathy	Lower limb weakness	Normal sensory conduction studies
Inflammatory/infectious myelitis	Subacute onset with systemic symptoms	Normal CSF findings
Paraneoplastic syndrome	Presence of paraproteinemia	Negative paraneoplastic antibodies and imaging
Spinocerebellar ataxia	Gait disturbance	Negative genetic testing

Discussion

This case demonstrates a rare hemiplegic presentation of ALS consistent with Mills' syndrome [4,5]. The defining features include progressive unilateral spastic hemiparesis, preservation of sensory function, and electrophysiological evidence of widespread lower motor neuron involvement [5,7]. The early presentation with back and limb pain may have contributed to initial consideration of radiculopathy or disc disease, particularly given the MRI findings of disc protrusions. However, the absence of myelopathic changes and the progressive involvement beyond a single root distribution argued against a purely compressive etiology [2,6].

The widespread chronic neurogenic changes on EMG, combined with reduced motor evoked potentials and preserved sensory conduction, are characteristic of ALS and are emphasized in current electrophysiological diagnostic frameworks [3,8]. The slow progression and hemibody predominance align with previously described cases of Mills' variant [4,5].

The presence of paraproteinemia is noteworthy but, in the absence of clinical or laboratory evidence of a plasma cell disorder causing neuropathy or myelopathy, was considered incidental [9]. This case further emphasizes the importance of considering atypical ALS variants in patients with asymmetric motor presentations.

Conclusion

This case highlights the diagnostic challenges posed by unilateral, slowly progressive motor symptoms. Comprehensive clinical, radiological, laboratory, and electrophysiological evaluations excluded alternative etiologies. The combination of progressive unilateral spastic hemiparesis, preserved sensory function, and widespread chronic denervation supported the diagnosis of the hemiplegic variant of ALS (Mills' syndrome) [4,5].

Early recognition of this rare phenotype is crucial for appropriate counseling, monitoring, and management [1,3].

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NATURAL AKSIL AS ADSORBENT FOR REMOVAL OF HEXAVALENT CHROMIUM FROM WATER RESOURCES: EQUILIBRIUM AND KINETICS

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Abstract

One of the most important problems today is the pollution of water resources with heavy metals, especially pollution with hexavalent chromium. The removal of Cr(VI) from wastewater is important due to its toxicity to living organisms and the environment. For this reason, in this paper we have focused on the removal of Cr(VI) ions using a natural mineral adsorbent such as aksil (Kriva Palanka). Adsorption experiments were conducted at room temperature, at different initial concentrations of Cr(VI) ions and different amounts of adsorbent. The results obtained from this work have been used to model the balance of the adsorption process, through several adsorption isotherms, using the MATLAB software package. For the equilibrium analysis of the adsorption system Cr(VI) with aksil, the following adsorption isotherms were applied: Langmuir, Freundlich, Langmuir-Freundlich and Redlich-Peterson. In order to define the kinetics of the investigated Cr(VI)-aksil system, these models have been applied: I and II order, pseudo I and pseudo II order and model of Elovic.

Keywords: hexavalent chromium, aksil, wastewater, adsorption, kinetics.

Introduction

Environmentally responsible wastewater disposal requires a reduction in the concentration of Cr(VI), up to its complete elimination. In this direction, numerous techniques have been developed for the removal of hexavalent chromium from wastewater, such as: adsorption, Advanced Oxidation Processes (AOPs), nanofiltration (NF), reverse osmosis (RO), ion exchange with resins and the use of membrane systems. The negative sides of these techniques are incomplete removal, high energy requirements, generation of toxic waste and large capital and investments (Babel *et* al., 2007). In recent years, adsorption has emerged as an alternative method for the removal of metal ions from wastewater, including Cr(VI). To reduce capital costs, extensive research has been conducted into the use of cheaper adsorbents, which can be various types of earths and clays (Gupta et al., 2001). Various minerals have been used suche as: carbonized eggshells (Berihu et al., 2026), walnut-derived biosorbents (Rajni et al., 2023), activated carbon (Wang et al., 2023), eucalyptus tereticornis bark (Sharma et al., 2011), powdered leaves of Prosopis cineraria (Soleimani et al., 2024), unmodified and modified biomass (Tripathi et al., 2024), green algae (Valli et al., 2013). The use of materials in solid form to remove certain substances from gases and liquid solutions is a process known as adsorption and in essence this process involves the distribution of substances from gas or liquid phase on the surface of a solid substrate, this process is most widely used for separation and purification purposes. In this process, the substances used for adsorption, in this case, change the concentration of heavy metals. An adsorbent is a solid body on which adsorption takes place, while the adsorbate is the substance that is adsorbed. In terms of the molecular layers that are created during adsorption, we have polymolecular adsorption. The division into physical and chemical adsorption is also known and they refer to the actions of the adsorbate molecules in relation to the surface of the adsorbent. In chemical adsorption, we have the formation of a chemical bond, while in physical adsorption, we have the appearance of the action of Van der Waals forces (Chamarthy et al., 2001).

Materials and Methods

2.1 Adsorbent: To investigate the removal of hexavalent chromium from polluted waters in this work, we have used aksil (trade name/natural mineral complex). The adsorbent is mechanically prepared in a ball mill until granulation occurs, with the 0,25-0,5 mm fraction dominates. Aksil is a sedimentary complex sample with significant presence of amorphous SiO_2. The macroscopic image of the aksil is shown in Figure 1.



Figure 1. Aksil

The results of the scanning electron microscopy of the material-aksil show the presence of particles in various irregular shapes and dimensions in which there are no pores.
The morphological characteristics of the aksil with the Electronic Scanning Microscope are shown in Figure 2.

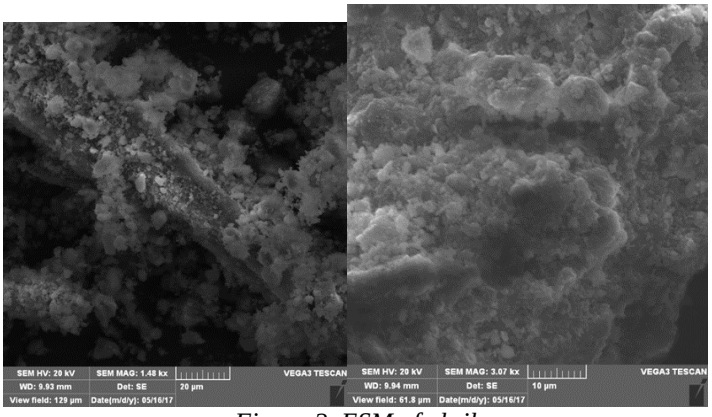


Figure 2. ESM of aksil

2.2 Adsorption experiment: A series of experiments were conducted in order to define the equilibrium and kinetics of the Cr(VI) ion separation process. The working mineral raw material that is the subject of the research of this paper was examined in a batch, laboratory reactor with a volume of 2,5 dm3, at room temperature, at a constant mixing mode of 500 rpm with a magnetic stirrer, during which the effect of the following operating parameters was monitored: pH of the medium (1, 2), initial concentration of Cr(VI) ions (0.3, 0.4, 0.5, and 0.6 mg/l), adsorption time (5, 10, 20, 30, 60, 90, 120 and 180 minutes), concentration of adsorbent (0.5; 1.5; 2.5; 3.5; 4.5; and 5.5 g/l). Aqueous solution of K2Cr2O7 was used to prepare the standard solutions.

Results and Discussion

The decrease in the concentration of chromium ions, with the adsorption time, for different initial concentrations, is given in Figure 3,4. From the diagrams, a similar effect of contact time on the change in the concentration of Cr (VI) ions can be observed for used adsorbent. For all tested initial metal concentrations, rapid adsorption occurs in the first 30 min and maximum efficiency in the removal of Cr(VI) ions is achieved.

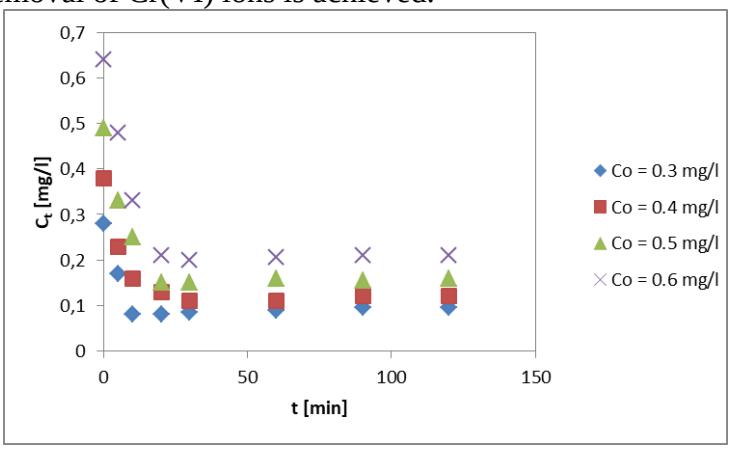


Figure 3. Dependence of Cr(VI) concentration from time of adsorption for the system Cr(VI)-aksil, pH=1

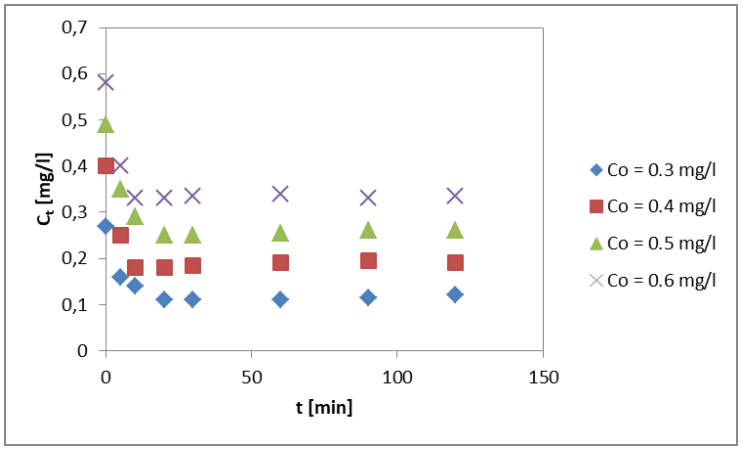


Figure 4. Dependence of Cr(VI) concentration from time of adsorption for the system Cr(VI)-aksil, pH=2

From the figures it can be seen that, adsorption equilibrium is reached in about 30 min. After this adsorption time, there is almost no change in the adsorbed amount of the tested adsorbate.

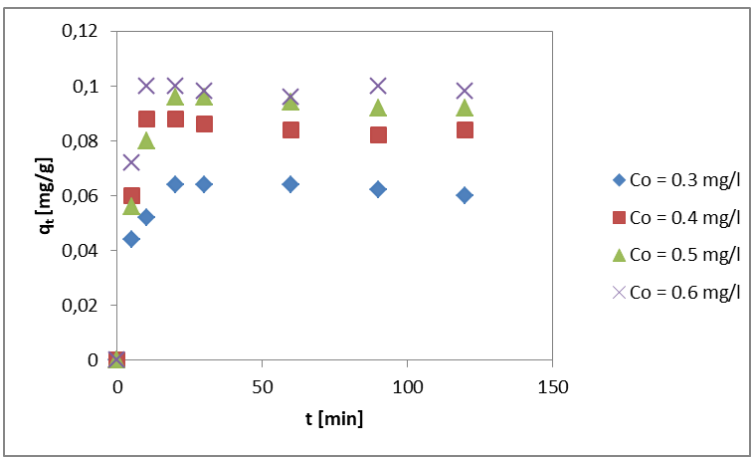


Figure 5. Dependence of adsorbed amount from time of adsorption for the system Cr(VI)-aksil pH=2

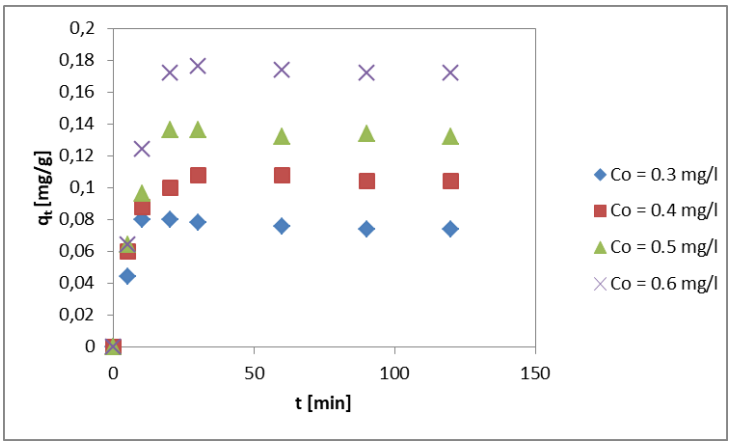


Figure 6. Dependence of adsorbed amount from time of adsorption for the system Cr(VI)-aksil pH=1

From the presented graphical dependences for the change in adsorption capacity with time, it is evident that at lower pH values, due to the phenomenon of protonation on the surface of the adsorbent, rapid adsorption occurs in the first 20-35 minutes.

Adsorption isotherms describe the equilibrium of the adsorbed material on the surface of the adsorbent. In this paper, the Langmuir, Freundlich, Langmuir-Freundlich and Redlich-Peterson isotherms are used in order to predict the adsorption behavior of Cr(VI) in aksil as an adsorbent. The diagram of the adsorption isotherms for the examined system is given in Figure 7. The fitting of the experimental results was performed using the MATLAB/Curve Fitting Toolbox software package. Table 1 presents the data resulting from the examination of the adsorption isotherms. The values of the model parameters are given as well as the values of the correlation coefficients, R^2.

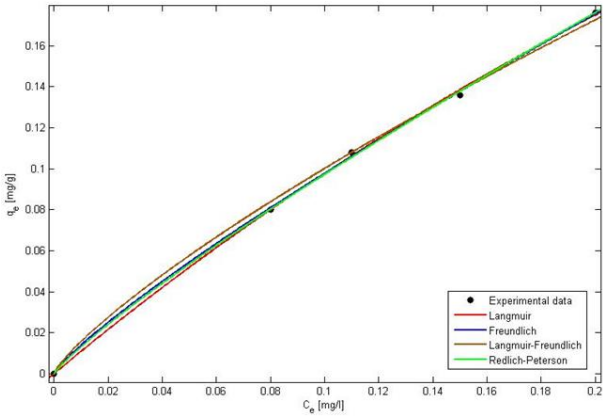


Figure 7. Adsorption isotherms for the adsorption of Cr(VI) with aksil

Table 1. Equilibrium isotherm parameters for the adsorption of Cr(VI) by aksil

Isotherm	Parameters and correlation coefficients	Aksil
Langmuir	q_m [mg/g]	0,1942
	K_L [l/mg]	21,34
	R^2	0,9972
Feundlich	K_F [l/g]	0,2571
	n	2,247
	R^2	0,9994
Langmuir-Freundlich	q_m [mg/g]	1,632
	K_C [l/mg]	0,1478
	n	1,72

	R^2	0,9853
Redlich-Peterson	K_{RP} [l/g]	92,408
	A [l/mg]	657
	β	0,458
	R^2	0,9985

The values of the parameters and correlation coefficients for the Cr(VI)-aksil system are given in Table 1. The correlation coefficient is the parameter according to which we select the isotherm that best matches the experimental results. From this Table we can conclude that the value of the correlation coefficient for the Freundlich isotherm is 0.9994. Accordingly, the Freundlich isotherm model is the better for fitting the experimental data compared to other isotherm models for the sorbent aksil.

The kinetics of Cr(VI) were analyzed using the following kinetic models: I and II order, pseudo I and pseudo II order and model of Elovic. The agreement between experimental and model values is expressed by the correlation coefficient R^2. The largest value of R^2 for a kinetic model means that model successfully describes the kinetic adsorption of Cr(VI).

From Table 2, it can be seen that the correlation coefficient R^2 has the highest value for the given pseudo II order model, from here we can conclude that the kinetic adsorption of Cr(VI) by aksil can be described by the pseudo II order model.

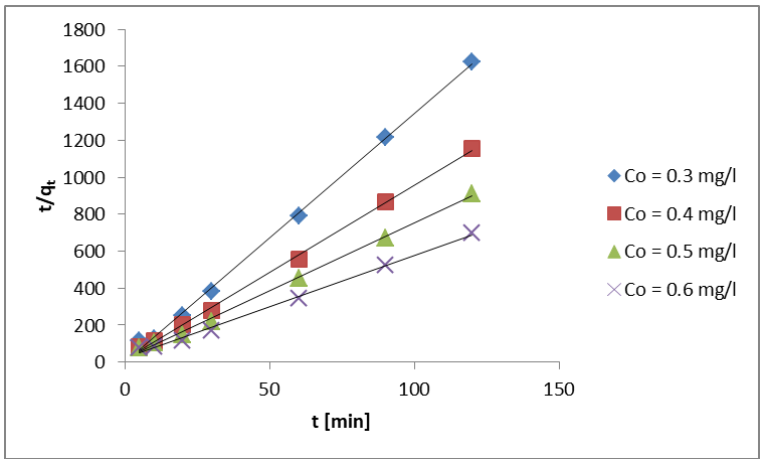


Figure 8. Pseudo II order kinetic model, Cr(VI)-aksil, pH=1

Table 2. Kinetic adsorption parameters, Cr(VI)-aksil, pH=1

Kinetic models	Parameters	A metal ion Cr(VI)			
	C_0,екс. [mg/l]	0,3	0,4	0,5	0,6
	q_e,екс. [mg/g]	0,08	0,108	0,136	0,176
I - order	k_1 [min^{-1}] C_0 [mg/l] R^2	0,0042 0,1310 0,171	0,0062 0,1997 0,3825	0,0065 0,2736 0,3965	0,0068 0,3727 0,4242
II - order	k_2 [l/mg·min] C_0 [mg/l] R^2	0,0261 0,1149 0,122	0,0349 0,1815 0,4164	0,0268 0,2472 0,4021	0,0213 0,3374 0,4397

Pseudo I order	k_1 [min^{-1}] q_e [mg/g] R^2	0,0169 0,0229 0,3317	0,0221 0,0379 0,6895	0,032 0,0697 0,821	0,0293 0,0518 0,5472
Pseudo II order	k_2 [g/mg·min] q_e [mg/g] R^2	7,2553 0,0744 0,9984	6,1857 0,1064 0,9985	2,7879 0,1367 0,9976	1,4510 0,1799 0,9955
Elovic	α [mg/g·min] β [mg/g] R^2	76,1573 178,57 0,265	1,0803 81,9672 0,6796	0,2826 51,0204 0,6692	0,1555 33,4448 0,6809

Research on the kinetics of the Cr(VI)-aksil system has also been done at pH=2, from which we can conclude that the correlation coefficient R^2 has a higher value in the given pseudo II order model, from here we can conclude that the kinetics of Cr(VI) adsorption with aksil at pH=2 can be described by the pseudo II order model. The results for the Cr(VI)-aksil system at pH=2 are given in Figure 9 and Table 3.

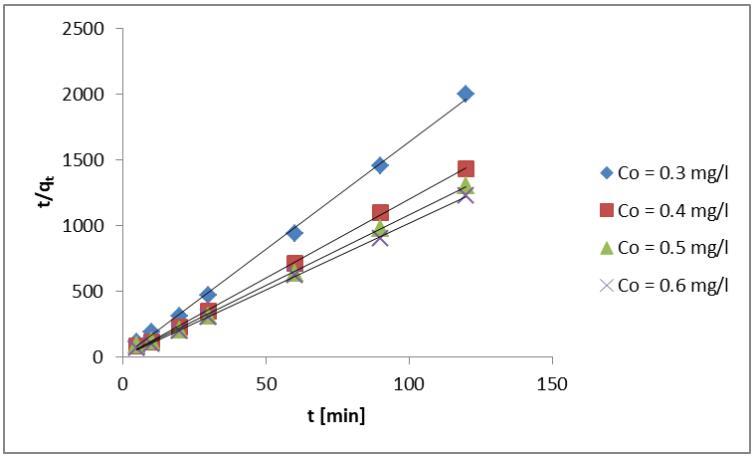


Figure 9. Pseudo II order kinetic model, Cr(VI)-aksil, pH=2

Table 3. Kinetic adsorption parameters, Cr(VI)-aksil, pH=2

Kinetic models	Parameters	A metal ion Cr(VI)			
	C_0,екс. [mg/l]	0,3	0,4	0,5	0,6
	q_e,екс. [mg/g]	0,064	0,088	0,096	0,1
I - order	k_1 [min^{-1}] C_0 [mg/l] R^2	0,0037 0,1579 0,2758	0,0027 0,2387 0,1884	0,003 0,3312 0,3007	0,0022 0,4001 0,2309
II - order	k_2 [l/mg·min] C_0 [mg/l] R^2	0,0233 0,1493 0,2861	0,0103 0,2270 0,1781	0,009 0,3205 0,3129	0,0052 0,3903 0,2409
Pseudo I order	k_1 [min^{-1}] q_e [mg/g] R^2	0,0207 0,0265 0,7259	0,0187 0,0229 0,396	0,0244 0,0357 0,6592	0,0265 0,0266 0,5556

Pseudo II order	k_2 [g/mg·min] q_e [mg/g] R^2	0,2483 0,0613 0,998	0,2534 0,0835 0,9992	0,0120 0,0933 0,9988	0,0169 0,0990 0,9994
Elovic	α [mg/g·min] β [mg/g] R^2	0,0106 200 0,5637	$3{,}91 \cdot 10^4$ 238,095 0,2511	3,1988 106,38 0,5674	$7{,}96 \cdot 10^3$ 185,185 0,3799

Conclusions

This paper examines the removal of Cr(VI) from water resources using aksil. An aqueous solution of $K_2Cr_2O_7$ was used to prepare the working solutions. To determine the concentration before and after the Cr(VI) adsorption process, an atomic adsorption spectrophotometric method and UV/VIS Spectrophoto-meter were used. A series of experiments were conducted in order to define the equilibrium and kinetics of the Cr(VI) ion separation process. The working mineral raw material that is the subject of the research of this paper was examined in a batch, laboratory reactor with a volume of 2,5 dm^3, at room temperature, at a constant mixing mode of 500 rpm with a magnetic stirrer, during which the effect of the following operating parameters was monitored: pH of the medium (1,2), the initial concentration of Cr(VI) ions (0.3, 0.4, 0.5 and 0.6 mg/l), adsorption time (5,10,20,30,60,90,120 and 180 minutes), adsorbent concentration (0.5; 1.5; 2.5; 3.5; 4.5; and 5.5 g/l). To describe the adsorption equilibrium, we used the following adsorption isotherms: Langmuir, Freundlich, Langmuir- Freundlich and Redlich-Peterson using the MATLAB/Curve Fitting Toolbox software package. From the experimental values in this paper we can conclude that the value of the correlation coefficient for the Freundlich isotherm is 0.9994. Therefore, the Freundlich isotherm model is better for fitting the experimental data compared to other isotherm models for the sorbent aksil. From the kinetic adsorption parameters it can be seen that the correlation coefficient R^2 has the highest value for thr given pseudo II order model, from here we can conclude that the kinetic adsorption of Cr(VI) with the working raw materials can be better described by the pseudo II order model.

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INTEGRATED NON-INVASIVE VASCULAR PHENOTYPING USING ANKLE-BRACHIAL INDEX (ABI) AND PULSE WAVE VELOCITY (PWV) FOR EARLY DETECTION OF SUBCLINICAL ATHEROSCLEROSIS. BRIDGING EVIDENCE FROM COMPREHENSIVE LITERATURE REVIEW AND CASE-BASED CLINICAL EVALUATION

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Abstract

Cardiovascular disease remains the leading global cause of morbidity and mortality, often preceded by a prolonged subclinical phase characterized by early vascular alterations. This study aims to evaluate the clinical utility of integrated non-invasive vascular phenotyping using ankle–brachial index (ABI) and pulse wave velocity (PWV) for the early detection of subclinical atherosclerosis, combining a comprehensive literature review with a case-based clinical evaluation.

A 36-year-old male with cardiometabolic risk factors, including smoking, physical inactivity, and dyslipidemia, underwent detailed vascular assessment using a four-limb oscillometric system (BPlab® with Vasotens®). Despite normal findings on conventional cardiovascular testing—including ECG, echocardiography, and exercise stress testing—advanced vascular evaluation revealed subtle abnormalities. ABI values were within the upper-normal range on the right (1.28) but elevated on the left (1.44), suggesting increased arterial stiffness rather than overt peripheral arterial disease. PWV analysis demonstrated mildly increased brachial–ankle and aortic PWV, while carotid–femoral PWV remained within normal limits, indicating early peripheral arterial stiffening. Central hemodynamic parameters were preserved, although wave reflection indices suggested early vascular functional changes.

These findings highlight the discordance between standard diagnostic approaches and advanced vascular biomarkers, emphasizing the added value of combined structural (ABI) and functional (PWV) assessment. The observed vascular phenotype is consistent with early vascular aging associated with cardiometabolic dysregulation.

In conclusion, integrated vascular phenotyping enhances early detection of subclinical vascular disease, improves cardiovascular risk stratification, and may guide timely preventive interventions, particularly in younger individuals with modifiable risk factors.

Keywords: Ankle–brachial index; Pulse wave velocity; Subclinical atherosclerosis; Arterial stiffness; Vascular phenotyping

Introduction

The cardiovascular disease remains the leading global cause of morbidity and mortality, with pathological vascular alterations developing insidiously and often undetected during a prolonged subclinical phase that may precede overt clinical events by many years (WHO, 2025; Fuster et al., 2024). In this instances identifying subclinical markers of atherosclerosis is essential for timely diagnosis and intervention.

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis that affects over 200 million people worldwide, particularly older adults and those with diabetes, smoking history, or chronic kidney disease (Zemaitis et al., 2026). Nearly half (42.6%) residing in low- and middle-sociodemographic regions (GBD 2019 and Injuries collaborators, 2020).

The overall global prevalence is estimated at 1.52%, rising markedly with advancing age, reaching nearly 15% among individuals aged 80–84 years, and demonstrating a higher prevalence in females compared to males within the same age group (18.03% vs. 10.56%) (Lin et al., 2022; GBD 2019 Peripheral artery disease collaborators, 2023).

This condition results from progressive arterial narrowing and stiffness most often in the aortoiliac, femoropopliteal, and infrapopliteal segments, leading to reduced or impaired blood flow to the lower extremities and it is associated with a substantially increased risk of major adverse cardiovascular events (MACE), including myocardial infarction (MI), stroke and cardiovascular mortality, reflecting the diffuse nature of atherosclerotic disease. Early detection of vascular damage, arterial stiffness, subclinical atherosclerosis, and cardiovascular risk is critical for effective prevention and management of cardiovascular diseases (CVD), but PAD remains underdiagnosed and untreated, largely due to its frequently asymptomatic or atypical presentation. Consequently, early identification through non-invasive diagnostic tools, such as the ABI, is essential for timely risk stratification and implementation of preventive and therapeutic strategies.

Non-invasive vascular biomarkers such as the ABI, PWV (including aPWV (aortic), baPWV (brachial-ankle) and cfPWV (carotid-fermoal)), central aortic pressure (CAP), and related arterial stiffness parameters have emerged as valuable tools for identifying individuals at increased risk before overt clinical disease develops.

- **Ankle–Brachial Index (ABI)** is calculated as the ratio of systolic blood pressure at the ankle to that at the brachial artery on each side. It is highly specific for PAD diagnosis when measured by Doppler ultrasound but can also be assessed using oscillometric or automated devices with varying sensitivity/specificity (Fendrik et al., 2023; Stone et al. 2023).
  Normal ABI ranges from 0.90 to 1.40 and PAD is defined as an ABI of 0.90 or less (Mazzolai et al., 2024; Aboyans et al., 2012). Patients with ABI 0.70 to 0.90 are categorized as mild PAD and typically are asymptomatic or present with intermittent claudication (Birkett et al., 2021). Those with ABI 0.50 to 0.70 have moderate PAD and typically present with more frequent claudication and reduced walking distance (Gommans et al., 2014). An ABI of less than 0.50 indicates severe PAD or chronic limb-threatening ischemia (CLTI) and often presents with ischemic rest pain, non-healing wounds, or tissue loss (Sprengers et al., 2010). Values greater than 1.40 may indicate non-compressible, calcified arteries, often seen in patients with diabetes or chronic kidney disease (Zemaitis et al., 2026; Mazzolai et al., 2024). In such cases, the ABI value is unreliable, and alternative testing like for example the toe-brachial index (TBI) or duplex ultrasound, is required to evaluate for PAD (Aboyans et al., 2012; Collins et al., 2007). The TBI, which is less affected by arterial calcification, provides a more accurate assessment; a TBI of less than 0.70 suggests the presence of PAD (Mazzolai et al., 2024; Collins et al., 2007; Suzuki et al., 2024).
- **Pulse Wave Velocity (PWV)** is an important and well-established measure of arterial stiffness that is strongly associated with aging and the faster the pulse wave travels between two points (e.g., carotid-femoral or brachial-ankle), the stiffer the arteries (Laurent et al., 2006). PWV, particularly cfPWV and baPWV, is widely recognized as a gold-standard measure of arterial stiffness and an independent predictor of CVD events across diverse populations (Zemaitis et al., 2026 ; Fendrik et al., 2023; Kim et al., 2019). In a landmark study by the Reference Values for Arterial Stiffness' Collaboration in 2010, normative values for pulse wave velocity (PWV) were established in a large population-based cohort (Reference Values for Arterial Stiffness' Collaboration, 2010). The authors reported a mean PWV of 6.0 m/s (95% CI 5.8–6.1), demonstrating a significant increase in PWV with advancing age and higher blood pressure categories (both $p < 0.001$). While no sex-related differences were observed in normotensive individuals, women exhibited significantly higher PWV values compared to men in the hypertensive subgroup (>140/90 mmHg;

p=0.005). Additionally, interpercentile ranges were narrower in individuals younger than 55 years, whereas greater variability and higher upper limits of PWV were observed in participants aged ≥55 years, particularly among those with elevated blood pressure (Reference Values for Arterial Stiffness' Collaboration, 2010); Van Hout et al., 2021). Beyond its role as a marker of arterial stiffness, PWV has substantial clinical relevance. Evidence indicates that increased PWV is independently associated with subclinical target organ damage, including coronary artery calcification, cerebral white matter hyperintensities, and albuminuria (Reference Values for Arterial Stiffness' Collaboration, 2010); ; Kim et al., 2019; Van Hout et al., 2021). Importantly, PWV also predicts future cardiovascular events and all-cause mortality, even after adjustment for traditional cardiovascular risk factors (Fuster et al., 2024; Zemaitis et al., 2026; Vlachopoulos et al., 2019; Ohkuma et al., 2017; Claessens et al., 2023).

In parallel, growing attention has been directed toward central hemodynamic parameters. **Central aortic systolic blood pressure** provides a more direct estimate of left ventricular afterload compared with peripheral blood pressure measurements (Williams et al., 2006). Furthermore, pulse wave analysis enables the assessment of additional indices such as the **augmentation index** and **reflected wave transit time (RWTT)**, which reflect the timing and magnitude of wave reflections and are associated with early vascular alterations (Mitchell et al., 2010). However, their routine clinical application still requires further validation in large-scale prospective studies.

The combined assessment of ABI and PWV enhances risk stratification for adverse cardiovascular outcomes compared with either marker alone. This integrated approach is particularly valuable in high-risk populations, including patients with diabetes mellitus or acute myocardial infarction, where the coexistence of structural (atherosclerotic burden) and functional (arterial stiffness) vascular abnormalities confers additive prognostic significance.

In the context of the present case, this dual evaluation allowed a more nuanced interpretation of vascular status, highlighting the interplay between PAD and increased arterial stiffness, which may otherwise remain underrecognized if assessed in isolation.

Beyond this, a comprehensive vascular phenotyping strategy incorporating ABI, PWV, central aortic pressure and RWTT enables simultaneous evaluation of macrovascular obstruction and arterial stiffness. This multidimensional approach improves early detection of subclinical vascular disease and refines cardiovascular risk prediction beyond traditional factors. In our patient, the integration of this parameters provided a more detailed characterization of vascular function and structure, offering clinically relevant insights that may inform individualized preventive and therapeutic strategies.

Such findings underscore the potential value of incorporating advanced vascular assessment into routine clinical practice, particularly in complex or high-risk cases where conventional evaluation may underestimate the true burden of vascular disease.

Case presentation

A 36-year-old male patient presented for cardiovascular evaluation with intermittent left lower limb tingling and episodic palpitations, described as brief, self-limited, and not previously documented on electrocardiography. His cardiovascular risk profile included active smoking, physical inactivity, and overweight status (BMI 26.7 kg/m²).

On physical examination, vital parameters were within normal limits: blood pressure 128/77 mmHg, heart rate 94 bpm, and oxygen saturation 97%. No signs of overt cardiovascular or peripheral vascular disease were observed on routine clinical examination. Resting 12-lead ECG demonstrated sinus rhythm, left axis deviation, and a PR interval of 0.20 s (upper limit of normal), with normal QRS duration, isoelectric ST segments, and normal QT interval.

Ambulatory rhythm monitoring (Holter ECG) revealed a second-degree atrioventricular block (Mobitz type I, Wenckebach) occurring during sleep, a finding generally considered benign and often associated with increased vagal tone, particularly in physically conditioned individuals. Exercise stress testing was clinically and electrically negative for ischemia, with the patient achieving maximal predicted workload. Isolated ventricular extrasystoles (VES) were observed during the recovery phase without clinical significance.
Transthoracic echocardiography demonstrated normal cardiac structure and function, with a preserved left ventricular ejection fraction (LVEF) of 67%, normal chamber dimensions, and no evidence of diastolic dysfunction. A localized chronic pericardial thickening, more pronounced at the apical region, was noted without hemodynamic compromise.
Laboratory findings revealed largely preserved metabolic and organ function parameters, with some notable findings: Glucose: 6.6 mmol/L (borderline elevated), HbA1c: 5.7% (upper-normal range, suggestive of prediabetes), Triglycerides: 4.2 mmol/L (elevated), HDL cholesterol: 1.0 mmol/L (low) , LDL cholesterol: 3.1 mmol/L, Uric acid: 421 µmol/L (borderline elevated), ALT: 64 U/L and GGT: 149 U/L (elevated, suggestive of possible hepatic/metabolic involvement) , Inflammatory markers (CRP), renal function (creatinine 77 µmol/L), electrolytes, and hematological indices were within normal limits. These findings indicate a metabolic risk profile consistent with early cardiometabolic dysfunction.

Vascular Assessment, ABI and Pulse Wave Analysis protocol



Fig.1 BPlab® device with Vasotens® Office+ software

A comprehensive vascular evaluation was performed using the BPlab® device with Vasotens® Office+ software, which enables simultaneous non-invasive assessment of ankle–brachial index (ABI), pulse wave velocity (PWV), central blood pressure, and wave reflection indices. The system is consisted of a measurement module, four cuffs, four hoses, power supply unit, USB cable, dongle, and TensOffice+ software. The system was connected to a PC via USB, with the software activated using the supplied dongle. After connecting the hoses according to the device markings, correct system readiness was confirmed by the green indicator lights (see figure 1).
The patient was examined in a supine position, barefoot, with both arms and ankles exposed (fig.2). Before cuff placement, upper-arm and ankle circumferences were measured to ensure correct cuff size. Arm cuffs were positioned with the arrow directed toward the brachial artery, ensuring they were neither too tight nor too loose. Ankle cuffs were then applied according to the measured ankle circumference.
In the first step of the protocol anthro-pometric distances were measured according to the device protocol, including the distance from the sternal notch to the os pubis (La), sternal notch to the middle of the brachial cuff (Lb), from the sternal notch to the femoral artery (Lc), and from the femoral artery to the middle of the ankle cuff (Ld) (fig. 3). The patient remained resting in the supine position for several minutes before measurement. Speaking or movement during the procedure was avoided, as these may affect signal quality and cause erroneous results, particularly in the presence of arrhythmia.



In the first measurement phase, arm and ankle cuffs were inflated simultaneously on both sides. The system recorded: *systolic blood pressure, diastolic blood pressure, ankle–brachial index, ABI classification, reflected wave transit time, aortic blood pressure, and aortic pulse wave velocity.*

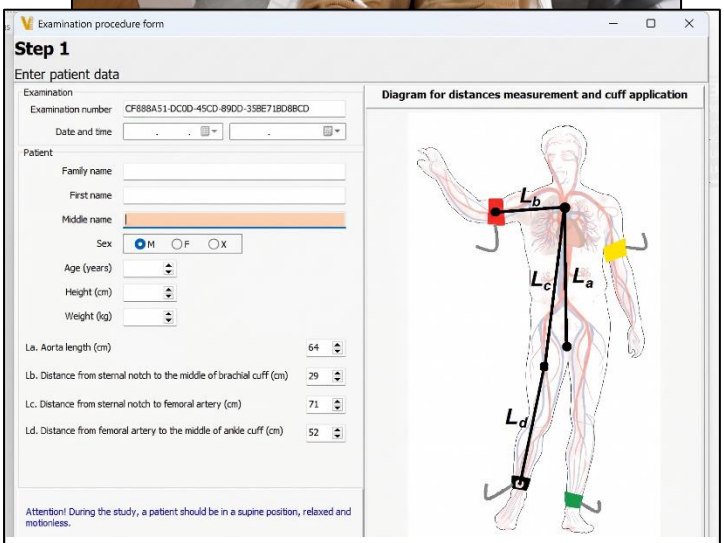


Fig.3 Measuring anthropometric distances before initiating the procedure according to the device protocol. **La** (distance from the sternal notch to the os pubis) **Lb**

In the second phase, simultaneous pulse wave analysis of all four limbs was performed using volume sphygmography. The target cuff pressure corresponded to the previously measured diastolic pressure of each limb. Pulse waves were recorded online until satisfactory signal quality was achieved. This phase provided right and left brachial–ankle pulse wave velocity, estimated carotid–femoral pulse wave velocity, and estimated aortic pulse wave velocity.

After completion, the software generated a detailed editable medical report, including ABI and arterial stiffness parameters (fig.5).

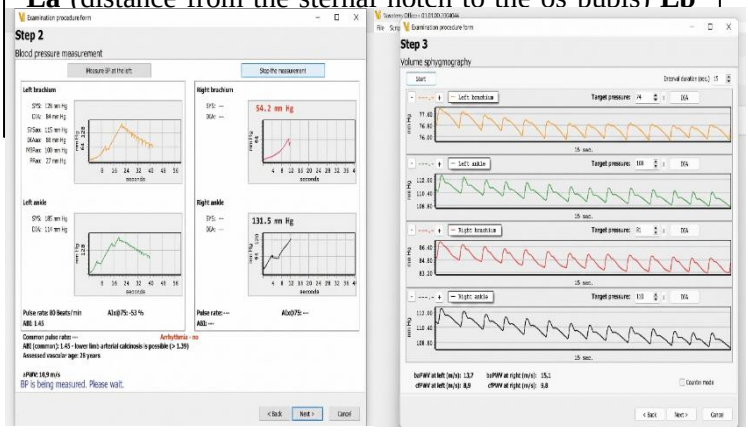


Fig.4 (A) Step 2, simultaneous four-limb blood pressure measurement. (B) Step 3, pulse waveforms from four limbs indicating reliable volume sphygmography.

Hemodynamic and vascular parameters were assessed using simultaneous four-limb oscillometric measurement. Brachial blood pressure values were within the normotensive range, measuring 113/74 mmHg on the right arm and 111/78 mmHg on the left arm, with no clinically significant inter-arm difference (ASYS ≈ 2 mmHg), normal peripheral and central blood pressure, indicating the absence of significant inter-arm asymmetry reached 15 mmHg.

- **ABI results**

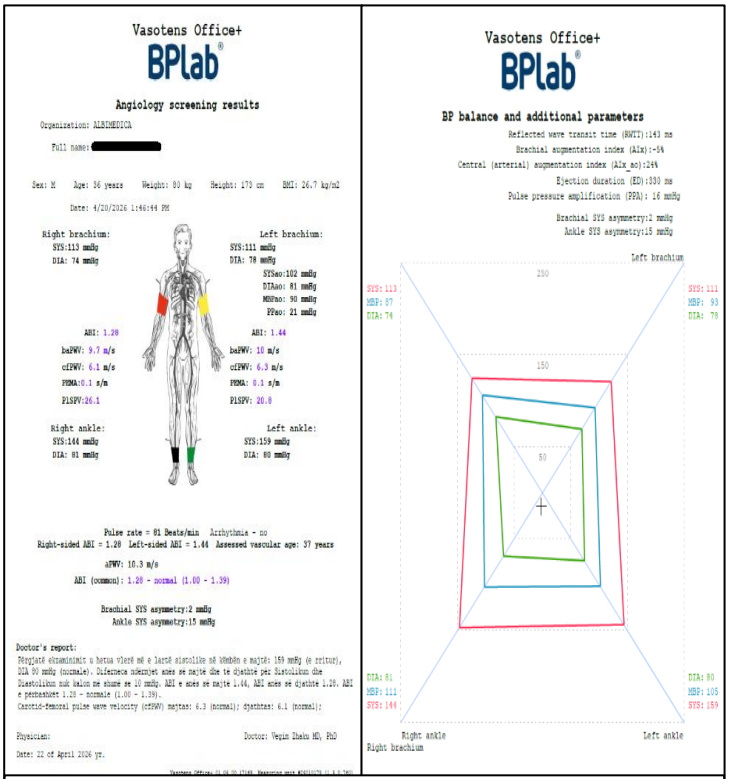


Fig.5 The final report generated by Vasotens/BPLab vascular showing all the parameters.

Ankle systolic blood pressure was higher compared to brachial measurements, as expected physiologically, with values of 144/81 mmHg on the right side and 159/80 mmHg on the left side. The calculated ABI was 1.28 on the right and 1.44 on the left, yielding a mean ABI of 1.28. While the right-sided ABI fell within the normal range (1.00–1.39), the left-sided ABI exceeded the upper normal threshold suggesting increased arterial stiffness, potentially reflecting early medial arterial calcification rather than obstructive peripheral arterial disease.

- **PWV results**

The PWV analysis demonstrated brachial–ankle PWV (baPWV) values of 9.7 m/s on the right and 10.0 m/s on the left (mildly increased values relative to expected norms for age). Estimated carotid–femoral PWV (cfPWV) values were 6.1 m/s and 6.3 m/s for the right and left sides, respectively which is within the normal limits. The calculated aortic PWV (aPWV) was 10.3 m/s. This pattern is consistent with early functional vascular alterations predominantly affecting peripheral arterial segments.

- **Central hemodynamic parameters**

Central hemodynamic parameters (SYSao: 102 mmHg; DIAao: 81 mmHg; PPao: 21 mmHg) were within normal physiological limits, with preserved pulse pressure amplification (PPA: 16 mmHg), suggesting maintained central arterial compliance.

Wave reflection indices revealed a RWTT of 143 ms, consistent with normal arterial elasticity. The brachial augmentation index (AIx: −5%) was within expected values for age, while the central augmentation index (AIx_ao: 24%) was within the normal-to-mildly elevated range. Ejection duration (330 ms) was appropriate for the recorded heart rate.

Additional indices (PEMA: 0.1 s/m bilaterally; PlSPV: 20.8–26.1) were within expected ranges, although their clinical interpretation remains supplementary due to limited standardization.

Overall, the findings are consistent with preserved central hemodynamics and absence of overt peripheral arterial disease, with evidence of early peripheral arterial stiffening**,** particularly reflected by elevated left-sided ABI and mildly increased baPWV/aPWV values.

Discussion

This case reinforces the concept that subclinical vascular dysfunction may be present despite normal findings on conventional cardiovascular testing, highlighting the limitations of standard diagnostic approaches in detecting early-stage vascular disease. The integration of ABI, PWV,

central hemodynamics, and wave reflection indices allowed identification of early vascular remodeling, supporting the paradigm that vascular alterations precede overt clinical manifestations of atherosclerosis by years or even decades.

A central observation in this patient is the discordance between an overall normal ABI and a borderline elevated left-sided ABI (1.44). While ABI values above 1.40 have traditionally been associated with arterial incompressibility, recent evidence suggests that such findings may reflect functional and structural vascular changes related to increased arterial stiffness**,** even in younger populations without advanced calcific disease (McDermott et al., 2010; Ix et al., 2010). Moreover, asymmetrical ABI elevation may indicate regional vascular heterogeneity, a phenomenon increasingly recognized as an early manifestation of vascular dysfunction rather than simply a measurement artifact.

The PWV profile further supports this interpretation. The preservation of cfPWV within normal limits, contrasted with mildly elevated baPWV and aPWV values, reflects a differential involvement of central versus peripheral arterial segments. This pattern aligns with contemporary evidence demonstrating that peripheral muscular arteries may exhibit functional stiffening earlier than central elastic arteries, particularly in individuals with cardiometabolic risk factors (Townsend et al., 2015; Tomizama et al., 2003). Such findings underscore the importance of multi-site PWV assessment, as reliance on a single parameter may underestimate early vascular changes.

Central hemodynamic measurements in this patient were within normal limits; however, the analysis of wave reflection indices provides additional pathophysiological insight. The RWTT of 143 ms and central augmentation index (AIx_ao: 24%), while within expected ranges, may reflect early alterations in arterial wave reflection dynamics, which are sensitive to changes in vascular tone, endothelial function, and arterial geometry (Vlachopoulos et al., 2011; Chirinos et al., 2012). Notably, the relatively low brachial AIx (−5%) is consistent with the patient's age and heart rate, but does not exclude the presence of early vascular dysfunction.

The observed ankle systolic asymmetry (15 mmHg)**,** although not diagnostic of peripheral arterial disease, may represent an early marker of localized vascular impairment. Emerging data suggest that even subclinical inter-limb differences are associated with increased cardiovascular risk and may reflect early atherosclerotic or functional vascular changes (Su e tal., 2014). This reinforces the importance of bilateral assessment in vascular screening protocols.

From a broader perspective, the vascular phenotype observed in this patient is consistent with early vascular aging (EVA), a condition characterized by accelerated arterial stiffening relative to chronological age. EVA has been strongly linked to modifiable risk factors such as smoking, sedentary lifestyle, dyslipidemia, and insulin resistance, all present in this case. Importantly, EVA is increasingly recognized as a critical intermediate stage in cardiovascular disease progression and a potential target for early (Nilson P, 2008; Benetos et al., 2019).

The metabolic abnormalities identified in this patient further support this interpretation. Elevated triglycerides, reduced HDL cholesterol, borderline glycemic status, and hepatic enzyme abnormalities are indicative of early cardiometabolic dysregulation, which is known to contribute to endothelial dysfunction, oxidative stress, and vascular remodeling. These processes play a central role in the pathogenesis of arterial stiffness and subclinical atherosclerosis (Saklayen M, 2018).

Clinically, this case highlights the incremental value of combining structural and functional vascular markers. ABI provides information on arterial obstruction and vessel compressibility, while PWV and wave reflection indices capture arterial stiffness and hemodynamic load. When integrated, these markers offer a comprehensive vascular phenotype, improving early risk stratification beyond traditional scoring systems.

However, several limitations must be acknowledged:

1. The interpretation of novel indices such as PEMA and PlSPV remains constrained by limited validation and lack of standardized reference values.
2. Variability between measurement devices and algorithms may affect reproducibility.
3. The clinical significance of mild asymmetries and borderline abnormalities requires further confirmation in longitudinal studies.

And finally, while this case demonstrates early vascular changes, the absence of long-term follow-up limits conclusions regarding prognostic implications.

Conclusion

This case demonstrates that integrated non-invasive vascular phenotyping provides a sensitive approach for detecting early vascular alterations that are not captured by conventional cardiovascular assessment.

Despite normal routine investigations, the patient exhibited evidence of early peripheral arterial stiffening, vascular asymmetry, and subtle alterations in wave reflection, consistent with an early vascular aging phenotype associated with cardiometabolic risk factors.

These findings emphasize the importance of adopting a multimodal vascular assessment strategy, particularly in younger individuals with modifiable risk profiles. Early identification of subclinical vascular dysfunction offers an opportunity for timely intervention, including lifestyle modification, metabolic optimization, and targeted cardiovascular prevention.

Future research should focus on:

- standardization of emerging vascular indices
- validation of inter-limb asymmetry as a prognostic marker
- integration of vascular phenotyping into routine clinical practice
- and evaluation of cost-effectiveness and outcome-driven strategies

Ultimately, comprehensive vascular assessment has the potential to significantly enhance early detection, risk stratification, and prevention of cardiovascular disease**.**

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BLACKOUT IN THE ELECTRICAL GRID CAUSED BY FLUCTUATIONS OF RENEWABLE ENERGY –CASE STUDY

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Abstract

The rapid integration of renewable energy sources into modern electrical power systems has created new operational challenges for transmission system operators worldwide. Renewable energy sources such as solar and wind power are inherently intermittent and weather-dependent, causing fluctuations in power generation that can significantly affect grid stability. In weak or developing transmission systems, sudden variations in renewable energy production may lead to voltage instability, frequency deviations, power oscillations, and ultimately large-scale blackout events. This paper investigates the impact of renewable energy fluctuations on the electrical grid of North Macedonia, with a particular focus on the role of the transmission system operator, MEPSO. The study analyzes the operational challenges faced by MEPSO during periods of high renewable energy penetration and examines the partial blackout event that occurred on 18 May 2025.The research evaluates the relationship between high photovoltaic generation, low system demand, overvoltage conditions, and transmission instability within the Macedonian power network. According to investigations conducted by ENTSO-E, unusually high voltages in the transmission system contributed to the separation of the 400 kV and 110 kV networks, resulting in the loss of approximately 79% of the country's electrical load. The paper further discusses the technical limitations of traditional transmission infrastructure when integrating large quantities of variable renewable energy sources. Particular attention is given to insufficient reactive power compensation, lack of energy storage systems, reduced system inertia, and inadequate flexibility mechanisms. The study also reviews preventive measures adopted by MEPSO, including temporary disconnection of photovoltaic plants during periods of low demand and excessive solar generation.

Key words: [Keywords]infrastructure.

Introduction

The global transition toward clean and sustainable energy systems has significantly increased the integration of renewable energy sources into national electrical grids. Countries worldwide are investing heavily in solar photovoltaic (PV) systems, wind farms, and other renewable technologies to reduce greenhouse gas emissions and dependence on fossil fuels. However, unlike conventional thermal or hydroelectric power plants, renewable energy sources are characterized by intermittent and variable generation patterns that depend on weather conditions and environmental factors.

This variability introduces serious technical challenges for electrical grid operators responsible for maintaining stable voltage levels, frequency balance, and continuous electricity supply. Rapid fluctuations in renewable energy generation can disturb the equilibrium between production and consumption, causing overloads, instability, and cascading failures across interconnected transmission systems.

North Macedonia has experienced rapid growth in renewable energy investments in recent years, particularly in photovoltaic power plants connected to the transmission and distribution networks. MEPSO, as the national transmission system operator, plays a crucial role in maintaining the stability and reliability of the country's electrical grid. According to MEPSO, more than 80 applications for renewable energy connections totalling approximately 9,000 MW have been submitted, representing a major transformation of the national power system.

Despite the environmental and economic benefits of renewable energy, the increased penetration of variable generation has exposed weaknesses in the existing transmission infrastructure. The partial blackout event of May 2025 demonstrated how excessive voltage

levels and insufficient grid flexibility can threaten system stability under conditions of low demand and high renewable generation.
This paper investigates the causes and consequences of blackout events associated with renewable energy fluctuations in North Macedonia and evaluates possible technical and operational solutions for improving grid resilience.

Renewable Energy and Grid Stability

and hydroelectric plants provide rotational inertia that stabilizes grid frequency during disturbances. In contrast, solar PV systems are connected through power electronic converters that contribute little or no natural inertia to the system.
The increasing penetration of renewable energy can therefore create several technical problems:
Voltage fluctuations
Frequency instability
Reduced system inertia
Reverse power flows
Transmission congestion
Reactive power imbalance
Difficulty in maintaining reserve margins
In North Macedonia, periods of low electricity demand combined with high solar generation create conditions where excess electricity cannot be adequately absorbed by the grid. These situations are especially critical during spring and holiday periods when consumption decreases but solar production remains high.
Modern transmission systems require advanced balancing mechanisms to maintain operational security under these changing conditions.

Overview of the Macedonian Transmission System

The transmission system of North Macedonia forms part of the Continental European interconnected electrical network. The system is operated by MEPSO and consists primarily of:
400 kV transmission lines
110 kV regional transmission network
Interconnection lines with neighbouring countries
High-voltage substations and transformers
National dispatch and control centre’s
The 400 kV network serves as the backbone of the transmission system and provides interconnection with neighbouring Balkan countries. The 110 kV network distributes electricity to regional substations and end consumers throughout the country.
Historically, the system was designed around centralized thermal and hydroelectric generation. However, increasing renewable energy penetration has significantly altered power flow patterns and voltage regulation requirements.
Renewable energy technologies differ fundamentally from conventional synchronous generators. Traditional thermal
The system has recently experienced periods of elevated voltage caused by low electricity demand combined with high reactive power generation from transmission lines and renewable energy sources. According to the ENTSO-E investigation, similar overvoltage conditions had been observed repeatedly before the blackout event

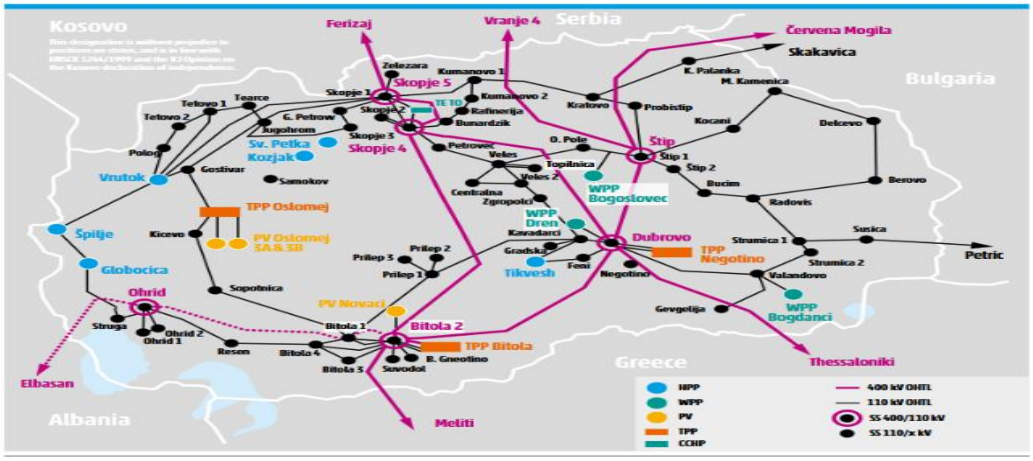


Figure 1 Topology of the transmission system of North Macedonia

Historically, the system was designed around centralized thermal generation and predictable demand patterns. However, the rapid growth of distributed renewable energy generation has introduced operational conditions that were not fully considered in the original network design. According to MEPSO reports, maintaining voltage stability has become increasingly challenging due to variable renewable production and changing electricity flow patterns.

Case Study: The 18 May 2025 Blackout

On 18 May 2025, North Macedonia experienced a significant disturbance in its electrical transmission system that resulted in a large-scale blackout affecting most consumers connected to the 110 kV network.
According to the investigation conducted by ENTSO-E, unusually high voltages were observed in the Macedonian transmission network before the event occurred. The overvoltage condition eventually caused the separation of the 400 kV and 110 kV transmission levels.
The blackout caused:
Loss of approximately 79% of national electricity load
Collapse of the entire 110 kV transmission network
Interruption of industrial and residential electricity supply
Regional operational instability
Emergency restoration procedures by MEPSO
The restoration process lasted less than three hours, during which MEPSO operators gradually re-energized substations and restored synchronization with the European interconnected system.
The incident highlighted several important vulnerabilities:
Excessive voltage caused by low demand and high renewable generation
Limited reactive power compensation capabilities
Insufficient flexibility resources
Lack of large-scale battery storage systems
Aging transmission infrastructure
Reduced system inertia due to inverter-based generation

Chronology of the Blackout Event

5.1 System Conditions before the Blackout: During the early morning hours of 18 May 2025, the electrical system was operating under low-load conditions typical for spring weekends. Electricity demand was significantly reduced, while reactive power generation in the transmission network remained high.
The ENTSO-E investigation identified persistent overvoltage conditions in the 400 kV network prior to the disturbance. Voltages exceeded acceptable operational limits and approached dangerous levels above 420 kV.
The transmission system was already operating close to stability limits due to:
Low electricity consumption
Excess reactive power
Weak voltage control capability
Limited transformer regulation margins
High voltage conditions across multiple substations

5.2 Initial Transformer Trips: According to the ENTSO-E factual report, several 400/110 kV transformers experienced automatic disconnection due to activation of overvoltage protection systems. Transformer trips occurred at major substations including:
Bitola 2
Skopje 5
Initial transformer disconnections occurred around 02:26 CEST and were followed by repeated unsuccessful reconnection attempts. Additional transformer trips occurred at 02:59 and 03:34 as overvoltage conditions persisted.
These transformer outages weakened the connection between the 400 kV and 110 kV systems and reduced the capability of the network to maintain stable voltage conditions.

5.3 Network Separation and Collapse: At approximately 04:59 CEST, the electrical system experienced complete separation between the 400 kV transmission network and the 110 kV network. This separation caused immediate instability within the 110 kV system and resulted in widespread loss of supply.
The blackout affected nearly the entire 110 kV network, leading to:
Loss of approximately 79% of national load
Interruption of electricity supply to consumers
Shutdown of industrial facilities
Temporary loss of regional power system stability
Despite the collapse of the 110 kV network, the 400 kV transmission backbone remained operational throughout the incident.

Technical Causes of the Blackout

6.1 Overvoltage in the 400 kV System: The primary technical cause of the blackout was excessive voltage within the 400 kV transmission network. According to the ENTSO-E final report, the system operated above the defined voltage limit of 420 kV.
Overvoltage conditions were intensified by:
Low active power demand
High reactive power generation from transmission lines
Insufficient reactive power compensation
Limited voltage control resources
Reduced loading of transmission corridors

Long high-voltage transmission lines naturally generate reactive power under light-load conditions. When system demand is low, this reactive power cannot be sufficiently absorbed, causing voltage to rise throughout the network.

6.2 Reactive Power Imbalance: Reactive power management is essential for maintaining stable voltage profiles in transmission systems. In the North Macedonian network, reactive power absorption capability was insufficient during the event.
Factors contributing to reactive power imbalance included:
Lack of sufficient shunt reactors
Limited transformer tap adjustment capability
Insufficient dynamic voltage control devices
Increased contribution from inverter-based generation
The inability to absorb excess reactive power allowed voltage levels to increase continuously until protective systems activated.

6.3 Reduced System Inertia: Modern renewable energy sources connected through power electronic converters provide significantly less mechanical inertia compared to conventional synchronous generators.
Reduced inertia decreases the system's capability to resist rapid disturbances and maintain stable operation during abnormal conditions.
The blackout highlighted how modern power systems with increasing renewable penetration become more sensitive to:
Voltage oscillations
Frequency deviations
Dynamic instability
Cascading protection operations

6.4 Protection System Operation Restoration Process: The overvoltage protection systems installed on 400/110 kV transformers operated correctly according to their design parameters. However, repeated transformer disconnections progressively weakened the connection between transmission voltage levels.
Once all major transformers disconnected simultaneously, the 110 kV system lost stability and collapsed.
Immediately after the blackout, operators from MEPSO initiated emergency restoration procedures.
The restoration strategy included:
Stabilization of the 400 kV network
Gradual re-energisation of substations
Controlled synchronization of transmission corridors
Sequential restoration of consumer load
Coordination with neighboring transmission operators
According to ENTSO-E, the restoration process was completed by 07:47 CEST, less than three hours after the blackout occurred.
The rapid restoration demonstrated effective emergency response procedures and coordination capabilities within MEPSO's control centres.

Impact of the Blackout

The blackout produced significant technical and economic consequences throughout North Macedonia.

which includes among others
Collapse of the entire 110 kV network
Loss of approximately 485 MW of load
Interruption of generation units
Temporary suspension of balancing markets
Increased operational risk in neighboring systems
Industrial production interruptions
Commercial activity disruption
Financial losses for businesses
Emergency operational costs
Increased balancing energy expenses
Although the rest of the Continental European power system remained stable, neighboring countries experienced elevated voltage conditions and increased operational alert levels during the event.
7.1. Lessons Learned
The blackout revealed several important weaknesses in the North Macedonian transmission system.
Modern transmission systems require advanced reactive power compensation devices such as:
Shunt reactors
STATCOM systems
SVC compensators
Dynamic voltage regulators
Regarding Renewable energy integration they must be accompanied by:
Grid modernization
Energy storage deployment
Synthetic inertia capability
Grid-forming inverter technology
Improved coordination between Southeast European transmission system operators is necessary to manage regional voltage stability under changing operating conditions.
Aging infrastructure must be upgraded to support modern operational requirements and renewable energy integration.

Recommendations

To reduce the probability of future blackout events, the following measures are recommended:
Installation of additional reactive power compensation equipment
Deployment of large-scale battery energy storage systems
Improvement of voltage monitoring and forecasting systems
Strengthening of transformer protection coordination
Expansion of regional operational cooperation
Implementation of smart grid technologies
Increased operational flexibility during low-load periods
Improved renewable generation forecasting
The ENTSO-E final report also recommended establishment of a coordinated action plan for the Southeast European region to mitigate high-voltage operating conditions.

Conclusion

The blackout that occurred in the North Macedonian power system on 18 May 2025 represents a significant example of the operational challenges facing modern electrical grids during the energy transition process.

The event was primarily caused by uncontrolled overvoltage in the 400 kV transmission network under low-load operating conditions. The resulting transformer protection operations caused separation of the 400 kV and 110 kV systems and led to collapse of the national 110 kV network.

The incident demonstrated that modern power systems require substantial modernization to ensure stable operation under conditions of increasing renewable energy penetration and reduced conventional generation.

Although the blackout exposed vulnerabilities in voltage control and system flexibility, the rapid restoration carried out by MEPSO demonstrated effective emergency response capability and operational professionalism.

Future prevention of similar incidents will require coordinated investments in smart grid technologies, reactive power compensation systems, energy storage, and advanced voltage management strategies across the Southeast European region.

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INTEGRATION OF IAAS AND SERVERLESS COMPUTING FOR E-COMMERCE ORDER PROCESSING

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Abstract

Infrastructure as a Service (IaaS) and serverless computing represent complementary paradigms within modern cloud architectures. IaaS provides persistent virtualized infrastructure for hosting applications and databases, whereas serverless computing enables event-driven execution without direct server management. This study examines their integration in e-commerce order-processing systems through a hybrid architectural approach.
The proposed model combines IaaS-based virtual machines with serverless functions responsible for transaction validation, inventory synchronization, and customer notification workflows. AWS Lambda and Azure Functions are analyzed as representative serverless platforms within commercial cloud ecosystems. The study adopts a conceptual architectural analysis methodology focused on scalability, modularity, workload responsiveness, and separation of processing logic from persistent infrastructure services.
The analysis demonstrates that integrating serverless execution with IaaS environments can improve resource utilization and operational flexibility in systems characterized by fluctuating transaction workloads. Event-driven processing reduces unnecessary infrastructure allocation while maintaining responsiveness during periods of increased activity. The study contributes a structured hybrid cloud framework that supports the development of scalable, adaptive, and cost-aware e-commerce architectures.

Keywords: Infrastructure as a Service (IaaS), serverless computing, AWS Lambda, Azure Functions, cloud computing, e-commerce.

Introduction

Infrastructure as a Service (IaaS) represents a fundamental cloud computing model that provides virtualized computing resources over the internet, including processing power, storage, and networking capabilities. These resources are hosted and managed by external providers, allowing organizations to allocate infrastructure according to operational needs without maintaining physical hardware (Minarolli, 2014).
In this model, responsibility is shared between provider and user. While the provider manages physical infrastructure, users configure and maintain operating systems, applications, and deployed services. This separation supports flexible scaling and adaptation to changing workloads. Virtualization enables multiple virtual machines to operate on shared physical resources while remaining isolated. This improves resource utilization and supports dynamic workload distribution across applications.
Serverless computing has emerged as a complementary approach within cloud architectures. It allows application functions to execute in response to events without direct server management, while resource allocation and scaling are handled automatically by the provider (Hassan et al., 2021).
Unlike traditional always-on infrastructure, serverless systems are better suited for intermittent and event-driven workloads such as data updates, user requests, and transaction processing. Services such as AWS Lambda and Azure Functions provide execution environments for such tasks within cloud ecosystems.
E-commerce systems represent a typical environment where workload variability is significant. Traffic and transaction volume fluctuate depending on user activity, requiring architectures that can scale efficiently without excessive resource provisioning (Shi & Dustdar, 2016; Li et al., 2020).

Recent research has explored the combined use of IaaS and serverless computing as a hybrid approach for improving scalability and workload distribution in cloud-based systems.
This study examines how virtualized infrastructure and event-driven serverless functions can operate together within e-commerce order-processing environments to improve scalability and operational efficiency.

1.1.Research Contribution

This study contributes to cloud architecture research in three specific ways.
First, it presents a structured hybrid model that explicitly combines Infrastructure as a Service (IaaS) with serverless computing within a unified e-commerce order-processing framework. Unlike conventional studies that treat these paradigms separately, this work focuses on their operational interaction within a single workflow.
Second, the study introduces a comparative architectural mapping between AWS Lambda and Azure Functions in relation to equivalent IaaS components. This allows a clearer understanding of how vendor-specific ecosystems influence system design decisions.
Third, the research identifies key architectural criteria—scalability behavior, modularity, workload responsiveness, and separation of concerns—as analytical dimensions for evaluating hybrid cloud systems. These criteria can be reused in future studies examining similar cloud integration patterns.

Integration of Infrastructure as a Service (IaaS) and Serverless Computing for E-Commerce Order Processing

The integration of Infrastructure as a Service (IaaS) and Serverless Computing provides a flexible approach for managing cloud-based e-commerce systems. In this model, IaaS resources are used to maintain the core infrastructure components of the platform, while serverless functions handle dynamic processing tasks that require automatic scaling and event-driven execution.
E-commerce applications typically involve multiple operations, including user authentication, product management, inventory control, payment processing, and customer notifications.
These processes generate workloads that may vary significantly depending on user activity and transaction volume. Combining IaaS and serverless technologies allows organizations to distribute these workloads more efficiently across different cloud services.
In the proposed architecture, virtual machines hosted within the IaaS environment are responsible for maintaining the main website, application services, and databases. These components require continuous availability and stable resource allocation in order to support customer access and data management operations.
At the same time, serverless computing services are used for processing customer orders and executing event-driven tasks. When a customer places an order, a serverless function is automatically triggered to validate the transaction, update inventory records, store order information, and generate notifications. This execution model enables automatic resource scaling according to demand without requiring manual server management.
AWS Lambda and Azure Functions are examined as representative serverless platforms that support this architecture. Both services provide event-driven execution, integration with cloud storage systems, and automatic scaling capabilities that are suitable for e-commerce environments.
Combining persistent infrastructure with event-driven execution can reduce unnecessary resource allocation while improving scalability in cloud-based commerce systems. In addition, separating persistent infrastructure components from dynamic processing functions allows organizations to manage workloads more efficiently while maintaining flexibility within the cloud environment.

Methodology

This study adopts a conceptual architectural analysis approach focused on hybrid cloud system design. The objective is to examine how Infrastructure as a Service (IaaS) and serverless computing can be structurally integrated within e-commerce order-processing environments.
The research design is qualitative and model-based. Instead of implementing a live system or performing performance benchmarking, the study evaluates architectural configurations, service interactions, and functional distribution across cloud layers.
Evaluation is guided by four analytical dimensions: scalability behavior, system modularity, responsiveness to workload variation, and separation between infrastructure and processing logic. These dimensions are used to assess the suitability of serverless integration within IaaS-based systems.
The analysis combines workflow modeling with technology mapping across AWS and Azure environments. This includes identifying how event-driven functions interact with virtualized infrastructure components to support core e-commerce operations such as order validation, inventory synchronization, and notification delivery.
The study focuses on design-level interpretation of hybrid cloud behavior under variable workloads, rather than empirical performance measurement.

System Architecture and Workflow Design

Based on the defined evaluation framework, the system architecture is developed as a conceptual model of hybrid cloud interaction.

The proposed model combines Infrastructure as a Service (IaaS) and Serverless Computing to support order-processing operations within an e-commerce environment. The architecture is designed to separate persistent infrastructure components from event-driven processing tasks in order to improve scalability and operational efficiency.
Within the IaaS environment, virtual machines are used to host the main e-commerce website, application services, and databases. These virtualized resources maintain continuous system availability and support customer interactions, product management, and data storage operations. The databases store product information, customer profiles, inventory records, and order history.
Serverless computing services handle event-triggered processing, reducing reliance on continuously running infrastructure and enabling dynamic resource allocation.
The workflow begins when a customer accesses the e-commerce platform through the web application hosted on the IaaS infrastructure. After selecting products and completing the checkout process, the system generates an event that activates a serverless function responsible for order processing.
The serverless function performs several operations, including:

- retrieval of order information,
- validation of transaction data,
- updating inventory records,
- storing order details in the database,
- and generating customer notifications.

After the processing stage is completed, the updated information is synchronized with the database hosted within the IaaS environment. Notification services may also be triggered to inform customers about order confirmation and delivery status.
This architecture allows the platform to respond dynamically to varying transaction volumes while minimizing the need for manual infrastructure management. In addition, the separation

between web hosting services and processing functions supports modular system design and improves scalability during periods of increased customer activity.

Azure Functions Implementation

Azure Functions was selected as one of the serverless platforms examined in this study due to its integration capabilities within Microsoft Azure cloud environments. Azure Functions supports event-driven execution and automatic scaling, enabling applications to process workloads without maintaining continuously active servers (Microsoft, 2023a).
In the proposed implementation, Azure Functions are responsible for handling order-processing tasks triggered by customer transactions. The serverless function communicates with supporting Azure services to manage data storage, inventory tracking, and notification delivery.
The following Azure services are integrated within the architecture:

- **Azure Blob Storage** is used for storing product-related information, customer data, and order records.
- **Azure Cosmos DB** maintains inventory information and supports real-time updates of order status.
- **Azure Service Bus** enables communication between services and supports customer notification delivery.

When a customer confirms a purchase, the Azure Function is automatically triggered. The function retrieves transaction details, validates the request, updates inventory records, and stores order information in the associated database services. The system then generates a notification confirming successful order processing. This implementation supports scalable execution while reducing the administrative overhead associated with traditional server management.

AWS Lambda Implementation

AWS Lambda is examined as an alternative serverless platform within the proposed architecture. AWS Lambda enables developers to execute application functions without directly managing servers or infrastructure resources. The platform automatically scales according to incoming requests and supports integration with multiple AWS cloud services (Amazon Web Services, n.d.).
Within the AWS-based implementation, order events initiate Lambda execution when customers complete transactions on the e-commerce platform. The functions process order-related operations and communicate with supporting AWS services for storage and notification management.
The supporting AWS ecosystem includes the following components:

- **Amazon S3** is used for storing customer information, product data, and order records.
- **Amazon DynamoDB** maintains inventory status and supports real-time database operations.
- **Amazon SNS (Simple Notification Service)** is used for sending order confirmation and status notifications to customers.

Once an order is submitted, the AWS Lambda function validates transaction information, updates inventory data, stores order records, and initiates notification services. Automatic scaling mechanisms allow the platform to handle varying transaction loads without requiring manual allocation of additional infrastructure resources. The AWS Lambda implementation demonstrates how serverless computing can support efficient and scalable order-processing operations within IaaS-based e-commerce systems.

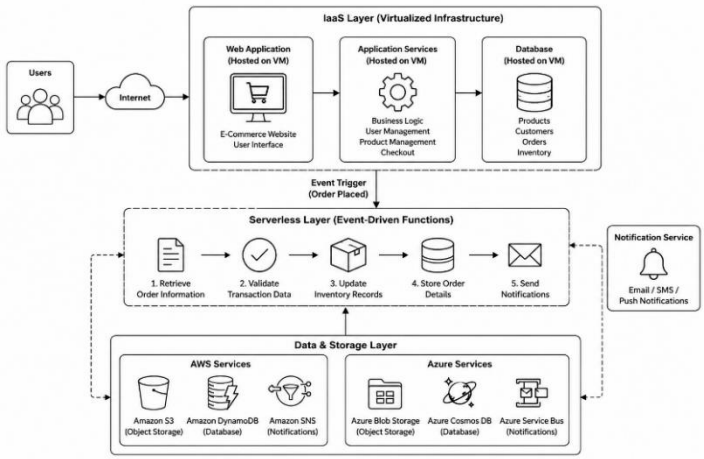


Figure 1. Proposed Hybrid IaaS and Serverless Architecture for E-Commerce Order Processing

The proposed architecture consists of three layered components that collectively support scalable e-commerce order processing.

At the **presentation layer**, users interact with a web application hosted on virtual machines within the IaaS environment. This layer handles user requests, product browsing, and checkout operations.

The **processing layer** is composed of serverless functions deployed on AWS Lambda and Azure Functions. These functions are triggered by order-related events and are responsible for transaction validation, inventory updates, and notification handling.

The **data layer** includes cloud-based storage and database services such as Amazon S3, DynamoDB, Azure Blob Storage, and Cosmos DB, which store persistent application data including product information, customer profiles, and order history.

The interaction between these layers follows an event-driven flow where user actions generate triggers that activate serverless execution, while persistent services maintain system state and data consistency.

Comparative Analysis and Discussion

AWS Lambda and Azure Functions both provide event-driven execution environments that can be integrated into IaaS-based e-commerce systems. Although they follow similar architectural principles, their practical use is often shaped by ecosystem alignment and system dependencies rather than functional differences alone.

AWS Lambda is more frequently adopted in systems built around Amazon Web Services, where integration with services such as Amazon S3, DynamoDB, and SNS enables consistent workflow design across storage, computation, and messaging components. In contrast, Azure Functions is more naturally aligned with Microsoft Azure environments, integrating with services such as Blob Storage, Cosmos DB, and Service Bus.

Scalability is a shared feature of both platforms, allowing automatic adjustment of computing resources based on workload demand. This is particularly relevant in e-commerce systems, where traffic patterns are irregular and often unpredictable.

From a cost perspective, both platforms follow usage-based billing models, where charges depend on execution time and consumed resources rather than provisioned capacity. However, actual operational cost may vary depending on execution frequency, memory configuration, and external service dependencies.

In practice, platform selection is often influenced by organizational familiarity with a specific cloud ecosystem rather than technical superiority. This reduces integration complexity and simplifies long-term maintenance. Overall, both services are suitable for implementing serverless order-processing functions in IaaS-based architectures, provided that they are aligned with the surrounding cloud infrastructure.
Table 1 presents a general comparison between AWS Lambda and Azure Functions within the context of e-commerce order processing.

Table 1. Comparison of AWS Lambda and Azure Functions

Feature	AWS Lambda	Azure Functions
Cloud Ecosystem	Amazon Web Services	Microsoft Azure
Main Storage Service	Amazon S3	Azure Blob Storage
Database Integration	DynamoDB	Cosmos DB
Notification Service	Amazon SNS	Azure Service Bus
Scaling Mechanism	Automatic	Automatic
Billing Model	Pay-per-use	Pay-per-use
Infrastructure Management	Managed by AWS	Managed by Azure
Suitable for Event-Driven Tasks	Yes	Yes

Conclusions

This study focused on the integration of Infrastructure as a Service (IaaS) and serverless computing in the context of e-commerce order-processing systems. The proposed framework combines persistent virtualized infrastructure with event-driven processing functions to support scalable cloud-based operations.
The analysis showed that IaaS is suitable for hosting core system components such as web applications and databases, while serverless computing is more efficient for handling dynamic processing tasks triggered by user activity. AWS Lambda and Azure Functions were used as representative technologies to demonstrate this integration.
The findings indicate that separating infrastructure hosting from transactional processing can improve system scalability and reduce operational complexity. In addition, serverless execution enables more efficient handling of workload variations without continuous resource allocation.
Both AWS Lambda and Azure Functions were found to be effective for implementing such workflows, with selection depending mainly on the underlying cloud ecosystem and organizational requirements.
The proposed hybrid model demonstrates that combining IaaS infrastructure with serverless execution can support scalable and operationally flexible e-commerce environments.

Recommendations and Future Work

The integration of Infrastructure as a Service (IaaS) and Serverless Computing continues to attract attention in cloud system design due to its potential for improving scalability and operational flexibility. In practice, however, its effectiveness depends on workload

characteristics and system configuration, which should be further examined in applied environments.

Additional research may also compare the execution efficiency of AWS Lambda and Azure Functions using performance indicators such as response time, scalability, execution latency, and operational cost. Experimental benchmarking in high-demand environments could provide more detailed insight into the behavior of serverless platforms during periods of increased workload.

Organizations implementing cloud-based e-commerce systems should consider monitoring and cost-management mechanisms as part of their deployment strategy. Services such as AWS CloudWatch and Azure Cost Management may assist in tracking resource utilization and identifying operational inefficiencies.

Security and access control remain important considerations in cloud architectures. Future implementations should incorporate authentication policies, identity management mechanisms, and data protection strategies in order to support secure transaction processing and compliance with organizational requirements.

Another area for future investigation involves the development of vendor-independent architectures capable of operating across multiple cloud providers. Such approaches may improve portability and reduce dependency on a single cloud ecosystem.

Finally, future studies may examine the applicability of combining IaaS and serverless computing in domains beyond e-commerce, including healthcare systems, logistics platforms, and financial applications that require scalable and event-driven cloud infrastructure.

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INSTRUMENTAL PHARMACEUTICAL ANALYSIS OF VITAMIN B12 IN PHARMACEUTICAL PRODUCTS AND DIETARY SUPPLEMENTS: A REVIEW

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Abstract

Vitamin B12, or cobalamin, is a water-soluble vitamin that is vital for the proper functioning of the human body. It plays important roles in the formation of red blood cells, DNA synthesis, and the functioning of the nervous system. A deficiency in this vitamin can result in megaloblastic anemia, fatigue, weakness, neurological issues, and memory problems. Consequently, Vitamin B12 supplements are commonly utilized, particularly among older adults, vegetarians, vegans, and individuals with gastrointestinal absorption disorders.
The growing use of dietary supplements has made the analysis of Vitamin B12 essential in pharmaceutical and food quality control. The primary goal of this analysis is to assess the actual quantity of vitamin present in the product and confirm whether it aligns with the value stated on the label. LC-MS/MS is an advanced analytical technique used for determining Vitamin B12 in dietary supplements and pharmaceutical preparations. Furthermore, the analysis is used to examine the stability of the vitamin during storage, detect potential degradation, and ensure the safety and effectiveness of the supplement.

Keywords: vitamin B12, public health, dietary supplements, analysis

Introduction

Vitamins are a category of organic compounds that are necessary in minimal quantities for the proper functioning of the human body. They have diverse chemical and physiological roles and are commonly found in a variety of natural food sources. Vitamins are not produced by the body, so they must be obtained from food. They are categorized into water-soluble and fat-soluble types. Fat-soluble vitamins D, A, E, and K are easily processed by the kidneys and eliminated from the body. Water-soluble vitamins, including folate, riboflavin, vitamin C, vitamin B12, vitamin B6, niacin, and thiamine, are stored in the body's cells (Alija *et al.* 2024).
Vitamin B12 is a complex water-soluble vitamin, is a term that refers to four cobamides, which share a common lower ligand known as 5,6-dimethylbenzimidazole (DMBI) at the α-position and one of four upper ligands—adenosyl, methyl, hydroxo, or cyano—at the β-position. These forms are identified as adenosylcobalamin (AdoCbl), methylcobalamin (MeCbl), hydroxocobalamin (OHCbl), and cyanocobalamin (CNCbl). A central cobalt (Co) atom is coordinated with four pyrrole rings, with the lower ligand connected through a phosphate–sugar bond and the upper ligand linked via a metal–carbon bond.
AdoCbl and MeCbl are the coenzyme forms necessary for the function of the enzymes methionine synthase and methylmalonyl-CoA, is shown in Figure 1. (Chamlagain, 2016).

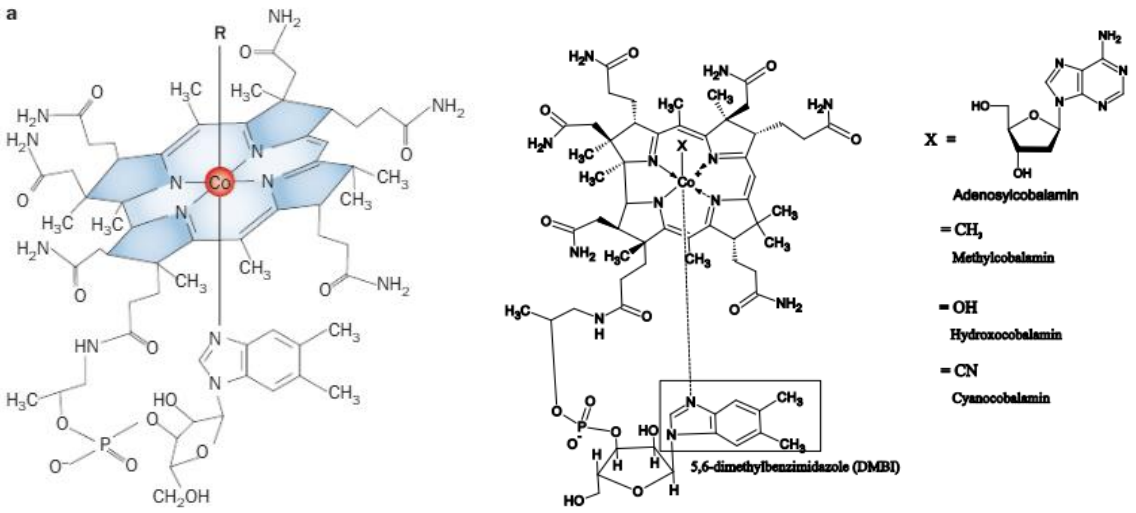


Figure 1. Structure of vitamin B12 ((Nielsen et al. 2012, Chamlagain 2016)

Vitamin B12 is vitamin essential for hematological and neurological functions. It serves as a cofactor in the processes of DNA synthesis, fatty acid metabolism, erythrocyte formation, aminoacid metabolism, nervous system function and cellular energy production. It is crucial for DNA synthesis, which directly influences cell division and growth. Without it, the maturation of blood cells can be hindered, resulting in megaloblastic anemia. Furthermore, vitamin B12 is vital for the upkeep of myelin, an important element for the proper functioning of the nervous system. (Green, 2011; Herrmann & Obeid, 2008).

Vitamin B12 is essential for two enzymatic processes: the conversion of homocysteine to methionine through methionine synthase, and the conversion of methylmalonyl-CoA to succinyl-CoA via methylmalonyl-CoA mutase (Nielsen *et al.* 2012).

Humans cannot synthesize vitamin B12 and therefore depend on dietary sources as well as a complex intracellular process for the vitamin's processing and delivery to its intended locations. (O'Leary & Samman, 2010).

Its absorption requires several steps: first, it is released from food proteins in the stomach, then it binds to intrinsic factor, followed by absorption in the terminal ileum, and finally, it is transported in the blood via trans cobalamin. Any disruption in these steps may result in a deficiency. Deficiency in vitamin B12 caused by malabsorption and insufficient intake is a global public health concern, is shown in Figure 2 (O'Leary & Samman, 2010; Hannibal *et al*., 2016; Allen, 2008).

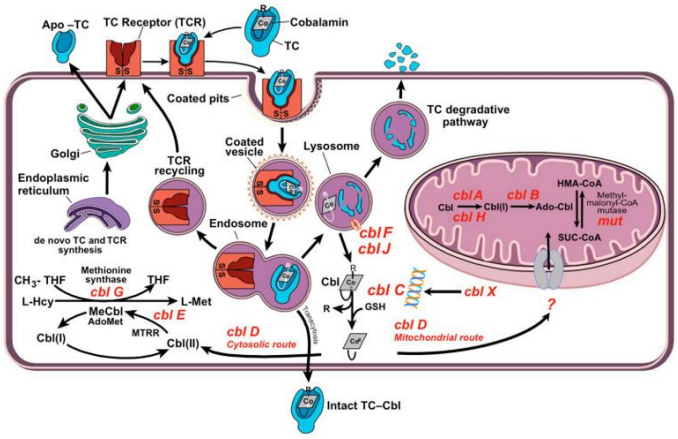


Figure 2. Cellular processing and trafficking of dietary vitamin B12 (Hannibal et al., 2016)

Vitamin B12 deficiency in humans is characterized by anemia and neuropathy. The anemia is clinically similar to that caused by folate deficiency and results from the inactivity of a vitamin B-dependent enzyme involved in folate metabolism. When megaloblastic anemia occurs due to a vitamin B12 deficiency, it is referred to as pernicious or Addisonian anemia. The neurological changes are not related to folate deficiency and arise from the inability to produce the lipid component of myelin, leading to a general demyelination of nerve tissue. Neuropathy initially affects the peripheral nerves, starting with the feet and fingers, and then progresses to the spinal cord and brain. If there is a deficiency in vitamin B12, taking folic acid supplements without including vitamin B12 may lead to irreversible neurological damage. While folate treatment may alleviate the apparent symptoms of anemia, it can also allow nerve degeneration to go unnoticed. Therefore, preventative vitamin supplementation should always include vitamin B12 along with folic acid (Stabler, 2013; Ball, 2005).

Proper evaluation of vitamin B12 levels in the body is important for the early detection and prevention of permanent complications.

A more typical presentation involves low or marginal levels of cobalamin ranging from 200 to 300 pg/mL (148–221 pmol/L) without accompanying symptoms. The groups most affected include older adults, individuals with pernicious anemia, pregnant and lactating women, and those with gastrointestinal disorders. People following a vegan diet may want to consider supplementation, in addition to the elderly population. High doses of cobalamin are generally considered safe and unlikely to result in toxicity (Hanna *et al*. 2022)

As a result, laboratory analysis of Vitamin B12 is essential to ensure the quality, efficacy, and safety of dietary supplements.

Vitamin B12 is available in multiple chemical forms, including cyanocobalamin, methylcobalamin, hydroxocobalamin, and adenosylcobalamin.

1. Cyanocobalamin is a more stable form and is most commonly found in supplements.
2. Methylcobalamin is the biologically active form and is frequently used for neurological disorders.
3. Hydroxocobalamin is administered through injections and has a longer duration of action.
4. Adenosylcobalamin is the metabolically active form found in mitochondria.

The most widely used form in supplements is cyanocobalamin due to its stability. The structure of Vitamin B12 is complex and features a cobalt atom at the center of the molecule.

The molecular formula of cyanocobalamin is $C_{63}H_{88}CoN_{14}O_{14}P$ (Ball, 2005)

The main purpose of the analysis is to assess the actual quantity of vitamin in the product and to confirm if it corresponds with the value stated on the label. Furthermore, the analysis is conducted to examine the stability of the vitamin during storage, detect any potential degradation, and ensure the supplement's safety and effectiveness.

Methods for assessing vitamin B12 include polarographic, spectrophotometric, and electrophoretic techniques, as well as various chromatographic procedures such as paper, thin-layer, open-column, gas chromatography (GC), liquid chromatography (LC), and liquid chromatography combined with mass spectrometry (LC-MS). Other methods include microbiologic and radio-ligand binding techniques (Eitenmiller, 2008)

One of the frequently utilized techniques for Vitamin B12 analysis is ultraviolet-visible spectroscopy. This technique relies on Vitamin B12's capacity to absorb electromagnetic radiation in the ultraviolet and visible regions of the spectrum. The concentration of the vitamin is calculated using the Beer–Lambert law: $A=\varepsilon \cdot b \cdot c$

which states that absorbance (A) is related to the molar absorptivity coefficient (ε), the path length of the cuvette (b), and the concentration of the analyte (c). This method is straightforward, quick, and economical, although it may be influenced by interference from other substances present in the supplement (Mendham, 2000).

Spectrophotometric methods are used for the analysis of high concentration pharmaceutical products. Özgür and Koyuncu (2002) employed second derivative spectrophotometry to analyze vitamin B6, thiamin, and vitamin B12 in pharmaceuticals. The calibration graphs were linear for thiamin at 228.9 nm, vitamin B6 at 309.6 nm, and vitamin B12 at 361.7 nm, up to a concentration of 20 $\mu g\ mL^{-1}$. An analysis of tablets with 1 mg of vitamin B12 yielded results that were close to the labeled amount, with a %RSD of 3.58 (Özgür & Koyuncu, 2002).

Nepote et al. developed a simultaneous analysis method for vitamin B6, dexamethasone, and vitamin B12 using UV-vis spectral measurements in conjunction with partial least squares (PLS-1) multivariate calibration. When applied to injectable products containing vitamin B12, the results were comparable to those obtained through capillary electrophoresis (Nepote *et al.* 2006).

Several methods utilizing chemiluminescence for the assay of vitamin B12 have been published. Most of these methods are suitable for flow injection analysis (FIA), which allows for rapid throughput procedures. For instance, Song and Hou (2003) presented a method that enhances the chemiluminescence reaction between luminol and dissolved oxygen in a flow injection system through the addition of cobalt (II). This method demonstrated high sensitivity, with a detection limit of $5 \times 10^{-11}\ g\ L^{-1}$. It is applicable to pharmaceuticals, serum, and foods. The evaluation by the authors highlighted the speed and simplicity of the procedure, positioning it as a useful routine analytical method (Song & Hou, 2003).

The analysis of Vitamin B12 in dietary supplements is a significant component of pharmaceutical and food quality control. Research has shown that modern analytical techniques allow for more precise and selective measurement of Vitamin B12 in multivitamin products and dietary supplements.

The analysis of Vitamin B12 using liquid chromatography coupled with mass spectrometry (LC-MS/MS) is regarded as a highly advanced and reliable analytical technique in pharmaceutical and food analysis. This method integrates the separation capability of high-performance liquid chromatography with the sensitivity and selectivity of mass spectrometry, facilitating accurate identification and quantification of Vitamin B12, even at trace concentrations.

Liquid chromatography can be effectively used to analyze vitamin B12 in high-concentration supplements and pharmaceutical formulations. It can successfully separate natural cobalamins. However, due to the low concentrations of the analytes, early studies often employed isotope dilution and radio-ligand binding assays to quantify eluted cobalamins. Currently, the integration of mass spectrometry with liquid chromatography has been limited (Li *et al*.2000; Wongyai,2000).

The analytical procedure typically starts with sample preparation. Solid dosage forms like tablets and capsules are crushed and homogenized, while liquid formulations are thoroughly mixed. The vitamin is extracted using solvents such as water, methanol, or acetonitrile, sometimes combined with buffer solutions to enhance extraction efficiency and stability. The resulting solution is then filtered and diluted before being injected into the chromatographic system.

Chromatographic separation is carried out using reverse-phase columns, commonly C18 columns, where compounds are separated based on polarity and interaction with the stationary phase. The mobile phase usually consists of water and organic solvents like methanol or acetonitrile, often containing formic acid to improve ionization efficiency during mass spectrometric detection.

Following chromatographic separation, the analyte enters the mass spectrometer, where ionization occurs, typically through electrospray ionization (ESI) in positive ion mode. During this process, Vitamin B12 molecules become protonated and form charged ions that are detected based on their mass-to-charge ratio (m/z) (Wongyai,2000; Lindemans *et al*. 2000).

Nonetheless, Lindemans (2000) indicates that soft ionization techniques suitable for nonvolatile and thermolabile compounds will be relevant for LC-MS methods for vitamin B12. Improved LC-MS instrumentation and LC interfaced with inductively coupled plasma emission mass spectrometry (LC-ICP-MS) have been identified as yielding sensitive and specific methods for the analysis of cobalamins.

A notable study conducted in North Macedonia was published by Stefova *et al.* which focused on developing a high-performance liquid chromatography (HPLC) method for determining Vitamin B12 in multivitamin tablets. The authors found that the HPLC method offered good sensitivity and precision for the routine analysis of supplements. This study was significant as it illustrated the applicability of modern chromatographic techniques in pharmaceutical laboratories in Macedonia and contributed to the enhancement of quality control for multivitamin preparations (Stefova *et al.1997).* HPLC provides greater selectivity than conventional spectrophotometric methods and minimizes interference from other components in the supplement matrix. The advancement of analytical techniques, particularly Mass Spectrometry coupled with Liquid Chromatography (LC-MS/MS), has significantly enhanced Vitamin B12 analysis. Research from various international studies indicates that LC-MS/MS allows for highly precise identification and quantification of various cobalamin forms, such as cyanocobalamin, methylcobalamin, and hydroxocobalamin, even at low concentrations.

The research conducted by Chamlagain *et al.* showed that LC-MS/MS offers high sensitivity and specificity for analyzing Vitamin B12 in food and dietary supplements. The authors noted that this method is particularly useful for detecting degradation products and for examining complex samples that may contain interfering compounds. These results suggest that LC-MS/MS is a current standard for vitamin analysis in both the pharmaceutical and food industries (Chamlagain *et al.* 2015).

Yanes and Miller-Ihli demonstrated that CNCbl, OHCbl, AdoCbl, and MeCbl were effectively resolved by LC-ICP-MS, resulting in clear chromatographs due to the element specificity of ICP-MS. The method proved to be robust and suitable for the analysis of foods and supplements, with minimized matrix interference (Yanes & Miller-Ihli, 2004).

There are limited methods that utilize LC-MS technology.

Chassaigne and Łobiński compared various detection modes, including spectrophotometric, ICP-MS, and electrospray ionization mass spectrometry (MS-ESI) paired with microbore reversed-phase LC on C8. When using standards such as CNCbl, AdoCbl, OHCbl, MeCbl, and cobinamide dicyanide (CN)2Cbn, ICP-MS demonstrated greater sensitivity compared to other online detection systems; however, total ion current chromatograms facilitated clear species identification (Chassaigne & Łobiński, 1998).

The authors Jiang *et al*. describe a straightforward LC-MS quantification method for Vitamin B12. Using the Waters Atlantis C18 Column, Vitamin B12 exhibited good retention and peak shape. A simple binary gradient was employed without the addition of a buffer.

The quantification linear range spanned from 5 ppb to 4000 ppb, with a limit of detection of 2 ppb for a 10 μL injection (Jiang *et al*. 2003)

Conclusion

Vitamin B12 is important for cellular metabolism and neurological health. A deficiency in vitamin B12 is a significant public health concern worldwide, especially among older adults, vegetarians, and individuals with malabsorption disorders. Proper evaluation of vitamin B12 levels is essential for early diagnosis and the prevention of complications. As a result, vitamin B12 supplements are commonly used as prophylactic therapy. The increasing use of dietary supplements has made vitamin B12 analysis essential in pharmaceutical and food quality control.

LC-MS/MS is an advanced analytical technique used for determining Vitamin B12 in dietary supplements and pharmaceutical preparations. This method provides enhanced sensitivity, selectivity, and precision when compared to traditional analytical techniques. Its capability to accurately identify and quantify various forms of Vitamin B12 is important for pharmaceutical quality control, food analysis, and research applications.

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THE ROLE OF NUTRITION IN SKIN DISEASES

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Abstract

Nutrition is essential for maintaining the structure, function, and health of the skin. As the largest organ of the human body, the skin acts as a protective barrier against environmental, chemical, and microbial factors. There is growing evidence that nutritional status plays a significant role in the development, progression, and management of various skin conditions. Nutrients including vitamins, minerals, essential fatty acids, proteins, and antioxidants contribute to skin regeneration, immune response, collagen synthesis, and protection against oxidative stress.
Various dermatological conditions, such as acne vulgaris, atopic dermatitis, psoriasis, rosacea, and eczema, have been linked to dietary factors and nutritional deficiencies. Diets that are high in processed foods, high glycemic index carbohydrates, saturated fats, and excessive dairy may lead to inflammation and worsen certain skin issues. Conversely, diets that include fruits, vegetables, omega-3 fatty acids, probiotics, and antioxidant-rich foods may enhance skin health and decrease inflammation. Micronutrients like Vitamin A, Vitamin C, Vitamin D, Vitamin E, zinc, selenium, and biotin play significant roles in maintaining skin integrity and aiding dermatological treatments. Furthermore, gut microbiota and the gut-skin axis have gained attention as relevant elements connecting nutrition and skin diseases.
This review aims to summarize existing knowledge about the connection between nutrition and skin diseases, emphasizing the effects of dietary patterns, micronutrients, and nutritional interventions on skin health. Understanding nutrition's role in dermatology may enhance prevention strategies and supportive treatment approaches for different skin conditions.

Keywords: nutrition, skin diseases, minerals, vitamins, tretman

Introduction

The role of nutrition in skin health and disease has received great attention in recent years, showing the importance of dietary factors in maintaining skin homeostasis **(**Katta *et al*., 2014; Barrea *et al*., 2025). As we know, the skin is the largest organ of the body, whose function is a protective barrier against external factors and which actively participates in metabolic and immunological processes (Katta *et al.*, 2014). Its structural and functional integrity directly depends on the adequate supply of nutrients, including proteins, lipids, vitamins, and minerals, which are essential for cell regeneration, collagen synthesis, and the maintenance of oxidative balance (Katta *et al.*, 2014; Barrea *et al*., 2025).
Scientific research suggests that diet has an impact on a variety of biological processes related to the pathogenesis of dermatological diseases (Katta *et al.*, 2014; Barrea *et al*., 2025). For example, foods with a high glycemic index can increase insulin levels and growth factors such as IGF-1, stimulating keratinocyte proliferation and sebum production, processes associated with the development of acne vulgaris.
On the other hand, a diet rich in antioxidants, such as vitamins A, C, and E, as well as bioactive compounds such as polyphenols, helps neutralize oxidative stress and reduce inflammation, having a protective effect against skin damage **(**Barrea *et al*., 2025).
It should be noted that some dietary ingredients affect the worsening of certain skin diseases. Consumption of dairy products and processed foods has been linked to worsening acne, while a lack of essential fatty acids and micronutrients may contribute to epidermal barrier disorders, such as in atopic dermatitis (Katta *et al.*, 2014; Barrea *et al.*, 2025). In this context, nutrition should not only be seen as a supporting factor, but as an integral component in the prevention and management of skin diseases. Understanding the interactions between diet, metabolism,

and skin functions is essential for the development of effective therapeutic and preventive strategies in dermatology (Katta *et al.*, 2014; Barrea *et al*., 2025).
This review aims to summarize current knowledge regarding the relationship between nutrition and skin diseases, focusing on the impact of dietary patterns, micronutrients, and nutritional interventions on skin health. Recognizing the role of nutrition in dermatology may improve prevention strategies and supportive treatments for various skin conditions.

Results and discussions

Skin Diseases

Acnet vulgaris-

Acne vulgaris is a chronic dermatosis, very prevalent in the Western population and common in adolescents (Khan *et al*., 2022; Rygula *et al*.,2024). It is characterized by follicular keratinization, intense sebum secretion, colonization of Propionibacterium acnes, with excessive intrafollicular growth and inflammation**.** There are different types of lesions: open and closed comedones (non-inflammatory lesions), papules, pustules, cysts and nodules (inflammatory lesions)**.** Acne is usually treated as an aesthetic problem, but it also affects psychologically by lowering self-esteem, with emotional and social consequences for some people (Khan *et al*., 2022; Rygula *et al*.,2024). They usually appear during adolescence, due to hormonal changes. The main etiological factors, currently accepted in the literature, are genetics (heredity), age (hormonal changes in adolescence), physical condition (body composition and insulin resistance) and finally nutrition (diet, supplements and phytotherapy) (Smith *et al*., 2022; Kowalska *et al.*, 2024). Among these, physical condition and nutrition are factors that can be modified. Classic treatments for acne vulgaris are various including mainly antibiotics and reduction of fat production (oral and topical). These are effective but can cause side effects and nutritional damage to the body. In this context, nutrition has been indicative of potential beneficial interactions (Smith *et al*., 2022). Evidence related to nutrition and dermatology is still scarce but it already suggests possible interventions (Rygula *et al*., 2024). Nutrients with a negative impact on acne-Milk is an extremely specialized functional food designed through evolution to support anabolic reactions and the growth of newborn mammals. Milk consumption significantly increases the amount of IGF-1 (Rygula *et al*., 2024). We know that 80% of milk protein from cows is casein, while 20% is whey protein. Whey protein is involved in the insulinotropic action of milk, and casein is more likely to stimulate IGF-1 than whey (Rygula *et al*., 2024). Athletes used whey protein for oral supplements in order to increase muscle weight. Thus, hyperinsulinemia caused by the insulinotropic function of such proteins significantly increases the concentration of IGF-1 during puberty, which explains why these people are more likely for the onset or worsening of acne lesions (Rygula *et al*., 2024). Also, cow's milk, mainly from pregnant cows, contains not only placental progesterone but also other dihydrotestosterone precursors, such as 5-alpha pregnandione and 5-alpha androstendione. It is worth noting that dihydrotestosterone is the most biologically reactive type of testosterone, which is important in the formation of acne lesions through increased androgen receptor expression (Rygula *et al*., 2024). But according to some case studies it is generally suggested that the effects of acne-causing dairy products are unlikely to be due to the fat content but rather due to the hormones and other bioactive molecules contained in milk (Rygula *et al*., 2024). Theses proposed to clarify the potential impact of chocolate intake on acne symptoms. One suggestion is that the saccharides present in chocolate and milk cause insulin secretion causing signaling pathways that ultimately imply increased keratinocyte tendencies,resulting in acne lesions (Rygula *et al*., 2024). Saturated fatty acids which include, for example, palmitoleic,

stearic and myristic acids and isomers of trans fatty acids, the main source of which is hydrogenated vegetable fats which are found in margarine, sweets or fast foods, negatively affect the skin affected by acne vulgaris (Rygula *et al*., 2024). The high content of palmitic acid leads to the progression of skin infection, increased blackheads and increased sebum production. Also, many cross-border surveys in the European and Asian populations have shown that alcohol abusers have a significantly higher probability of acne than those who do not drink. It is worth noting that alcohol has been shown to increase testosterone values as well as the secretion of pro-inflammatory cytokines (Rygula *et al*., 2024). In longer use it damages the immune system, linking the tendency of bacteria to changes in the skin microbiome and worsening acne and when expelled with sweating it works as a food ingredient for Cutibacterium acnes (Khan *et al*., 2022; Rygula *et al*.,2024).

Case Study-(Rubin *et al.*,2008)

In this study of 5 patients with inflammatory acne vulgaris, the initial condition was characterized by the presence of active acnetic lesions (papules and pustules), visible inflammation of the facial skin and moderate to pronounced severity of the disease, which in some cases was also associated with psychological impact. The diagnosis was inflammatory acne vulgaris, while the intervention consisted of food supplementation with omega-3 (EPA from fish oil) and antioxidants such as zinc and selenium in order to reduce systemic inflammation and oxidative stress. After a few weeks of treatment, there was a significant clinical improvement, with a reduction in acne lesions, a reduction in inflammation and fewer appearances of new acne, suggesting a positive effect of the nutritional intervention in controlling inflammatory acne (Rubin *et al.*,2008)



Fig.1-before use of omega-3 poly-nutrient capsules

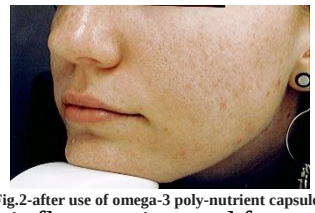


Fig.2-after use of omega-3 poly-nutrient capsules

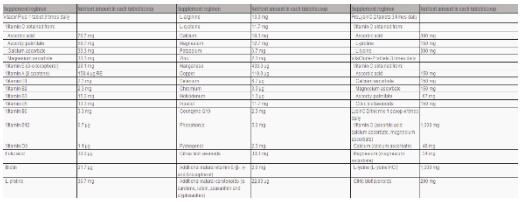
Psoriasis-

Psoriasis is considered to be a T-cell-mediated inflammatory skin disease, which is characterized by hyperproliferation and poor differentiation of epidermal keratinocytes (Ricketts *et al*., 2010). While susceptibility to psoriasis is hereditary, the disease is influenced by environmental factors, such as infections and stress (Ricketts *et al*., 2010). Diet has been suggested to be involved in the etiology and pathogenesis of psoriasis (Ricketts *et al*., 2010). The fasting period, low-energy diets, and vegetarian diets have been shown to improve psoriasis symptoms in several studies, and the diet rich in polyunsaturated fatty acids from fish oil have also shown beneficial effects (Ricketts *et al*., 2010). Consuming vegetables and fruits can be beneficial in psoriza due to their high content with antioxidant action (vitamins C, E, B2, zinc, selenium), improved energy metabolism (vitamin B complex, magnesium, vitamin C), modulation of immune function (vitamins A, D, C, folic acid, selenium, copper) and stimulation of collagen synthesis (vitamin C, lysine, proline) (Ricketts *et al*., 2010).

Here we have a case study-(Wong *et al*., 2015**)**



A 36-year-old woman presented to the clinic with psoriasis since the age of 22. She stated that the psoriasis outbreak originated on the scalp and slowly descended down towards her feet. Eventually, the psoriatic lesions covered a large area of her body, with the exception of the face (Fig. 1). That He had been prescribed topical steroid cream for the past 14 years. The possible cause may be the use of anti-dandruff



shampoo (which contains charcoal tar) since adolescence. The patient stopped using anti-dandruff shampoo from the first consultation. Discontinuing shampoo would not relieve psoriasis in the current study timelines, but it may help speed up healing. At the beginning of the treatment, the patient was advised to consume a healthy diet with plenty of vegetables, minimal meat, no fast foods, and to avoid taking any form of sugar in food or beverages. The following supplements were prescribed: Vitacor Plus-1 tablet 3 times a day, ProLysinC-2 tablets 3 times a day, VitaCforte-2 tablets 3 times a day, and LysinC Drink mix-1 tablespoon 4 times a day. Table I shows the list of ingredients in these supplements. The patient was advised to stop using the steroid cream immediately at the beginning of treatment. Return appointments were scheduled once a month. During the first month, the patient experienced worsening of the skin condition with the removal of the dead skin. From the second month onwards, the psoriasis spots looked thinner. Spots on the upper body (neck, shoulder, upper arms) seemed to heal faster than the lower parts of the body. This healing process continued and the psoriatic spots on the legs were the last to heal. By the end of 6 months, the patient's psoriasis had completely disappeared (Fig. 2). The patient reported worsening of itching and pain in the first month, followed by gradual improvement of these symptoms over 6 months. The patient had no complaints/side effects related to the diet (Wong *et al*., 2015**)**

Atopic dermatitis-

Atopic dermatitis (AD) is a chronic eczematous disease characterized by allergic immunity displaced by T helper 2(Th2), skin barrier damage and itching (Khan *et al.*, 2022). Oral intake of certain nutrients may help regulate AD. Serum 25-hydroxyvitamin D levels are often low in these patients, and oral vitamin D supplementation improves AD. The way vitamin D acts is by increasing regulatory T(Market) cells which promote allergen tolerance and prevent allergic inflammation by promoting the expression of filagrin and catelicide in keratinocytes (Khan *et al.*, 2022). Vitamin A strengthens regulatory T cells by promoting the expression of the P3 forkhead box and inhibits the release of mediators by mast cells and hosinophils. Serum levels of γ-linolenic acid (GLA) and its metabolism, dihomo-γ-linoleic acids (DGLA), are also low. Thus, GLAs improve AD through DGLA-derived prostaglandin D1 and E1. OMEGA-3 (Ac. eicosapentaenoic and Ac. docosahexaenoic) acts by decreasing the production of leukotriene B4, increasing ceramides in the stratum corneum, and through their metabolites, rezolvine E1 and D1, which resolve inflammation (Khan *et al.*, 2022). It should be noted that the level of zinc is also low. Zinc induces the expression of the P3 forkhead box and increases Treg cells, and the zinc-finger protein A20 decreases the nuclear-factor-κB-dependent expression of inflammatory cytokines. Oral supplementation of the above nutrients may have a therapeutic or preventive role in AD (Khan *et al.*, 2022).

Rosacea

Rosacea is a chronic inflammatory skin disease that mainly affects the face and is characterized by recurrent redness, persistent erythema, telangiectasis and some papules and pustules with progress that passes into phases of deterioration. It is divided into several subtypes (erythematothelangiectatic, papulopustular, phimatous and ocular), often with mixed symptoms in the same patient. Its cause is not clear, but it is related to a combination of factors: immune disorder born with increased inflammatory mediators, dysfunction of the nervous and vascular system that increases sensitivity and vasodilation, as well as the influence of skin microorganisms such as Demodex Folliculorum and various bacteria that can promote inflammation. External factors such as food, heat and irritants can worsen the condition. Treatment often includes topical creams and in more severe cases oral antibiotics, but their

long-term use is limited due to side effects and bacterial resistance, so lifestyle modification is also becoming important.
Dietary triggers are often cited by patients, although there is a lack of research in this area. In a survey by the National Rosacea Association over 400 patients, 78% had changed their diet due to rosacea. Of this group, 95% reported a later decrease in deterioration. The reported triggers in this group can be divided into heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related. Specifically, hot beverages acted as triggers, including hot coffee (33% describe it as the trigger) and hot tea (30%). Alcohol was another frequent trigger, including wine (52%) and hard liquor (42%). Capsaicin is found in some spices and peppers. Respondents frequently reported spices as triggers (75%), as well as spicy sauce (54%), cayenne pepper (47%), and red pepper (37%). Lastly, cinnamdehyde is found in some seemingly unrelated foods, including tomatoes, citrus fruits, cinnamon, and chocolate. In this study, foods containing cinnamaldehyde were also described as frequent triggers, including tomatoes (30%), chocolate (23%), and citrus fruits (22%) -(Weiss *et al.,* 2017)

The role of vitamins and minerals

Vitamins and minerals are micronutritions essential for the proper functioning of the human body, required in small amounts. They play various chemical and physiological roles and are commonly present in many natural food sources (Alija *et al.* 2024).

Vitamin C

Vitamin C (ascorbic acid) plays an important role in the functioning and health of the skin, which is not produced by the body but must be obtained externally. It is part of the synthesis of collagen in the dermis contributing directly to the structure, elasticity and strength of the skin, as well as to the formation of the barrier. In addition, vitamin C acts as a powerful antioxidant, protecting the skin from oxidative damage caused by external factors such as UV radiation, and thus helps slow down the aging process and reduce wrinkles. At the cellular level, it participates in the signalling pathways that regulate cell growth and differentiation, processes associated with the development of various skin diseases. An important characteristic of vitamin C is its dual role as an antioxidant and pro-oxidant. Under certain conditions, especially in the presence of transition metals such as iron (Fe^{2+}), it can generate reactive oxygen species (ROS). While in normal cells this balance is controlled, in tumor cells where the antioxidant system is impaired the increase in ROS can lead to DNA damage, decreased ATP and failure of cellular metabolism hindering their survival. For this reason, vitamin C is also of interest in the context of anticancer therapies. Also, vitamin C helps reduce melanogenesis (melanin production), which makes it important in the treatment of hyperpigmentation, and stimulates keratinocyte differentiation, improving skin regeneration. Its deficiency leads to serious systemic disorders, the most well-known being scorpion, which is characterized by weakening of connective tissues due to impaired collagen synthesis (Wang *et al*., 2018)

Vitamin E

Vitamin E is an essential fat-soluble antioxidant that's primarily obtained through diet, especially from vegetable oils, nuts, seeds, and green leafy vegetables. From a nutritional perspective, it plays a key role in protecting cell membranes as it settles in their lipid layers and protects them from lipid peroxidation caused by free radicals. By donating an electron, vitamin E neutralizes these reactive molecules and interrupts chain reactions of oxidative

damage. At the skin level, this translates into protection against damage caused by UV radiation, environmental pollutants and chemical substances, factors that contribute to premature aging and the development of inflammatory processes. Additionally, vitamin E has anti-inflammatory effect, helping to reduce erythema, irritation, and damage to the epidermal barrier. Metabolically, vitamin E does not act alone. It is part of an antioxidant network where it interacts with other vitamins, especially vitamin A and vitamin C, contributing to the maintenance of the redox balance in the body. In this context, it helps stabilize vitamin A, which is essential for epithelial cell differentiation and skin regeneration. Although the main function of vitamin E is antioxidant, under certain conditions (such as the high presence of free radicals or a lack of other antioxidants) it may also exhibit pro-oxidant activity, reflecting the complexity of its role in the body. Getting enough through diet is essential for maintaining the structural and functional integrity of the skin, improving the immune response, and protecting against chronic inflammatory and degenerative processes.
On the other hand, vitamin E deficiency, while rare, can lead to increased susceptibility to oxidative stress and tissue damage (Cassano *et al.*, 2012**)**

Vitamin A

Vitamin A is an essential fat-soluble vitamin obtained through the diet in the form of retinoids (from animal sources) and carotenoids (from plant sources like beta-carotene). From a nutritional point of view, it plays a key role in the differentiation, growth, and function of epithelial cells, making it one of the most important vitamins for skin health. At the skin level, vitamin A is essential for maintaining the integrity of the epidermal barrier and for cell regeneration. It regulates the keratinization process, preventing excessive thickening of the corneal layer and clogging of pores, which makes it particularly important in acne management. Additionally, vitamin A stimulates collagen production in the dermis, contributing to improved skin elasticity and reduced wrinkles. Functionally, vitamin A also plays a role in modulating the skin's immune system, helping to protect against infections and control inflammatory processes. It also affects the activity of melanocytes, playing a role in regulating skin pigmentation. Vitamin A acts in synergy with other antioxidants such as vitamins E and C, contributing to redox balance and protecting against oxidative damage caused by environmental factors such as UV radiation and pollution. Vitamin A deficiency leads to obvious skin disorders, such as dryness, hyperkeratosis and loss of the protective function of the epidermal barrier, while in more severe cases it also affects other systemic functions. On the other hand, adequate intake through diet is essential for maintaining healthy, functional, and damage-resistant skin (Park *et al.* 2015).

Zinc-

Zinc is an essential micronutrient that should be taken regularly through the diet, as the body does not store it in large quantities. It is mainly found in meat, fish, dairy products, nuts and grains and is better absorbed from animal sources. The specific roles zinc plays in skin health and function are less well known but likely to be equally critical based on manifestations of zinc deficiency in the diet, which include moderate to severe dermatitis. The skin is in a constant state of rejuvenation, placing a high demand for enzymes and zinc-based proteins that drive this process. The importance of zinc physiologically is particularly evident in studies of wound healing and inflammation reduction. During these processes, high zinc needs can be met externally, generally increasing the rates of natural processes (Schwartz *et al*., 2006)
The findings of this review emphasize the increasing evidence that nutrition influences the development, progression, and management of various skin diseases. Historically,

dermatological conditions were viewed as unrelated to diet; however, recent studies have shown that nutritional factors can significantly affect skin health outcomes (Draelos, 2010, Boelsma *et al*. 2001).

The results indicate that dietary patterns high in refined carbohydrates, saturated fats, and processed foods may lead to increased inflammation and exacerbate conditions such as acne, psoriasis, and atopic dermatitis. Conversely, diets that are rich in antioxidants, vitamins, and minerals seem to provide protective and supportive effects on skin function.

These observations are in line with earlier research indicating that Vitamin A, Vitamin C, Vitamin E, and Zinc play important roles in preserving skin integrity, aiding collagen synthesis, and minimizing oxidative stress.

Moreover, nutrition seems to hold particular significance in chronic inflammatory diseases like psoriasis, where dietary changes can support pharmacological treatments and enhance overall patient outcomes. Likewise, in the case of acne, there is evidence that low-glycemic diets might alleviate disease severity by affecting hormonal and inflammatory mechanisms.

In summary, this discussion reinforces the idea that nutrition should be regarded as a key factor in both the prevention and management of dermatological conditions. Nonetheless, additional large-scale clinical studies are required to establish standardized dietary guidelines for the management of skin diseases.

The review emphasized the adverse impacts of high-glycemic diets and processed foods on skin inflammation. Likewise, Smith et al. (2007) found that individuals adhering to a low-glycemic-load diet experienced a reduction in acne severity, reinforcing the idea that insulin and IGF-1 pathways play a role in the development of acne (Smith *et al*. 2007).

Wolters (2005) primarily focused on psoriasis and its relationship with obesity, metabolic syndrome, and chronic inflammation. In contrast to studies that concentrate on acne, this research highlighted the systemic aspects of psoriasis and proposed that weight loss and anti-inflammatory diets could lead to improved disease outcomes. Both studies indicate that changes in diet may have a beneficial impact on inflammatory skin disorders, though the underlying mechanisms may vary (Wolters, 2005).

Stahl and Sies (2007) investigated the protective effects of antioxidants like carotenoids and flavonoids against oxidative damage caused by ultraviolet exposure. Their research differs from studies related to acne and psoriasis, as it emphasizes the prevention of premature aging and skin cancer rather than direct inflammatory processes. Nonetheless, all studies highlight the significance of minimizing oxidative stress for maintaining skin health (Stahl & Sies 2007).

Boelsma et al. (2001) and Draelos (2010) focused on the importance of micronutrients in maintaining healthy skin. Their research indicated that vitamins and minerals, including Vitamin A, Vitamin C, Vitamin D, zinc, and selenium, play a role in collagen synthesis, antioxidant protection, and skin regeneration. Although these studies emphasized skin physiology and aging rather than inflammatory diseases, they align with research on inflammatory skin conditions by highlighting the necessity of proper nutrition for overall skin health (Boelsma *et al*. 2001; Draelos, 2010).

Research in North Macedonia has identified a connection between systemic health, metabolism, and skin diseases. Damevska et al. noted a higher prevalence of metabolic syndrome among patients with psoriasis, indicating that nutritional and metabolic factors may affect the severity and progression of the disease. Additionally, studies from dermatology centers in Skopje highlighted the impact of chronic inflammation and systemic conditions on skin-related issues. These findings align with the increasing evidence that links nutrition and metabolic health to skin diseases (Damevska *et al.* 2013).

Conclusion

Skin diseases are influenced by obesity, metabolic and dietary factors, emphasizing the need for an integrated and multidisciplinary approach to clinical management involving dermatologist, endocrinologist and nutritionist. Medical nutrition therapy offers promising results not only in improving obesity, metabolic changes, and cardiovascular risk, but, leading to reduced inflammation and oxidative stress, directly and indirectly reduces the clinical severity of major inflammatory skin diseases. While observational studies suggest beneficial associations between dietary patterns and skin disease severity, the lack of large-scale, randomized controlled studies limits the definitive conclusions. Future research should prioritize well-designed RCTs to determine causality, refine dietary recommendations, and standardize assessment methods for adherence to the diet. Personalized nutrition strategies should be incorporated into routine dermatological care to increase treatment efficiency and improve patient quality of life.

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CLINICAL MANIFESTATIONS OF HERPES ZOSTER OPHTHALMICUS

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Abstract

Background: Herpes zoster ophthalmicus (HZO), which accounts for 10–20% of herpes zoster (HZ) cases, involves the first division of the trigeminal nerve.It is considered a medical emergency due to its potential to significantly affect visual function and quality of life.
The aim of this study was to evaluate the clinical manifestations of hospitalized patient with HZO and to identify potential factors associated with the time to improvement of skin rash and the duration of ocular symptoms at discharge.
Material and methods: Our case report is a 33-year-old man who presented with left-sided orbital and temporal stabbing pain, accompanied by swelling in the left frontal region that later extended to the left ocular area, with upper eyelid edema, burning, and tearing.
Due to the persistence of swelling and pain, the patient was referred to the Department of Infectious Diseases, hospitalized for further evaluation and treatment.
Results and Conclusion:
Varicella-zoster virus–specific cell-mediated immunity, which maintains latent VZV under control and is reinforced by periodic re-exposure, represents a key mechanism in preventing viral reactivation and the development of HZ.
Clinical manifestations include dermatomal vesicular rash, acute ocular pain, and prodromal symptoms. Slit-lamp biomicroscopy is necessary to identify ocular complications, while corneal sensation testing is recommended to detect neurotrophic keratopathy. Initial treatment consists of systemic antivirals, including acyclovir, with assessment for possible immunocompromise.
Advanced age is not the sole risk factor for HZO, as the disease may occur at any age. This case indicates that stress and other factors may contribute to VZV reactivation in middle-aged patients.. Whereas older age appears to be mainly associated with delayed healing of skin lesions.

Keywords: Herpes Zoster Ophthalmicus, Clinical Manifestations, Acyclovir,Varicella-Zoster Virus, Trigeminal nerve.

Introduction

Herpes zoster ophthalmicus (HZO) is a special type of HZ, accounting for 10–20% of HZ cases, which involves the first division of the trigeminal nerve (ophthalmic division).[1] HZ or shingles, results from reactivation of latent infection with varicella- zoster virus, which also causes chicken-pox. Anyone who has had chickenpox, even in subclinical form, is at risk for developing HZ. It is estimated that the lifetime risk of HZ is 30%, and 1 million new cases are reported annually in the United States.[2] HZO is a medical emergency because it can significantly compromise visual function and quality of life.
The combination of vision loss and chronic pain creates a dual burden, with profound psychosocial and economic consequences. Patients with HZO often experience reduced productivity, higher healthcare utilization, and increased risk of depression and social isolation.[4]
Herpes zoster classically results in a unilateral neurocutaneous reaction in the dermatome served by a particular neurosensory nucleus, causing pain and a pustular rash; serious complications such as superinfection, long-term pain, and ophthalmic involvement can result in significant morbidity. Up to 4% of patients presenting with herpes zoster require hospitalization to aid in management of complications.[3]

Objective

The aim of this study was to evaluate the clinical manifestations of hospitalized patient with HZO and to identify potential factors associated with the time to improvement of skin rash and the duration of ocular symptoms at discharge, emphasizing the need for close multidisciplinary collaboration among infectious disease specialists, ophthalmologists, and dermatologists.
The specific objectives include:
To identify the main clinical, dermatological, and ophthalmological manifestations of herpes zoster ophthalmicus.
To describe the pathophysiological pathway of HZO.
To evaluate the clinical course and variability of symptoms in relation to age and associated risk factors.
To analyze the potential ocular complications arising from this condition.
To emphasize the importance of early diagnosis and timely therapeutic intervention in preventing permanent damage, particularly ocular sequelae.

Epidemiology,risk factors and prevention measures

Epidemiological study results indicate that the lifetime risk of herpes zoster is nearly 30%, with approximately 1 in 3 individuals expected to develop shingles during their lifetime. Among these, nearly one-quarter will experience ophthalmic involvement, translating into millions of individuals at risk for HZO-related complications worldwide. [5]
Global Burden
Worldwide, the incidence of herpes zoster is estimated at 3 to 5 cases per 1000 person-years, with rates increasing sharply in older populations to over 10 cases per 1000 person-years in individuals aged 60 years and older; approximately 10% to 20% of these manifest as HZO, equating to millions of cases annually. With global increases in life expectancy and a higher prevalence of immunosuppressive conditions, the burden of HZO is expected to rise significantly in the coming decades.[6]
Sex Distribution
Most population-based studies show a slightly higher incidence in females than males, mirroring trends in herpes zoster more broadly. This difference may reflect both immunological and healthcare-seeking factors. However, no strong sex predilection is consistently observed in all cohorts.[7]
Of all risk factors, reactivation along the trigeminal nerve has been implicated in developing HZO. Of the branching fibers (nasocil-iary, frontal, and lacrimal), frontal nerve involvement is the most frequently doc-umented. Risk factors for both acute and recurrent HZO include immuno-compromised status, female sex, au-toimmune disorders, and an age of 50 years or older. Additional risk factors for recurrence of disease include 30 or more days of zoster-associated pain during acute infection, ocular hypertension, and uveitis following acute infection.[2]
The CDC recommends use of varicella zoster immune globulin preparation for postexposure prophylaxis in patients at high risk of severe disease who lack immunity to varicella or for whom vaccination is contraindicated. This includes neonates or those who are immunocompromised or pregnant. The CDC recommends administration of immune globulin as soon as possible after exposure to varicella and within 10 days. Patients affected by herpes zoster are advised to remain under contact and respiratory isolation until full crusting of lesions is achieved, to prevent transmission to others.[8].

The first line of defense against HZO is prevention through vaccination. Compared to the live attenuated vaccine (Zostavax), the newer subunit vaccine (Shingrix) is more effective at reducing the incidence of HZ (51% vs. 97%, respectively, over three years). [9]

Pathophysiology

VZV is a double-stranded DNA virus that initially invades the upper respiratory tract via virus-laden respiratory droplets, replicating and invading adjacent lymph nodes. [10]
During primary infection, viral particles are believed to spread from the infected skin along sensory nerve endings, ultimately reaching the nerve ganglia. An alternative hypothesis suggests that hematologic spread during the viremic phase leads to access to the ganglia. [11]
Following primary infection, the host's immune system suppresses viral replication; however, viral particles can then remain dormant for years, most commonly in spinal root and cranial nerve ganglia.The virus moves anterograde toward superficial tissue in the reactivation phase, reemerging as herpes zoster. [10]
After latency, when cell-mediated immunity declines due to aging, immunosuppression, or stress, the virus reactivates and spreads centrifugally along the ophthalmic branch of the trigeminal nerve, reaching the skin, cornea, conjunctiva, and ocular adnexa.[12]
Reactivation results when host immunity fails to suppress the virus and the reactivation leads to the classic dermatomal rash and neuropathic pain in the distribution of the dermatome of the involved cranial or spinal nerve. Additionally, inflammation in the ganglion itself can lead to neuronal necrosis. At the time of reactivation, the immune system demonstrates a T-cell proliferation with subsequent production of interferon-alfa and herpes virus-specific antibodies.[13]
The ophthalmic division of the trigeminal nerve provides sensory innervation to the cornea, conjunctiva, sclera, iris, eyelids, and forehead. Viral reactivation in this distribution explains the dermatomal rash and high frequency of ocular manifestations. Viral replication in the affected nerves causes neuritis, leading to acute pain and neuralgia. Inflammatory mediators and immune cell infiltration further contribute to nerve injury, predisposing to chronic postherpetic neuralgia.[14]
The ophthalmic division gives rise to 3 terminal branches: the lacrimal, frontal, and nasociliary branches. The nasociliary branch innervates the skin of the tip of the nose and divides further into the long ciliary nerves, which provide sensory innervation to the globe, including the cornea and uvea. For this reason, involvement of the tip of the nose, or Hutchinson sign, is highly correlated with ophthalmic involvement.[15]
As the virus replicates, viral particles migrate peripherally along the sensory nerves, triggering a local inflammatory immune response. In the early stages of replication and inflammation, this pain is often mildly neuropathic in nature, with sensations of burning and tingling; however, as the virus continues to replicate, the inflammation becomes severe, leading to intense pain in the affected dermatome. Once the virus reaches the skin, it penetrates the epidermis, resulting in a pustular lesion. Ophthalmic involvement follows a similar paradigm, as viral replication along the long ciliary nerves results in inflammation that can involve the cornea, sclera, conjunctiva, iris, retina, and optic nerve. As the virus migrates along these nerves, inflammatory sequelae can cause optic neuritis, retinal necrosis, and uveitis, as well as corneal stromal and epithelial sequelae. [16].

Case presentation

We conducted an observational study on a 33-year-old male who presented with left-sided orbital and temporal stabbing pain, accompanied by additional symptoms that began three days

prior to examination. The initial presentation included swelling in the left frontal region, which subsequently extended to the left ocular area, associated with upper eyelid edema, burning sensation, and tearing.The patient had no significant past medical history and no known drug allergies, and presented with dermatological and ocular symptoms. His chief complaint was a rash and pain localized to the left frontal and orbital region.

Three days prior to admission, the patient developed a rash in the left frontal region, which progressively spread to the left orbital area. The condition was associated with a burning sensation, itching, and severe pain. The patient was initially evaluated by an ophthalmologist and started on topical therapy with Tobramycin and Dexamethasone. He was subsequently assessed by a dermatologist and initiated on oral Acyclovir (five times daily). Despite treatment, the pain and swelling persisted, leading to referral and hospital admission to the Department of Infectious Diseases for further evaluation and management.

Prior to hospitalization, ophthalmological examination revealed no pathological changes in the cornea. Fluorescein staining (FLNA) was negative, and corneal sensitivity was preserved. Following the initial evaluations by the ophthalmologist and dermatologist, antiviral therapy with Acyclovir was initiated. Due to persistent symptoms, the patient was referred for inpatient care.

The patient reported no chronic diseases, and his family and epidemiological history were non-contributory.

The patient was in good general condition, conscious, afebrile, eupneic, and with a normal heart rate. The skin had normal coloration, while in the left frontal and orbital region a maculopapulovesicular rash was observed, accompanied by edema of the left upper eyelid.

On systemic examination, the respiratory system revealed normal vesicular breath sounds. The cardiovascular system showed a regular cardiac rhythm with normal heart sounds and no pathological murmurs. Examination of other systems did not reveal any pathological findings.

The patient received combined multidisciplinary treatment, including both topical ophthalmic and systemic therapy. Local treatment consisted of moxifloxacin eye drops (Vigamox) administered four times daily, artificial tears (Proculin Advance) six times daily, chloramphenicol ophthalmic ointment once daily in the evening, and acyclovir 3% ophthalmic ointment applied three times daily.

Upon admission, systemic therapy was initiated immediately and included intravenous fluid replacement with 0.9% sodium chloride, parenteral third-generation cephalosporin (ceftriaxone 2 g/day), antiviral therapy with acyclovir, serrapeptase, as well as vitamin supplementation (pyridoxine and ascorbic acid) and additional symptomatic treatment.

Throughout hospitalization, the patient remained afebrile and demonstrated a favorable clinical course. Progressive improvement was observed, including reduction of eyelid edema and evolution of the skin lesions into the crusting stage. At discharge, continuation of therapy at home was recommended, including topical tobramycin/dexamethasone combination and systemic acyclovir.



Dg.herpes zoster ophthalmicus lat.sin

Figure 1&2. A 33 year old man with V1 dermatomal rash, ptosis, and periorbital edema.

* The images were obtained on the fifth day of hospitalization.

Clinical MANIFESTATIONS

The physical exam begins with an external evaluation of lesion distribution, including the eyelids and scalp. The rash often appears maculopapular before transitioning to vesicles and pustules that ultimately rupture and scab over. Although the rash is usually limited to a single unilateral dermatome, immunocompromised individuals may develop disseminated disease, with a possible bilateral presentation. Particular attention should be paid to eyelid involvement, which is frequently associated with blepharitis, conjunctivitis, and episcleritis. A thorough ocular exam must include visual acuity, slit-lamp examination with fluorescein staining, and ocular tonometry; a thorough dilated funduscopic exam is also necessary.[17]

Depending on the severity of infection, patients may develop significant ptosis secondary to edema, resulting in inability to close the eyelid and dry eye. Red eye, excessive tearing, eye pain, blurred vision, photophobia, and decreased visual acuity are common complaints. The most common ocular presentations include mucopurulent conjunctivitis, anterior uveitis, and keratitis (nummular and disciform). Episcleritis and chemosis are often seen in acute disease, as well. [2]

The rash may involve the tip of the nose or nasal ridge, known as Hutchinson sign. This region is innervated by the nasociliary fibers, which also serve the conjunctiva, sclera, cornea, iris, and choroid. Hutchinson sign is associated with an increased risk of HZO. The absence of this sign does not rule out disease, however, as up to 30% of patients with HZ but without Hutchinson sign will develop HZO.[18]

Beyond ocular pathology, HZO is strongly associated with postherpetic neuralgia, a chronic neuropathic pain syndrome resulting from VZV-induced damage to sensory nerves. PHN can persist for months to years, significantly impairing quality of life. [4]

Treatment

Following a complete history and physical examination, management goals in the patient with herpes zoster ophthalmicus include shortening disease course, providing analgesia, and preventing potential complications. Treatment ultimately depends on the degree of ocular involvement. However, nearly all patients with acute manifestation of herpes zoster ophthalmicus require treatment with systemic antiviral medications, as the disease process is not limited to the ocular surface. Systemic antivirals have been shown to reduce viral shedding from skin lesions, reduce the chance of viral dissemination, and reduce the incidence and severity of ocular complications. Therapy started within 72 hours can also decrease the duration of postherpetic neuralgia, which may occur later in the disease process. [2]

Options for treatment include oral acyclovir, famciclovir, and valacyclovir. Famciclovir (500 mg 3 times a day) and valacyclovir (1 g 3 times a day) have been shown to be as effective as

acyclovir (800 mg 5 times a day),15 both in the treatment of herpes zoster and in reduction of complications. The simpler dosing regimen of famciclovir and valacyclovir may enhance patient compliance. Intravenous acyclovir is recommended in immunocompromised hosts, particularly to prevent disseminated disease such as encephalitis.[19]

The standard duration of antiviral therapy is 7-10 days. However, varicella DNA has been shown to persist in the cornea for up to 30 days, particularly in elderly individuals.[20]

In disseminated HZ or in immunocompromised patients, IV acyclovir is indicated; if the disease is resistant to acyclovir, IV foscarnet may be considered.

For HZO in particular, adjuvant therapy is used. Analgesics or steroids are given to reduce pain. If blinking is impaired, lubricating and antibiotic ophthalmic ointments may be used. Nonophthalmic topical antibiotics and dressings with adhesive are typically avoided, as they can exacerbate the rash and delay healing.

For stromal keratitis and uveitis, topical corticosteroids are used judiciously with close monitoring. Be aware that tapering prior to resolution of inflammation can prolong healing time. For optic neuropathy or orbitopathy, IV acyclovir is used at a dosage of 10 to 15 mg/kg three times daily for two to three weeks. The treatment for retinitis is similar, with the addition of several months of oral antiviral therapy.[21]

DISCUSSION

HZO is a serious condition characterized by various symptoms and complications, including postherpetic neuralgia, conjunctivitis, keratitis, uveitis, and even retinal vasculitis and necrosis. Previous studies have reported an incidence rate of ocular symptoms in HZO patients ranging from around 50% to 80%.This may be attributed to the fact that hospitalized patients generally have more severe symptoms. Patients with more pronounced and severe ocular involvement are more likely to be advised for hospitalization by doctors. Hence, the incidence rate of ocular symptoms among our patients is expected to be higher. Conjunctivitis, keratitis, and uveitis have been reported as the most common ocular manifestations of HZO.[22]

The evaluation of a patient suspected of having herpes zoster ophthalmicus begins with a complete history. When possible, a history of primary varicella infection should be solicited. Careful questioning to elicit potential immunocompromise should be undertaken, as the disease entity can be more severe and prolonged in immunocompromised individuals. The physical examination should be complete and thorough to evaluate for dermatomal involvement of herpes zoster. Varicella virus serologies are not part of the typical work-up because diagnosis can usually be made by history and physical examination alone. [8]

In developing countries, there are few studies on the prevalence of HZO infection, which allow the implementation of promotion and prevention strategies. It is important to create a higher awareness in the context of promotion to make an earlier diagnosis and avoid complications.

If there is a suspicion for ophthalmic involvement, a consultation with an ophthalmologist is recommended due to the significant morbidity that can occur.

In addition to the characteristic dermatologic findings, HZO can present with a variety of ocular findings, which occur in up to 50% of patients who do not receive antiviral treatment.

A trend of HZO occurrence at younger ages! However, previous studies have shown that specific cell-mediated immunity to VZV may decrease with age, leading to an increased incidence and severity of HZO.

CONCLUSION

This study provides the clinical manifestations and some risk factors of HZO patients. This review also describes the pathophysiology, evaluation, treatment, and prevention of herpes zoster ophthalmicus. First-line interventions include treatment with systemic antiviral medication, such as acyclovir, and testing to uncover potential immunocompromise.

Aging is not the only risk factor for HZO, since its occurrence does not know age and this case shows that stress with other factors help in the reactivation of VZ even in middle age as we

showed in our case. Therefore, we can say that advanced age is an independent risk factor for delayed healing of skin lesions.
Herpes zoster ophthalmicus causes significant ophthalmic morbidity if not adequately diagnosed and treated.
It can lead to serious sequelae, the most adverse involving the eyes, which may require more aggressive treatment for patients with severe facial rash.
For those whose symptoms persist after discharge from the hospital, further studies and follow-up are necessary.

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VANISHING ACT: THE TRUTH BEHIND THE CT FOGGING PHENOMENON IN ISCHEMIC STROKE - A CASE REPORT

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Abstract

The fogging phenomenon is a well-recognized yet frequently underappreciated imaging pitfall in neuroimaging, particularly during the subacute phase of cerebral infarction. It is characterized by the transient normalization of previously hypodense ischemic brain tissue on computed tomography (CT), which may lead to misinterpretation as lesion resolution.
We present a case of subacute ischemic stroke in an 89-year-old patient, demonstrating the fogging effect on CT imaging, accompanied by a review of its pathophysiology, temporal evolution, and clinical implications. Recognition of this phenomenon is essential for neurologists and radiologists to prevent diagnostic errors and ensure appropriate patient management.

Keywords: ischemic stroke; fogging phenomenon; computed tomography (CT).

Introduction

Cranial CT remains a first-line imaging modality in the evaluation of acute and subacute stroke due to its accessibility and speed. However, its sensitivity varies depending on the timing of imaging. One notable limitation is the fogging phenomenon, first described in the 1970s, in which infarcted brain tissue transiently appears isodense relative to normal parenchyma.
Non-contrast CT is widely used in the evaluation of acute stroke; however, its sensitivity varies with time and anatomical location. Posterior fossa infarctions remain challenging due to technical limitations. The fogging phenomenon, first described in ischemic stroke imaging, represents a transient phase in which infarcted tissue becomes isodense, potentially obscuring diagnosis.
The progression of an ischemic stroke on imaging during the subacute phase can exhibit a variety of changes that reflect the underlying pathophysiological processes of tissue damage and repair. One notable phenomenon observed during this phase is the gradual disappearance of density or signal abnormalities within the infarcted region, a process commonly referred to as the “fogging effect”, which typically occurs in the second and third weeks [1,2].
This phenomenon may falsely suggest lesion resolution or lead to underestimation of infarct size. Recognizing this temporal imaging pattern is essential, especially when clinical findings remain discordant with imaging.
Case Report
An 89-year-old patient was admitted due to generalized weakness, gait instability, and left-sided limb weakness, with symptoms developing approximately 10 days prior to the initial neurological evaluation. Because of suspected cerebrovascular insult, an urgent brain computed tomography (CT) scan was performed.
The initial CT demonstrated advanced global cortical atrophic changes without evidence of an expansive lesion. In the left cerebellar hemisphere, involving the anterior lobe and part of the

superior cerebellar peduncle, a well-demarcated hypodense area with cortico-subcortical distribution and mild surrounding edema was observed, without significant effect on the ventricular system. The findings were consistent with a late subacute/early chronic ischemic infarction.

Past medical history was notable for arterial hypertension treated with regular therapy. Admission ECG revealed atrial fibrillation, after which the patient was evaluated by an internist and admitted to the neurology department.

Neurological examination showed preserved consciousness and orientation without speech disturbances. Cranial nerve examination was unremarkable. Coordination testing was normal on the right side, while dysmetria was noted on the left. Mild left-sided weakness was present, characterized by drifting and slow descent of the left extremities during positional testing. Reflexes were symmetric, and plantar responses were flexor bilaterally.

Follow-up brain CT demonstrated increased density and less distinct demarcation of the previously described left cerebellar post-ischemic lesion, prompting a recommendation for brain magnetic resonance imaging (MRI). Although MRI was scheduled, the examination could not be completed due to technical reasons. A subsequent follow-up CT demonstrated near-complete resolution of the previously observed hypodensity in the left cerebellar hemisphere, a finding suggestive of the "fogging phenomenon." No new focal lesions were identified in the remaining brain parenchyma.

As part of the etiological workup, cardiology evaluation confirmed atrial fibrillation. In addition, Doppler ultrasonography of the carotid and vertebral arteries demonstrated atherosclerotic but hemodynamically insignificant changes. During hospitalization, the patient was treated as having a cardioembolic ischemic stroke with antiedematous, anticoagulant, antihypertensive, statins, and symptomatic therapy. Regular monitoring of vital signs was performed.

The patient was managed as a cardioembolic ischemic stroke. During hospitalization, the general condition deteriorated due to cardiogenic decompensation with subsequent cardiac arrest which ultimately resulted in a fatal outcome.

Discussion

Ischemic stroke is one of the leading causes of morbidity and mortality worldwide, second only to myocardial infarction in terms of cardiovascular disease burden. It results from cerebral injury due to the abrupt interruption of blood flow in a vascular territory, leading to ischemia and neuronal necrosis [1]. Hypoperfusion may result from an in-situ thrombus, embolic migration, or reduced blood flow (due to conditions such as heart failure, dissection, or stenosis from vasculitis), all of which cause a reduction in cerebral blood flow, leading to impaired cellular exchanges and cytotoxic edema. Clinically, it manifests as motor or sensory deficits, aphasia, or altered consciousness, with a sudden onset [1].Ischemic stroke progresses through four stages, corresponding to varying degrees of injury, whose CT characteristics are described in the table below (Table 1).

Temporal Evolution of CT Findings in Ischemic Stroke

Phase	CT Appearance
Hyperacute (0–6 h)	Often normal, especially in posterior fossa
Acute (6–72 h)	Hypodensity becomes more apparent
Subacute (7–21 days)	Fogging phenomenon (isodense phase)
Chronic (>3 weeks)	Hypodensity with encephalomalacia and atrophy

The progression of cerebral infarction (in the absence of early reperfusion) leads to the formation of infarcted tissue, which is manifested in imaging by a progressive exaggeration of hypodensity on CT, the appearance of hyperintensity on FLAIR and T2 sequences, with a decrease in diffusion-weighted imaging hyperintensity and pseudonormalization of Apparent diffusion coefficient (ADC) values around 10–14 days post-infarct. During the subacute phase, between the second and third week, there is migration of lipid-rich macrophages and leukocytes, capillary proliferation, extravasation of red blood cells, and reduction of the edematous component [1]. These processes are reflected on CT by an increase in density, which may obscure the infarcted area and can be a source of confusion. This phenomenon corresponds to the "fogging effect," which occurs in 10% to 54% of cases and may lead to confusion due to the radiological pseudonormalization of the cerebral tissue [2,3]. The fogging phenomenon has been reported in 20–50% of infarctions, most commonly between days 10–20. It is associated with reperfusion and larger infarcts but may occur in posterior circulation strokes as well. This pseudonormalization of density is transient, and hypodensity reappears on follow-up CT scans [4]. The administration of contrast agents helps refine the diagnosis by showing gyriform enhancement due to the disruption of the blood-brain barrier, thus delineating the affected territory. In cases where perfusion CT is performed, a "luxury perfusion" pattern is noted, reflecting an adaptive increase in blood flow, which better highlights the infarcted area [5]. On MRI, the fogging effect is characterized by either the disappearance of signal abnormalities on T2/FLAIR and diffusion sequences or by blurring and attenuation of T2/FLAIR hyperintensity [1]. The "fogging effect" may be visible on SWI as signal voids caused by the presence of deoxyhemoglobin and methemoglobin within extravasated red blood cells [1]. These signal voids should be interpreted as hemorrhagic transformation if they present as punctate lesions exceeding 5 mm in size, or as microbleeds if smaller [4]. The fogging phenomenon is an important diagnostic pitfall in both supratentorial and cerebellar infarctions. In elderly patients and posterior circulation strokes, awareness is crucial. Familiarity with the "fogging effect" phenomenon helps prevent diagnostic errors, such as mistaking it for improvement or resolution of ischemia, which could lead to inappropriate discontinuation of treatment or secondary prevention strategies [6].

Conclusion

The "fogging effect" is a well-recognized phenomenon in the subacute phase of ischemic stroke imaging, where the infarcted area appears isodense or isointense with surrounding tissue and may sometimes be misinterpreted as improvement of the ischemic injury. The fogging phenomenon is an important diagnostic pitfall in both supratentorial and cerebellar infarctions. In elderly patients and posterior circulation strokes, awareness is crucial Familiarity with the "fogging effect" phenomenon helps prevent diagnostic errors, such as mistaking it for improvement or resolution of ischemia, which could lead to inappropriate discontinuation of treatment or secondary prevention strategies

The fogging phenomenon has been reported in 20–50% of infarctions, most commonly between days 10–20. It is associated with reperfusion and larger infarcts but may occur in posterior circulation strokes as well.

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BONE AUGMENTATION IN IMPLANT DENTISTRY; COMPARATIVE EVALUATION OF LATERAL WINDOW VERSUS CRESTAL APPROACH FOR MAXILLARY SINUS FLOOR AUGMENTATION — A SYSTEMATIC REVIEW

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Abstract

Insufficient bone volume in the posterior maxilla remains one of the principal challenges in implant dentistry. Progressive alveolar bone resorption and maxillary sinus pneumatization frequently compromise implant placement, necessitating sinus floor augmentation procedures. The lateral window and crestal (transcrestal) approaches are the most commonly utilized surgical techniques for maxillary sinus augmentation. Despite their high clinical success rates, controversy persists regarding indications, surgical morbidity, implant survival, and complication rates between these methods.

The purpose of this systematic review was to comparatively evaluate the lateral window and crestal approaches for maxillary sinus floor augmentation in implant dentistry, focusing on implant survival, bone gain, surgical complications, postoperative morbidity, and long-term clinical outcomes.

An electronic search of PubMed, Scopus, Web of Science, Cochrane Library, and ScienceDirect databases was conducted for articles published between January 2020 and March 2026. Thirty-six studies fulfilled the inclusion criteria. The lateral window approach demonstrated superior vertical bone augmentation in severely atrophic maxillae with residual bone height below 5 mm, achieving implant survival rates between 92% and 98%. The crestal approach showed lower postoperative morbidity, reduced surgical trauma, and shorter healing time, with implant survival rates ranging from 94% to 99% in moderately resorbed posterior maxillae. Membrane perforation represented the most common complication and was more frequently associated with the lateral approach.

Both techniques are clinically predictable and highly successful when appropriately indicated. The lateral window technique remains the gold standard in severe maxillary atrophy requiring extensive bone augmentation, whereas the crestal approach offers a minimally invasive alternative with lower patient morbidity in cases with adequate residual bone height. Appropriate case selection and surgical expertise remain fundamental determinants of long-term success.

Keywords Bone augmentation; sinus lift; lateral window; crestal approach; dental implants; maxillary sinus augmentation; implant dentistry

Introduction

Bone augmentation is a fundamental surgical procedure in contemporary implant dentistry aimed at increasing the quantity and quality of alveolar bone in areas where insufficient bone volume prevents ideal implant placement. Successful osseointegration and long-term implant stability depend heavily on adequate bone height, width, density, and vascularity. However, after tooth extraction, traumatic injury, periodontal disease, congenital defects, cystic lesions,

or prolonged edentulism, the alveolar ridge undergoes progressive physiological resorption that may significantly compromise implant rehabilitation.

The posterior maxilla represents one of the most anatomically challenging regions in implant dentistry due to rapid alveolar bone resorption combined with pneumatization of the maxillary sinus. Following tooth loss, the sinus progressively expands inferiorly, resulting in reduced vertical bone height and poor bone density, frequently classified as type III or IV bone quality according to Lekholm and Zarb classification. Consequently, implant placement in this region often becomes impossible without prior augmentation procedures.

Bone augmentation therefore plays a crucial role in restoring adequate bone architecture necessary for predictable implant-supported rehabilitation. The primary objective of augmentation procedures is to regenerate sufficient hard tissue volume capable of supporting osseointegrated implants under long-term functional loading. In addition to increasing bone quantity, augmentation procedures aim to improve bone quality, vascularization, biological stability, and biomechanical support around implants.

The importance of bone augmentation extends beyond implant placement alone. Adequate bone volume is essential for:

Achieving primary implant stability
Ensuring long-term osseointegration
Improving biomechanical load distribution
Enhancing peri-implant tissue stability
Optimizing esthetic outcomes
Reducing implant failure risk
Preventing prosthetic complications

Several augmentation techniques have been developed in modern implantology, including:

Guided bone regeneration (GBR)
Onlay grafting
Ridge splitting
Block grafts
Sinus floor augmentation (lateral window approach and crestal approach)

Distraction osteogenesis

Among these procedures, maxillary sinus floor augmentation has become one of the most predictable and extensively studied techniques for rehabilitation of the atrophic posterior maxilla.

The biological success of bone augmentation depends greatly on the regenerative capacity and quality of the newly formed bone. Ideal regenerated bone should demonstrate:

Adequate mineralization
Sufficient vascular supply
Mechanical stability
Favorable remodeling potential
High osteoconductive and osteoinductive properties

Bone quality significantly influences implant survival and long-term clinical outcomes. Poor bone density may compromise primary stability, delay osseointegration, and increase micromovement at the bone–implant interface. Consequently, achieving high-quality regenerated bone has become a major focus of contemporary regenerative implant dentistry.

Modern regenerative protocols utilize various grafting materials including:

Autogenous bone grafts
Allografts
Xenografts

Alloplastic biomaterials
Growth factors and biologics
Autogenous bone remains the gold standard because of its osteogenic, osteoinductive, and osteoconductive properties. Nevertheless, xenografts and synthetic biomaterials have gained increasing popularity due to reduced donor-site morbidity and favorable long-term volumetric stability. Advances in tissue engineering, biomaterials, piezosurgery, platelet concentrates, and digital surgical planning have substantially improved the predictability and safety of augmentation procedures. Contemporary literature demonstrates implant survival rates exceeding 90–95% in augmented bone when proper surgical protocols and patient selection criteria are respected.
Within sinus floor augmentation procedures, two principal surgical approaches dominate current clinical practice:
The lateral window approach
The crestal (transcrestal) approach
Both methods aim to elevate the Schneiderian membrane and create sufficient vertical bone height for implant placement. However, they differ considerably in surgical invasiveness, achievable bone gain, complication profile, healing dynamics, and clinical indications.
The lateral window approach was initially introduced for severely atrophic maxillae requiring substantial vertical bone gain. It involves preparation of a lateral bony window followed by Schneiderian membrane elevation and graft placement. This approach provides direct surgical visualization and extensive augmentation capacity but is associated with greater surgical invasiveness and postoperative morbidity. Still remains the preferred technique in cases of severe posterior maxillary atrophy requiring substantial augmentation.
Conversely, the crestal approach utilizes osteotomes or osseodensification through the alveolar crest to elevate the sinus membrane indirectly. It is considered minimally invasive, demonstrates lower morbidity, and is generally indicated in cases with moderate residual bone height.
Recent advances in implant surface technology, biomaterials, guided surgery, piezosurgery, and osseodensification techniques have significantly modified the indications and outcomes of both approaches. Contemporary literature suggests excellent implant survival rates with both methods, although significant differences remain regarding complication frequency, patient comfort, surgical indications, and achievable bone gain.
Understanding the biological principles, indications, limitations, and clinical outcomes of both augmentation techniques is essential for achieving predictable implant rehabilitation and long-term functional success in modern implant dentistry.
This systematic review critically analyzes recent evidence from relevant medical and dental journals to comparatively evaluate lateral window and crestal sinus augmentation approaches in implant dentistry.

Materials and methods

Focused Question

The review addressed the following PICO question:
“In patients with atrophic posterior maxilla requiring implant rehabilitation, does the lateral window approach provide superior clinical outcomes compared with the crestal approach regarding implant survival, bone augmentation, and complication rates?”
Electronic database searches were conducted in:
PubMed/MEDLINE
Scopus

Web of Science
Cochrane Library
ScienceDirect
The search period included studies published between January 2020 and March 2026. The following search terms were utilized: “maxillary sinus augmentation” , “lateral window sinus lift” , “crestal sinus lift” , “transcrestal sinus floor elevation” , “bone augmentation in implant dentistry” , “osseodensification sinus lift” , “implant survival sinus augmentation” , “sinus membrane perforation” .

Inclusion Criteria
The following studies were included:
Randomized controlled clinical trials
Prospective studies
Retrospective cohort studies
Systematic reviews
Human clinical studies
Publications from the last 5 years
Exclusion Criteria
Excluded studies included:
Animal studies
Case reports
Studies without implant survival data
Publications before 2020

Data Extraction
The following variables were extracted:
Residual bone height (RBH)
Implant survival rate
Vertical bone gain
Schneiderian membrane perforation
Biological complications
Prosthetic complications
Postoperative pain and swelling
Healing period
Follow-up duration

Results

Study Selection
The initial electronic search identified 1,547 studies. After duplicate removal and eligibility screening, 36 studies fulfilled the inclusion criteria for qualitative analysis.
The included literature comprised:
10 systematic reviews
8 randomized clinical trials
11 prospective studies
7 retrospective cohort analyses

Lateral Window Approach

Surgical Characteristics
The lateral window approach, also known as the lateral antrostomy technique or direct sinus lift procedure, is a surgical method used for maxillary sinus floor augmentation in patients with insufficient vertical bone height in the posterior maxilla. It is considered the gold standard technique for severe maxillary atrophy and allows direct visualization and elevation of the Schneiderian membrane with simultaneous placement of grafting material and, in many cases, dental implants.
This technique is generally recommended in:
Severe posterior maxillary atrophy
Residual bone height below 4-5 mm
Extensive vertical augmentation requirements
Prior implant rehabilitation
The fundamental principle of the technique is:
Creation of a bony window in the lateral wall of the maxillary sinus
Careful elevation of the Schneiderian membrane
Formation of a subantral compartment
Placement of bone graft material beneath the elevated membrane
Simultaneous or delayed implant placement depending on primary stability
The elevated sinus membrane acts biologically as a compartment that protects the graft material and facilitates new bone formation.

Clinical importance

The lateral window approach remains one of the most predictable regenerative procedures in implant dentistry. It enables implant rehabilitation in patients who otherwise would not qualify for implant treatment because of severe posterior maxillary bone deficiency. Long-term studies report implant survival rates exceeding 95%,
Implant Survival Rates
Recent systematic reviews reported implant survival rates ranging between 92% and 98% for the lateral approach making this procedure highly reliable when proper surgical principles and patient selection criteria are respected. Long-term implant success appears comparable to implants placed in native bone.
Several studies concluded that lateral sinus augmentation provides excellent primary stability even in severely atrophic maxillae.
Bone Gain
The lateral approach demonstrated the highest vertical augmentation capacity among all sinus lift techniques.
Average vertical bone gain:
8–12 mm
This substantial augmentation makes the technique ideal for complex implant rehabilitation in severely resorbed posterior maxillae.
Complications
The most frequently reported complication was Schneiderian membrane perforation. Recent evidence demonstrated perforation rates between:
10% and 35%
Additional complications included:
Bleeding
Sinus infection

Graft migration
Postoperative edema
Delayed healing
Small residual ridge height was identified as an important risk factor for membrane perforation.

Crestal Approach

Surgical Characteristics
The crestal approach, also known as the transcrestal sinus lift, osteotome sinus floor elevation, or indirect sinus lift technique, is a minimally invasive surgical procedure used for maxillary sinus floor augmentation through the alveolar crest. The technique was originally introduced by Robert B. Summers and is widely utilized in implant dentistry for patients with moderate posterior maxillary bone deficiency.
Unlike the lateral window approach, the crestal technique elevates the Schneiderian membrane indirectly through the implant osteotomy site without creating a lateral bony window. The crestal or transalveolar approach elevates the sinus membrane indirectly through the alveolar crest using osteotomes or osseodensification instruments.
This minimally invasive technique is recommended when:
Residual bone height exceeds 5 mm
Limited vertical augmentation is required
Reduced postoperative morbidity is desired
Simultaneous implant placement is planned
The crestal approach has gained increasing popularity due to improvements in osseodensification and minimally invasive implant protocols.
Biological principle of the crestal approach
The biological concept of the crestal sinus lift is based on:
Controlled fracture of the sinus floor
Elevation of the Schneiderian membrane
Creation of a subantral compartment
Placement of graft material beneath the membrane
Formation of new regenerated bone around the implant apex
The elevated membrane acts as a biological barrier that protects the graft material and promotes bone regeneration within the sinus cavity.
Implant Survival Rates
Implant survival rates reported for the crestal approach ranged between:
94% and 99%
Several recent studies demonstrated no statistically significant difference in implant survival between lateral and crestal approaches.
Bone Gain
The crestal technique generally achieved:
3–5 mm vertical augmentation
Although less extensive than the lateral approach, this bone gain is clinically sufficient for moderately resorbed posterior maxillae.
Advantages
Major advantages included:
Minimal surgical trauma
Reduced operative time
Lower postoperative pain
Faster recovery
Reduced swelling

Higher patient acceptance
Farina et al. reported significantly lower postoperative morbidity with transcrestal sinus elevation compared with lateral sinus augmentation.

Comparative Analysis Of Both Approaches

Parameter	Lateral Window Approach	Crestal Approach
Surgical invasiveness	High	Low
Bone gain	8–12 mm	3–5 mm
Residual bone height indication	<5 mm	>5 mm
Membrane perforation risk	Higher	Lower
Postoperative discomfort	Greater	Reduced
Surgical visibility	Direct	Blind technique
Healing period	Longer	Shorter
Implant survival	92–98%	94–99%

Discussion

Maxillary sinus augmentation remains one of the most predictable surgical procedures in implant dentistry. However, the choice between lateral and crestal approaches remains dependent upon multiple anatomical and clinical factors.
The present review demonstrated that both techniques provide excellent implant survival and predictable long-term outcomes. Nevertheless, important differences exist regarding invasiveness, augmentation potential, complication rates, and patient morbidity. The lateral window approach continues to represent the gold standard for severe maxillary atrophy because of its superior augmentation capability and direct surgical visualization. Recent literature confirms that this technique remains indispensable in cases with residual bone height below 5 mm.
Despite its effectiveness, the lateral approach remains technically demanding and is associated with increased complication rates, particularly Schneiderian membrane perforation. Recent systematic reviews indicate that reduced residual ridge height significantly increases perforation risk.
Conversely, the crestal approach has become increasingly popular due to advances in osseodensification and minimally invasive surgical concepts. Modern transcrestal techniques demonstrate excellent implant survival with significantly reduced postoperative morbidity. Several studies now suggest that the crestal approach may even be feasible in cases with residual bone height below 4 mm when advanced surgical protocols are utilized. Furthermore, technological innovations including piezosurgery, dynamic navigation, stereolithographic surgical guides, and advanced biomaterials continue to improve safety and predictability in both techniques.
Current evidence therefore supports individualized treatment planning based on:
Residual bone height
Sinus anatomy
Surgeon experience
Required augmentation volume
Patient-centered outcomes

Conclusion

Both lateral window and crestal approaches represent highly successful and evidence-based methods for maxillary sinus floor augmentation in implant dentistry.
The lateral window technique remains superior in:
Severe posterior maxillary atrophy
Extensive vertical bone augmentation
Complex anatomical cases
The crestal approach offers substantial advantages regarding:
Minimal invasiveness
Reduced postoperative morbidity
Faster healing
Improved patient comfort
Current evidence demonstrates comparable implant survival rates between both approaches when proper indications are respected.
Long-term treatment success depends primarily upon:
Accurate diagnosis
Appropriate case selection
Surgical expertise
Careful management of sinus anatomy
Modern evidence-based surgical protocols
Future randomized clinical trials with extended follow-up periods remain necessary to establish definitive evidence-based guidelines for sinus augmentation procedures in implant dentistry.

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DIAGNOSTIC VALUE OF DOPPLER ULTRASONOGRAPHY IN CAROTID ARTERY ATHEROSCLEROSIS

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Abstract

The carotid arteries are two major pairs of blood vessels in the neck, the internal and external carotids, that supply oxygen-rich blood to the brain, neck, and face. The right common carotid originates from the brachiocephalic trunk, while the left arises directly from the aortic arch. Carotid artery disease is caused by a buildup of fatty deposits, known as plaques, in the arteries that send blood to the brain. Plaques are clumps that include cholesterol, fat and blood cells that form in the artery. This process is called atherosclerosis. Carotid arteries narrow when they are clogged with plaques. A clog in carotid arteries makes it hard for oxygen and nutrients to reach the brain. The first line diagnosis of atherosclerotic plaques in carotid arteries is a Carotid Duplex Ultrasound, which uses high-frequency sound waves combined with Doppler technology to detect plaque buildup, stenosis and blockages in the carotid arteries, helping diagnose risks for stroke. It evaluates blood flow speed and vessel structure to assess carotid artery disease, blood clots and arterial damage. Duplex ultrasound (DUS) is a highly accurate, non-invasive primary screening tool, generally offering over 90% sensitivity for identifying high-grade (70-99%) stenosis and occlusion. Its diagnostic accuracy for high-grade stenosis often exceeds 85-90%, making it the preferred initial imaging test. Because of the low cost, minimal risk, and accuracy of duplex sonography, some carotid surgeons advocate endarterectomy on the basis of these results alone. A recent survey revealed that most vascular surgeons (75%) accept endarterectomy without preoperative arteriography for appropriate indications.

Keywords: Atherosclerosis, Common Carotid Artery, Plaque formation, Doppler Ultrasonography.

Introduction

The head and neck receive the majority of their arterial blood supply from the carotid and vertebral arteries. The common carotid arteries (CCAs) constitute the primary vessels delivering blood to the brain and face, with a total flow of approximately 600-700 ml/min.
There are two Common Carotid Arteries:

1. Right common carotid artery- originates from brachiocephalic trunk.
2. Left common carotid artery – arises directly from aortic arch.

Both arteries ascend in the neck within the carotid sheath, alongside the internal jugular vein and vagus nerve. They do not give off branches in the neck and typically divide at the level of the upper border of the thyroid cartilage (around the C4 vertebral level).
In the level of bifurcation these arteries divide into:

1. The internal carotid artery (ICA)
2. The external carotid artery (ECA)

ICA gives blood supply to brain and eyes and has no neck branches, whereas ECA supplies blood to face, scalp, tongue and neck structures.
Other important structures:
The carotid sinus is a widened area of the internal carotid artery that contains baroreceptors, which detect blood pressure changes and help regulate heart rate and vessel tone.
The carotid body is a small chemoreceptor cluster near the carotid bifurcation that senses oxygen, carbon dioxide, and pH levels in the blood, helping control breathing.
The most common disease of carotid artery is atherosclerosis occurring at the carotid artery bifurcation, typically involving the distal common carotid and proximal internal carotid artery, and to a lesser extent the proximal external carotid artery.
The fact that atherosclerosis develops next to branch ostia, bifurcations, and bends suggests that flow dynamics are important in this process. Low flow velocity and high shear stress are

typical environments for the development of atherosclerotic plaque· Constricted arteries and the carotid sinus, which have slower blood flow, are affected by the pulsing pattern of the cardiac cycle's blood flow, which results in fluctuating shear rates. A thrombus occlusion or embolization may occur as a consequence of the carotid artery gradually narrowing or of plaque rupture, both of which can induce transient ischemic attack (TIA) or strokes. (6,4)
Carotid artery disease account for between 10-20% of ischemic stroke.
Understanding the anatomy of carotid blood supply is crucial in diagnosing and treating these vascular conditions and diseases.

Understanding Atherosclerosis

Carotid artery plaque is a measure of atherosclerosis and is associated with future risk of atherosclerotic cardiovascular disease (ASCVD), which encompasses coronary, cerebrovascular, and peripheral arterial diseases.
Atherosclerosis is principally a lipid-driven process initiated by the accumulation of low-density lipoprotein and remnant lipoprotein particles and an active inflammatory process in focal areas of arteries particularly at regions of disturbed non-laminar flow at branch points in the arteries.
The development of these plaques lead to progressive narrowing and hardening of arteries, resulting in reduced blood flow and impaired oxygen delivery to tissues. Plaques may also become unstable and rupture, leading to thrombus formation and arterial occlusion.
The risk factors of atherosclerosis include:

- Diabetes
- Family history
- Blood pressure
- Inflammatory diseases such as rheumatoid arthritis and psoriasis
- Older age (male >45 and female > 55 years old)
- Smoking
- Unhealthy diet

After understanding the anatomy of the carotid arteries and the pathophysiological process of atherosclerotic plaque formation, the next essential step is to evaluate how these changes can be detected in clinical practice. (4.3)

Diagnosis of atherosclerotic plaques in carotid artery disease

Carotid artery atherosclerotic plaques are diagnosed primarily through non-invasive imaging:

- Carotid Duplex Ultrasound
- CT Angiography (CTA)
- MR Angiography (MRA)
- Contrast Enhanced Utrasound
- Positron Emission Tomography
- Digital Subtraction Angiography

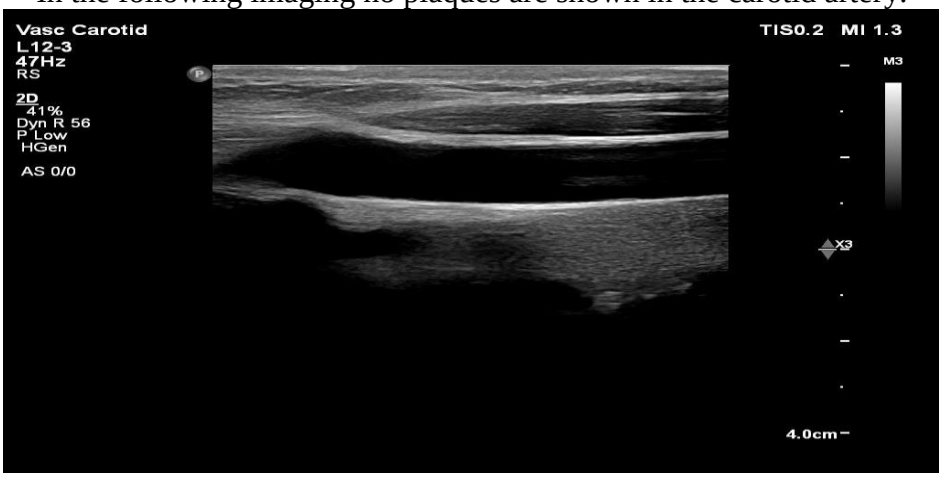
Carotid Duplex Ultrasound

One of the most widely used imaging methods for assessing carotid artery disease is duplex ultrasonography (DUS). This technique combines two complementary ultrasound modes. B-mode (grey-scale) imaging uses reflected sound waves to create real-time images of the carotid

artery, allowing evaluation of the vessel wall, lumen structure, and the presence of atherosclerotic plaque.

In addition, color and Doppler ultrasound assess blood flow by detecting changes in sound frequency caused by moving red blood cells. This provides both visual information about flow patterns and measurable data such as blood flow velocity, which are important for identifying and grading carotid artery stenosis. (1,2,5)

In the following imaging no plaques are shown in the carotid artery.

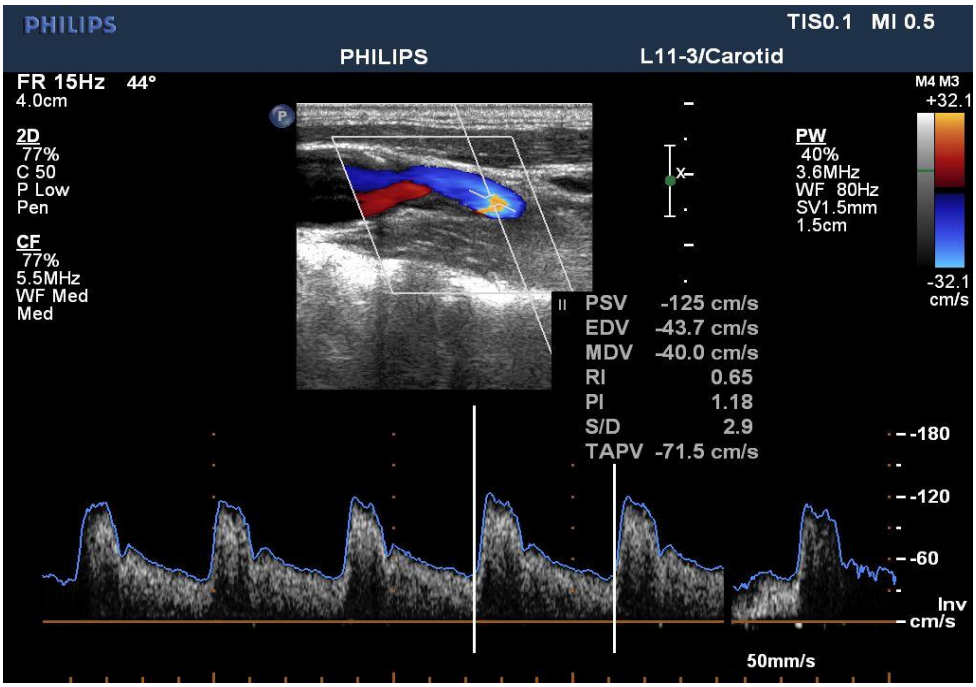


In the figure shown below, we have an atherosclerotic plaque of 1.77mm in bulbus caroticus.





In the picture shown above, a borderline plaque of 0.91mm is shown.



In the figure above, an approximately 75% of stenosis is shown.

Conclusion

Carotid ultrasonography is a safe, non-invasive, widely available imaging method, while still providing a real-time assessment of both structural changes and functional impact without exposing the patient to radiation. In addition, carotid ultrasound has high sensitivity and specificity for detecting moderate to severe stenosis**,** making it highly effective for identifying patients at increased risk of ischemic stroke. Color duplex ultrasound has replaced carotid arteriography as the preferred screening test for carotid artery occlusive disease. Because of the low cost, minimal risk, and accuracy of duplex sonography, some carotid surgeons advocate endarterectomy on the basis of these results alone. A recent survey revealed that most vascular

surgeons (75%) accept endarterectomy without preoperative arteriography for appropriate indications. (1,2,4)

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CORRELATION BETWEEN PERCEIVED STRESS, RESTING HEART RATE, BODY MASS INDEX, AND BLOOD PRESSURE AMONG MEDICAL FACULTY STUDENTS AT THE UNIVERSITY OF TETOVA. A CROSS-SECTIONAL STUDY.

Rida SALIJA, Esra RAKPI, Vegim ZHAKU

Abstract

Psychological stress is a common issue among medical students and may negatively affect important cardiometabolic parameters such as resting heart rate, blood pressure, and body mass index (BMI). Academic workload, emotional pressure, and lifestyle factors often contribute to increased stress levels in this population. Identifying the relationship between perceived stress and physiological parameters may help promote health and prevent early cardiovascular risk factors among students.

The aim of this study is to evaluate the correlation between perceived stress level, resting heart rate, BMI, and blood pressure among students of the Faculty of Medical Sciences at the University of Tetova.

This study will be observational and cross-sectional and will include 40 General Medicine students, consisting of 21 males and 19 females. Data will be collected anonymously after obtaining informed consent. Stress level will be assessed using the Perceived Stress Scale (PSS-10). Resting heart rate, systolic and diastolic blood pressure, body weight, and height will be measured for BMI calculation. Statistical analysis will be performed using Excel, SPSS, or JASP through descriptive analysis, t-test, ANOVA, and Pearson or Spearman correlation analysis depending on data distribution. Statistical significance will be considered at $p < 0.05$.

Expected results suggest that students with higher levels of perceived stress will present increased resting heart rate and higher blood pressure values. Additionally, a relationship between stress and BMI is expected, as well as possible gender differences.

This study is expected to contribute to a better understanding of the impact of psychological stress on the cardiometabolic health of medical students and to serve as a basis for preventive strategies and the promotion of stress management in the university environment.

Keywords: perceived stress, medical students, BMI, blood pressure, resting heart rate, cardiometabolic health.

Stress can be defined as a state of worry or mental tension caused by a difficult situation. Stress is a natural human response that prompts us to address challenges and threats in our lives. Everyone experiences stress to some degree.[3]

Physiological responses to stress include the complex changes the human body undergoes when faced with stressors. When the brain perceives a threat, it activates the sympathetic nervous system, initiating a "fight or flight" response characterized by increased heart rate, elevated blood pressure, and accelerated breathing. These changes prepare the body for immediate action by diverting blood flow to vital organs while suppressing non-critical functions such as digestion. Chronic exposure to stress can lead to serious health consequences, including cardiovascular disease, gastrointestinal disorders, and weakened immune function.

Study Objective

To assess the correlation between perceived stress, resting heart rate, BMI, and blood pressure among Medical Faculty students.

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Study Hypotheses

Primary Hypothesis

There is a positive correlation between the level of perceived stress and physiological parameters in Medical Faculty students, where students with higher perceived stress levels exhibit higher resting heart rates and higher blood pressure values.

Secondary Hypotheses

- The level of perceived stress differs between genders.
- Female students may exhibit higher levels of perceived stress compared to males.
- There is a relationship between body mass index (BMI) and perceived stress.
- Higher BMI may be associated with higher blood pressure values.

This is a cross-sectional study conducted among students of the Medical Faculty at the University of Tetova.
The study was carried out over a defined period of time and aimed to assess the correlation between perceived stress level, resting heart rate, body mass index (BMI), and blood pressure. Data were collected simultaneously through the PSS-10 questionnaire and physiological measurements of the participants.

Study on Stress and Cardiometabolic Parameters

Faculty of Medicine – University of Tetova | Comparison by Gender

Total Sample:	**40**	**Males:**	**21**	**Females:**	**19**

Parameter	**Males — Mean**	**Males — SD**	**Females — Mean**	**Females — SD**	**Difference (M-F)**
Stress PSS-10 (points)	16.9	4	21.1	4	**-4.2**
BMI (kg/m²)	24.24	2.68	21.68	4.02	**2.56**
Resting Heart Rate (bpm)	75.3	8.6	78.8	10.1	**-3.5**
Systolic Blood Pressure (mmHg)	122.6	8.6	115.7	13.7	**6.9**
Diastolic Blood Pressure (mmHg)	78.8	7.6	71.9	11.1	**6.9**

SD = Standard Deviation | Positive difference = Males have higher value | Negative difference = Females have higher value

Lifestyle Factors

Category	**Males (n)**	**Males (%)**	**Females (n)**	**Females (%)**
Physical Activity — Never	2	9.5%	2	10.5%
Physical Activity — 1–2 times/week	11	52.4%	11	57.9%

Physical Activity — 3–4 times/week	6	28.6%	4	21.1%
Physical Activity — 5+ times/week	2	9.5%	2	10.5%
Smoking — No	16	76.2%	13	68.4%
Smoking — Occasionally	1	4.8%	4	21.1%
Smoking — Regularly	4	19.0%	2	10.5%
Sleep — < 5 hours	1	4.8%	2	10.5%
Sleep — 5–6 hours	6	28.6%	3	15.8%
Sleep — 7–8 hours	12	57.1%	13	68.4%
Sleep — > 8 hours	2	9.5%	1	5.3%

PSS-10 — Perceived Stress Scale — Analysis Per Question

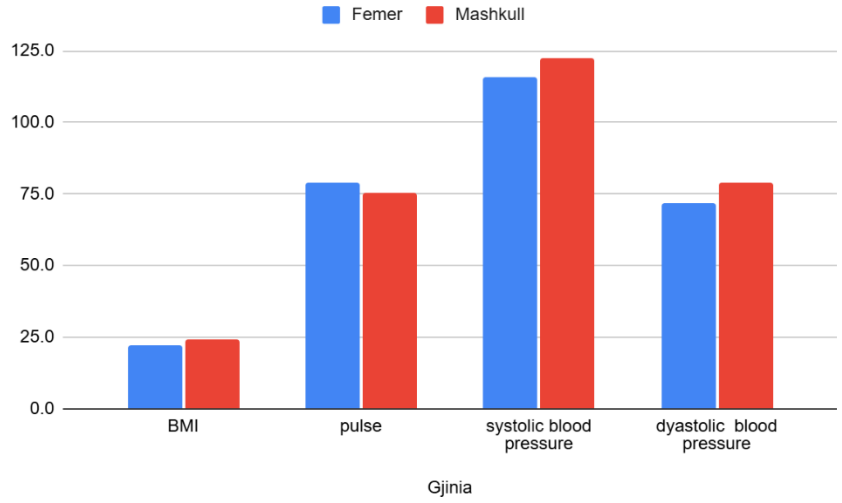
Question (PSS-10)	Males Mean	Males SD	Females Mean	Females SD	Difference	Direction
Q1. How often have you felt upset about something unexpected?	2.81	1.17	3.74	0.81	**-0.93**	Females ↑
Q2. How often have you felt nervous and stressed?	3.33	0.86	3.95	0.85	**-0.62**	Females ↑
Q3. How often have you felt confident in your ability? [R]*	3.9	1.0	3.68	0.67	**0.22**	Males ↑
Q4. How often have you felt that things were going according to plan? [R]*	3.29	1.15	2.84	0.83	**0.45**	Males ↑
Q5. How often have you felt unable to cope with your tasks?	2.38	0.92	3.11	0.81	**-0.73**	Females ↑
Q6. How often have you been able to control irritations? [R]*	3.43	0.87	3.32	0.95	**0.11**	Males ↑
Q7. How often have you felt "on top of things"? [R]*	3.48	1.03	3.0	0.94	**0.48**	Males ↑
Q8. How often have you felt angered by things outside your control?	3.52	1.17	3.63	1.01	**-0.11**	Females ↑
Q9. How often have you felt that difficulties were piling up?	2.9	1.14	3.47	0.9	**-0.57**	Females ↑
TOTAL PSS-10 (0–40 points)	**16.9**	**4**	**21.1**	**4**	**-4.2**	**Females ↑**

[R] = Reverse-scored question (4 minus original value). Total score: 0 = no stress, 40 = maximum stress.

PSS-10 Scores Per Question by Gender

Gender	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Female	3.5	3.7	3.7	3.7	2.8	3.1	3.3	3.0	3.6	3.5
Male	2.8	2.8	3.9	3.9	3.3	2.4	3.4	3.5	3.5	2.9

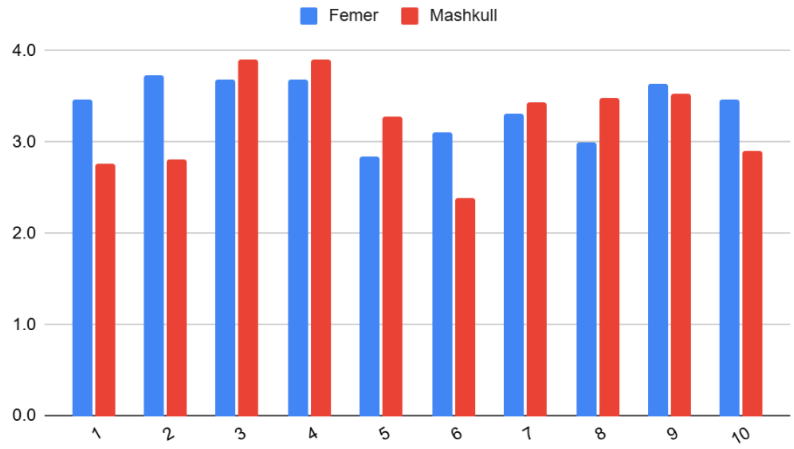
Gender	BMI	Resting Heart Rate	Systolic BP	Diastolic BP
Female	22.0	78.8	115.7	71.9
Male	24.2	75.3	122.6	78.8



PSS-10 — Perceived Stress Scale

The PSS-10 is a scale measuring perceived stress over the past month, consisting of 10 questions:

1. How often have you felt upset about something unexpected?
2. How often have you felt that you were unable to control the important things in your life?
3. How often have you felt nervous and stressed?
4. How often have you felt confident about your ability to handle your personal problems? (reverse)
5. How often have you felt that things were going your way? (reverse)
6. How often have you felt that you were unable to cope with all the things you had to do?
7. How often have you been able to control irritations in your life? (reverse)
8. How often have you felt that you were on top of things? (reverse)
9. How often have you been angered because of things that were outside of your control?
10. How often have you felt difficulties were piling up so high that you could not overcome them?



Physiological Parameters by Gender

Analysis of physiological parameters revealed differences between genders.
Males had:

- Higher BMI
- Higher systolic blood pressure
- Higher diastolic blood pressure

Females exhibited:

- Higher resting heart rate[4]

Mean values were:

- BMI: 24.2 in males vs. 22.0 in females
- Resting heart rate: 78.8 bpm in females vs. 75.3 bpm in males
- Systolic BP: 122.6 mmHg in males vs. 115.7 mmHg in females
- Diastolic BP: 78.8 mmHg in males vs. 71.9 mmHg in females

Results

Perceived Stress Level by Gender

Analysis of the PSS-10 scale showed that female students had a higher level of perceived stress compared to males.
The mean total PSS-10 score was:

- Females: 21.1 ± 4
- Males: 16.9 ± 4

A difference of 4.2 points suggests a higher perception of stress among the female gender.
In questions related to:

- worry
- nervousness
- emotional overload
- accumulating difficulties females reported higher mean values.

Meanwhile, males showed higher scores on reverse-scored questions, which reflect:

- emotional control
- self-confidence

[4] Physiological responses to stress | EBSCO [Internet]. EBSCO Information Services, Inc. | www.ebsco.com. 2024

- better coping with stressful situations

Conclusion

This cross-sectional study analyzed the relationship between perceived stress, resting heart rate, body mass index (BMI), and blood pressure among Medical Faculty students at the University of Tetova.
Results showed that female students exhibited higher levels of perceived stress compared to males, while males had higher BMI and blood pressure values. Females also showed a higher resting heart rate.
The findings suggest that perceived stress may be associated with physiological changes in the cardiovascular system and metabolic parameters. These results highlight the importance of identifying and managing stress among medical students, with the aim of preserving both physical and psychological health.[5]
Further studies with larger samples and more advanced statistical analyses are needed to more accurately assess the relationship between stress and physiological parameters.

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FORMS OF TREATMENT AND PREVENTIVE MEASURES OF PUERPERAL PARESIS ON SOME FARMS

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Abstract

Cow's milk fever (puerperal paresis or calving hypocalcemia) is an acute disorder of mineral metabolism. It occurs at the beginning of lactation, which is followed by hypocalcemia and hypophosphatemia. Animals with a genetic predisposition for high milk production are most at risk, immediately before calving and up to 72 hours after calving. It occurs in approximately 6% of dairy cows. In diseased cows, the hormonal mechanism that naturally maintains the calcium concentration in the blood plasma within normal limits (9 to 10 mg/dl) does not function. Clinical symptoms of milk fever appear when the calcium concentration in the blood plasma drops to 4 mg/dl. Predisposing factors that affect the occurrence of the disease are: nutrition, housing conditions, breed and age of the animals. Based on clinical signs, the disease manifests itself with clinical or subclinical signs. High-yielding dairy cows are more susceptible to puerperal paresis during the pre- and post-calving period. Milk yield, parity, age, breed, and diet composition of the cows are the most common factors contributing to the occurrence, incidence, and severity of milk taint. It is usually treated with oral calcium solutions and intravenous (I/V) calcium borogluconate. During the treatment of puerperal paresis, the primary focus should be on therapeutic treatment to restore blood calcium levels. Prevention of puerperal paresis is economically important to dairy producers to minimize production losses, mortality losses, and veterinary costs associated with the disease. Multiple strategies have been used to prevent hypocalcemia, including feeding anionic salts, low-calcium diets, vitamin D supplementation, dietary magnesium supplementation, and management of cow body condition during the calving period.

Keywords: calving paresis, milk fever, hypocalcemia, prevention.

Introduction

Milk fever (paresis puerperalis), the clinical manifestation of calving hypocalcemia, is one of the most common mineral-related metabolic diseases in dairy cows that occurs shortly before or immediately after calving as a result of low blood calcium levels. Although treatment with intravenous infusion of calcium salt solutions cures most clinical cases of hypocalcemia, such cows are later more susceptible to other metabolic and infectious diseases (Curtis et al. 1983, Curtis et al. 1984). In many countries, the prevention of hypocalcemia during calving is given high priority.

During the dry period, the demand for calcium is relatively low. Therefore, intestinal absorption and bone resorption of calcium are relatively inactive during this time. The onset of lactation results in a sudden loss of calcium through milk. When the calcium homeostatic mechanism is unable to meet the calcium demand for milk production, hypocalcemia occurs (Tsioulpas A, et al., 2007). About 50% of dairy cows in their second lactation and above have blood calcium concentrations that fall below the threshold for subclinical hypocalcemia after calving (Reinhardt T, et al., 2011).

Milk fever can be clinical or subclinical based on whether or not an animal can show clinical signs. Clinical signs include ataxia, poor appetite, reduced rumen movement, low body temperature, slow respiration, rapid and weak heart rate, paresis due to decreased muscle function that can progress to complete paralysis and coma (Goff J., 2008). It can be diagnosed based on the animal's history at the time of calving, clinical signs, maternal age, and response to intravenous calcium borogluconate solution (Radostits O., et al., 2007). Treatment of puerperal paresis should be done as soon as possible for a good recovery and to avoid

complications. Calcium borogluconate is most commonly used for the treatment of puerperal paresis (Oetzel G., 2011).

Milk fever is a common metabolic disease of dairy cows worldwide, affecting cows most distinguished by the amount of milk secreted. Risk factors for hypocalcemia can be divided into intrinsic risk factors, which are related to genetic factors, condition, and constitution of the animal itself, and extrinsic risk factors, which are related to breeding, care, welfare, and usually environmental factors.

The key to preventing puerperal paresis is close dry cow management or management during late pregnancy. Multiple strategies should be developed to manage hypocalcemia and increase calcium mobilization in dairy cows, especially in the peri-parturient period (Amaral-Phillips D., 2017).

General characteristics of milk fever. Milk fever is a non-febrile disease of adult dairy cows caused by acute calcium deficiency (Oetzel G., 2011). Low blood calcium levels can lead to the cow's inability to lift her feet off the ground, as calcium is vital for muscle and nerve function, resulting in a metabolic disorder called milk fever. This disease has been known by a number of names, including milk fever, postpartum paresis, puerperal paresis, and calving apoplexy. It generally affects high-yielding breeds in their productive phase and older dairy cows that have a reduced ability to mobilize calcium from their bones.

Treatment. Animals affected by the most severe form of puerperal paresis should be treated as soon as possible. Puerperal paresis is usually treated with oral calcium solutions and intravenous calcium borogluconate (Goff J., 2008). Oral calcium borogluconate supplementation is the best approach for hypocalcemic cows that are still standing, such as cows in stage I hypocalcemia or those with undetected subclinical hypocalcemia (Oetzel G., 2011). Cows in later stages (II and III) of milk fever should be treated immediately with a slow intravenous administration of 500 ml of 23% calcium borogluconate (Melendez P,. et al., 2008,). Extremely high doses of calcium can cause fatal cardiac complications (Doze J,. et al., 2008.). Subcutaneous calcium administration can also be used to support blood calcium concentrations around calving (Goff J., 2008).

Intravenous calcium borogluconate, administered early in the course of severe cases, is generally the treatment of choice. The solution should be given slowly because rapid infusion of calcium can result in cardiac arrest. The combined use of calcium borogluconate, initially intravenously, then subcutaneously, may prevent recurrence by slowly releasing biologically available calcium from the tissues into the bloodstream (Bhanugopan MS, Lievaart J., 2014).

Prevention and control of puerperal paresis. Many programs are used to prevent hypocalcemia and mobilize calcium ions in dairy cows. We can mention nutritional management, including: feeding with anionic salts, low calcium ion feeds, low potassium forages and vitamin D supplements (Boda J., Cole H., 2003). A large body of literature suggests that when the incidence of milk fever increases above 10% in their third or subsequent lactations, attention should be paid to a specific control program (Oetzel G., 2011). Several principles and factors of milk fever control are applied today in commercial dairy farms. These include oral calcium feeding during parturition with easily absorbed calcium supplements, feeding acidifying rations with anionic salt supplements during the last weeks of pregnancy, feeding low calcium rations during the last weeks of pregnancy, and management practices such as body condition monitoring and shortening the dry period (Goff J., 2008).

Providing adequate magnesium supplementation is vital for the prevention of milk fever. This is because magnesium (Mg) plays a very important role in Ca metabolism, as it is a key mediator in the resorption of Ca from bone by parathyroid hormone. In a recent review, increasing Mg supplementation was found to have the greatest impact among nutritional programs for the prevention of milk fever (Jesse PG, Nicholas JK., 2018). A common preventive strategy is to add anionic salts to reduce the cation-anion difference in the diet (Patel

VR, et al., 2011). Since diets high in potassium are commonly associated with milk fever, pre-calving potassium levels should be kept as low as possible. Since dry feed contains more potassium, feeding dairy animals higher amounts of dry feed should be discouraged to prevent milk fever.

Material and methods

The aim of this study is to present the forms of treatment and preventive measures of the disease of cows with the diagnosis of puerperal paresis. In our ten-year practice, from 2016 to 2025, in different farms in the area we have treated a total of 40 dairy cows with clinical signs of puerperal paresis and stretching before and after calving (Table 1).

Table 1. Number of cows treated during the 10-year period

Year of treatment	Number of cows
2016	3
2017	3
2018	5
2019	5
2020	7
2021	5
2022	4
2023	2
2024	2
2025	4
Total cows treated:	= 40

In the treatment of cows diagnosed with milk fever, we used 3 forms of application of calcium preparations (Table 2). In the first form, we treated cows intravenously with puerperal paresis with more severe clinical signs resulting in gradual loss of consciousness to the point of coma. In the second form, cows treated in two ways: intravenously and subcutaneously were restless and sensitive to external stimuli, with slight tremors in the muscles of the back, neck and limbs, with difficulty in standing and unsteady while walking. In the third form, we treated cows subcutaneously, with signs of subclinical hypocalcemia resulting in less severe Ca disorders, animals that cannot stand up, apathetic and do not respond to external stimuli, with their head tilted to the side and resting on their chest. These animals may also experience slight tremors in the muscles of the back, neck, and limbs. They have difficulty standing up and are unsteady when walking.

Cows lying down with more severe clinical signs, those that cannot stand up, were treated intravenously with slow intravenous administration of 500 ml of 23% calcium borogluconate, while cows with clinical signs of paresis to the point that they cannot stand up were treated with calcium preparations (Calciject 40%, containing calcium borogluconate and Calci-kel 300, containing calcium gluconate, magnesium chloride). Of the cows that were treated intravenously, there were 21, of which 15 cows stood up within 8 hours after the start of treatment and 3 cows did not stand up. After the second treatment, 6 stood up on the second day, while 3 cows remained lying down in the following days. Of the cows that were treated subcutaneously, there were 13 cows, of which after applying subcutaneous calcium, 12 cows stood up within 2 to 4 hours, while one cow did not stand up, as it was physically weaker, so one of them recovered, while one did not stand up for 4 days, but remained in a lying position for up to 13 days and then stood up and recovered completely. Two cows with severe paralysis

and one cow with paresis were recommended to the owner to eliminate from the herd, and another died of cardiac insufficiency during treatment. Cows with mild tremors in the muscles of the back, neck and limbs, with difficulty in standing and unsteadiness while walking were treated subcutaneously. All cases treated in this way stood up and recovered completely, without any recurrence.

Table 2. Forms of treatment of cows with milk fever and number of animals treated

Treatment form	Number of cows	Cows That Stood Up	Cows That Didn't Stand Up
Intravenous	21	18	3
Subcutaneous	13	12	1
Combined (i/v and s/c)	6	6	0

In all treated cases of cows with milk fever, the following preventive measures for post-calving paresis were recommended to farmers: low-calcium feed (< 20g per day), oral feeding around calving with easily absorbed calcium supplements, feeding acidifying rations with anionic salt supplements during the last weeks of pregnancy, feeding low-calcium rations during the last weeks of pregnancy, and pre-calving administration of vitamin D, vitamin D metabolites, and its analogues. There is another possibility to prevent hypocalcemia, and by limiting calcium intake during the dry period, calcium deficiency in the blood can be prevented. As already mentioned, the entire calcium regulation system in the body is regulated by the parathyroid glands, which secrete two hormones: parathyroid hormone (PTH) and calcitonin. PTH and calcitonin act in different ways. When there is not enough calcium in the blood, the parathyroid glands secrete PTH, which participates in the extraction of calcium from the bones and intestinal contents and stimulates the production of vitamin D, which is a calcium transporter. When there is too much calcium, the glands secrete calcitonin, which prevents the production of vitamin D and the breakdown of bone tissue, and all excess calcium is excreted from the body. It is especially important that PTH acts immediately before calving, because then the need for calcium increases drastically.

Results and discussions

From the results of the treatment, it can be seen that in the 10 years of field work, there were fluctuations in the incidence of milk fever. There were more cases of this disease in 2020, while fewer in 2023 and 2024. This is an indication that the occurrence of milk fever is also affected by the dry climate, in particular the alfalfa growing season, because alfalfa contains twice as much calcium as all forage crops, so it would be advisable to avoid feeding cows during the drying period. Only corn silage has very little potassium, so it is a good food for cows in the drying season. From the results of the forms of treatment, we can conclude that the intravenous application of calcium preparations in severe cases, with gradual loss of consciousness, was reasonable given the fact that the applications of other forms could endanger the life of the animal. The application of calcium solutions was performed slowly in the jugular vein, but we previously performed a subcutaneous injection of caffeine, as an analeptic drug that affects the awakening of the central nervous system and the acceleration of the heartbeat (bradycardia). After the treatment, we stood next to the animal, waiting for its reaction to the applied therapy. The action of caffeine and then calcium woke the animal from its serious clinical condition, then muscle tremors began from the front of the body, continuing to the rear parts. After 8 hours of application, most of the cows stood up and stood tiredly, trying to get a little food. After standing up, we gave recommendations to the farmers that the newly recovered animals should be left calm, without disturbance, offering them a little food and water. The very

important recommendation was that the cow should not milk within the next 48 hours, because this would cause the depletion of calcium reserves in the body and the recurrence of the disease. Of course, there were cases when some farmers did not respect these recommendations, so we had cases of repeated treatment of the disease.
Combined treatment (intravenous and subcutaneous), that is, a smaller amount of the drug was applied intravenously, in order to quickly act calcium, while the rest was applied subcutaneously. This form was carried out in cows with signs of subclinical hypocalcemia that resulted in less severe Ca disorders, animals that could not stand up, but with a lighter clinical picture. The animals treated in this form were not treated with preliminary caffeine therapy, because the animals were awake, with slowed breathing, temperature within normal limits and with their heads raised. Almost all the cows treated in this form, within 2 to 4 hours, stood up, only one of them did not stand up.
Subcutaneous treatment was performed on cows that were anxious and sensitive to external stimuli, with slight tremors in the muscles of the back, neck and limbs, with difficulty in getting up and unsteady while walking. Treatment in this form gave good results, almost all treated cows got up and stood on their feet until complete recovery. Even in these cases, we recommended to farmers that the cows should not be milked within the next 48 hours, because this would cause the depletion of calcium reserves in the body and the recurrence of the disease.

Conclusion

Metabolic diseases usually affect animals that are about to reach their maximum production potential. Milk fever or calving paresis is a common metabolic disorder in dairy cows that results from hypocalcemia that occurs in older, high-producing dairy cows in their third to sixth lactations that are about to calve or have recently calved. It is characterized primarily by progressive muscle weakness and depression that progresses to coma if not treated promptly. Calving causes a high volume of milk production and with it, a high demand for calcium from the cow's body. If the body is unable to respond quickly to this demand, the cow develops hypocalcemia. Hypocalcemic cows will begin to tremble and will no longer be able to stand. The cow will then lie down, first in a sternal position and then on its side. Calving paresis is favorable for early treatment with intravenous calcium supplements. Economically, it reduces milk yield and fertility. There are also losses due to the cost of treatment, the time the farmer spends dealing with the sick animal, and the increased risk of associated health problems. As with most diseases, prevention is key. Management practices such as body condition management and shortening the dry period are also critical to preventing the disease.

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MATHEMATICAL MODELING FOR OPTIMIZATION OF FOOD TRANSPORTATION

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Abstract

Food transportation is a critical component of the food supply chain because it directly affects delivery cost, product availability, service reliability, and the quality of perishable goods. In many practical situations, food products must be transported from several warehouses, production facilities, or distribution centers to several markets, supermarkets, restaurants, or institutional consumers. The main operational question is how to determine the quantity of goods that should be shipped from each origin to each destination so that total transportation cost is minimized while all supply and demand requirements are satisfied.

This paper presents a mathematical modeling approach for optimizing food transportation using the classical transportation problem from linear programming. The problem is formulated through decision variables, an objective function, supply constraints, demand constraints, and non-negativity conditions. A numerical example is developed for the distribution of food pallets from three distribution centers to four retail markets. The example is solved using the transportation simplex method, including the initial feasible allocation and the optimality test based on the MODI method. The results show that mathematical optimization can significantly support decision-making in food logistics by identifying the least-cost distribution plan and by providing a structured basis for operational planning. Knowledge of mathematical modeling techniques provides significant information for simulation and further design and optimization purposes

Keywords: Food transportation, mathematical modeling, transportation problem, linear programming, simplex method, logistics optimization, supply chain management

Introduction

Food transportation is one of the most important activities in the logistics and supply chain system. Unlike many other types of goods, food products often have specific requirements related to delivery time, temperature control, hygiene, storage conditions, and shelf life. Inefficient transportation can increase costs, cause delays, reduce product quality, and generate unnecessary losses. Therefore, food transportation requires careful planning and the use of rational decision-making methods. In practice, food companies frequently operate with several distribution centers and several delivery locations. Each distribution center has a limited available quantity of products, while each destination has a specific demand that must be satisfied. The planner must decide how much product should be transported from each origin to each destination. If the decision is made intuitively, the final transportation plan may be expensive or inefficient. Mathematical modeling provides a systematic method for finding an optimal or near-optimal distribution plan.

The increasing complexity of modern food supply chains has encouraged the development of advanced optimization techniques, intelligent transportation systems, and machine learning methods for improving logistics efficiency and reducing food spoilage. Intelligent routing and navigation algorithms developed for autonomous robotic systems have demonstrated that optimized movement planning can significantly reduce operational inefficiencies and transportation delays (Antoska Knights et al., 2017; Antoska Knights et al., 2018). Similar principles are increasingly applied in food transportation systems where route optimization contributes to reduced delivery time, minimized fuel consumption, lower operational costs, and preservation of product freshness.

Dynamic transportation environments frequently involve uncertainty related to traffic congestion, weather conditions, fluctuating demand, delivery deadlines, and perishability constraints. Therefore, adaptive optimization models and intelligent transportation systems have become essential for modern logistics management. Research involving dynamic modeling and intelligent control systems has shown that optimization under disturbances and uncertain environments can significantly improve system stability and operational performance (Knights & Petrovska, 2024; Antoska Knights et al., 2013). In addition, IoT technologies and AI-supported monitoring systems enable real-time decision-making and continuous tracking of transportation conditions (Antoska Knights & Gacovski, 2024; Knights et al., 2024).

Mathematical modeling is defined as a new solution to such 'old' questions which has been made possible by methods and fundamental changes used in the way problems are approached. The transportation problem is a special type of linear programming problem widely applied in logistics, production planning, and supply chain optimization. The objective is usually to minimize total transportation cost, although the same model can also be adapted to minimize transportation distance, travel time, carbon emissions, spoilage risk, or a weighted combination of several criteria (Dantzig, 1951; Laporte, 1992; Toth & Vigo, 2014).

Recent studies in sustainable food logistics increasingly focus on integrating environmental objectives, food quality preservation, and intelligent optimization methods. Pérez-Lechuga et al. (2024) proposed a green cold-chain routing model for perishable food distribution, while Wang et al. (2025) developed sustainable transportation planning approaches considering environmental and quality objectives simultaneously. Multi-objective optimization models integrating production, inventory, and routing decisions have also shown promising results in perishable food logistics systems (Chan et al., 2020).

The use of intelligent logistics systems and digital simulation tools has become particularly important in reducing food losses and improving transportation efficiency. Jedermann et al. (2014) emphasized the importance of intelligent food logistics systems for reducing spoilage and improving monitoring capabilities. Tsang et al. (2019) proposed an intelligent model for quality assurance in multi-temperature food distribution centers, while Fikar (2018) developed a decision-support system for investigating food losses in e-grocery deliveries. More recent approaches combine stochastic optimization, machine learning, and hybrid heuristics to address uncertainty in food transportation networks (Yu et al., 2023; Chen et al., 2026).

Optimization algorithms in food logistics vary depending on network complexity, perishability constraints, uncertainty levels, and computational requirements. Exact optimization methods such as Mixed Integer Linear Programming (MILP), branch-and-bound algorithms, and transportation simplex methods are highly effective for structured deterministic transportation problems. However, heuristic and metaheuristic approaches such as Genetic Algorithms (GA), Particle Swarm Optimization (PSO), and Ant Colony Optimization (ACO) are increasingly preferred for large-scale and dynamic logistics systems involving uncertainty and perishability (Kennedy & Eberhart, 1995; Dorigo & Stützle, 2004; Holland, 1992).

Machine learning methods, including neural networks, predictive analytics, and intelligent routing systems, additionally support adaptive logistics planning and real-time transportation management (Goodfellow et al., 2016; Bishop, 2006). Recent studies have demonstrated that AI-supported transportation systems can improve route optimization, reduce spoilage risk, and increase sustainability in urban food delivery networks (Kumar et al., 2024). Furthermore, statistical process control and intelligent optimization models contribute to sustainable food production and logistics management aligned with Sustainable Development Goals (Knights et al., 2026).

The purpose of this paper is to explain how mathematical modeling can be used to optimize food transportation and to demonstrate the procedure through a solved numerical example. The example is based on a balanced transportation problem and is solved using the transportation

simplex method. The integration of mathematical optimization, intelligent transportation systems, IoT technologies, and AI-based logistics planning provides important opportunities for improving supply chain performance, reducing food waste, minimizing transportation costs, and supporting sustainable food distribution systems. Different optimization approaches used in food logistics exhibit different advantages and limitations depending on the size of the transportation network, perishability constraints, uncertainty level, and computational complexity. Exact optimization methods are generally suitable for deterministic transportation problems, while heuristic, metaheuristic, and machine learning approaches provide greater flexibility for large-scale and dynamic logistics systems. A comparative overview of the most commonly applied optimization algorithms in food transportation is presented in Table 1.

Table 1. Comparison of Optimization Algorithms Used in Food Logistics

Algorithm Type	**Examples from Literature**	**Strengths in Food Logistics**	**Limitations**	**Typical Use Cases**
Exact Methods (MILP, Branch-and-Bound, Transportation Simplex)	Dantzig (1951); Laporte (1992); Yu et al. (2023)	Provides optimal solutions and precise cost minimization; highly suitable for balanced transportation problems	Computationally expensive for large-scale systems; limited adaptability to uncertainty	Small and medium deterministic transportation networks
Metaheuristics (Genetic Algorithms, Simulated Annealing)	Holland (1992); Singh et al. (2025)	Fast near-optimal solutions; adaptable to dynamic routing and spoilage reduction	Requires parameter tuning; solutions may not be globally optimal	Large-scale food distribution with time windows
Swarm Intelligence & Hybrid Heuristics (PSO, ACO, Hybrid GA-ML)	Kennedy & Eberhart (1995); Dorigo & Stützle (2004); Chan et al. (2020)	Handles uncertainty in demand, spoilage, and shelf-life variability; improves sustainability	Higher implementation complexity; computational tuning required	Dynamic logistics systems with stochastic behavior
Machine Learning Methods (Neural Networks, k-NN, Predictive Analytics)	Goodfellow et al. (2016); Bishop (2006); Kumar et al. (2024)	Real-time adaptation to traffic, spoilage risk, and environmental conditions	Requires large datasets and training procedures; reduced interpretability	Urban food delivery and intelligent transportation systems

The Role of Optimization in Food Transportation

Food transportation includes the movement of products from farms, factories, warehouses, cold-storage facilities, or distribution centers to final points of sale or consumption. The efficiency of this process depends on several factors, including transport cost, available vehicle capacity, distance, road network conditions, delivery time windows, product perishability, and demand uncertainty. In modern food supply chains, transportation efficiency has become increasingly important because perishable products are highly sensitive to delays, temperature fluctuations, and inadequate handling conditions (Jedermann et al., 2014; Tsang et al., 2019).
Optimization is important because even small improvements in transportation planning can result in considerable savings. For example, a company that distributes food every day may reduce fuel consumption, vehicle operating costs, labor time, and product losses by selecting better shipment quantities and routes. In addition, optimized transportation contributes to better customer service because demand can be satisfied on time and with lower operational risk. Recent studies have shown that intelligent routing systems and sustainable transportation planning approaches can significantly reduce spoilage risk, improve freshness preservation,

and decrease environmental impact in food logistics systems (Pérez-Lechuga et al., 2024; Wang et al., 2025).
The integration of intelligent transportation systems, machine learning, and optimization algorithms has additionally improved the adaptability and efficiency of food logistics operations. AI-supported transportation models and IoT-based monitoring systems enable real-time route optimization, traffic prediction, and continuous monitoring of transportation conditions (Antoska Knights & Gacovski, 2024; Knights et al., 2024). Similar optimization principles have previously been applied in autonomous robotic navigation and intelligent control systems where efficient movement planning reduced operational inefficiencies and transportation delays (Antoska Knights et al., 2017; Antoska Knights et al., 2018).
The classical transportation model is particularly useful when the main decision is the allocation of product quantities between origins and destinations. In its basic form, the model assumes that the unit transportation cost from each origin to each destination is known, the supply at each origin is known, and the demand at each destination is known. The model then determines the optimal shipping plan. Classical transportation optimization methods based on linear programming and transportation simplex algorithms remain highly applicable for balanced food distribution problems because they provide structured and computationally efficient solutions for minimizing transportation costs (Dantzig, 1951; Toth & Vigo, 2014).

Mathematical Formulation of the Transportation Problem

Let there be (m) origins and (n) destinations. In the context of food transportation, origins may represent distribution centers, warehouses, production plants, or cold-storage facilities. Destinations may represent supermarkets, local markets, restaurants, hotels, or public institutions.
The mathematical notation is defined as follows:

- (i = 1, 2, …, m) denotes the origins;
- (j = 1, 2, …, n) denotes the destinations;
- (s_i) denotes the available supply at origin (i);
- (d_j) denotes the demand at destination (j);
- (c_{ij}) denotes the unit transportation cost from origin (i) to destination (j);
- (x_{ij}) denotes the quantity transported from origin (i) to destination (j).

The objective is to minimize the total transportation cost:

$$Z = \sum_{i=1}^{m} \sum_{j=1}^{n} C_{ij} x_{ij} \quad (1)$$

subject to the supply constraints:

$$\sum_{i=1}^{m} x_{ij} = s_{i\,,} \quad i = 1,2,\dots,m \quad (2)$$

and the demand constraints:

$$\sum_{i=1}^{m} x_{ij} = d_{j\,,} \quad j = 1,2,\dots,n \quad (3)$$

with non-negativity constraints:

$$x_{ij} \geq 0, \quad i = 1,2,\dots,m, \; j = 1,2,\dots,n \quad (4)$$

For a balanced transportation problem, total supply is equal to total demand:

$$\sum_{i=1}^{m} s_i = \sum_{j=1}^{n} d_j \quad (5)$$

If total supply and total demand are not equal, the problem can be balanced by adding a dummy origin or a dummy destination. The dummy row or column usually has zero transportation cost or a penalty cost, depending on the practical interpretation of the shortage or surplus.

Transportation Simplex Method

The transportation simplex method is a specialized form of the simplex method developed for transportation problems. It is more efficient than the general simplex method because it uses the specific structure of the transportation table. The solution procedure generally includes the following steps:

1. Formulate the transportation table with supplies, demands, and unit costs.
2. Find an initial basic feasible solution.
3. Test the solution for optimality.
4. If the solution is not optimal, improve it by creating a closed loop and reallocating quantities.
5. Repeat the optimality test until no further improvement is possible.

Several methods may be used to obtain the initial feasible solution, including the North-West Corner Method, the Least Cost Method, and Vogel's Approximation Method. After an initial solution is obtained, the optimality test can be performed using the MODI method, also known as the (u-v) method. For a minimization problem, the MODI method calculates opportunity costs for all non-basic cells. If all opportunity costs are non-negative, the current solution is optimal. If at least one opportunity cost is negative, the solution can be improved.

4.1 Numerical Example: Food Transportation Problem: A food distribution company supplies fresh food pallets from three distribution centers to four retail markets. The company wants to minimize the total cost of transportation while satisfying the demand of each market. The available supply and demand are given in pallets per day. The unit transportation costs are expressed in monetary units per pallet.

Problem Data: The company has three distribution centers:

- Distribution Center A with 120 pallets available;
- Distribution Center B with 80 pallets available;
- Distribution Center C with 100 pallets available.

The company must deliver products to four retail markets:

- Market 1 requires 100 pallets;
- Market 2 requires 60 pallets;
- Market 3 requires 80 pallets;
- Market 4 requires 60 pallets.

The total supply is:

$$[120 + 80 + 100 = 300]$$

The total demand is:

$$[100 + 60 + 80 + 60 = 300]$$

Since total supply is equal to total demand, the problem is balanced. The transportation cost matrix is shown in Table 2.

Table 2. Unit transportation costs

Origin / Destination	**Market 1**	**Market 2**	**Market 3**	**Market 4**	**Supply**
Distribution Center A	4	6	8	8	120
Distribution Center B	6	8	6	5	80
Distribution Center C	7	5	4	6	100
Demand	100	60	80	60	300

4.2 Linear Programming Model for the Example:

Let:

$$x_{ij} = quantity\ transported\ from\ distribution\ center\ i\ to\ market\ j \quad (6)$$

where:

- (i = A, B, C);
- (j = 1, 2, 3, 4).

The objective function is:

$$Z = 4x_{A1} + 6x_{A2} + 8x_{A3} + 8x_{A4} + 6x_{B1} + 8x_{B2} + 6x_{B3} + 5x_{B4} + 7x_{C1} + 5x_{C2} + 4x_{C3} + 6x_{C4} \quad (7)$$

subject to supply constraints:

$$x_{A1} + x_{A2} + x_{A3} + x_{A4} = 120$$
$$x_{B1} + x_{B2} + x_{B3} + x_{B4} = 80$$
$$x_{C1} + x_{C2} + x_{C3} + x_{C4} = 100$$

and demand constraints:

$$x_{A1} + x_{B1} + x_{C1} = 100$$
$$x_{A2} + x_{B2} + x_{C2} = 60$$
$$x_{A3} + x_{B3} + x_{C3} = 80$$
$$x_{A4} + x_{B4} + x_{C4} = 60$$

with: $x_{ij} \geq 0, \quad i = A, B, C, \; j = 1,2,3,4$

Figure 1 presents the optimal transportation plan obtained from the balanced transportation problem. The diagram illustrates the distribution of food products from three distribution centers (A, B, and C) to four demand locations (1–4). The labels on the arrows represent the transported quantity and the corresponding unit transportation cost. The transportation simplex solution minimizes the total transportation cost while satisfying all supply and demand constraints. The optimal solution demonstrates efficient allocation of shipments and balanced utilization of available supply capacities.

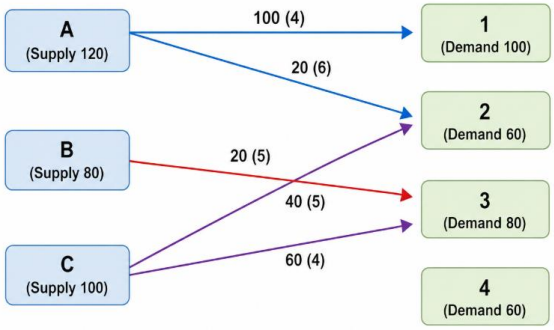


Figure 1. Optimal Transportation Plan for Food Distribution Using the Transportation Simplex Method

Solution Using the Transportation Simplex Method

The Transportation Simplex Method is a specialized optimization technique used to solve transportation problems in linear programming. Its main objective is to determine the most cost-effective way to transport goods from multiple supply points to multiple demand locations while satisfying all supply and demand constraints. The method begins with the formulation of a transportation matrix that contains transportation costs, supply quantities, and demand requirements. An initial feasible solution is first obtained using methods. After obtaining the

initial solution, the Transportation Simplex Method iteratively improves the transportation plan by evaluating unused routes and calculating opportunity costs. The method identifies whether transportation costs can be reduced by reallocating shipment quantities among different routes. During each iteration, the algorithm searches for an improved solution while maintaining all constraints related to supply and demand. The optimization process continues until no further reduction in total transportation cost is possible, indicating that the optimal solution has been reached. The Transportation Simplex Method is widely used in logistics, supply chain management, and distribution planning because it enables efficient allocation of transportation resources, minimizes operational costs, and improves overall distribution efficiency. An optimal feasible allocation for the example is shown in Table 3

Table 3. Optimal transportation plan

Origin / Destination	**Market 1**	**Market 2**	**Market 3**	**Market 4**	**Supply**
Distribution Center A	100	20	0	0	120
Distribution Center B	0	0	20	60	80
Distribution Center C	0	40	60	0	100
Demand	100	60	80	60	300

The total transportation cost is calculated as follows:
Z = 100(4) + 20(6) + 20(6) + 60(5) + 40(5) + 60(4)
Z = 400 + 120 + 120 + 300 + 200 + 240
Z = 1,380

Therefore, the minimum total transportation cost is:

$$Z_{min} = 1{,}380$$

5.1 Optimality Test by the MODI Method: For the optimality test, the basic occupied cells are: [(A,1), (A,2), (B,3), (B,4), (C,2), (C,3)]

The number of basic variables is:

$$m + n - 1 = 3 + 4 - 1 = 6$$

This confirms that the solution is non-degenerate.The MODI method assigns potentials (u_i) to rows and (v_j) to columns. For each occupied cell, the following relation must hold:

$$u_i + \vartheta_j = c_{ij} \qquad (8)$$

Let:

$$u_A = 0$$

From the occupied cells, the potentials are calculated as follows:

$$u_A + v_1 = 4 \Rightarrow v_1 = 4$$
$$u_A + v_2 = 6 \Rightarrow v_2 = 6$$
$$u_c + v_2 = 5 \Rightarrow v_c = -1$$
$$u_c + v_3 = 4 \Rightarrow v_3 = 5$$
$$u_B + v_3 = 6 \Rightarrow v_B = -1$$
$$u_B + v_4 = 5 \Rightarrow v_4 = 4$$

The potentials are therefore:

Potential	Value
u_A	0
u_B	1
u_c	-1

Potential	Value
v_1	4
v_2	6
v_3	5
v_4	4

For all unoccupied cells, the opportunity cost is calculated as:

$$\Delta_{ij} = c_{ij} - (u_i + v_j) \quad (9)$$

The opportunity costs are shown in Table 4.

Table 4. Opportunity costs for unoccupied cells

Cell	Calculation	Opportunity cost
((A,3))	(8 - (0+5))	3
((A,4))	(8 - (0+4))	4
((B,1))	(6 - (1+4))	1
((B,2))	(8 - (1+6))	1
((C,1))	(7 - (-1+4))	4
((C,4))	(6 - (-1+4))	3

Discussion of Results

The optimal solution indicates that the food distribution company should organize the daily transportation plan as follows:

- Distribution Center A should deliver 100 pallets to Market 1 and 20 pallets to Market 2.
- Distribution Center B should deliver 20 pallets to Market 3 and 60 pallets to Market 4.
- Distribution Center C should deliver 40 pallets to Market 2 and 60 pallets to Market 3.

No deliveries should be made on the remaining routes because they would increase the total transportation cost under the given assumptions. The result is important from a managerial perspective. Instead of distributing food products according to subjective judgment or historical habits, the company can use a mathematical model to determine the least-cost allocation. This can support daily planning, contract negotiations with transport operators, warehouse coordination, and operational control.

The obtained results are consistent with previous studies in transportation optimization and food logistics. Classical transportation optimization methods based on linear programming and transportation simplex algorithms have been widely recognized as effective tools for minimizing operational costs in deterministic distribution systems (Dantzig, 1951; Toth & Vigo, 2014). Similar findings were reported by Laporte (1992), who emphasized that optimal route and allocation planning can significantly improve transportation efficiency and reduce unnecessary logistics expenses.

The results are also aligned with recent studies in perishable food transportation and sustainable logistics systems. Pérez-Lechuga et al. (2024) demonstrated that optimized routing in cold-chain food distribution contributes to reduced spoilage risk and improved freshness preservation. Wang et al. (2025) additionally showed that transportation optimization models integrating environmental and quality objectives can simultaneously reduce operational costs and environmental impact.

Compared with more advanced intelligent logistics approaches, the proposed model represents a simplified deterministic framework because supply, demand, and transportation costs are assumed to be known and constant. In real transportation systems, uncertainty related to traffic congestion, weather conditions, delivery delays, and fluctuating demand may significantly affect logistics performance. Recent studies therefore increasingly combine classical

optimization models with machine learning, IoT technologies, and intelligent routing systems to improve adaptability and real-time decision-making (Knights et al., 2024; Antoska Knights & Gacovski, 2024).

Similar optimization principles have also been applied in autonomous robotic navigation systems, where efficient path planning reduces unnecessary movement and operational inefficiencies (Antoska Knights et al., 2017; Antoska Knights et al., 2018). The integration of intelligent optimization algorithms with transportation planning may therefore provide additional improvements in food logistics systems, especially in large-scale and dynamic supply-chain environments.

In real food logistics, the model may also be expanded by adding practical constraints. These may include maximum vehicle capacity, delivery time windows, cold-chain requirements, maximum travel time, driver working hours, road restrictions, fuel consumption, and emissions. If the products are highly perishable, the objective function can include not only transportation cost but also the cost of product deterioration or delay.

Advantages and Limitations of the Model

The classical transportation model represents an important foundational tool in food logistics because of its mathematical simplicity, transparency, and computational efficiency. The model enables planners to evaluate different allocation scenarios between distribution centers and demand locations while minimizing total transportation cost. Classical linear programming approaches and transportation simplex methods can efficiently solve balanced transportation problems even for moderate logistics networks, such as the 3×43 \times 43×4 distribution example presented in this study, where the optimal transportation cost was determined to be 1380 monetary units (Dantzig, 1951; Toth & Vigo, 2014).

Despite these advantages, the classical transportation model also has several important limitations. The model assumes that transportation costs, supply quantities, and customer demand are fixed and known in advance. In practical food logistics systems, however, transportation conditions are often dynamic and uncertain. The model does not explicitly consider traffic congestion, vehicle routing sequences, delivery time windows, cold-chain requirements, fuel consumption, or product perishability. These limitations are particularly important for highly perishable food products, where transportation delays may significantly increase spoilage risk and reduce product quality (Jedermann et al., 2014; Tsang et al., 2019).

To overcome these limitations, researchers have proposed several advanced extensions of the classical transportation problem. Stochastic optimization models are used to address uncertainty in customer demand and supply variability through probabilistic or chance-constrained approaches (Yu et al., 2023; Chen et al., 2026). Vehicle Routing Problems (VRP) extend the transportation model by determining optimal delivery sequences for vehicles serving multiple destinations within a single route (Laporte, 1992). Metaheuristic algorithms such as Genetic Algorithms (GA), Particle Swarm Optimization (PSO), and Ant Colony Optimization (ACO) are frequently applied in large-scale food logistics systems because they can generate near-optimal solutions under complex routing and perishability constraints (Holland, 1992; Kennedy & Eberhart, 1995; Dorigo & Stützle, 2004).

Multi-objective optimization models have additionally become increasingly important in sustainable food logistics. These models simultaneously minimize transportation cost, carbon emissions, delivery delays, and spoilage risk (Pérez-Lechuga et al., 2024; Wang et al., 2025). Time-dependent transportation models further improve logistics efficiency by considering dynamic travel times and traffic conditions during different periods of the day. Intelligent transportation systems integrating machine learning and IoT technologies also support adaptive route optimization and real-time transportation monitoring in modern food supply chains

(Knights et al., 2024; Antoska Knights & Gacovski, 2024).
A comparative overview of the most common transportation model extensions used in food logistics is presented in Table 5.

Table 5. Extensions of the Classical Transportation Model in Food Logistics

Extension	Purpose	Example Application	References
Stochastic Models	Handle demand uncertainty	Random market orders ±20%; uses chance constraints	Yu et al. (2023); Chen et al. (2026)
Vehicle Routing Problem (VRP)	Optimize multi-stop delivery routes	One truck serving Markets 1–4; integrates with GA/PSO	Laporte (1992); Toth & Vigo (2014)
Multi-Objective Optimization	Simultaneously minimize cost, emissions, and spoilage	Minimize transportation cost and CO_2 emissions using Pareto optimization	Pérez-Lechuga et al. (2024); Wang et al. (2025)
Time-Dependent Models	Incorporate dynamic travel times and congestion	Peak-hour traffic adaptation and delivery scheduling	Fikar (2018); Tsang et al. (2019)
Metaheuristic Algorithms (GA, PSO, ACO)	Generate near-optimal solutions for complex logistics systems	Large-scale food logistics and cold-chain routing optimization	Holland (1992); Kennedy & Eberhart (1995); Dorigo & Stützle (2004)
AI and IoT-Based Models	Real-time monitoring and adaptive routing	Intelligent food logistics and smart transportation systems	Antoska Knights & Gacovski (2024); Knights et al. (2024); Kumar et al. (2024)

Conclusions

This paper presented a mathematical modeling approach for the optimization of food transportation. The transportation problem was formulated as a linear programming model with the objective of minimizing total transportation cost. A numerical example was developed for the delivery of food pallets from three distribution centers to four retail markets. The example demonstrated that the transportation simplex method can be effectively used to determine the optimal distribution plan. The minimum transportation cost obtained in the example was 1,380 monetary units. The MODI optimality test confirmed that the solution was optimal because all opportunity costs were non-negative.
The analysis shows that mathematical modeling is a useful decision-support tool in food logistics. It enables companies to reduce transportation costs, improve resource allocation, and make more objective operational decisions. Although the classical transportation model is simplified, it provides a strong basis for further development of more complex logistics models that include time, vehicle capacity, product perishability, environmental impact, and uncertainty. Since all opportunity costs are non-negative, no further reduction of the total transportation cost is possible. Therefore, the solution shown in Table 3 is optimal.

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COMPARISON OF EXISTING AND PLANNED HYDROPOTENTIAL AND ADDITIONAL ACTIVITIES TO ENCOURAGE THE USE OF HYDROPOWER PLANTS IN THE REPUBLIC OF NORTH MACEDONIA

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Abstract

Hydropower plants as the most ecologically acceptable sources of electricity are expensive investment projects which in a longer time interval are economically sustainable due to low operating costs.
In the Republic of North Macedonia there is a considerable unused hydro potential for the construction of large and small hydropower plants (HPPs). Recently, an increase in interest in small HPPs has been noted. In the Development Program of the Republic of North Macedonia, the government's investment in large and small HPPs is one of the priority parts in the development of the energy sector. In our country, the concession for the construction of small HPPs has started with the Ministry of Economy announcing four calls for applications for concession over 140 locations for small HPPs with installed capacity from 35 kW to 2500 kW.
The aim of this paper is to provide an overview of hydropower plants as a facility for generating electricity from renewable energy sources. The current situation in the Republic of North Macedonia is discussed. The paper highlights the needs and opportunities for the construction of HPPs in the Republic of North Macedonia. Hydropower potential: technically available hydropower potential and also the hydropower potential used with small and large HPPs are given through concrete data. The thesis discusses future plans and scenarios for the use of hydropower potential in the Republic of North Macedonia.
In the Republic of North Macedonia, the use of hydropower potential for energy needs is below 50%. Although the largest hydropower plants were built 60 years ago, they still remain certain locations and opportunities for the construction of hydropower facilities. The installed capacity is around 1500 MW, with an average annual production of 1200 GWh, although due to the growing electricity needs in the Republic of Macedonia, the participation of hydropower in total consumption is below 15%.

Keywords: Hydropower plant; Electric power system; Hydroelectric power plant; Capacity; Potential; Annual production; Hydropower; hydropotential.

Introduction

Water is a natural resource of every country that is not only used for drinking, irrigation or other purposes, but is also used to produce electricity.
In 1882, the first hydroelectric power plant was built on the Fox River in Wisconsin, United States of America. After this event, the first hydroelectric power plant was built at Niagara Falls, marking the beginning of the era of hydropower.
Hydropower plants use water as energy, which is the main source of energy, but in general, hydroelectric power plants also use the sun as energy, because the hydrological process by which the earth is supplied with water is initiated by the sun. A small part of the precipitation, in fact atmospheric water as well as that of snow when it melts, evaporates, while the greater part sinks into the ground and flows to the surface of the earth to then flow into lakes, seas, artificial reservoirs/accumulations and oceans.
Part of the water that flows to the surface of the earth through underground streams or springs, goes to the water masses, while part has the possibility of remaining as stored water, which in periods of drought can return to the atmosphere through evaporation, which condenses into fog and returns to the surface of the earth in the form of precipitation, with which the hydrological process is complete.

The economic and agricultural benefits of hydroelectric power plants would be greatest if, in addition to the energy effect, hydro facilities would also have multiple purposes (for irrigation, water supply, for tourist sites, etc.). With the largest deficit compared to the large needs of electricity in the region and beyond, the opportunity for investment also opens up in this part of the energy sector.

The use of the hydropower potential of each country depends on the level of economic, technical and social development of the country itself. In developed European countries, the rate of utilization of hydropower potential ranges from 65 to 95%. This rate in the Republic of North Macedonia is below 50%. Compared to developed European countries, we see that our country is not at the right level in terms of maximum utilization of hydropower potential for electricity production.

The Macedonian energy policy was built within the framework of the collective Yugoslav policy until the country's independence in 1991. At that time, almost 50% of the electricity needs in the Republic of North Macedonia were provided by domestic production, while the remaining 50% were provided by the common Yugoslav electricity network. Immediately after independence, the overall electricity needs in the Republic of North Macedonia were provided by domestic production, which came as a result of the transition process, the degradation of industrial production, the closure of many factories, the deterioration of living standards, etc. In recent years, the restart of some larger industrial facilities as well as the start of some new facilities resulted in an increase in electricity consumption. Nowadays, electricity imports are important and it is expected that this trend will continue. Hydropower plants are currently the second largest electricity production capacity, after thermal power plants. The Ministry of Environment of the Republic of North Macedonia has conducted feasibility studies for the exploitation of hydropower potential through more than 400 small hydroelectric power plants, where they state that these hydroelectric power plants do not destroy the habitats of animals and plants, do not pollute the environment, do not require the construction of large dams and lakes, which means that they protect the environment.

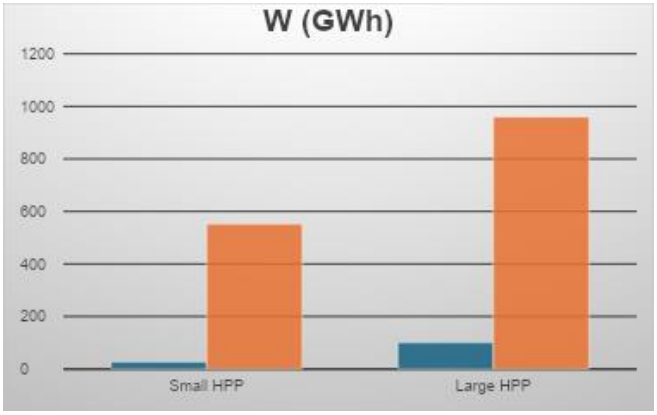
Comparison of existing and planned hydropotentials

Regarding the hydro potential, an overview of the existing built hydropower potential in the R.M.V, as well as planned hydropower facilities is provided. Table no. 1 provides an overview of the existing and planned hydropower potential in the R.M.V. A graphical overview of the installed capacity and the corresponding production, for permanent, planned and total hydropower plants in the country, is also provided.

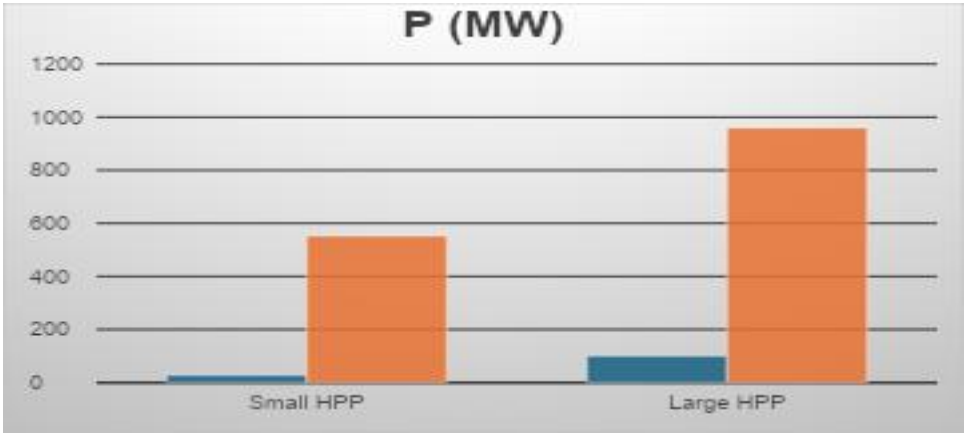
Table 1. Overview of existing and planned hydro potential.

Hydropower plants	Existing		Planned		TOTAL	
	P inst. (MW)	W year. (GWh)	P inst. (MW)	W year. (GWh)	P inst. (MW)	W year. (GWh)
Large HPP	552	1392	960	2280	1512	3672
Small HPP	27	76	100	267	127	343
TOTAL	579	1468	1060	2547	1639	4015

(Energy Agency in the Republic of North Macedonia, n.d.)



Graph 1. Average annual production of existing and planned HPPs.



Graph 2. Installation of existing and planned HPPs.

The planned hydropower plants to be built in the coming period in the Republic of North Macedonia have a total installed capacity of about 1060 MW, of which 960 MW are larger hydropower capacities, and about 100 MW are in small hydropower plants. The corresponding total average annual production amounts to about 2550 GWh, of which about 2280 GWh are from larger hydropower plants and about 270 GWh are from small hydropower plants. With the announcements for the concession of additional locations for the construction of small hydropower plants, it is expected that in the coming period the contribution of new small hydropower plants will reach an installed capacity in the range of 80 to 120 MW with an annual production of 210 to 310 GWh. In the period (2025-2035) the construction of the remaining small hydropower plants is expected. By revitalizing existing hydropower plants, additional electricity production can be achieved. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)

With the hydropower plants planned in this way, North Macedonia should increase its hydro potential to a total installed capacity of around 1,700 MW and an average annual production of around 4,400 MWh in the coming period until 2035. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)

Incentive and the future of hydro power plants

According to the Law on Energy of the Republic, the incentive fees and the installed capacity of hydropower plants for obtaining the right to use incentive fees are determined by the Regulatory Commission of the Republic. Regarding the incentive fees for HPPs, the Regulatory Commission has adopted the Regulation on the manner and procedure for

determining and approving the use of incentive fees for the sale of electricity produced in small hydropower plants. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)
According to the rules, incentive fees apply to the quantities of electricity supplied by newly constructed run-of-river HPPs with an installed capacity of up to 10,000 kW, which have acquired the status of a preferential producer. The preferential producer is obliged to use the incentive fees, for the use of which it has made a Decision for approval, for a period of 20 years. (Causevski, A.; Nikolova, S., 2011)
The electricity market operator is obliged to purchase the entire amount of electricity supplied by the preferential producer at the incentive fees for which the Energy Regulatory Commission adopted a Decision on the approval of the use by this preferential producer. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)
Also, the Energy Regulatory Commission has adopted a Decision on the determination of fees for the sale of electricity produced and supplied by small hydropower plants that have acquired the status of preferential producers. These fees are given in Table No. 2.

Table 2. Incentive fees for electricity produced and furnished by HPPs.

Unit	Monthly electricity supplied (kWh)	Annual power supplied (kWh)	Incentive fees (€ cent/kWh)
I	1 – 85000	1 - 1020000	12,00
II	85001 – 170000	1020000 - 2040000	8,00
III	1700001 - 350000	2040001 - 4200000	6,00
IV	350001 – 700000	4200001 – 8400000	5,00
V	Over 700001	Over 8400001	4,50

(Energy Agency in the Republic of North Macedonia, n.d.)

In the future, it is planned to increase the use of energy from renewable sources. According to the Strategy for the Development of Energy in North Macedonia until 2040, there is a technical potential of hydropower for annual electricity production of about 5500 GWh. So far, there are hydropower plants with a total installed capacity of 580 MW and an average production of about 150 GWh, which represents 27% of the available potential. According to the aforementioned study, it is planned to use additional hydropower plants with a production of about 2500 GWh, so that the total production increases to 4000 GWh or 73% of the available technical potential.
The base scenario of the aforementioned Strategy is the planning of the construction of 6 large hydropower plants in the period until 2035 with a total installed capacity of about 690 MW and an average annual production of about 1200 GWh. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)
Considering that the concession tenders ended in failure in some cases, there is a possibility for a certain extension of the construction of these 152 hydropower plants. In this case, in 2040 the production from the new large hydropower plants would be around 600 GWh.
In the period until 2040, in addition to the above-mentioned ones, the construction of the Veles HPP and the remaining 10 smaller HPPs of the Vardar Valley is also foreseen. Thus, the total installed capacity of the newly built hydropower plants will be 960 MW with an average annual production of around 2280 GWh.
The available potential for the construction of small hydropower plants in 400 possible locations is estimated at 255 MW. According to the average production of small hydropower plants available, the annual production from these 255 MW would be 670 GWh. (Causevski, A.; Nikolova, S., 2011)

The locations for the construction of small hydropower plants have been granted by concession through tender by the Ministry of Economy. Small hydropower plants are also planned for the construction of water supply systems, as well as in irrigation systems. Despite some administrative problems and problems with the unclear hydrology of the locations, the realistic scenario foresees the construction of small hydropower plants with an installed capacity of 80 MW and an annual production of 210 GWh by 2035; and by 2040, 160 MW in small hydropower plants with an annual production of 420 GWh are expected. There is also an optimistic scenario which foresees the construction of small hydropower plants with an installed capacity of 120 MW and an annual production of 310 GWh by 2040; and by 2035, 240 MW is projected in small hydropower plants with an annual production of 620 GWh.

Additional activities to encourage the use of hydropower plants

The construction of the Galishte and Cebren HPPs should be carried out through a public-private partnership. As a first step, a program should be prepared to find at least one strategic partner interested in a Public Private Partnership with the inclusion of the Tikvesh HPP, and based on the Energy Strategy and mutually agreed terms, a tender should be signed. An investment consultant should be hired for the tender, who will prepare the tender documentation according to the conditions clearly defined by the state and will assist in the selection of strategic partners. An additional incentive for attracting strategic partners and at the same time a selection criterion would be the possibility of building a hydro-nuclear complex (if a positive decision is made at the state level for the construction of a nuclear power plant).

AD ELEM can build small hydropower facilities. Accordingly, it is recommended to prepare an action plan for the construction of the Lukova Plain association with the Guri i Zi HPP and the Ura e Boshkos HPP by AD ELEM, with state support within the Public Investment Program. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)

Regarding the Vardar Valley project, as a first step it is necessary to announce a tender for the creation of an innovative study for the Vardar Valley that will provide accurate answers regarding the railway (time of relocation or relocation of a new route already determined or the first. construction of a new modern railway) and regarding transporters (the idea of Vardar navigability has been definitively abandoned, and consequently the transition to optimal energy use). As in the case of Çebren and Galishte, at least one interested investor must be found and the tender announced. An investment consultant should be hired for the tender, who will prepare the tender documentation according to the conditions clearly defined by the state and will assist in selecting the most favorable bidder.

Of primary importance for supporting small hydropower plants is the simplification of water concession procedures, which should also include a requirement for a previously defined land use. The procedure should ensure the right of priority for obtaining a concession for the construction of a small hydropower plant for private landowners. (Causevski & Bosevski : Model for Generation Planning in an Electric Power System, 2004)

The Energy Agency should be authorized to accurately monitor all stages of the preparation and construction of the first ten small hydropower plants and provide assistance in removing administrative and legal obstacles for their rapid implementation. Also, based on the experience gained, the Energy Agency should prepare a manual with a clearly defined procedure for the construction of small hydropower plants, which will be used by future investors.

Considering the unreliability and complexity of the available data on hydropower potential, before further tenders for small hydropower plants are announced, it is necessary to prepare and implement a project to update the data on hydropower potential and other relevant parameters (preferably in the level solution concept) for each of the identified locations. (Panovski & Janevska, Hydroenergy in Macedonia, 2010)

Conclusions and suggestions

Renewable energy sources, with the exception of large hydropower plants, are, as a rule, not concentrated and can be used to produce electricity in smaller production units distributed over a large area and much closer to consumers.
The distribution of production capacities and their connection to distribution networks and their proximity to consumers reduces electricity losses in the network and improves the reliability of electricity supply. But on the other hand, this concept creates additional problems in the management and management of systems from a technical and economic point of view.
The existing hydropower plants in the Republic of North Macedonia have a total installed capacity of about 579 MW, of which 552 MW are large hydropower plants, and 27 MW are small hydropower plants. The planned hydropower plants to be built in the coming period in the Republic of North Macedonia have a total installed capacity of about 1060 MW, of which 960 MW are large hydropower capacities (investments for all facilities are estimated at about 1.53 billion euros), and about 100 MW are small hydropower plants.
In the Republic of North Macedonia there is considerable hydropower potential, estimated to be about 5600 GWh of technically usable hydropotential. Today, about 1470 GWh is used, which is only about 26% of this potential.
The Strategy for the Use of Renewable Energy Sources in the Republic of North Macedonia provides four scenarios depending on the share of renewable energy in the total final energy consumption.
In all four scenarios, it can be expected that the Republic of North Macedonia can realistically achieve a 21% share of renewable sources by 2035. Scenarios C2 and C3 appear as the most likely.
Scenario C3 is based on the final energy consumption scenario with enhanced energy efficiency measures according to the Strategy for the Development of Energy in North Macedonia, in order to represent a targeted option.
Scenario C2 predicts the final energy consumption as in the baseline scenario of the Strategy.
For the realization of scenarios C2 and C3 or any option between them, by 2035, the use of hydropower from large HPPs in the amount of 2000 - 2350 GWh is required, as well as hydropower from small HPPs in the amount of 350 - 360 GWh.
Furthermore, the percentage of participation of large and small HPPs in the total amount of renewable energy by 2035 is: according to the C2 scenario, large HPPs participate with 34.1% and small HPPs with 5.2%, and according to the C3 scenario, large HPPs participate with 30.9% and small HPPs with 5.4%.
The strategy foresees the participation of HPP production in final energy consumption in the range of 3430 - 4410 GWh from large HPPs and in the range of 510 - 710 GWh from small HPPs by 2035.
Construction of all planned HPPs (including large and small ones as well as HPPs from the Vardar Valley), the expectation for electricity production for 2040, could be from 2000 GWh for dry hydrology, about 4000 GWh for medium hydrology and over 6000 GWh for wet hydrology. This means that the share of hydro production in covering the electricity demand could be over 20% for medium and wet hydrology.

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USING MARKET BASKET ANALYSIS TECHNIQUE TO FIND CONSUMER PURCHASING PATTERNS AND OPTIMIZE INVENTORY MANAGEMENT

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Abstract

Market Basket Analysis (MBA) is a data mining technique that plays a key role in finding consumer purchasing patterns to aid in optimizing inventory management and marketing strategies. It assists in the decision-making process and increases the success of the marketing strategy. A competitive market requires businesses to observe the market using data to further optimize their marketing and business strategy. Retail stores need to use all of the available resources, including data, to improve their inventory management but also their marketing strategy. Data processing is able to provide details that can be used to support marketing strategies. One of the data processing methods that is often used in marketing strategies is the use of data mining techniques. This study uses association rule mining and the Apriori algorithm to analyze transaction data from a German dataset, which included over 541,000 transactions from December 2010 to December 2011. The analysis found important product associations and customer behavior patterns using metrics such as confidence, lift, leverage, conviction, and certainty to find the strength and dependability of the discovered associations. Results showed strong associations between specific product pairs, offering insight for marketing strategy and inventory optimization.

Keywords: Market Basket Analysis, Data Mining Techniques, Inventory Management, Datasets, Apriori Algorithm

Introduction

With the advances in information technology, corporations can obtain and store transactional and demographic data on individual customers from purchases made on their stores. However, a key challenge for companies that have heavily invested in customer data collection is identifying valuable insights within their vast databases to gain an advantage.[9] Market basket analysis (MBA), also known as association rule mining, is a data mining technique employed to discover customer purchasing patterns by identifying associations or co-occurrences within transactional data. For instance, recognizing that supermarket customers frequently buy milk, bread, and cheese together.[16] The fact that bank customers commonly use specific services in combination can assist managers in optimizing store layouts, websites, product offerings, bundling strategies, and other marketing initiatives.[17] Furthermore, predictive modeling of data mining regression technique applied in a prototype presents a practical application of linear regression for predicting business profit based on product sales.[18] Using a small dataset from a one-week sales period, it demonstrates how regression coefficients are calculated and used for forecasting. It clearly can explain the methodology and offers a simple prototype with a claimed 99% confidence level in its predictions.[19] While the approach is well-suited for educational or introductory purposes, it lacks rigorous validation, scalability, and testing for model assumptions. The dataset can be too limited to generalize the results or ensure robustness. Overall, it's a useful beginner-level demonstration of regression in predictive modeling, but Market Basket Analysis helps businesses uncover hidden patterns in customer purchasing behavior, enabling smarter decision-making [9]. Inventory management is responsible for the planning and control of resources and goods that sustain manufacturing functions, maintenance activities, and customer service.[14] Due to the high level of cost that stocks can reach in an organization, the latent demand to optimize costs and customer service

has positioned inventories as a vital area for improvement in firms. This study delves into the purchasing patterns of the data from an online retail market based in Germany. By using the Apriori Algorithm, we aimed to identify popular product combinations and uncover consumer preferences.

Literature Review

[8] analyzes transaction data from "Mizan Computer Shop", a computer and accessories store, to create marketing strategies. MBA, alongside the Apriori algorithm, was used to uncover purchasing patterns that can be used for marketing strategy. They built the application using the waterfall method, with UML diagrams for design, and implemented it in PHP. The authors deduced that these patterns can help the shop create differentiation and advantageous marketing strategies. Key findings found that customers buy Laptop chargers alongside keyboards, and customers who buy Laptops also buy mice, which tracks. [6]. This research paper applied the Apriori algorithm to analyze consumer purchasing patterns in a minimarket. The objective was to generate insights for developing marketing strategies, specifically determining which items are frequently bought together. The authors used transaction data as their primary data. They processed this data by applying a minimum support value of 10% and a minimum confidence value of 65%. The method involved sorting and calculating association rules based on these thresholds. The results showed that the Apriori algorithm successfully produced combinations of consumer purchase patterns. The authors concluded that their information system can support sales decision-making by providing actionable pattern combinations derived from real transaction data. Similar patterns are applied in this paper, mostly focusing on a bigger and broader dataset. [11] provides an overview of the strategic role played by North Macedonia's FITD in fostering technological innovation. The authors trace FITD's evolution through its call cycles, mentorship programs, and partnerships with international bodies like the World Bank, UNICEF, and foreign embassies. They emphasize FITD's financial support strategy, including finance grants, innovation vouchers, and startup competitions, which have funneled millions of euros into SMEs and startups regionally. However, the MBA advantage is that it shows patterns in customer purchasing behavior, allowing companies to make data-driven decisions that boost profits. [5] This is a paper that uses data mining techniques, specifically the Apriori algorithm, to analyze consumer purchasing patterns in the "O! Fish restaurant", a restaurant in the rapidly growing food and beverage culinary industry. The authors aim to assist other restaurant owners by performing better in a competitive market by using transaction data to show consumer purchasing patterns, which can be used to improve marketing strategy. They apply data mining techniques, specifically the Apriori algorithm, to generate association rules identifying which menu items are often purchased together. These patterns are intended to be used to improve strategies and boost sales. The outcome of the study is a website-based application that analyzes consumer purchasing patterns and provides recommendations based on item associations. The authors conclude that these association rules can guide O! Fish restaurant in developing more effective and targeted promotion strategies. In paper [10], the authors examine how AI integration can enhance IoT applications in the Western Balkans, using energy optimization, smart cities, and sustainable practices. It proposes a PHP/MySQL-based web application featuring citizen profiles, region-wide fire detection, air quality monitoring, and demographic data access to support regional digital governance. However, it lacks validation of the prototype's effectiveness, scalability assessments, and user studies. Despite the limitations, the paper presents a different regional perspective on AIoT deployment and a tangible starting point for future digital transformation efforts.

Data Mining

Data mining is a technology that blends traditional data analysis methods with sophisticated algorithms for processing large volumes of data. It has also opened up exciting opportunities for exploring and analyzing new types of data and for analyzing old types of data in new ways. Data mining is the process of automatically discovering useful information in large data repositories. Data mining techniques are deployed to scour large databases in order to find novel and useful patterns that might otherwise remain unknown. They also provide capabilities to predict the outcome of a future observation, such as predicting whether a newly arrived. customer will spend more than $100 at a department store. In business data collection have allowed retailers to collect up-to-the-minute data about customer purchases at the checkout counters of their stores.[12] Retailers can utilize this information, along with other business-critical data such as Web logs from e-commerce[13]. Web sites and customer service records from call centers, to help them better understand the needs of their customers and make more informed business decisions.[14][15] Data mining techniques can be used to support a wide range of business intelligence applications such as customer profiling, targeted marketing, workflow management, store layout, and fraud detection. It can also help retailers answer important business questions such as "Who are the most profitable customers?" "What products can be cross-sold or up-sold?" and "What is the revenue outlook of the company for next year?" Some of these questions motivated the creation of association analysis, a new data analysis technique[4].

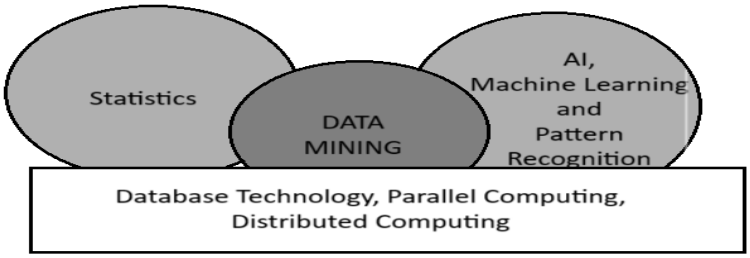


Figure 1. Core components and supporting technologies of data mining.

Data mining tasks

Data mining tasks are generally divided into a few categories: Predictive tasks - The objective of these tasks is to predict the value of a particular attribute based on the values of other attributes.[1] The attribute to be predicted is commonly known as the target or dependent variable, while the attributes used for making the prediction are known as the explanatory or independent variables. Descriptive tasks - Here, the objective is to derive patterns (correlations, trends, clusters, trajectories, and anomalies) that summarize the underlying relationships in data. Descriptive data mining tasks are often exploratory in nature and frequently require postprocessing techniques to validate and explain the results[1]. Predictive modeling – is the task of building a model for the target variable as a function of the explenatory variables. There are two types of predictive modeling tasks: classification and regression. Classification is used for discrete target variables. For example, predicting whether a Web user will make a purchase at an online bookstore is a classification task because the target variable is binary-valued. Regression is used for continuous target variables. For example, forecasting the future price of a stock is a regression task because price is a continuous-valued attribute[1]. Association Analysis – is used to discover patterns that describe stronlgy associated features in the data. These patterns are usually expressed as implication rules or feature subsets. Association

analysis efficiently extracts the most meaningful patterns. This technique has various applications such as recognizing frequently accessed Web pages, detecting groups of genes with similar functions, and analyzing connections between different components of Earth's climate system[1]. Example 1 (Market Basket Analysis). The transactions shown in Table 1.1 illustrate point-of-sale data collected at the checkout counters of a grocery store. Association analysis can be applied to find items that are frequently bought together by customers. For example, we may discover the rule association rules which suggests that customers who buy diapers also tend to buy milk. This type of rule can be used to identify potential cross-selling opportunities among related items. Cluster analysis seeks to find groups of closely related observations so that observations that belong to the same cluster are more similar to each other than observations that belong to other clusters. Clustering has been used to group sets of related customers, find areas of the ocean that have a significant impact on the Earth's climate, and compress data.

Table 1.1 Market basket data

Transaction ID	Items
1	{Bread, Butter, Diapers, Milk}
2	{Coffee, Sugar, Cookies, Salmon}
3	{Bread, Butter, Coffee, Diapers, Milk, Eggs}
4	{Bread, Butter, Salmon, Chicken}
5	{Egg", Bread, Butter}
6	{Salmon, Diapers, Milk}
7	{Bread, Tea, Sugar, Eggs}
8	{Coffee, Sugar, Chicken, Eggs}
9	{Bread, Diapers, Mi1k, Salt}
10	{Tea, Eggs, Cookies, Diapers, Milk}

Example 2 – Document Clustering: The news articles in Table 1.2 can be categorized based on their topics. Each article is represented as a set of word-frequency pairs (t,c)(t, c)(t,c), where ttt is a word and ccc is its occurrence count in the article. The dataset naturally forms two clusters: the first four articles focus on economic news, while the last four pertain to healthcare. An effective clustering algorithm should be able to detect these clusters by analyzing the similarity of words appearing in the articles[1].

Table 1.2 Collection of news articles

Article	Words
1	dollar: 1, industry: 4, country: 2, loan: 3, deal: 2, government: 2
2	machinery: 2, labor: 3, market: 4, industry: 2, work: 3, country: 1
3	job: 5, inflation: 3, rise: 2, jobless: 2, market: 3, country: 2, index: 3
4	domestic: 3, forecast: 2, gain: 1, market: 2, sale: 3, price: 2
5	patient: 4, symptom: 2, drug: 3, health: 2, clinic: 2, doctor: 2
6	pharmaceutical:2, company: 3, drug: 2,vaccine:1, flu: 3
7	death: 2, cancer: 4, drug: 3, public: 4, health: 3, director: 2
8	medical: 2, cost: 3, increase: 2, patient: 2, health: 3, care: 1

Anomaly detection is the task of identifying observations whose characteristics are significantly different from the rest of the data. Such observations are known as anomalies or outliers. The goal of an anomaly detection algorithm is to discover the real anomalies and avoid falsely labeling normal objects as anomalous[1]. Example 3 – Credit Card Fraud Detection: A credit card company tracks each cardholder's transactions and stores personal details, including

credit limit, age, annual income, and address. since the number of fraudulent cases is relatively small compared to the number of legitimate transactions, anomaly detection techniques can be applied to build a profile of legitimate transactions for the users. When a new transaction occurs, it is evaluated against the user's profile. If its characteristics significantly deviate from the established profile, the transaction is flagged as potentially fraudulent[1].

Data Mining Technique

Data mining techniques and tools help enterprises to predict future trends and make more informed business decisions. There's different types of data mining techniques such as: classification, Clustering, Regression, Association Rule Mining, Anomaly Deteciton, Text Mining, Apriori Algorithm etc.
The Association Rules and the Apriori Algorithm will be the main topics of this paper and experiment.
One data mining technique for finding significant connections or patterns among several variables in a dataset is association rules. These guidelines are frequently used in market basket analysis to determine which products are frequently bought in tandem. An association rule might indicate, for example, that consumers who purchase bread and butter are also likely to buy milk.
There are two primary parts to any association rule:

- Antecedent (X): The item or items that show up in the rule's "if" section.
- Consequent (Y): The item or items mentioned in the rule's "then" section.

The rule is typically expressed as follows: Y is likely to occur if X occurs.

Key Metrics

Support measures how frequently an itemset X appears in all transactions. It calculates the probability that a transaction contains X. A higher support score means X occurs more often in the dataset.

$$Support(X \Rightarrow Y) = \frac{(Transactions\ containing\ both\ X\ and\ Y)}{(Total\ No.of\ transactions)}$$

Confidence measures probability that an item Y will be bought when an item X is bought, given the antecedent item, it measures the conditional probability of the succeeding item. A higher confidence score means that there is a greater chance that item Y will be bought when item X is bought.

$$confidence(X \Rightarrow Y) = \frac{Support(X \Rightarrow Y)}{Support(X)}$$

Lift evaluates the strength of the association between two items by comparing the observed probability of them being bought together to the expected probability if the items were independent. A lift value greater than 1 suggests that the items are positively correlated and are more likely to be bought together than by random chance. Lift helps identify relationships that might not be immediately obvious based on frequency alone

$$lift(X \Rightarrow Y) = confidence(X \Rightarrow Y) / support(X)$$

Leverage is a metric that helps assess how much more often X and Y appear together compared to what would be expected if the two items were independent. A positive leverage value indicates a stronger association than expected, while a negative value suggests that the items occur together less frequently than expected by chance.

$$leverage(X \Rightarrow Y) = support(X \Rightarrow Y) - support(X) \cdot support(Y)$$

Conviction measures the degree to which an association rule is reliable. It is based on how often the rule holds true compared to how often the consequent item is expected to occur in the

absence of the antecedent. A high conviction value suggests a strong, reliable rule, while a low conviction value indicates that the rule is less reliable or possibly coincidental

$$Conviction(X \Rightarrow Y) = support(Y)/confidence(X \Rightarrow Y)$$

The Apriori algorithm focuses on item combinations that exceed a predetermined support limit by assessing transactional data, such as store data records. The identification of these frequently occurring itemsets produces association rules, offering important information about the connections between the items[2].

Datasets

A dataset is a group of data used for analysis, research, and or machine learning that is usually arranged in a structured manner.[1][2]
We use transactional data in this work, which is defined as records that record the specifics of business transactions and are frequently collected by systems like banking systems, e-commerce platforms, and point-of-sale systems.

Transaction ID	Customer ID	Product	Quantity	Date	Total Amount
1	101	Milk	2	2024-12-01	5.00
1	101	Bread	1	2024-12-01	2.50
2	102	Butter	1	2024-12-01	3.00
2	102	Milk	1	2024-12-01	2.50
3	103	Eggs	12	2024-12-02	6.00
3	103	Cheese	1	2024-12-02	4.00
4	104	Milk	3	2024-12-03	7.50
5	105	Butter	1	2024-12-03	3.00
5	105	Bread	2	2024-12-03	5.00

Figure 2. An example of transactional data

The transactional dataset was originally collected by Daqing Chen from a UK-based online retailer operating without physical store locations. The dataset was sourced from the UCI Machine Learning Repository and contains all transactions recorded between 01/12/2010 and 09/12/2011 [7]. While primarily consisting of UK transactions, the dataset also includes international purchases.

Experiment

Cleaning & Preparing the data

The first step was removing all transactions marked with cancellation indicators like "C" or "A" to ensure only valid purchases remained. The dataset was then filtered to include transactions only from customers in Germany, removing all UK and other international records. The transactional data was reformatted into a binary matrix suitable for Market Basket Analysis, where each row represented an invoice, and each column indicated the presence or absence of a product. This prepared the transaction data for pattern mining using Apriori.
Execution of Algorithm

antecedents	consequents	antecedent support	consequent support	support	confidence	lift	leverage	conviction
PLASTERS IN TIN WOODLAND ANIMALS	PLASTERS IN TIN CIRCUS PARADE	0.13786	0.11597	0.06783	0.49206	4.24289	0.05185	1.74043
PLASTERS IN TIN CIRCUS PARADE	PLASTERS IN TIN WOODLAND ANIMALS	0.11597	0.13786	0.06783	0.58491	4.24289	0.05185	2.07698
ROUND SNACK BOXES SET OF 4 FRUITS	PLASTERS IN TIN CIRCUS PARADE	0.15755	0.11597	0.05033	0.31944	2.75445	0.03206	1.29898
PLASTERS IN TIN CIRCUS PARADE	ROUND SNACK BOXES SET OF 4 FRUITS	0.11597	0.15755	0.05033	0.43396	2.75445	0.03206	1.48833
ROUND SNACK BOXES SET OF4 WOODLAND	PLASTERS IN TIN CIRCUS PARADE	0.24508	0.11597	0.05689	0.23214	2.00168	0.02847	1.15129
PLASTERS IN TIN CIRCUS PARADE	ROUND SNACK BOXES SET OF4 WOODLAND	0.11597	0.24508	0.05689	0.49057	2.00168	0.02847	1.48189
PLASTERS IN TIN WOODLAND ANIMALS	PLASTERS IN TIN SPACEBOY	0.13786	0.10722	0.06127	0.44444	4.14512	0.04649	1.60700
PLASTERS IN TIN SPACEBOY	PLASTERS IN TIN WOODLAND ANIMALS	0.10722	0.13786	0.06127	0.57143	4.14512	0.04649	2.01167
PLASTERS IN TIN WOODLAND ANIMALS	ROUND SNACK BOXES SET OF4 WOODLAND	0.13786	0.24508	0.07440	0.53968	2.20210	0.04061	1.64001
ROUND SNACK BOXES SET OF4 WOODLAND	PLASTERS IN TIN WOODLAND ANIMALS	0.24508	0.13786	0.07440	0.30357	2.20210	0.04061	1.23795
WOODLAND CHARLOTTE BAG	RED RETROSPOT CHARLOTTE BAG	0.12691	0.07002	0.05908	0.46552	6.64817	0.05019	1.73996
RED RETROSPOT CHARLOTTE BAG	WOODLAND CHARLOTTE BAG	0.07002	0.12691	0.05908	0.84375	6.64817	0.05019	5.58775
ROUND SNACK BOXES SET OF 4 FRUITS	ROUND SNACK BOXES SET OF4 WOODLAND	0.15755	0.24508	0.13129	0.83333	3.40030	0.09268	4.52954
ROUND SNACK BOXES SET OF4 WOODLAND	ROUND SNACK BOXES SET OF 4 FRUITS	0.24508	0.15755	0.13129	0.53571	3.40030	0.09268	1.81451
ROUND SNACK BOXES SET OF4 WOODLAND	SPACEBOY LUNCH BOX	0.24508	0.10284	0.07002	0.28571	2.77812	0.04482	1.25602
SPACEBOY LUNCH BOX	ROUND SNACK BOXES SET OF4 WOODLAND	0.10284	0.24508	0.07002	0.68085	2.77812	0.04482	2.36543
WOODLAND CHARLOTTE BAG	ROUND SNACK BOXES SET OF4 WOODLAND	0.12691	0.24508	0.06346	0.50000	2.04018	0.03235	1.50985
ROUND SNACK BOXES SET OF4 WOODLAND	WOODLAND CHARLOTTE BAG	0.24508	0.12691	0.06346	0.25893	2.04018	0.03235	1.17814

Figure 3. Results of algorithm execution

In Figure 3, we can see the raw results of the algorithm. Strong associations can be observed between themed items such as "PLASTERS IN TIN WOODLAND ANIMALS," "PLASTERS IN TIN CIRCUS PARADE," and "ROUND SNACK BOXES SET OF 4 WOODLAND." The high confidence and lift suggest to us that people who purchase one of these products are significantly more likely to purchase the related product as well.
This means that customers are influenced by the product themes, collections or complementary designs while deciding on a purchase. The results may be useful for product placement management, bundle offer creation and inventory management.

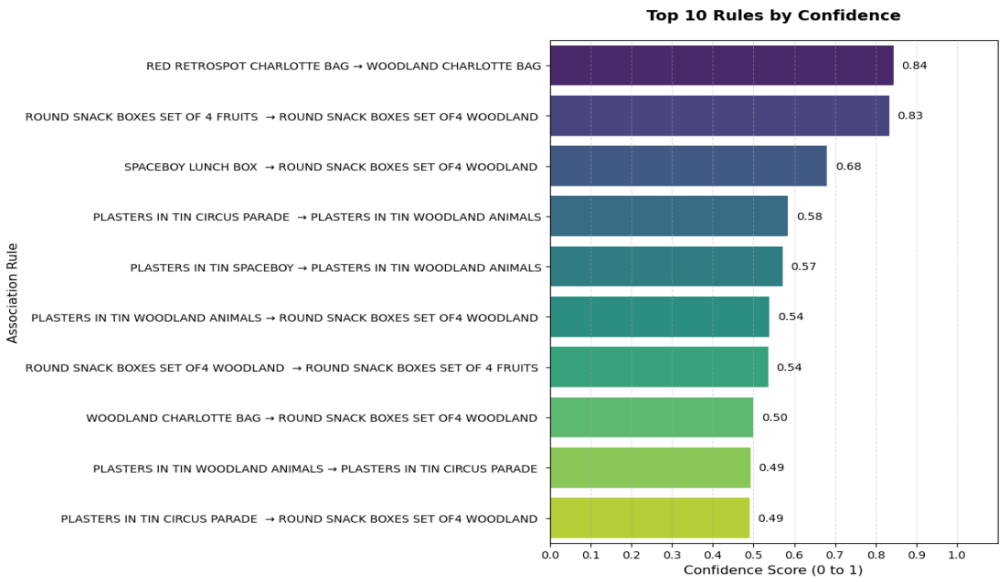


Figure 4. Results by arranged by confidence

Figure 4 shows us the results generated by the algorithm, based on confidence scores. They show a few strong product associations, mostly within matching product categories. The “Red Retrospot” and “Woodland Charlotte bags” have the strongest association, which means that these products are often bought together. It can be seen that customers who buy the “Round Snack Boxes Set of 4 Fruits” are also likely to buy the Woodland version, meaning a trend to buy multiple versions of similar products. The plaster tins explain thematic purchasing patterns, with the space-themed products showing association with other products in the space theme, while the woodland items form their own distinct grouping When comparing different product pairs, the confidence values reveal that certain combinations such as the Charlotte bags, exhibit stronger associations than others like the snack box and plaster tin combinations. These patterns suggest that customers tend to purchase complementary items that share either functional relationships or thematic consistency.

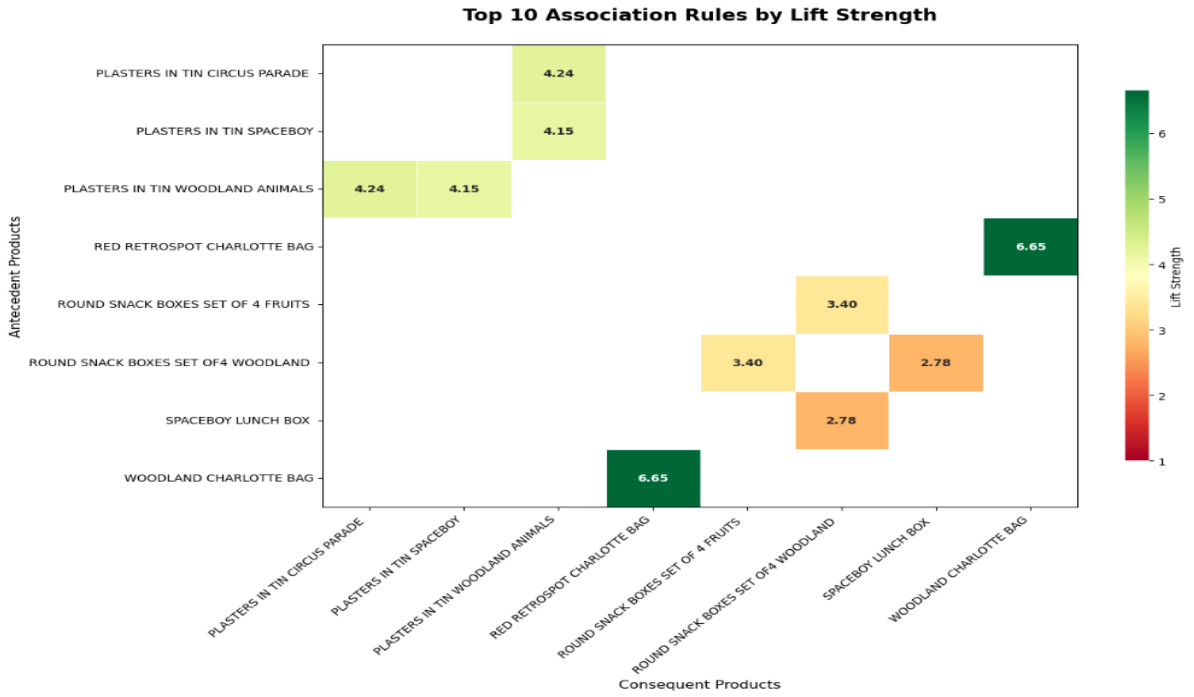


Figure 5. Results arranged by lift strength

Figure 5 shows us the top association rules ranked by lift, showing the most noteworthy product relationships. The results show particularly strong associations between specific itemsets with the highest lift showing especially notable patterns. A few product pairs demonstrate lift values above the threshold of 1 suggesting these combinations occur together more frequently than would be expected by random chance. The "Plasters In Tin" products show multiple strong associations with each other, while the "Charlotte Bags" exhibit the most apparent relationship. "Snack Box" also shows us meaningful associations, particularly between different variants. Space-themed items form their own distinct cluster of associations. These results indicate that customer purchasing behavior follows consistent patterns, with clear preferences for combining certain complementary products

Inventory Management

Due to the complexity and importance of inventory control in the age of globalization, new innovations have been proposed to enhance the computerized procedures for establishing, maintaining, or updating inventory records[3]. For example, an inventory management system

can automatically determine which items in the inventory may need replenishment most likely. Another computer system uses a linear programming engine to choose the priority of customer orders and arrange limited inventory accordingly.
Using the data from Figures 3, 4, and 5, we can come to the conclusion that placing frequently bought-together items near each other can encourage additional purchases. Whether it be space-themed boxes or boxes of different materials. With the usage of MBA, businesses can optimize inventory placement and promotions to increase sales and efficiency

Conclusion and future work

The purpose of this study was to analyze customer purchasing patterns by analyzing transaction data to identify significant associations between frequently bought items. The analysis showed several interesting correlations, highlighting strong and medium relationships between products. From the results, we can conclude that the Apriori algorithm is still used to an effective extent with useful data for marketing strategy and inventory management, but compared to other techniques, such as the FPGrowth Algorithm, it isn't as effective at tackling larger datasets[16]. While the dataset used with the Aprior algorithm provided valuable insights into customer behavior, it is important to acknowledge potential limitations.
This analysis was based on a dataset that was collected over 13 months., from December 2010 to December 2011, which includes 541,911 rows and 8 columns. While the data provides useful insights, the limited timeframe and sample size may influence the reliability of the results. With the dataset also being older than 10 years, an efficient and reliable marketing strategy based on it wouldn't be effective. A broader dataset covering a longer period could offer more accurate and comprehensive findings, leading to more precise predictions and associations. Future research could improve by incorporating larger, more diverse datasets to refine the analysis and enhance decision-making for inventory management and marketing strategies.

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