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## Original scientific paper



## Profesional paper



## Review



## Case report

Medical Journal

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## Case report

# *Betimi i Hipokratit*

*Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.*

*Kolegët e mi do t'i konsideroj si vëllezër të mi.*

*Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.*

# *The Oath of Hippocrates*

*Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.*

*My colleagues will be my brothers.*

*I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor*

Medical Journal

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# ASSOCIATION OF TUMOR NECROTISATION FACTOR ALPHA WITH MULTIVESSEL CORONARY DISEASE IN PATIENTS WITH ACUTE CORONARY SYNDROME

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## ABSTRACT

Acute coronary syndrome (ACS) represents a clinical syndrome, which could manifest with or without changes in the electrocardiogram and with or without elevated cardiac biomarkers. ACS comprises of unstable angina and myocardial infarction with or without ST segment elevation. Depending on the presence of these signs, the treatment method for these patients is planned. In addition to the well-established cardiac biomarker troponin, tumor necrosis factor alpha can also be included in the diagnosis, as independent or in combination with the former for better diagnosis and creating a treatment plan in future cardiac events. In our study, we aimed to demonstrate the association between serum TNF-α levels and angiographic prevalence of atherosclerosis in patients with acute myocardial infarction undergoing coronary angiography and subsequent percutaneous coronary intervention. According to the results of our study, it can be seen that serum levels of TNF-α are correlated with the occurrence of acute myocardial infarction and higher values of TNF-α suggest greater involvement of the coronary arteries by atherosclerosis.

keywords: acute coronary syndrome, cardiac biomarkers, multivessel coronary disease, tumor necrosis factor alpha, cardiac troponin

## INTRODUCTION

Acute coronary syndrome includes a spectrum of conditions in patients who present with recent changes in the clinical picture, with or without changes in the 12-lead electrocardiogram, and with or without acute elevated values of cardiac biomarkers, mainly cardiac troponin [1]. Patients suspected of having acute coronary syndrome (ACS) may have a clinical diagnosis of acute myocardial infarction (which may be with or without ST segment elevation) or unstable angina. The diagnosis of acute myocardial infarction (AMI) is associated with cardiomyocyte necrosis and elevated serum cardiac troponin levels. Unstable angina (UA) is defined as myocardial ischemia at rest or with minimal physical exertion in the absence of acute injury or necrosis of cardiomyocytes. It is characterized by specific clinical signs such as prolonged angina (> 20 minutes), the appearance of new angina of a more severe degree, or angina after a previous episode of myocardial infarction [2].

Acute coronary syndrome is associated with a wide range of clinical presentations, from patients who are asymptomatic on examination to patients with prolonged chest discomfort, cardiac arrest, electrophysiological or hemodynamic instability, or cardiogenic shock [1,2]. Patients with acute coronary syndrome are further classified based on changes in the electrocardiogram and serum cardiac troponin values at examination. The indicated changes have great importance in risk stratification of patients and guide the initial treatment strategy [3].

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine that plays a critical and complex role in myocardial infarction and subsequent heart failure [4]. Elevated serum levels of TNF-α are associated with adverse cardiac remodeling, impaired pump function, and increased mortality [4,5]. TNF-α promotes atherosclerosis, impairs endothelial function, and contributes to inflammatory damage to the heart [4,5]. There are studies that confirm the role and predictive power of TNF-α in acute coronary syndrome and the occurrence of major adverse cardiac events after an episode of acute myocardial infarction [6].

## MATERIAL AND METHODS

Our study was designed as an observational cohort study that included 50 patients hospitalized for acute myocardial infarction in Department of Cardiology at Clinical Hospital Stip in the period from March 2023 to June 2023.

Inclusion criteria: patients with acute coronary syndrome, hospitalized during the aforementioned period and agreeing to participate in the study and providing signed informed consent.

Exclusion criteria: patients who did not consent to participate in the study, patients who had in-hospital mortality, patients with a previous episode of acute coronary syndrome.

Demographic data, risk factors for cardiovascular disease, comorbidities, ECG signs of myocardial injury and necrosis, cardiac biomarkers, heart function data via transthoracic echocardiography, data on angiographic disposition of the disease through coronary angiography and eventual percutaneous coronary intervention and intrahospital outcome in the early period of hospitalization, were collected from the study population.

## STATISTICAL ANALYSIS

IBM SPSS statistical software, version 27, was used for statistical analysis. Comparative and descriptive statistical methods such as Chi-square test for variables with dichotomous distribution, T-test and ANOVA for continuous variables with two or more defined categories, risk ratio with 95% confidence interval, ROC curves for predictive power were used. In addition to these, correlation, univariate and multivariate linear and logistic regression analyses were used to identify significantly associated variables. Significance was determined at a level of <0.05.

## RESULTS

A total of 50 patients with acute myocardial infarction (AMI) who underwent successful percutaneous coronary intervention (PCI) were included in the study. Their demographic characteristics, clinical features of the disease and echocardiographic parameters of the study population are shown in the following tables.

Table 1. Descriptive statistics and demographics

| Characteristic | Total (H/%)<br>50 (100%) |
|---|---|
| Gender<br>Female<br>Male | (p<0,0000)<br>22 (44%)<br>28 (56%) |
| Age (years) | 61.2±9.5 |
| HTA | 40 (89%) |
| Diabetes mellitus | 16 (32%) |
| Smoking | 33 (66%) |
| HLP | 35 (70%) |
| Obesity (BMI >30) | 13 (26%) |
| AMI<br>NSTEMI<br>STEMI | 50 (100%)<br>20 (40%)<br>30 (60%) |
| Biochemical characteristics | |
| hscTn (mean) | 7289.0±9810.4 |
| TNF-α (mean) | 13.9±2.1 |
| Stress glycemia | 8.18±3.02 |

Authors research

Legend: HTA – arterial hypertension; HLP – hyperlipidemia; AMI – acute myocardial infarction; NSTEMI –myocardial infarction without ST segment elevation; STEMI – myocardial infarction with ST segment elevation hscTn – troponin; TNF-α – tumor necrotizing factor alpha

Table 2. Functional parameters of the left ventricle during the index event obtained by transthoracic echocardiography

| | |
|---|---|
| LVEDd (mm) | 52.3±5.0 |
| LVESd (mm) | 38.3±4.2 |
| EF (%)<br>EF<40%<br>Mid-range EF 41-49%<br>EF>50% | 53.2±4.7<br>8 (16%)<br>17 (34%)<br>25 (50%) |
| Diastolic dysfunction | 18 (36%) |

Authors research

Legend: LVEDd – left ventricular end diastolic diameter; LVESd - left ventricular end systolic diameter; EF – ejection fraction

The following table presents the angiographic disposition of the disease as shown by coronary angiography, i.e. whether there is involvement of one or more coronary arteries in the studied population.

Table 3. Angiographic staging of disease by coronary angiography

| Coronary arteries in AMI | Total (H/%)<br>50 (100%) |
|---|---|
| MonoVD | 40 (80%) |
| MVD | 10 (20%) |

Authors research

Legend: AMI – acute myocardial infarction; MonoVD – monovessel disease; MVD – multivessel disease

The following table presents the mean value of TNF-α in the two subclasses of patients with acute myocardial infarction.

Table 4. TNF-α values in relation to angiographic disease disposition

| Biochemical characteristics | Total (H/%)<br>50 (100%) |
|---|---|
| TNF-α at MonoVD | 12.5±2.2 |
| TNF-α at MVD | 14.3±1.9 |

Authors research

Legend: TNF-a – tumor necrotizing factor alpha, MonoVD – monovessel disease; MVD –multivessel disease

## DISCUSSION

Our research identified the following risk factors for the occurrence of acute myocardial infarction: age, hyperlipidemia, arterial hypertension, and diabetes mellitus. In one study, it was proven that patients who have one or more of these comorbidities have a much higher risk of developing acute myocardial infarction with a more severe clinical picture and greater anatomical localization of atherosclerosis [7].

This study showed that the majority of patients with acute myocardial infarction have a left ventricular ejection fraction >50%. This represents a good basis for monitoring these patients for possible future occurrence of cardiac adverse events, primarily the occurrence of heart failure after an episode of acute myocardial infarction, which is a common complication in this patient population. TNF-α has been shown to be an important prognostic factor in these patients [8].

Regarding the geographical distribution of atherosclerosis in the studied patient population, it was shown that in 10% more than one coronary artery was affected. In the same population, mean TNF-α levels are higher than in patients with single coronary artery disease. Several studies have reported results that support this claim [9,10].

## CONCLUSION

The serum value of TNF-α alone and/or in combination with previously proven cardiac biomarkers, as well as clinical and paraclinical methods for the diagnosis of acute myocardial infarction, can be used to optimize the therapy of patients with AMI, also to improve the prevention of adverse cardiac events after an episode of acute coronary syndrome.

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Original scientific paper

# POST TONSILLECTOMY HEMORRHAGE: POSSIBLE RISK FACTORS

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## ABSTRACT

Introduction: Tonsillectomy and adenotonsillectomy are the most common surgical procedures performed by ear, nose, and throat (ENT) specialists. Bleeding after tonsillectomy is one of the most serious and common complications of tonsillectomy surgery. According to worldwide data, hemorrhage after tonsillectomy is about 2-5 % and can happen in the first 24 hours as primary bleeding or after 7 days when the scabs fall off as secondary bleeding.

Aim: Although it is a routine operation, the seriousness of regular monitoring, adherence to a hygienic diet, and postoperative course is necessary to prevent the risk of life-threatening complications.

Material and methods This study was conducted by retrospectively reviewing the medical history of patients who underwent tonsillectomy and adenotonsillectomy at the ENT clinic of our hospital for 7 year period. Evaluation of each individual, including their personal medical data (age and sex, coagulation status, CBC analysis, blood group with Rh factor, treatment, diagnosis, complication, and hospitalization time)

Results: A total of 667 tonsillectomy and adenotonsillectomy procedures were performed during the study period. Postoperative hemorrhage occurred in 59 patients (8.8%). The incidence was significantly higher in adults (21.3%) compared to children (4.3%) ($p<0.05$). Primary hemorrhage occurred in 5 patients (8.5%) and secondary hemorrhage in 54 patients (91.5%). Minor bleeding was observed in 56 cases (94.9%), while major bleeding occurred in 3 cases (5.1%). Bleeding was more common in patients operated on with cold dissection compared to hot dissection ($p<0.05$). Infection of the tonsillar fossa was detected in 25.4% of cases with hemorrhage. Most bleeding episodes occurred between the 5th and 10th postoperative day and were more frequent during colder months.

Conclusion: Post-tonsillectomy hemorrhage remains a significant postoperative complication. Advanced age, surgical technique, infection of the tonsillar fossa, and seasonal factors may contribute to the increased risk of bleeding.

Key words: tonsillectomy, bleeding, infection, surgical technique, hospitalization

## INTRODUCTION

While the first information about tonsillectomy was found in Hindu medical documents around 1000 BC (1), Aulus Cornelius Celsus described tonsillectomy with fingers in 30 AD. Tonsillectomy and adenotonsillectomy are the most common surgical procedures performed by ear, nose, and throat (ENT) specialists (3, 4). Indications for tonsillectomy include recurrent tonsillitis, peritonsillar abscess, tonsillar hypertrophy with apnoea, and suspected malignancy (5). Complications such as nausea, vomiting,

respiratory distress, difficulty swallowing, dehydration, fever, and bleeding can occur after tonsillectomy and adenotonsillectomy (6). Bleeding after tonsillectomy is one of the most serious and common complications of tonsillectomy surgery (6). Bleeding after tonsillectomy has been classified as primary (before 24 hours) and secondary (after 24 hours) bleeding in the literature (3,7-9). Bleeding after tonsillectomy has been classified as primary (before 24 hours) and secondary (after 24 hours) bleeding in the literature. According to worldwide data, hemorrhage after tonsillectomy is about 2-5 % and can happen in the first 24 hours as primary bleeding or after 7 days when the scabs fall off as secondary bleeding. (3,7-9).

## MATERIALS AND METHODS

In this study, we retrospectively analyzed the medical records of patients who presented to our clinic with bleeding after tonsillectomy and determined possible predisposing factors. Our goal was to highlight risk factors by drawing the attention of physicians. In a retrospective study conducted at the University Clinic for Ear, Nose and Throat, University Campus "St. Mother Teresa" in Skopje, S. Macedonia. This study was conducted by retrospectively reviewing the medical history of patients who underwent tonsillectomy and adenotonsillectomy at the ENT clinic of our hospital for 7 year period. From the medical detail records, we retrospectively tracked demographic, epidemiological, clinical, and surgical information. Based on medical data, patients who were hospitalized at the ENT clinic due to bleeding after tonsillectomy were identified. Evaluation of each individual, including their personal medical data (age and sex, coagulation status, CBC analysis, blood group with Rh factor, treatment, diagnosis, complication, and hospitalization time). The cases were divided into two groups: children and adults. A complete coagulation status included: prothrombin time (PT), activated partial thromboplastin time (aPTT), bleeding time, and clotting time. The complete medical documentation in PHI UK for Ear, Nose, and Throat is attached in ENT clinic. Additionally, cases that were followed up and treated with hospitalization for bleeding after tonsillectomy, the day or hour of bleeding, the number of days they were under observation, the severity of bleeding (minor/major bleeding) and the procedure for stopping the bleeding, the need for blood transfusion, the presence of infection in the tonsillar bed and its relationship to the seasons were evaluated. All patients were hospitalized for at least one night for observation, regardless the severity of bleeding. The first setting for bleeding control is cessation of oral intake, intravenous fluid support, and removal of the coagulum from the tonsillar bed under topical/local anesthesia and gargling with cold water (conservative treatment). Cases that did not respond to conservative treatment or had severe bleeding were treated under general anesthesia. Local compression, local application of adrenaline, bipolar electrocautery, and/or suture ligation were performed under general anesthesia. Patients whose hematocrit was below 30% were given a packed red blood cell count. Patients were discharged according to their general condition and hemoglobin values. Statistical analyses were performed using SPSS statistical software (SPSS 20.0 for Windows, Inc. Chicago, IL, USA). Results were evaluated with the Pearson chi-square test and a p value of <0.05 was considered significant.

## RESULTS

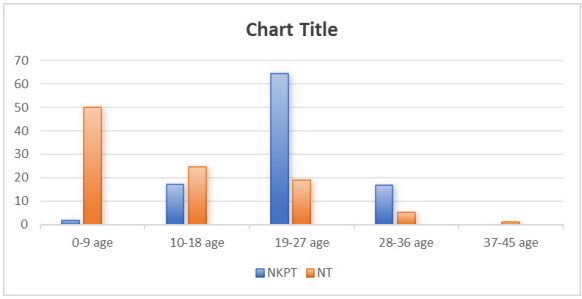
A total of 667 tonsillectomy and adenotonsillectomy operations were performed in our clinic in the last five years. Of the cases, 308 (46.2%) were female, 359 (53.8%) were male, the mean age was 8.5±12.5 (1-43), 498 (73.3%) were children, 178 (26.7) were adults, and the mean postoperative hospital stay was 3.92±1.7 (1-7) days. The overall incidence of bleeding was calculated as 8.8% 59 subjects of which, 4.3% in 28 children and 4.5% in 30 adults. This was shown to be significant in adults (p<0.05).

(table 1, chart 1)

Table 1. Distribution of patients with tonsillectomy and post-tonsillectomy bleeding by age group

| Age range: | 0-9 age (n,%) | 10-18 age (n,%) | 19-27 age (n,%) | 28-36 age (n,%) | 37-45 age (n,%) |
|---|---|---|---|---|---|
| NT n:667 | 333 (50) | 165 (24,7) | 127 (19) | 34 (5,1) | 8 (1,2) |
| NKPT n:59 | 1 (1.7) | 10 (17) | 38 (64,4) | 10 (16,9) | 0 |

(NT: Tonsillectomy number, NKPT: Post-tonsillectomy bleeding number)

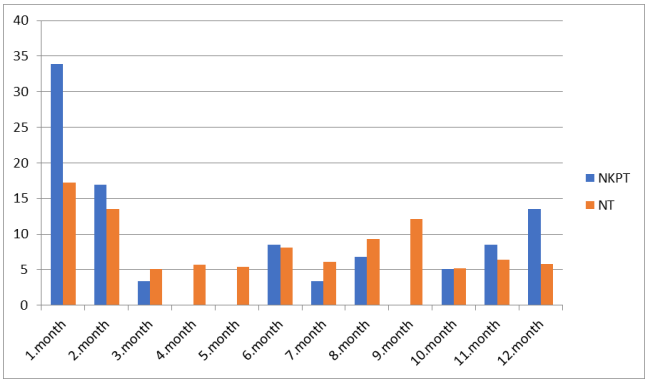



(NT: Tonsillectomy number, NKPT: Post-tonsillectomy bleeding number)

The mean age of the 59 patients with post-tonsillectomy bleeding was 22.7±5.2 (8–29) years, and 21 (35.6%) were children and 38 (64.4%) were adults. Five (8.5%) of these cases were primary, 54 (91.5%) were secondary, 56 (94.9%) were minor, and three (5.1%) were major. In addition, all patients with primary bleeding were pediatric patients (<18 years of age). Three (5.1%) cases required blood transfusion. Of these, two units of blood were transfused to one patient, and one unit of blood to two patients. Coagulation tests were within normal limits. As a tonsillectomy method, 320 (47.9%) of our cases were operated on with cold dissection and 347 (52.1%) with warm dissection. In addition, 35 (59.9%) of the cases with bleeding were operated on with cold dissection, and 24 (40.1%) with warm dissection. While the incidence of bleeding was 10.9% or 34 patients in the cases performed with the cold dissection method, it was found to be 6.9% or 25 in the cases performed with the warm dissection method. This was statistically significant against cold dissection ($p<0.05$). While there was active bleeding in 43 cases at the time of admission, no bleeding was observed in 16 cases at the time of admission. The mean length of stay of patients presenting with post-tonsillectomy bleeding was 5.8 (1–13 days). As a treatment approach, in addition to intravenous fluid support in 30 (51%) cases, conservative treatment, including gargling with cold water with removal of the coagulum from the tonsillar bed under local anesthesia, was used, and 29 (49%) underwent bipolar electrocautery or suturing under general anesthesia. Bipolar electrocautery and/or suturing were used in all patients (5/59) with primary bleeding, and 25/54 (46.3%) of patients with secondary bleeding under conservative and the remaining (29/54) under general anesthesia. No advanced surgical procedures were performed in any of the cases in which we controlled bleeding under general anesthesia. We had no cases of recurrent bleeding. In 15/59 (25.4%) of our cases with bleeding after tonsillectomy, there was infection in the tonsillar bed. There was no residual tonsillar tissue in any of our patients. When evaluated according to the seasons, it was observed that the majority of bleeding (76%) in 44 patients occurred in the cold months (1-3 and 10-12) (table 2, chart 2 )

Table 2. Distribution of patients with tonsillectomy and post-tonsillectomy bleeding by month

| Months | 1 (n,%) | 2 (n,%) | 3 (n,%) | 4 (n,%) | 5 (n,%) | 6 (n,%) | 7 (n,%) | 8 (n,%) | 9 (n,%) | 10 (n,%) | 11 (n,%) | 12 (n,%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NCPT : n(59) | 20 (33.9) | 10 (16.9) | 2 (3.4) | 0 0 | 0 0 | 5 (8.5) | 2 (3.4) | 4 (6.8) | 0 0 | 3 (5.1) | 5 (8.5) | 8 (13.5) |
| NT: n (667) | 117 (17.2) | 90 (13.5) | 34 (5.1) | 38 (5.7) | 36 (5.4) | 54 (8.1) | 41 (6.1) | 62 (9.3) | 81 (12.1) | 34 (5.2) | 42 (6.4) | 38 (5.8) |




(NT: Tonsillectomy number, NKPT: Post-tonsillectomy bleeding number)

## DISSCUSION

However, the effects of very few of the causes reported in studies on this topic of post-tonsillectomy bleeding are statistically significant (10, 11). Bleeding rates after tonsillectomy range from 0.3% to 13.9% (11). Hopkins C. found that the frequency of bleeding can increase up to 18% (12). In our study, the incidence of bleeding was found to be 8.8%. Bleeding after tonsillectomy is more common in adults than in children. Tomkinson et al. (13) reported

in their serial study of tonsillectomy in 17680 people that the risk of bleeding in patients older than 12 years of age was higher than before the age of 12 years. We found this rate to be 21.3% in adults and 4.3% in children. In our study, it was found that there was a very low bleeding rate in the pediatric group and a higher rate in the elderly group. In addition, the risk of bleeding increases with age. Bleeding as a complication can be observed in the early or late stage. Bleeding within the first 24 hours is called primary bleeding, and late bleeding seen after 24 hours is called secondary bleeding (8). Primary bleeding is the result of acute vascular injuries occurring during surgery, while secondary bleeding is associated with dissolution of the coagulum in previously coagulated foci due to various causes and destruction of fibrin, which can sometimes be observed due to infection of the surgical wound (3). Tomkinson et al. (13) reported that 270 (1.5%) of 17,480 patients who underwent tonsillectomy had postoperative bleeding, of which 128 were primary, and 142 were secondary. Some authors have reported the rate of primary bleeding as 1.2–7% and secondary bleeding as 7–9% after tonsillectomy (14, 15). In our study, the incidence of secondary bleeding was found to be higher (91.5%). The majority of patients with secondary bleeding were adults. The incidence of primary bleeding was 8.5%, and all of these cases were pediatric patients. In addition, postoperative tonsillar bleeding can be classified as minor depending on the amount of bleeding and as major bleeding when it is life-threatening (16). If the bleeding is major or if it recurs, it may require rehospitalization, intervention, or even reoperation (17). In our study, 56% (94.9%) of our patients with bleeding after tonsillectomy had minor bleeding and 3 (5.1%) had major bleeding. These patients received blood transfusions. Bleeding may cause readmission to the hospital after discharge. Patients presenting with bleeding after tonsillectomy may be managed with only close clinical observation initially, or they may require surgical intervention under local or general anesthesia for more severe bleeding (17). In our study, all our patients were hospitalized and followed up. All patients with primary bleeding, and 25/54 (46.3%) of patients with secondary bleeding, were treated conservatively; 29/54 patients under general anesthesia were treated with bipolar electrocautery and/or sutures.

Secondary bleeding is most common between 5-10 days (18). While secondary bleeding can be found in the literature up to the 54th day (4). Cakir A et al. (18) reported that they had patients who had bleeding problems on the 60th postoperative day in one of their studies. Primary hemorrhages are less common in children, and most of them occur in the first eight hours after surgery (19). In this study, we found that the admission time of patients who presented for bleeding after tonsillectomy was 5.9 days. In addition, all patients with primary bleeding were children.

Whether there is a seasonal distribution of bleeding and whether there is a relationship between ambient temperature and bleeding is another controversial point. Although Wall et al. (16) in their study stated that bleeding was not related to the seasons, it was reported that bleeding increased in July (20). In another study, it was reported that bleeding was most common in summer (44%) (16). In contrast, Lee et al. in their study, found that et al. in their study found that bleeding after tonsillectomy was more common in the winter months (9). In our study, we found that bleeding increased most in the cold months (1-3 and 10-12 months).

## CONCLUSION

Although the complication rates of tonsillectomy have been reduced with surgical techniques developed since ancient times, post-tonsillectomy bleeding is still a life-threatening complication today (7). Post-tonsillectomy bleeding is known to cause social and psychological distress to physicians, patients, and their relatives, as well as a financial burden (3). Post-tonsillectomy bleeding is one of the most serious and common complications of tonsillectomy surgery (3). To date, many studies have attempted to identify risk factors associated with post-tonsillectomy bleeding (8). Factors such as age and sex, surgical technique and experience, infections, hematological parameters, intraoperative blood loss, and postoperative blood pressure have been implicated in the etiology of secondary post-tonsillectomy bleeding (9, 10). We believe that the seasons should be taken into account when planning tonsillectomy surgery, and caution should be exercised as bleeding after tonsillectomy may be higher in the colder months. There are many studies examining the effects of surgical techniques on bleeding (21). In contrast to classical dissection (cold dissection), surgical methods that cut while coagulating at the same time cause less perioperative bleeding (22). Bipolar tonsillectomy comes after the cold surgery method in terms of bleeding safety (23). Electrocautery is also widely believed to reduce postoperative bleeding. Guida and Mattucci (24) found no significant difference in bleeding between electrocautery and classical (cold) dissection in

their series of 1000 tonsillectomy patients. Watson et al. (25) in their study of 1036 patients did not find more primary bleeding after cautery surgery compared with the literature. In this study, we found that the incidence of bleeding in the cold dissection method was statistically higher than in the warm dissection method. The two main factors responsible for bleeding after secondary tonsillectomy are residual tonsillar tissue and infection (10). In our study, the bleeding patients did not have residual tonsillar tissue. There was an infection in the tonsillar bed in 15/59 (25.4%) of our patients. The mean leukocyte count in these patients was 21450/µl. It should be remembered that infection can be a predisposing factor for bleeding after tonsillectomy and necessary precautions should be taken.

As a result, we consider it extremely important to pay attention to the highlighted recommendations and studies during tonsillectomy in order to prevent postoperative bleeding complications that can cause disturbing results. The warm dissection method should be chosen as the dissection method to be applied, the infection that may develop after surgery should be prevented and these factors should be carefully evaluated because the possibility of bleeding may increase with advanced age and in cold seasons. Patients who present with a complaint of bleeding after tonsillectomy should be hospitalized even for observation, vascular access should be established, examination, vital signs and hematological parameters should be carefully monitored.

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Original scientific paper

# FUNCTIONAL DISORDERS AFTER CONSERVATIVE TREATMENT OF MANDIBULAR FRACTURES

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## ABSTRACT

Mandibular fractures are among the most common injuries of the maxillofacial region and are frequently managed by conservative(non-surgical) treatment particulary in cases of minimaly displaced fractures.Althought this approach aims to preserve anatomical structures and avoid surgical complications ,functional disturbances may occur during the healing process.The aim of this study is to evaluate the most frequent functional disorders observed after conservative treatment of mandibular fractures and to analyse their clinical significance.

Functional complications following conservative management may include limited mouth opening,temporomandibular joint disfunction,malocclusion,masticatory inefficiency and pain during mandibular movements.These disorders can arise as a consequence of prolonged immobilisation,muscle stiffness,inadequate fracture alignment,or changes in occlusal relationships.Temporomandibular joint discomfort and reduced mandibular mobility are particularly common in patients treated with intermaxillary fixation for extended periods.

Clinical evaluation of patients after conservative treatment typically involves assessment of mandibular range of motion,occlusal stability,joint function and the presence of pain or muscular tenderness.Early physiotherapy and functional rehabilitation play a crucial role in minimizing long-term complications.Several studies emphasize that timely initiation of mandibular exercises significantly improves functional recovery and reduces the risk of persistent disfunction.

Despite the potential for certain functional disturbances,conservative treatment remains an effective option for appropriately selected mandibular fractures.Carefull case selection,regular follow-up,and adequate rehabilitation protocols are essential for achieving optimal functional outcomes.Understanding the nature and prevalence of these disorders contributes to improved treatment planning and better long-term patient quality of life.

Key words: Fractures, T.M.J., collum mandibulae, treatment, healing, consequences, intermaxilar fixation, ankylosis, microgenia, laterogenia,

## INTRODUCTION

The question of the consequences that occur after the conservative treatment of fractures of the lower jaw,is the subject of a large number of conflicting opinions in the professional literature and among maxillofacial surgeons. Therefore, there is a need for a wider evaluation of the results of conservative treatment of a large randomized series of fractures, which would include all aspects of fracture healing. This means, conducting a systematic and scientific examination of the causes, conditions for conservative treatment, vision, X-ray aspects of healing, and especially the functional results and consequences after the treatment is completed.

The results were tabulated in relation to age and sex, cause of the injury, associated injuries, occlusal relationships, appearance of the fracture, position of the fragments, or

combinations of the above parameters.

Thus,the obtained groups - tabulated in relation to the relevant parameters that are of interest for proving the set goals (hypothesis) were analyzed with appropriate standard statistical methods.

The statistical significance of the distribution of variables and the statistical significance observed associations were assessed using : proportions, ratios, rates, Student's t-test for large dependent and independent samples and non-parametric tests: , Kolmogorov - Smirnov test, and Friedman-ANOVA.

The findings indicated that the most frequent consequences of fractures in our study sample were:

-pain,which we did not find that is associated with the type, or the hight of the fracture,or the way of healing.

-difficulyt in opening of the lower jaw, observed in 28% of the examined patients ,which in most cases did not represent a major limitation for nutrition or the patient's daily activities.

-oclusal disorders are rare,,often at wrong treated patients , or untreated, especialy when there is no T.O.S. (Terminal Oclusal Support) because of any reason.

-Ankylosis in TMJ was not found in our material,as well as disturbance in mandibular growth and development.

With evaluation of all described consequences of fractures of the neck of the lower jaw,after decesive conservative treatment,we are on opinion that there are currently no indications for routine surgical treatment in this type of fractures.

## OBJECTIVES

Through this study,we aimed to define the following objectives:

- To determine the presence or occurrence of the consequences of the defect after the conservative treatment is completed, that is, to determine the presence of:

a).-pain in the condylar region

b).-appereance of difficualties in opening of the lower jaw

c).-changes in the functional movements of T.M.J

in relation to:

a) height of the fracture

b) type of fracture

v) patients age

- Based on the situation and the severity of the consequences, determine the indications for the need for surgical treatment.

## MATERIAL AND METHOD

The study was conducted on a randomized series of all subjects who were patients at the Clinic for Maxillofacial Surgery in the period from 01.01.2017 to 31.12.2025. The subjects were processed in two groups, of which the first group was a retrospective study, and the second group was a prospective study. The retrospective group consisted of patients for whom we had radiographs on admission in the period from 01.01.2017 to 31.12.2020, from which it was possible to conclude about the type of fracture, and its height and in some cases to make the appropriate measurements. From this group, 60 patients responded to the call, so only they were taken into consideration in the functional examinations, and examinations of the type of healing as the final result. The prospective group consisted of 76 patients who were treated in the period from 01.01.2021 to 31.12.2025, examined according to the specified methodology.

All subjects underwent examinations at the time of admission to treatment, when the IMF was removed, and at one, three, and six months after the removal of the intermaxillary fixation.

Clinical examinations: - anamnestic data and patient status at admission, with a questionnaire on the patient's status important for further treatment and prognosis.

Radiological examinations were performed on all patients at the Clinic for Maxillofacial Surgery,and the X-ray Institute at the Clinical Center in Skopje, as follows: - orthopantomogram, CBCT scan, 3D if necessary, TMJ tomograms (if necessary), submentovertical projection (if necessary. Orthopantomograms were measured according to the method proposed by Worsae, 1994,

The resulting groups - tabulated in relation to the relevant parameters that are of interest for proving the set goals (hypotheses) were tested with appropriate standard statistical methods.

The statistical significance of the distribution of the distributions and the statistical significance of the existence of significance were examined with:

proportions, ratios, rates, Student's t-test for large dependent and independent samples and non-parametric tests: x2 - test, Kolmogorov - Smirnov test, and Friedman-ANOVA,

SAMPLE

The gender and age of the patients showed a distribution that we also encountered in the findings from the literature and are presented in Chart. 1.

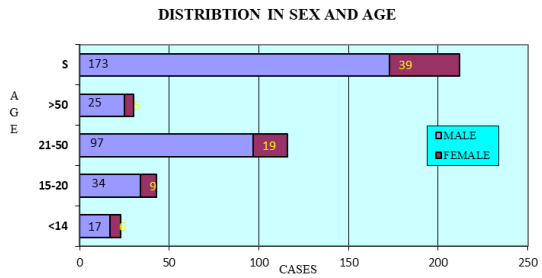



Chart 1

It is noticeable that the majority of patients are young and middle-aged men, which is directly due to the most common cause of injury. The percentages are generally in line with the cited literature.

The causes of injury are presented in Chart 2.

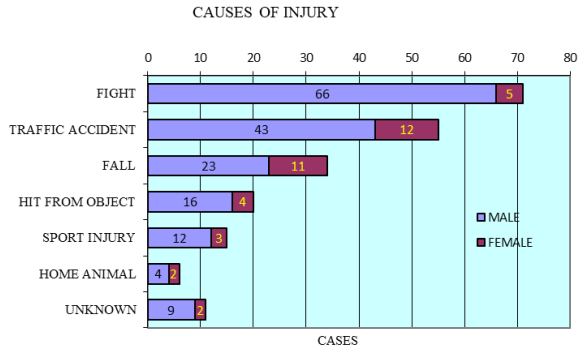



Chart 2

The most common cause of injury is physical abuse, which is most often practiced by males in adolescence and adulthood. Traffic accidents take second place as a cause of injury. In childhood and among the female population, falls from a height are still the most common cause of injuries of this type.

The injuries were most often solitary injuries to the neck of the mandible, and less often associated with other injuries to the mandible, face and neck or accompanied by polytrauma. The results are given in Chart 3.

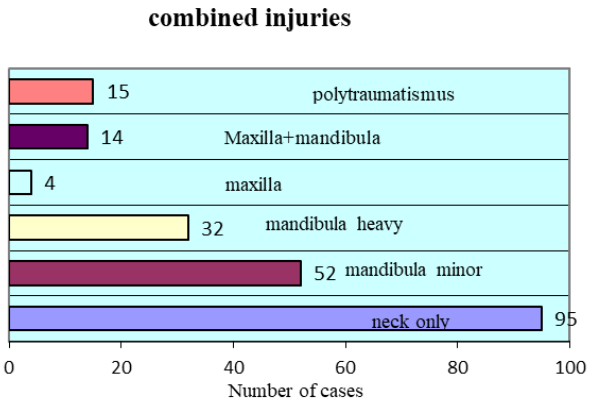



Chart 3

The nature of the injuries is a very important factor in determining the course of therapy. Polytraumatized patients, as well as patients who have other more extensive injuries to the bones of the facial skeleton are complicated to resolve, and according to several authors, they represent an indication for surgical treatment of the fracture of the neck of the lower jaw. The relationship of the neck fracture with other fractures of the lower jaw is presented as complementary, i.e. each fracture of the lower jaw, associated with a fracture of the neck of the lower jaw is in itself an indication for surgical treatment.

Occlusal conditions are data that are needed in the studies to determine the possibility of good occlusal support of conservative treatment. (chart 4). Patients who had less than 4 pairs of teeth in occlusion, without any molars, were classified as having no occlusal conditions, and we considered the occlusion to be "stable" when we had at least six pairs of molars or premolars in occlusion with more than eight pairs of teeth in occlusion.

Occlusal conditions are the crucial moment that guides us in determining the possibility of conservative treatment of fractures. Good occlusal conditions with more than eight pairs of teeth and an adequate number of molars are the guiding moment in deciding how to approach the treatment of fractures of the neck of the lower jaw. The absence of enough teeth and the inability to establish a correct occlusion that would correspond to the occlusion that the patient had before the injury are factors that predispose to poor results after the completed treatment.

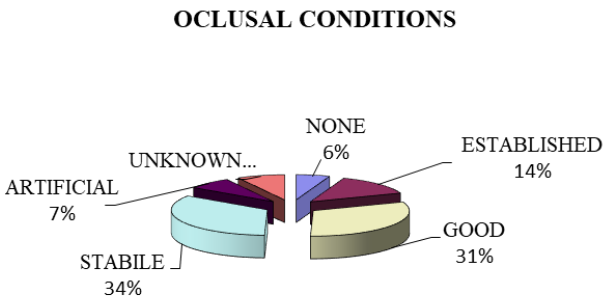



Chart 4

## RESULTS

### FUNCTIONAL MOVEMENTS

Opening, lateral movement, protrusion and retrusion, are called "functional mandibular movement". They are basically related to the movements of the capitulum mandibulae in TMJ, that is, to the "functional joint movements". The physiology of TMJ and the conditions that must be satisfied for smooth and proper development of functional joint movements are generally known. Their violation causes the impossibility of performing the correct rotations and propulsive movements of the capitulum mandibulae in TMJ, and as a result, a reduction of the functional mandibular movements occurs. Fractures of the neck of the lower jaw are basically bone-joint injuries that have the greatest consequences on strictures in the TMJ. Therefore, we can say that the functional mandibular movements are the best test for the functional ability of the TMJ, and thus it is the basic factor in relation to which we will evaluate the consequences of the neck of the lower jaw.

### RESTRICTIVE OPENING

The limited opening of the mouth is apostrophized by several authors as the most common consequence of the narrowing of the neck of the lower jaw.

The degree of opening has not been precisely defined in any effort, but everyone agrees that the opening is within the limits of 37-55 m.m. interincisal distance, depending on gender and age, is an acceptable level for which we can say that the patient has no restriction on opening. In our material, the largest part of the patients were subjectively satisfied with the possibility of opening under 37 mm., however, we do not consider these results to be objectively unsatisfactory.

The survey was conducted on a series of 129 respondents. Children were excluded from the examinations, due to a small interincisal distance that is variable next to it, adults without two incisors, and children who remained unprosthetic during the entire follow-up period.

From initial, 5-10 mm. the interincisal distance after the removal of the IMF led to a rapid increase in the degree of opening to normal limits.

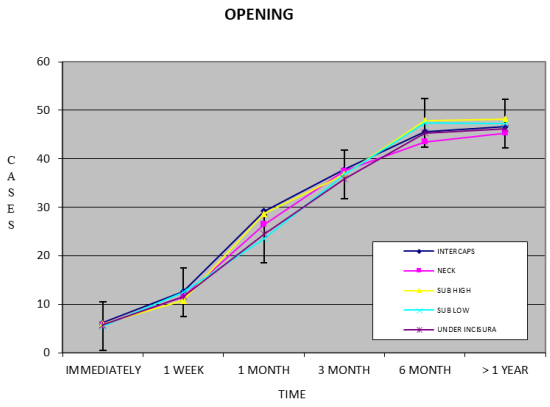



Chart 5

It can be seen from the graph that the fastest growth of the interincisal distance is up to the third month after the removal of the splints, and after the sixth month the finding can be taken as permanent, that is, it can be considered that the convalescent period is over. The largest number of authors who have reviewed the topics in their works agree with these findings. (Amaratunga NA, 1987, (1); Bell at al. 1983, (2); Thiele RB, Marcoot RM 1985 (3); Silvennoinen U.et al. 1994, (4))

We have already examined the phenomenon of limiting the opening in relation to the height of the hatch. The results were processed with the Student's t-test between all parameters and are presented in table 1.

| TABLE 1 | N | S.V. | S.D. |
|---|---|---|---|
| INTER CAPSUL | 4 | 42.1 | 8.5 |
| NECK | 18 | 41.8 | 7.9 |
| SUB HIGH | 41 | 43.4 | 7.3 |
| SUB LOW | 38 | 42.1 | 7.7 |
| UND.INCISURA | 28 | 41.9 | 8.1 |

The degree of opening of the lower jaw did not show a statistically significant relationship in relation to the height of the fracture. Site values show values for p> 0.05.

The results for the dependence of the degree of opening of the lower jaw, from the type of the fracture are presented in table 2.

TABLE 2

| | N | S.V | S.D |
|---|---|---|---|
| NO DISLOCAT. | 22 | 44.5 | 8.5 |
| ANGULATION | 10 | 43.8 | 7.9 |
| DISLOCATION | 81 | 43.2 | 9.2 |
| LUXATION | 16 | 41.2 | 9.4 |

Statistical tests were performed with comparative t-tests.

In this case too, the degree of opening of the lower jaw did not show a statistically significant relationship in relation to the type of the fracture. All values were in diapason : $p > 0.05$; $t < 1.96$.

In our results, we did not find that the limitation of the opening is causally related neither to the height, not to the type of the fracture . On the other hand, realistically, we found that dislocation and luxation fractures more often cause restriction of opening than other types of fractures, but we cannot say with certainty that the type of fracture completely determines the restriction of opening.

On the other hand, the fact that combined injuries to the facial skeleton and polytraumatized patients generally have more severe injuries, both in the joint segment and in the surrounding soft tissues, should not be overlooked, which would mean that there is a higher posibility of having more severe consequences. (Avrahami et al. 1993, (5); Dahlstrom L, Lindahl L, 1989, (6); Newman L. 1998, (7))

In order to clearly prove this hypothesis, the influence of these factors should be excluded, that is, a long-term IMF should be applied to isolated and easy fractures of the neck of the lower jaw, which in principle goes against medical ethics. Such experiments were made in the experimental life, (chapter II.E.), and the conclusion goes in support of the thesis that the limitation of the movements in the TMJ is due to the prolonged IMF, but this in itself will not lead to irreversible changes in the functional elements for limiting the opening, but it is only a factor that these changes are supplemented.

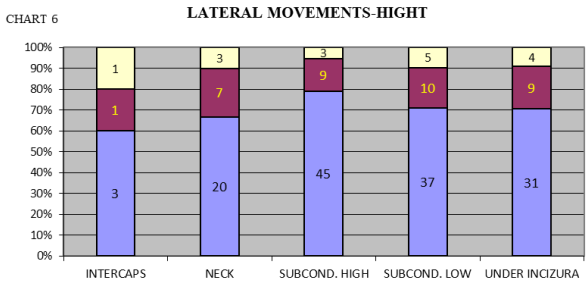
LATERAL MOVEMENTS

The lateral movements of the mandible, protrusion and retrusion, which we call “functional movements”, are in addition to opening, the basis of the functioning of the lower jaw and TMJ, and are one of the basic indicators for assessing the consequences of a violation of their function as a result of the shortening of the neck of the lower jaw.

Under normal conditions, the mandible moves laterally up to 12 mm., which mostly depends on the sex, constitution, and age of the patient. In our material, we examined the lateral movements in relation to the individual elements of the neck of the lower jaw. Due to the extreme differences in the various groups of patients, very small obtained values and huge standard deviation, the results are presented with the frequency of the patients, where the lateral movements towards the healthy side are presented as: free, restrictive, or impossible. Movenents are defined as “free” if it is larger than the size of the first upper incisor, “restrictive” if it is larger than half of its size and impossible if it is smaller than half of the first upper incisor.

Examining the sizes of the lateral movements in relation to the height of the fracture were performed on a group of 140 patients with unilateral injuries, and a group of 16 patients with bilateral injuries and are presented in chart 6.

CHART 6




The test was made with the Kolmogorov-Smirnov test for two primers. Relations are tested between the free and restrictive movements (p1) and the free and impossible movements (p2) in relation to the height of the fracture.

In both cases, there is a statistically significant difference between the height of the fracture and the possibility of lateral movement. (p1= 0.036; p2=0.036) It is seen that injuries to the neck at the level of the attachment can be considered as potentially increasing the risk of restriction

in mandibular physiological movements. Cases with a double violation did not show a deviation from this rule, so we do not present them in a separate table.

The results for the possibility of lateral movements in relation to the type of the fracture are presented in chart 7.

Statistical processing is performed with the Kolmogorov-Smirnov test for two examples of limited and impossible lateral movements. (p1,p2)

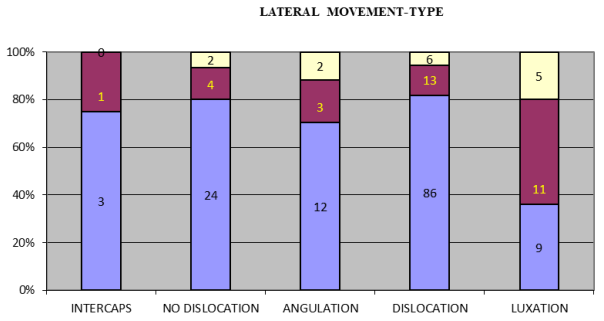



Chart 7

We did not find a statistically significant relationship between the appearance of the squint and the reduction of lateral movements (p1=0.699), while the relationship between the appearance of the squint and the inability to perform lateral movements is statistically significant. (p2=0.036) This means that the largest number of cases in which lateral movements are restrictive or impossible belong to the groups of dislocating and luxating injuries, while non-dislocating injuries and angulations generally show free joint movements. For their part, these two variables are interdependent and individually depend on the way of healing of the fractures of the neck of the lower jaw.

3). In order to separate these relationships, we asked for a correlation between the restriction in physiological movements in relation to the way the fracture heals. The results were processed with the same statistical procedure and are presented in chart 8.

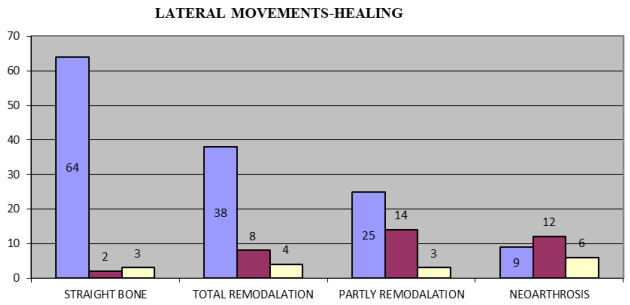
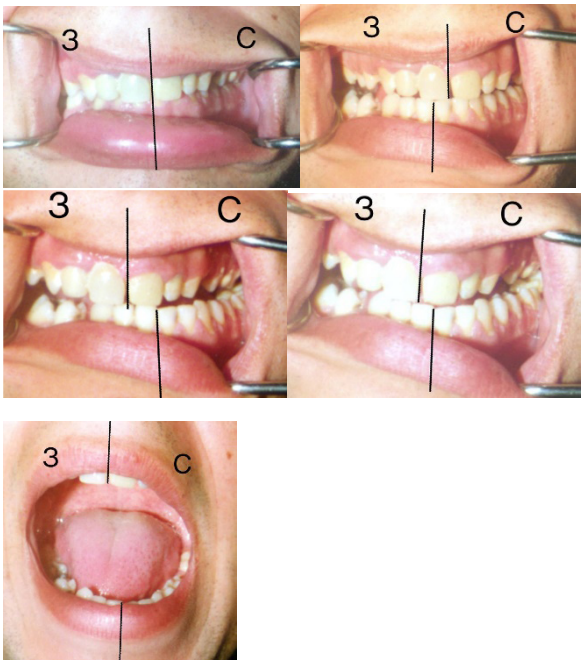



Chart 8

The results did not show the statistical significance of the finding of reduced lateral movements in relation to the way of fracture healing. (p=0.21) On the other hand, there is statistical significance of the finding for the impossibility of lateral movement and the way of healing. (p=0.036) Such joints that heal as neoarthrosis or as partial remodeling show in large part the impossibility of lateral movements, which is rare in joints that heal with bone fusion or complete remodeling.

This ratio is very interesting in light of the findings for the limitation of the opening, where we found a reduction in the size of the opening depending on the type of healing. This by itself imposes an answer that even in cases where the opening is not marked, there is a possibility of restriction of physiological movements.




Picture1

PROTRUSIVE MOVEMENTS

The protrusive movements were examined as a function of the lateral movements, that is, as part of the assessment of the functional ability of the TMJ. For them, we found that they can be free with protrusion over 6 mm., or reduced to a lesser degree and lateralization of the interincisive line in the direction of the affected joint.

The findings for reduced and lateralized protrusive movements completely coincide with the findings for the inability to perform lateral movements in the same patient, which completely proves the functional inability of the affected joint to perform propulsive movements. (picture 1/B)

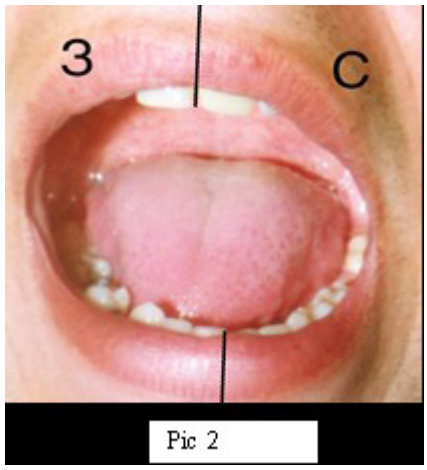
Only two cases with bilateral complete restriction of lateral movement showed complete impossibility for protrusive movements. In all other cases, the protrusive movements were preserved to a certain extent, so that the degree of lateralization and protrusion was in a different ratio and almost always individual.

DEVIATIVE OPENING

Patients who show restriction in the free movements of the mandible on the healthy side also show a characteristic picture of the deviation of the mandible on the side of the fracture at some stage of opening. This deviation of our material has been found in the order of sizes from 0 to 10 mm. This condition is another element that follows the functional disability of the affected joint.

The phase of the appearance of the deviation during the opening corresponds to the degree of restriction of the propulsive movements in the TMJ. The greater the restriction of the propulsive movements, the greater the restriction of the lateral movements and the earlier the deviation of the mandible occurs in the act of opening. (pic. 2)

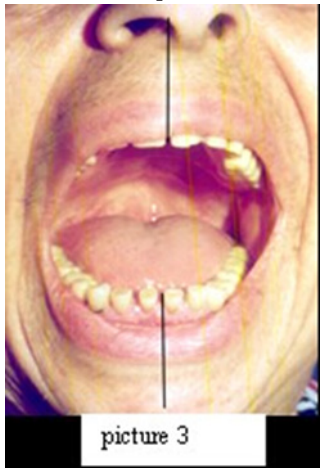
Lateralization during opening is often mentioned as a consequence of the neck of the lower jaw in the literature. Silevennionen et al., 1994, (4) the lack of occlusive stability on the fractured side and the strong dislocations of the capitulum are seen as the reason for their occurrence of the impossibility of lateral movement on the fractured side or deviation during opening. Feifel H et al, 1996, (8) found a 16.4% reduction in condylar length on the operated side, measured by lateral movement.



Pic 2

voluntary contraction of the musculature se izedna~i. I find Talwar RM, Ellis 3rd 1998, (9) says that after 8-10 months the difference in muscle action is lost, that is, we did not find a statistically significant correlation in the results of the patients in relation to the control group. Istite naodi gi opi{uvaat i Trockmorthon GS, 1999, (10); Stoll P et al., 1996, (11); Bell WH et al., 1983, (12) and other authors.

A large number of patients who showed a picture of neoarthrosis or partial remodeling showed a normal opening of the lower jaw. However, we found that in a large part of these patients, the impossibility of performing lateral movements, protrusion and deviation during opening is observed. This means that in this case there is an impossibility to perform free translational movements in addition to the existence of free rotational movements. (pic. 3)


picture 3

In our study, and also in the most cited authors, the impossibility of performing free translational movements was compensated by excessive rotational movements in the affected joint. Thus, in these patients, the function was apparently not disturbed, there is no lateralization

during the opening, but when performing the functional tests, it gives positive results.

In our material, we found that in combined injuries there is a significantly greater number of functional disorders than in isolated ones. This, of course, comes in addition to the extent of the injury with a large number of hematomas and the possibility of fibrosis of the surrounding extra-articular structures, and the need for prolonged IMF during their treatment.

## DISCUSSION

Fractures of the mandibular condyle represent a significant proportion of mandibular fractures and are often associated with functional disorders of the TMJ. The choice of therapeutic approach, especially between conservative and surgical approaches, remains a topic of numerous scientific discussions. Modern research indicates that non-operative, i.e. conservative treatment can provide satisfactory functional results in patients with minimal or partial dislocations of the fractured fragments and ensure stable occlusion (13).

The results of several studies have shown that after conservative treatment, certain functional disorders may occur, such as limited mouth opening, deviation during opening, impaired masticatory function and pain in the TMJ. These changes occur as a result of adaptive processes in the temporomandibular joint and in the masticatory system (17).

In most cases, however, a significant capacity for remodeling of the condylar process is observed. This process allows for the gradual establishment of functional adaptation of the joint and improvement of masticatory function over time (18). According to some authors, such modeling is especially pronounced in younger patients, in whom there is a greater potential for bone tissue regeneration.

On the other hand, bilateral fractures of the condylar process may result in more pronounced disorders of the masticatory system. Studies show that these fractures can lead to changes in masticatory patterns and asymmetry of the masticatory muscles (19).

Some authors point out that in patients with enormous dislocation of the fragments, conservative treatment can result in long-term functional impairment (13).

Despite possible complications, conservative treatment remains an important therapeutic option, especially in patients with minor dislocation of the fragments and stable occlusion. Appropriate functional rehabilitation, physiotherapy and regular patient monitoring play a significant role in achieving optimal functional results.

## CONCLUSION

Opening the lower jaw by 30-40 mm. interincisal distance was found in 22% of the respondents, which was not an obstacle for functional activities. Extreme limitation of opening under 30 mm. after conservative treatment we didn't find. Predictive moments for the occurrence of limited opening are:

-type od fracture: -luxation and dislocated fractures

-combined injuries of maxillofacial region

-duration of immobilisation-longer immobilisation

-patients age-not seen in younger patients

Functional joint movements are limited in 36% of patients as a result of articular and extra-articular fibrotic changes.

Predictive moments for their occurrence are:

-luxation and dislocation problems,

- healing of cartilage with neoarthrosis or partial remodeling,

- associated injuries, especially on the mandible,

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Profesional paper

# IMMUNE MODULATION OF PSA LEVELS IN RELATION TO PROSTATE VOLUME AFTER TREATMENT OF PROSTATITIS

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## ABSTRACT

Prostate-specific antigen (PSA) is widely used in the detection and monitoring of prostate diseases; however, PSA lacks cancer specificity. PSA levels may increase not only in prostate cancer but also in benign conditions such as prostatitis and benign prostatic hyperplasia. Inflammatory processes may influence PSA release through immune-mediated mechanisms, which complicates clinical interpretation and decision making prior to prostate biopsy.

The aim of this study was to investigate the relationship between PSA levels and prostate volume in patients with prostatitis and to evaluate PSA changes after antibiotic therapy.

A retrospective observational analysis included 25 adult men who underwent prostate biopsy because of elevated PSA levels or abnormal digital rectal examination. Patients were categorized according to biopsy findings into chronic prostatitis or prostate cancer. Serum PSA and prostate volume were measured at baseline, after antibiotic therapy, and at follow-up. Statistical analysis included Pearson correlation, Mann-Whitney testing, and evaluation of PSA dynamics over time.

A significant decline in PSA levels was observed after antibiotic therapy in men with chronic prostatitis, whereas prostate volume remained relatively stable. A strong correlation between prostate volume and PSA was present before treatment and weakened after therapy. In contrast, patients diagnosed with prostate cancer demonstrated persistent PSA elevation without meaningful correlation with prostate volume.

These findings suggest that inflammatory immune activity significantly influences PSA behavior. Immune modulation following treatment of prostatitis may reduce PSA levels without major changes in prostate volume. Recognition of this effect is important to improve interpretation of PSA dynamics and reduce unnecessary prostate biopsies.

Keywords: PSA, prostatitis, prostate volume, immune modulation, prostate cancer

## INTRODUCTION

Serum prostate-specific antigen (PSA) is widely used for early detection and risk stratification of prostate cancer; however, PSA lacks cancer specificity. Several benign conditions including benign prostatic hyperplasia, urinary retention, recent instrumentation, and

particularly prostatic inflammation and infection may lead to PSA elevation and create significant diagnostic uncertainty. Stopiglia et al. demonstrated that prostatic inflammation represents an important cause of PSA variability and may lead to false-positive PSA elevation in the absence of malignancy [1]. Similarly, Sfoungaristos et al. reported that inflammatory conditions of the prostate substantially reduce the positive predictive value of PSA in prostate cancer detection [2]. Based on these findings, repeat PSA testing and additional risk stratification tools are recommended before prostate biopsy when PSA levels are mildly or moderately elevated, as discussed by Karazanashvili and Managadze [3].

From an immunological perspective, prostatitis represents a spectrum of inflammatory conditions ranging from acute symptomatic infection to asymptomatic histological inflammation. Cai et al. described that immune cell infiltration, pro-inflammatory cytokine signaling, epithelial barrier disruption, and stromal remodeling increase epithelial permeability and facilitate PSA leakage into the systemic circulation [4]. Del Giudice et al. further demonstrated that immune-mediated tissue damage rather than bacterial presence alone may be a major driver of PSA variability in inflammatory prostate disease [5].

Clinical studies have shown that antibiotic therapy may reduce inflammatory activity and lead to a decrease in PSA levels in patients with prostatitis. Lee et al. reported significant PSA decline following antibiotic treatment in men with inflammatory prostate conditions [6]. Similar findings were described by Magri et al., who demonstrated that reduction of inflammatory burden may modify PSA behavior during follow-up [7]. However, persistent PSA elevation may occur when chronic immune activation remains unresolved or when an underlying malignancy is present, as emphasized by Magri et al. and Nickel et al. [8,9].

Prostate volume (PV) represents another important determinant of PSA levels. Larger prostates generally produce higher PSA values due to increased glandular tissue mass. Cai et al. demonstrated that the relationship between prostate volume and PSA in inflammatory prostate disease is strongly influenced by inflammatory burden rather than gland size alone [10]. More recently, Nickel et al. confirmed that immune-mediated inflammation modifies the PV–PSA association and may limit the reliability of PSA-based diagnostic thresholds [11]. Chronic inflammation of the prostate has been increasingly recognized as an important factor influencing PSA levels and prostate tissue remodeling through immune-mediated mechanisms. Inflammatory cell infiltration and cytokine signaling pathways may contribute to PSA elevation even in the absence of malignancy [13]. In addition, inflammatory mediators such as interleukins and tumor necrosis factor have been shown to influence prostate growth and immune responses within prostatic tissue [14].

The aim of this study was to quantify the relationship between prostate volume and PSA levels across serial measurements obtained before and after antibiotic therapy in men with prostatitis. Additionally, we aimed to compare these patterns between patients with biopsy-proven chronic prostatitis and those diagnosed with prostate cancer in order to better understand the role of inflammatory immune modulation in PSA dynamics.

## MATERIALS AND METHODS

Study design and patients:

This original retrospective observational study was conducted at the Department of Urology, General Hospital “Ferid Murad”, Gostivar, Republic of North Macedonia. The study included 25 adult men treated for clinical prostatitis. Serial laboratory and imaging measurements were extracted from clinical records. The dataset included age, prostate volume (PV), total PSA (tPSA), free PSA (fPSA), and the percent free-to-total PSA ratio.

Antibiotic regimen and follow-up:

Patients received levofloxacin 500 mg once daily for 28 days. Treatment then continued with trimethoprim-sulfamethoxazole 480 mg twice daily for 10 days. PV and PSA were recorded at three timepoints: baseline (pre-antibiotics), after levofloxacin therapy, and at follow-up. All patients underwent prostate biopsy one year after treatment initiation. Biopsy results were categorized as chronic prostatitis or prostate cancer.

Outcomes:

The primary outcome was the strength of association between PV and tPSA at each timepoint. Secondary outcomes included differences in PSA metrics between biopsy outcome groups.

Statistical analysis:

Continuous variables are summarized as mean ± standard

deviation. Pearson correlation coefficients were used to assess the PV–tPSA association. Group comparisons were performed using the Mann-Whitney U test. A two-sided p value < 0.05 was considered statistically significant. Analyses were performed in Python.

Ethics and data confidentiality:

Patient data were obtained retrospectively from hospital medical records at the Department of Urology, General Hospital "Ferid Murad", Gostivar. All data were anonymized prior to analysis and handled in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

## RESULTS

Baseline characteristics:

Mean age was 63.9 ± 5.4 years. Fourteen men had biopsy-proven chronic prostatitis and eleven were diagnosed with prostate cancer.

Trends in PSA and prostate volume:

Mean tPSA decreased from 11.28 ± 8.96 ng/mL at baseline to 9.59 ± 6.28 ng/mL after levofloxacin therapy and further to 6.96 ± 7.14 ng/mL at follow-up. Mean prostate volume demonstrated only minimal changes across the observation period.

PV–tPSA correlations:

In the full cohort, PV correlated with tPSA at baseline (r = 0.579, p = 0.002) and after levofloxacin therapy (r = 0.494, p = 0.012), but not at follow-up (r = 0.078, p = 0.710).

In subgroup analysis, men with chronic prostatitis demonstrated strong PV-tPSA coupling at baseline (r = 0.682, p = 0.007) and after levofloxacin therapy (r = 0.806, p < 0.001). In contrast, no meaningful PV–tPSA correlation was observed in men later diagnosed with prostate cancer at any timepoint.

Biopsy outcome differences:

After levofloxacin therapy, the cancer group had higher tPSA (11.59 ± 5.64 vs 8.01 ± 6.50 ng/mL, p = 0.043) and a lower percent free PSA ratio (17.65 ± 6.08% vs 27.27 ± 11.99%, p = 0.037). At follow-up, these differences were more pronounced.

Table 1 presents the characteristics, serial PSA and prostate volume metrics.

Table 1. Patient characteristics and serial PSA and prostate volume metrics.

| Variable | All patients (n=25) | Chronic prostatitis (n=14) | Prostate cancer (n=11) |
|---|---|---|---|
| Age (years) | 63.88 ± 5.36 | 64.29 ± 6.11 | 63.36 ± 4.46 |
| Prostate volume baseline (g) | 58.16 ± 8.98 | 60.43 ± 10.75 | 55.27 ± 5.20 |
| tPSA baseline (ng/mL) | 11.28 ± 8.96 | 11.10 ± 11.25 | 11.52 ± 5.29 |
| f/t PSA baseline (%) | 21.88 ± 8.63 | 23.80 ± 9.74 | 19.44 ± 6.62 |
| Prostate volume after levofloxacin (g) | 57.80 ± 8.92 | 59.79 ± 10.84 | 55.27 ± 5.06 |
| tPSA after levofloxacin (ng/mL) | 9.59 ± 6.28 | 8.01 ± 6.50 | 11.59 ± 5.64 |
| f/t PSA after levofloxacin (%) | 23.04 ± 10.82 | 27.27 ± 11.99 | 17.65 ± 6.08 |
| Prostate volume follow-up (g) | 57.04 ± 9.34 | 58.36 ± 11.51 | 55.36 ± 5.64 |
| tPSA follow-up (ng/mL) | 6.96 ± 7.14 | 3.26 ± 4.72 | 11.67 ± 7.05 |
| f/t PSA follow-up (%) | 35.00 ± 19.85 | 44.44 ± 17.64 | 22.98 ± 16.06 |

Pearson correlations between prostate volume and total PSA are shown on the Table 2, while Table 3 presents PSA metrics by biopsy outcomes, p values from Mann Whitney U test.

The association between prostate enlargement and inflammatory activity has been documented in recent studies showing that immune cell infiltration and chronic inflammation contribute to prostatic tissue remodeling and progression of benign prostatic hyperplasia [15]. Furthermore, reduction of inflammation after antimicrobial therapy may result in changes in PSA levels reflecting the resolution of inflammatory immune responses in prostatic tissue [16].

Table 2. Pearson correlations between prostate volume and total PSA.

| Timepoint | All (Pearson r) | Chronic prostatitis | Prostate cancer |
|---|---|---|---|
| Baseline | 0.579 (p=0.002) | 0.682 (p=0.007) | 0.216 (p=0.524) |
| After levofloxacin | 0.494 (p=0.012) | 0.806 (p=0.001) | 0.092 (p=0.787) |
| Follow-up | 0.078 (p=0.710) | 0.350 (p=0.219) | 0.083 (p=0.809) |

Table 3. PSA metrics by biopsy outcome, p values from Mann Whitney U test.

| Variable | Chronic prostatitis (mean±SD) | Prostate cancer (mean±SD) | Mann-Whitney p |
|---|---|---|---|
| TPSA 2 (ng/mL) | 8.01 ± 6.50 | 11.59 ± 5.64 | 0.043 |
| FPSA/TPSA 2 Ratio (%) | 27.27 ± 11.99 | 17.65 ± 6.08 | 0.037 |
| TPSA 4 (ng/mL) | 3.26 ± 4.72 | 11.67 ± 7.05 | 0.001 |
| FPSA/TPSA 4 Ratio (%) | 44.44 ± 17.64 | 22.98 ± 16.06 | 0.008 |

Figure 1 presents Baseline relationship between prostate volume and total PSA, stratified by biopsy outcome.

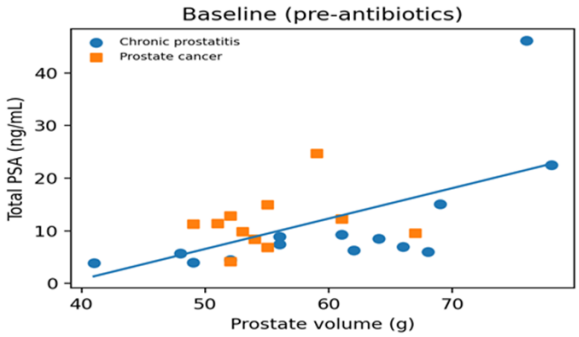


Figure 1. Baseline relationship between prostate volume and total PSA, stratified by biopsy outcome.

Figure 2 shows the relationship between prostate volume and total PSA after levofloxacin therapy, stratified by biopsy outcome, while Figure 3 presents the relationship between prostate volume and total PSA at follow up after antibiotic treatment, stratified by biopsy outcome.

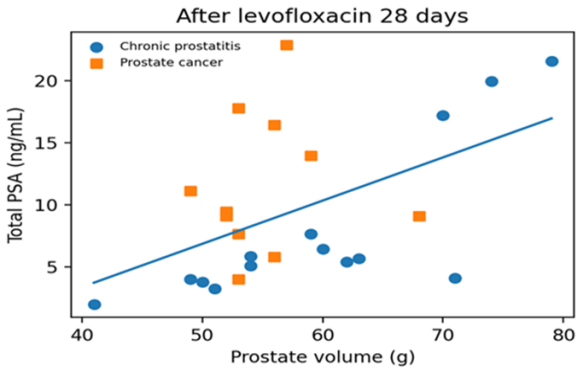


Figure 2. Relationship between prostate volume and total PSA after levofloxacin therapy, stratified by biopsy outcome.

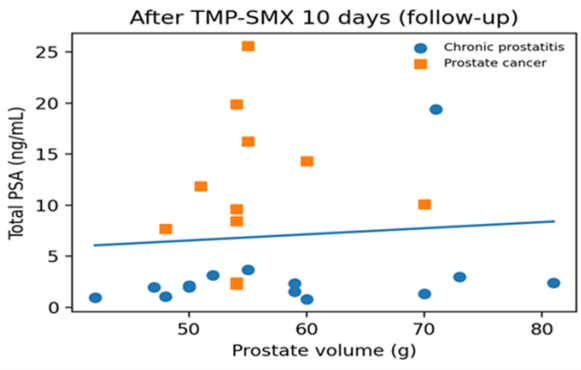


Figure 3. Relationship between prostate volume and total PSA at follow up after antibiotic treatment, stratified by biopsy outcome.

## DISCUSSION

The present study demonstrates that the relationship between prostate volume and PSA levels in men treated for prostatitis is strongly influenced by inflammatory immune activity and is modifiable following antibiotic therapy. Similar findings were reported by Stopiglia et al., who showed that PSA elevation in prostatitis frequently reflects inflammatory permeability changes rather than malignant PSA production [1].

The immunological basis of this phenomenon has been described by Cai et al. and Del Giudice et al., who demonstrated that cytokine-mediated epithelial disruption and immune-cell infiltration promote PSA leakage into the circulation independently of prostate size [4,5]. In this context, antibiotic therapy may act not only as an antimicrobial intervention but also as a modulator of immune-driven inflammation.

Clinical studies by Lee et al. and Magri et al. reported PSA reduction following antibiotic therapy, supporting the concept that inflammation control alters PSA dynamics [6,7]. However, persistent PSA elevation despite therapy may occur when chronic immune activation remains unresolved, as emphasized by Magri et al. and Nickel et al. [8,9].

An important finding of the present study is the divergence in PV–PSA behavior between biopsy-proven chronic prostatitis and prostate cancer. Gandaglia et al. demonstrated that PSA expression in prostate cancer is primarily driven by tumor biology rather than glandular volume or inflammatory burden [12]. Similarly, Nickel et al. highlighted that absence of inflammation-related PSA modulation may represent a distinguishing feature of

malignant disease [11].

The clinical implications of these findings are important. Monitoring PSA changes over time and evaluating inflammatory context may improve diagnostic accuracy and reduce unnecessary biopsies, as suggested by Karazanashvili and Managadze as well as Sfoungaristos et al. [2,3].

Taken together, these findings support the interpretation of PSA as a dynamic biomarker influenced by immune-mediated inflammation rather than a purely cancer-specific marker

## CONCLUSION

In men treated for prostatitis, prostate volume and PSA demonstrate an inflammation-linked relationship that is strongest before treatment and weakens as inflammatory burden decreases. Persistent PSA elevation together with loss of PV–PSA correlation and a lower free-to-total PSA ratio characterized men later diagnosed with prostate cancer. These findings support repeat PSA assessment and interpretation within an inflammatory clinical context prior to prostate biopsy decisions. Recognition of inflammation-driven PSA variability may improve clinical decision making and help avoid unnecessary prostate biopsies in patients with suspected prostatitis.

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Profesional paper

# CHOANAL POLYPS ACROSS AGE GROUPS: COMPARATIVE CLINICAL AND HISTOLOGICAL INSIGHTS FROM A RETROSPECTIVE STUDY

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## ABSTRACT

Purpose: To evaluate and compare the clinical and histopathological characteristics of choanal polyps (CPs) in pediatric and adult populations.

Methods: A retrospective analysis was conducted on patients who underwent surgical treatment for CPs. Evaluated parameters included demographics, symptoms, origin and laterality, histopathology, associated sinonasal disease, allergic rhinitis, and recurrence rates.

Results: The study included 78 patients (22 children, 56 adults). Primary nasal symptoms were comparable between groups. Oropharyngeal extension was significantly more frequent in children (27% vs. 7%, $p<0.01$). Angiomatous histology (18% vs. 5.3%, $p<0.05$), allergic rhinitis (32% vs. 18%, $p<0.05$), and ipsilateral CRSsNP (32% vs. 14%, $p<0.05$) were also more common in the pediatric group. Recurrence rates did not differ significantly (14% vs. 8%).

Conclusion: Pediatric CPs exhibit distinct features, including more frequent oropharyngeal extension, an angiomatous subtype, and a correlation with allergic rhinitis and ipsilateral CRSsNP.

Keywords: Choanal polyps; Pediatric; Allergic rhinitis; Chronic rhinosinusitis; Angiomatous polyp

## INTRODUCTION

Choanal polyps (CPs) are benign inflammatory lesions originating from the mucosa of the nasal cavity and paranasal sinuses, extending into the nasopharynx through the choana. They most commonly arise from the maxillary sinus mucosa, in which case they are referred to as antrochoanal polyps (ACPs) [1,2]. Typically, ACPs originate from the inner wall of the maxillary antrum and gradually enlarge, passing through an accessory ostium or, less frequently, through the natural ostium into the nasal cavity [1,2].

Although the maxillary sinus represents the most frequent site of origin, CPs may also arise from other regions within the sinonasal tract, including the ethmoid and sphenoid sinuses, nasal septum, and the middle or inferior turbinate [3]. These lesions are usually unilateral; however, rare cases of bilateral CPs have been reported in the literature [4,5].

The etiology and pathogenesis of CPs remain incompletely understood. Chronic inflammation, atopy, and impaired lymphatic drainage have been proposed as contributing factors in their development. CPs account for approximately 4–6% of all nasal polyps in the general population, whereas their prevalence is significantly higher in children, reaching up to 33% [8].

Diagnosis is primarily based on clinical examination, including anterior rhinoscopy and nasal endoscopy, complemented by computed tomography (CT) of the paranasal sinuses, which is essential for determining the site of origin and extent of the lesion. Surgical excision

remains the treatment of choice [6].

## MATERIALS AND METHODS

The present study aimed to evaluate and compare the clinical and histopathological characteristics of CPs in pediatric and adult patients. A review of the existing literature revealed only a limited number of studies addressing age-related differences in ACPs [9,10], with a lack of comprehensive analyses encompassing CPs as a broader clinical entity. To the best of our knowledge, this study represents the first report from our country examining both clinical and histopathological features of CPs across different age groups.

This retrospective descriptive study included 78 patients (47 males and 31 females) with a mean age of 38.7 years (range: 4–67 years), diagnosed with choanal polyps (CPs), who were treated and followed up at the ENT University Hospital, University Campus "Ss. Mother Theresa" between January 2010 and December 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Institutional Ethics Committee, and written informed consent was secured from all adult participants and from the parents or legal guardians of pediatric patients for the use of clinical data.

Demographic data, presenting symptoms, and clinical characteristics of CPs—including laterality, site of origin, surgical approach, histopathological findings, associated paranasal sinus disease, presence of allergic rhinitis, duration of postoperative follow-up, and recurrence rates—were retrospectively reviewed. Patients were stratified into two groups: pediatric (<18 years) and adult (≥18 years).

All patients underwent computed tomography (CT) of the paranasal sinuses in coronal, axial, and sagittal planes. Magnetic resonance imaging (MRI) was performed selectively in cases requiring further differential diagnosis. Endoscopic sinus surgery (ESS) was the primary treatment modality in the majority of cases.

In all pediatric patients with antrochoanal polyps (ACPs), as well as in adult patients in whom the site of origin was readily accessible, endoscopic middle meatal antrostomy was performed. In adult patients with polyps originating from the inferior or anterior wall of the maxillary sinus, the procedure was extended with an inferior meatal antrostomy to ensure adequate access.

In selected adult cases where the maxillary component of the ACP could not be adequately visualized or completely removed endoscopically, a combined approach was employed, consisting of endoscopic middle meatal antrostomy and a limited external (mini-Caldwell–Luc) procedure.

The postoperative follow-up period was at least 24 months for all included patients. Patients lacking adequate follow-up data, as well as those with recurrent polyps previously treated at other institutions, were excluded from the study.

All excised specimens were subjected to histopathological examination using hematoxylin and eosin staining and were evaluated by a single experienced pathologist to ensure consistency. Histological analysis focused on identifying specific subtypes and associated inflammatory changes.

Assessment of allergic status was performed in all patients based on clinical symptoms (nasal obstruction, rhinorrhea, sneezing, itching, hyposmia), endoscopic findings (edematous, pale mucosa and inferior turbinate hypertrophy), and results of skin prick testing and serological analysis. Skin prick testing was conducted using a standard panel of 15 inhalant allergens. Histamine dihydrochloride (1 mg/mL) served as the positive control, and saline as the negative control. Reactions were measured on the volar aspect of the forearm after 15 minutes. A test was considered positive when the mean wheal diameter was equal to or greater than that of the histamine control. Total serum IgE levels were measured using an enzyme-linked immunosorbent assay (ELISA), with values >100 IU/mL considered indicative of atopy.

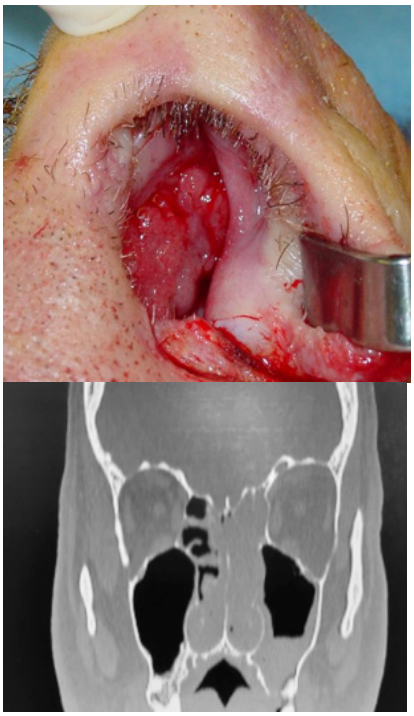
## RESULTS

The demographic and clinical characteristics of patients with choanal polyps (CPs) are summarized in Table 1. A total of 78 patients were included, comprising 22 (28%) pediatric and 56 (72%) adult patients. The pediatric group included 13 males and 9 females (mean age: 13.7±1.8 years; range: 4–17), while the adult group included 34 males and 22 females (mean age: 51.8±4.2 years; range: 19–67). The most common presenting symptoms in both groups were nasal obstruction, rhinorrhea, snoring, and epistaxis, with no significant intergroup differences.

All CPs were unilateral. The maxillary sinus was the predominant site of origin in both groups (17/22 in children; 50/56 in adults), followed by the anterior

ethmoid sinus and, less frequently, the middle and inferior turbinates. Oropharyngeal extension was significantly more common in pediatric patients compared to adults ($p<0.01$). (Photo 1, 2)

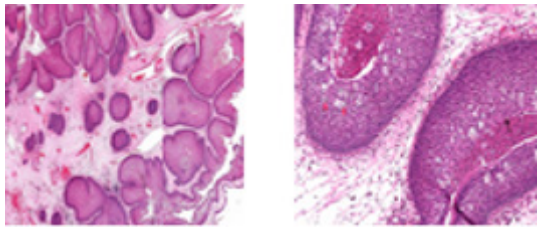
Photo 1, 2 (nasal polyp, CT scan)



Endoscopic surgery was performed in all pediatric patients and in 85% of adults. Middle meatal antrostomy was the standard approach in all pediatric cases with antrochoanal polyps (ACPs). In adults, combined middle and inferior meatal antrostomy was performed in 10 (20%) patients, while 8 (15%) underwent an additional mini-Caldwell–Luc procedure due to limited endoscopic access.

Histopathological analysis confirmed CPs in all cases. The lesions were lined by ciliated pseudostratified respiratory epithelium with mixed inflammatory stromal infiltrates. Dilated ductal retention cysts were observed in the antral component in 54% of pediatric and 67% of adult patients. Angiomatous CPs were identified in 4 pediatric and 3 adult patients, demonstrating a significantly higher prevalence in children ($p<0.05$) (Photo 3).

Photo 3. Patohistological findings



The association with allergic rhinitis was significantly more frequent in children than in adults ($p<0.05$). Ipsilateral chronic maxillary rhinosinusitis without nasal polyps (CRSsNP) was identified in 32% of pediatric and 14% of adult patients ($p<0.05$).

The mean postoperative follow-up was 58.8±28.5 months in children and 57.5±27.8 months in adults. Recurrence occurred in 3 (14%) pediatric and 5 (8%) adult patients, without a statistically significant difference. All recurrences were observed in patients with ACPs. Notably, in adults, recurrences occurred exclusively after isolated middle meatal antrostomy, whereas no recurrences were observed following combined surgical approaches. No correlation was found between the site of polyp attachment within the maxillary sinus and recurrence rates.

## DISCUSSION

Choanal polyps (CPs) demonstrate distinct histopathological features compared to bilateral inflammatory nasal polyps. While the latter are typically characterized by eosinophil-predominant inflammation, CPs exhibit a mixed inflammatory infiltrate composed mainly of lymphocytes, plasma cells, macrophages, and neutrophils [7]. In line with previous reports, we frequently observed stromal ductal retention cysts in the antral component of antrochoanal polyps (ACPs), likely reflecting glandular alterations during polyp growth. In the present study, no significant differences were identified in the prevalence of main nasal symptoms between pediatric and adult patients. However, oropharyngeal extension was significantly more common in children, suggesting either a higher growth potential or delayed diagnosis in this population, as previously reported [8]. We also found a higher prevalence of the angiomatous subtype of CPs in children, consistent with earlier studies [9,10]. This rare variant, characterized by prominent vascular proliferation, may represent either secondary vascular changes due to stromal compromise or a distinct entity

driven by angiogenesis [12–13]. Clinically, its presentation may mimic vascular tumors, emphasizing the importance of histopathological evaluation.

The relationship between CPs and allergic rhinitis remains controversial. In our cohort, allergic rhinitis and ipsilateral chronic maxillary rhinosinusitis without nasal polyps (CRSsNP) were significantly more frequent in pediatric patients. This may reflect the impact of mucosal edema and ostiomeatal obstruction in children, predisposing to chronic sinus inflammation. Our histological findings, showing limited eosinophilia, support the hypothesis that mechanical obstruction and impaired drainage, rather than allergy alone, play a key role in CP pathogenesis, as suggested by previous authors [14].

Surgical excision remains the treatment of choice; however, complete removal of the antral component is essential to prevent recurrence. In our series, all recurrences occurred in ACPs, with a higher, though not statistically significant, rate in children. This may be explained by a more conservative surgical approach in pediatric patients to preserve facial growth structures. In contrast, extended endoscopic techniques in adults, including inferior meatal antrostomy and combined approaches with mini-Caldwell–Luc, were associated with no recurrences, supporting previous evidence that improved access to the maxillary sinus reduces residual disease and recurrence rates [15, 16]. Nevertheless, external approaches should be used cautiously in children due to potential effects on maxillary growth and dentition [17].

This study has several limitations, including its retrospective design and relatively small sample size from a single center. Additionally, incomplete data on symptom duration, particularly in younger children, limited further analysis. Future multicenter studies with larger cohorts are warranted to validate these findings.

## CONCLUSION

This study demonstrates distinct clinical and histopathological features of choanal polyps (CPs) in children compared to adults. Oropharyngeal extension, association with allergic rhinitis and ipsilateral chronic rhinosinusitis, as well as the angiomatous subtype, are more frequently observed in the pediatric population. Endoscopic surgery represents a safe and effective treatment in both age groups; however, middle meatal antrostomy alone may be insufficient for complete removal of antrochoanal polyps (ACPs) and prevention of recurrence. In adults, extended approaches—including inferior meatal antrostomy and, in selected cases, combined procedures with mini-Caldwell–Luc—may improve surgical outcomes.

In children, surgical management remains challenging due to anatomical and developmental considerations, which may contribute to higher recurrence rates. Further studies are needed to establish optimal surgical strategies for pediatric ACPs.

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Profesional paper

# ЕФЕКТОТ НА КИНЕЗИТЕРАПЕВТИЧНИ ПРОЦЕДУРИ ВРЗ PROM НА КОЛКОТ КАЈ ДЕЦА СО ЦЕРЕБРАЛНА ПАРАЛИЗА

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## АПСТРАКТ

Церебралната парализа често е придружена со намален пасивен опсег на движење и развој на контрактури, особено во пределот на тазобедрените зглобови. Раната кинезитерапевтска интервенција може да има значајна улога во превенција на овие компликации.

Целта на истражувањето беше да се испита ефикасноста на професионална кинезитерапевтска процедура во зголемување на пасивниот опсег на движење на тазобедрената флексија кај деца со церебрална парализа.

Методи:Истражувањето претставува проспективна лонгитудинална интервенциска клиничка студија спроведена на примерок од 15 деца со церебрална парализа на возраст од 20–24 месеци. Биомеханички мерења на пасивниот опсег на движење PROM (Passive Range of Motion) на articulatio coxofemoralis / flexio, беа извршени на почетокот и по 24 месеци континуирана кинезитерапија. За статистичка анализа беше користен непараметриски тест.

Резултати: Средната вредност на PROM пред интервенцијата изнесуваше 81.83 ± 3.72°, додека по 24 месеци терапија изнесуваше 100.17 ± 3.72°. Разликата од 18.34° беше статистички значајна ($Z=3.41$; $p<0.001$). Големината на ефектот ($r=0.88$) укажува на многу голем клинички ефект.

Заклучок: Долготрајната и рана професионална кинезитерапија значајно го подобрува пасивниот опсег на движење на тазобедрената флексија кај деца со церебрална парализа и претставува важен фактор во превенција на контрактури и секундарни ортопедски компликации.

Клучни зборови: церебрална парализа, моторен развој, кинезитерапија, пасивен опсег на движење.

## ВОВЕД

Во современиот свет, бројот на деца со церебрална парализа е голем, а овој број е причина зошто модерната физиотерапија се развива максимално, а во разни клиники и центри за рехабилитација се користат различни методи и посовремени средства за рехабилитација на овие деца. Несомнено, кинезитерапијата игра голема улога во рехабилитацијата на овие деца. Церебралната парализа се јавува како резултат на лезии во мозокот во раните фази од развојот на поединецот.Таа е дефинирана како нарушување на движењето и држењето на телото како резултат на оштетување предизвикано од овие

лезии[1,2]. Церебралната парализа е комплексен збир на клинички состојби. Во класичната презентација, моторната дисфункција е истакната. Моторните дисфункции можат да се појават и заедно со многу невролошки нарушувања поврзани со централниот нервен систем. Примарните дефицити се состојат од абнормалности во мускулниот тонус кои влијаат на положбата, држењето на телото и движењето, нарушувања на рамнотежата и координацијата, намалена мускулна сила и губење на селективната моторна контрола. Секундарните мускулно-скелетни проблеми вклучуваат мускулни контрактури и деформитети на коските. Тие се развиваат прогресивно како одговор на примарните дефицити и водат до понатамошна моторна дисфункција. Поради овие сложени проблеми, рехабилитацијата на церебрална парализа бара мултидисциплинарен пристап кон рехабилитација и третман[3,5]. Проблемите што се јавуваат кај децата со церебрална парализа зависат од локацијата и степенот на оштетување на мозокот[5,7,9]. Најшироко користената класификација се базира на доминантниот тип на моторно оштетување. Според Surveillance of Cerebral Palsy in Europe – SCPE (1999) и Monbaliu et al., церебралната парализа е поделена на три главни типа: Дискинетична форма, вклучувајќи дистонија и атетоза, кај која се забележуваат несакани, бавни или нагли движења[2]. Спастична форма, која се карактеризира со зголемен мускулен тонус и патолошки рефлекси; тоа е најчестата форма на церебрална парализа. Атактична форма, кај која доминираат нарушувања на координацијата, рамнотежата и прецизноста на движењето (SCPE, 1999). Кај некои деца се забележуваат мешани форми, кои комбинираат карактеристики на повеќе од еден тип. Од функционална перспектива, современата клиничка пракса го користи Gross Motor Function Classification System (GMFCS), развиен од Палисано и др. (1997), кој ги класифицира децата со церебрална парализа на пет нивоа според нивните бруто моторни способности и потребата од помош при движење[12]. Имајќи ги предви овие последици, целта на оваа истражување е споредба на различни кинезитерапевтски пристапи за зголемување на функционалноста на детето и превенција од понатамошни мускулно-скелетни последици.

## МЕТОДОЛОГИЈА

Истражувањето претставува проспективна, лонгитудинална, интервенциска клиничка студија Студијата е реализирана во периодот 2023–2025 година, во времетраење на рехабилитацискатa интервенција од 24 месеци. Кај сите испитаници се извршени две мерења: почетна (влезна) проценка во 2023 година; завршна (излезна) проценка по завршување на 24-месечниот рехабилитациски период.

Популација и примерок-Во истражувањето се вклучени 15 деца со медицински и клинички потврдена дијагноза: Детска церебрална парализа – спастична диплегија. Примерокот е намерен (purposive sampling), со хомогеност во клиничката форма на заболувањето.

Критериуми за вклучување-клинички и медицински потврдена дијагноза Детска церебрална парализа–спастична диплегија; стабилна здравствена состојба; писмена информирана согласност од родител или законски старател.

Критериуми за исклучување-други клинички форми на Детска церебрална парализа; тешки когнитивни, сензорни или визуелни нарушувања; нередовност или прекин во рехабилитацискиот процес.

Инструменти за проценка-PROM– проценка на пасивен опсег на движење. Мерењата на коксофеморалниот зглоб беа направени во сагитална рамнина (флексија), ги тестиравме децата во почетна положба лежејќи на грб (супинација), истиот физиотерапевт ги направи мерењата и на почетокот и на крајот од 24-месечната програма за рехабилитација, заедно со асистент поради специфичноста на болеста, мерењето беше извршено со стандарден гониометар[6,10,11].

Анализата на податоците изведена е во Statistica 7.1. Дистрибуцијата на податоците тестирана е со: Kolmogorov-Smirnov test; Lilliefors test; Shapiro-Wilks test (p); разликата во вредностите на PROM, во релацијата пред кинезитерапија - после кинезитерапија, анализирана е со примена на Wilcoxon Matched Pairs Test (Z / p), Effect size (r = 0.88), сигнификантноста одредена е за $p<0,05$.

## РЕЗУЛТАТИ

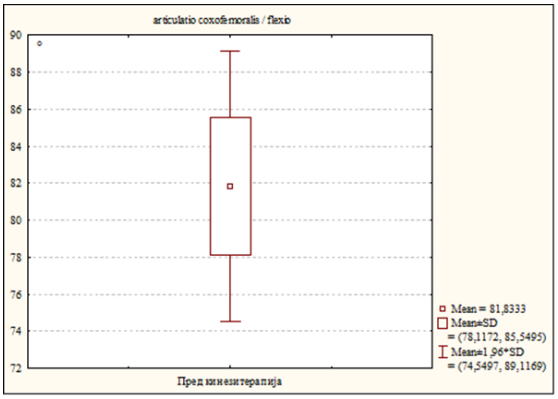
На табела 1. и графикон 1. прикажана е дескриптивна статистика на PROM (articulatio coxofemoralis / flexio) пред кинезитерапија.

Вредноста на аголот на движење пред кинезитерапија варира во интервалот 81,83±3,72°; ±95,00%CI:79,78-83,89; медијаната изнесува 82,50°, минималната вредност

изнесува 77,50° а максималната вредност изнесува 87,50°.

Табела 1. articulatio coxofemoralis / flexio / Пред кинезитерапија

| Variable | Valid N | Mean | Confidence -95,00% | Confidence +95,00% | Median | Minimum | Maximum | Std. Dev. |
|---|---|---|---|---|---|---|---|---|
| articulatio coxofemoralis / flexio / Пред | 15 | 81,83 | 79,78 | 83,89 | 82,50 | 77,50 | 87,50 | 3,72 |




Графикон 1.

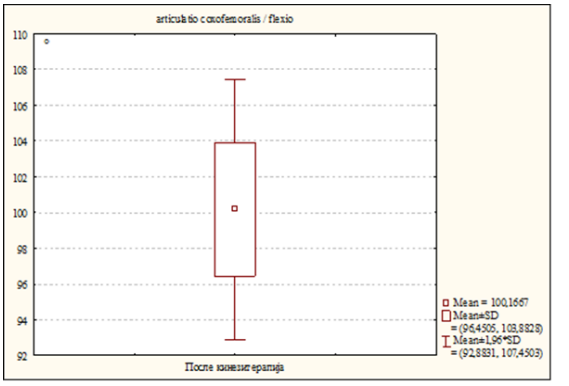
На табела 2. и графикон 2. прикажана е дескриптивна статистика на PROM (articulatio coxofemoralis / flexio) после кинезитерапија.

Вредноста на аголот на движење после кинезитерапија варира во интервалот 100,17±3,72°; ±95,00%CI:98,11-102,22; медијаната изнесува 97,50°, минималната вредност изнесува 97,50° а максималната вредност изнесува 107,50°.

Табела 2. articulatio coxofemoralis / flexio / После кинезитерапија

| Variable | Valid N | Mean | Confidence -95,00% | Confidence +95,00% | Median | Minimum | Maximum | Std. Dev. |
|---|---|---|---|---|---|---|---|---|
| articulatio coxofemoralis / flexio / После | 15 | 100,17 | 98,11 | 102,22 | 97,50 | 97,50 | 107,50 | 3,72 |

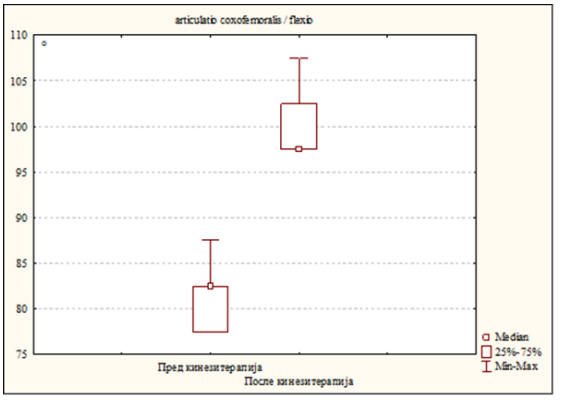
Графикон 2.




Вредноста на PROM (articulatio coxofemoralis / flexio) после кинезитерапија за Z = 3,41 и p<0,001(p=0,000) значајно е поголема во однос на вредноста на PROM (articulatio coxofemoralis / flexio) пред кинезитерапија (табела 3. и графикон 3.).

Табела 3. articulatio coxofemoralis / flexio / Преди & articulatio coxofemoralis / flexio / После / Разлика

| Pair of Variables | Valid | T | Z | p-level |
|---|---|---|---|---|
| articulatio coxofemoralis / flexio / Пред & articulatio coxofemoralis / flexio / После | 15 | 0,00 | 3,41 | 0,0007 |




Графикон 3. articulatio coxofemoralis / flexio / Пред кинезитерапија & articulatio coxofemoralis / flexio / После кинезитерапија

## ДИСКУСИЈА

Резултатите од оваа проспективна лонгитудинална интервенциска студија покажаа статистички значајно зголемување на пасивниот опсег на движење на флексија на коксофеморалниот зглоб (PROM articulatio coxofemoralis / flexio) по 24-месечна професионална кинезитерапевтска интервенција. Просечната вредност се зголеми од 81.83 ± 3.72° на 100.17 ± 3.72°, со

вкупна разлика од 18.34° (Z=3.41; p<0.001).

Овие резултати укажуваат на значаен позитивен ефект од долготрајната кинезитерапија врз одржувањето и подобрувањето на пасивната подвижност на колкот кај деца со церебрална парализа. Пресметаната големина на ефектот (r=0.88) дополнително потврдува дека станува збор за многу голем клинички ефект, што ја засилува релевантноста на интервенцијата.

Нашите наоди се во согласност со претходни истражувања кои покажуваат дека кинезитерапевтските интервенции можат да придонесат за подобрување на ROM кај деца со CP.[4]. Кој пријавуваат зголемување на PROM hip flexion по шестнеделна интервенција со whole-body vibration и истегнување (+10°), иако без силна статистичка значајност за пасивниот сегмент. Tornberg и Lauruschkus (2020) покажаа значајни подобрувања на PROM при динамички стоечки програми (p<0.001), но со пократко времетраење (4 месеци) [8,11].

Во споредба со овие студии, нашето истражување покажува поголем степен на подобрување, што најверојатно се должи на:

Долготрајната интервенција (24 месеци континуирана терапија)

Раната возраст на испитаниците (20–24 месеци), кога ткивната пластичност е повисока

Континуиран професионален и структуриран кинезитерапевтски пристап

Проспективниот дизајн со следење на истите испитаници

Раната интервенција е клучен фактор во превенција на мускулно-скелетни деформитети и контрактури кај деца со CP. Литературата покажува дека без адекватна терапија, пасивниот опсег на движење има тенденција на постепено намалување со возраста поради спастицитет и мускулна скратеност. Оттука, добиеното зголемување од 18.34° претставува не само терапевтски успех, туку и потенцијална превенција од идни ортопедски компликации.

Иако примерокот е релативно мал (n=15), конзистентноста на резултатите и големината на ефектот ја засилуваат валидноста на наодите. Сепак, идни истражувања со поголем примерок и контролна група би овозможиле дополнителна потврда на резултатите.

Заклучно, резултатите од ова истражување потврдуваат дека раната, долготрајна и професионално водена кинезитерапија значајно го подобрува пасивниот опсег на движење на флексија на коксофеморалниот зглоб кај деца со церебрална парализа, со изразен клинички ефект.

## ЗАКЛУЧОК

Оваа проспективна лонгитудинална интервенциска студија покажа дека 24-месечната професионална кинезитерапевтска програма доведува до статистички и клинички значајно зголемување на пасивниот опсег на движење на флексија коксофеморалниот зглоб (PROM articulatio coxofemoralis / flexio) кај деца со церебрална парализа на возраст од 20–24 месеци. Средната вредност на PROM се зголеми од 81.83 ± 3.72° на 100.17 ± 3.72°, со вкупна разлика од 18.34° (Z=3.41; p<0.001). Пресметаната големина на ефектот (r=0.88) укажува на многу голем терапевтски ефект на кинезитерапевтската интервенција врз пасивниот опсег на движење на тазобедрената флексија. Ова укажува дека забележаното подобрување не е само статистички, туку и клинички значајно. Зголемување од 18.34° кај деца во рана возраст е функционално релевантно, особено во контекст на превенција на контрактури и подобрување на моторниот развој.

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Profesional paper

# POSTOPERATIVE COGNITIVE DYSFUNCTION AFTER SPINAL AND GENERAL ANESTHESIA: A COMPREHENSIVE REVIEW

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## ABSTRACT

Postoperative cognitive dysfunction (POCD) is a common complication following surgical procedures requiring anesthesia, particularly among older adults. With an incidence ranging from 10–60%, POCD poses significant challenges to postoperative recovery, quality of life, and long-term cognitive outcomes. This manuscript reviews current evidence regarding the etiology, risk factors, pathophysiology, diagnostic criteria, and anesthetic considerations related to POCD. Clinical observations from a cohort of 35 elderly patients undergoing orthopedic surgery are incorporated to highlight practical implications. Advances in understanding POCD mechanisms have informed preventive strategies, although further research is required to optimize clinical management.

## INTRODUCTION

Postoperative cognitive dysfunction represents a frequently encountered complication after surgeries performed under spinal or general anesthesia. Defined as a decline in cognitive performance in individuals without prior mental disorders, POCD is especially prevalent among elderly surgical patients. Reported incidence rates vary widely, from 10% to 60%, depending on patient characteristics, surgical type, and diagnostic timing. Given its impact on functional recovery and long-term cognitive health, understanding POCD is of substantial clinical importance.

## PATHOPHYSIOLOGY

Research increasingly indicates shared pathophysiological mechanisms between POCD, mild cognitive impairment, and neurodegenerative diseases such as Alzheimer's disease. Potential mechanisms include neuroinflammation, neuronal apoptosis, synaptic dysfunction, mitochondrial abnormalities, abnormal tau protein metabolism, and chronic postoperative pain. These converging pathways suggest that surgery and anesthesia may accelerate underlying neurodegenerative processes in susceptible individuals.

The pathogenesis of POCD remains unclear, with

research focusing upon the role of neuronal death, neuro-inflammation and micro-emboli. Animal in vivo studies have shown that inhalational anesthetic agents potentiate neuronal death through the degradation of the cholinergic system by amyloid plaques and neurofibrillary tangles. These cholinergic pathways are a key element of consciousness, learning and memory. Conversely, there has been no relationship established between POCD and apolipoprotein- E genotype carriers, a strong risk factor for Alzheimer's disease, which is characterised by loss of basal forebrain cholinergic neurones. Neuro-inflammation occurs as inhalational agents increase the permeability of the endothelial cells in the cerebral vasculature, allowing cytokines to enter and damage neural tissue. Micro-emboli from the surgical site or air entrainment may cause cerebral infarcts, and have been studied using MRI, but no clear relationship was found.

## Etiology and Risk Factors

Advanced age is one of the most prominent risk factors for POCD. Evidence suggests that biological age—reflecting cumulative physiological decline—may better predict POCD risk than chronological age alone. Other predisposing factors include: - Low educational attainment - Preoperative cognitive impairment - Cardiovascular comorbidities - Long or complex surgeries - Significant intraoperative blood loss or hemodynamic instability - Use of specific anesthetic or sedative agents

Orthopedic surgeries, such as hip and knee arthroplasty, are particularly associated with higher POCD incidence due to prolonged duration, increased surgical trauma, and the potential for fat embolism.

**Table 2**
**Potentially modifiable risk factors for POCD**

| Risk Factor | Effect Size | Study Design | Reference |
|---|---|---|---|
| Bispectral index (EEG) guided anesthetic care (vs routine care) | OR 0.92 (0.66–1.29) at 1 wk $P = .06$<br>OR 0.62 (0.39–0.97) at 3 mo $P = .02$ | RCT | 51 |
| | 18.1% vs 23.9% at 7 d $P = .062$<br>8% vs 10.3% at 3 mo $P = .372$ | RCT | 52 |
| Fentanyl dosage | Low (10 μg/kg) vs high-dose fentanyl (50 μg/kg), POCD rates 23.6% vs 13.7% at 1 wk, respectively, $P = .03$. NS at 3 and 12 mo. | RCT | 141 |
| Ketamine treatment | 2 SD drop in overall cognition in 7/26 ketamine group vs 21/26 patients, $P<.001$ | RCT | 107 |
| Lidocaine vs no lidocaine | POCD 18.6% vs 40%, $P = .028$ | RCT | 142 |
| | Neurocognitive deficit 45.8% vs 40.7% at 10 wk $P = .577$<br>35.2% vs 37.7% at 25 wk $P = .710$ | RCT | 143 |
| | 45.5% vs 45.7%, $P = .97$ | RCT | 66 |
| Magnesium sulfate infusion | Multivariate OR for low dose 0.09 (0.02–0.50), $P = .01$; OR for high dose 0.45 (0.16–1.33), $P = .15$ | RCT | 144 |
| | 44.4% vs 44.9%, $P = .93$ | RCT | 106 |
| Piracetam vs no piracetam | Overall cognitive function preoperative 0.06 ± 1.02 vs −0.06 ± 0.99 postoperative −0.65 ± 0.93 vs −1.38 ± 1.11, $P<.0005$ | RCT | 145 |
| Intraoperative steroid treatment | No vs low-dose vs high-dose dexamethasone POCD<br>22.3% vs 20.6% vs 31.4%, $P = .003$ | RCT | 110 |
| | RR 1.87 (0.90–3.88) at 1 mo $P = .09$<br>RR 1.98 (0.61–6.40) at 1 y $P = .24$ | RCT | 109 |
| Postoperative delirium[a] | Multivariate OR 9.58 (4.62–19.9), $P<.001$ | RCT | 51 |
| | POCD vs no POCD[b]<br>1.5% vs 1.1% at discharge $P = .046$<br>6.7% vs 5.6% at 3 mo $P = .373$ | Prospective cohort study | 20 |
| | Delirium vs no delirium<br>MMSE scores:<br>24.1 vs 27.4 at 1 mo $P<.001$<br>25.2 vs 27.2 at 1 y $P<.001$ | Prospective cohort study | 9 |
| Postoperative infection[a] | Univariate OR 2.17 (1.50–3.15), $P = .001$ | RCT | 51 |
| Postoperative respiratory complication[a] | Univariate OR 1.69 (1.01–2.89), $P = .02$ | RCT | 51 |
| Metabolic syndrome[a] | POCD vs no POCD<br>43.3% vs 26.7%, $P<.02$ | Prospective cohort study | 127 |
| Cigarette abuse | Multivariate OR 2.04 (1.11–3.74), $P = .022$ | RCT | 146 |
| | NS | Prospective cohort study | 23 |
| Diabetes[a] | Multivariate OR 2.34 (1.22–4.51), $P = .01$ | Prospective cohort study | 11 |
| | POCD vs no POCD<br>40% vs 19.2%, $P = .021$ | Prospective cohort study | 104 |
| | Multivariate linear regression, parameter estimate 0.031 (−0.111–0.172), $P = .671$ | RCT | 66 |
| Duration of anesthesia | OR 1.1 (1.0–1.3), $P = .01$ | Prospective cohort study | 23 |
| | POCD vs no POCD at 3 mo<br>215.0 ± 92.8 vs 211.5 ± 103.2 min duration, $P = .52$ | Prospective cohort study | 20 |
| | POCD vs no POCD<br>5.6 ± 1 .5 vs 5.0 ± 1.2, $P = .026$ | Prospective cohort study | 104 |
| | POCD vs no POCD<br>4.6 ± 1.5 vs 3.8 ± 0.8, $P = .001$ | Prospective cohort study | 147 |
| Benzodiazepines before surgery | OR 0.4 (0.2–1.0), $P = .03$ | Prospective cohort study | 23 |
| Duration of hospital stay | POCD vs no POCD<br>6.6 ± 16.3 vs 4.8 ± 5.9 at discharge $P = .0003$<br>Multivariate OR 1.03 (1.00–1.05) at 3 mo $P = .2479$ | Prospective cohort study | 20 |
| Duration of surgery | POCD vs no POCD<br>4.7 ± 0.9 vs 4.2 ± 1.0, $P = .01$ | Prospective cohort study | 104 |
| Anesthetic type (general vs regional) | Mean Difference −0.08 (−0.17–0.01), $P = .094$ | Meta-analysis | 56 |
| | General vs nongeneral anesthesia, OR 1.34 (0.95–1.93), $P = .26$ | Meta-analysis | 55 |

(*continued on next page*)

| | | | |
|---|---|---|---|
| Hyperglycemia (ie, glucose >200 mg/dL at any point during CPB cases) | Associated with POCD in nondiabetic patients, N = 380, OR = 1.85 (95% CI 1.12–3.04), *P* = .017; NS (*P* = .81) in diabetic patients, n = 145 | Retrospective analysis of pooled data from multiple previous prospective studies | 153 |
| Slow rewarming vs normal rewarming (in CPB cases) | Multivariate linear regression variable estimate 0.35, *P* = .047 (favoring slow rewarming) | RCT | 154 |
| Continuous cell saver use (in CPB cases) | 6% vs 15% in controls, *P* = .038 | RCT | 155 |
| | 16.7% vs 15.9% in controls, relative risk: 1.05, 95% CI 0.58–1.90 at 3 mo. | RCT | 156 |
| Embolic load (in CPB cases) | No correlation between embolic load measured by transcranial Doppler ultrasound and POCD at 1 wk (*P* = .617) or at 3 mo (*P* = .110), n = 356 patients. | Pooled analysis of data from 2 other RCTs | 102 |
| Alpha stat vs pH stat blood gas management (in CPB cases) | 27% vs 44%, *P* = .047 | RCT | 157 |
| Hypothermia vs normothermia (in CPB cases) | Multivariate odds ratio 1.15 (95% CI 1.01−1.31), *P* = .042, for POCD at hospital discharge after intraoperative normothermia vs mild hypothermia. | Retrospective analysis of pooled data from 2 previous trials | 158 |
| | NS difference for POCD at 6 wk after surgery. | RCT | 159 |
| | Hypothermia vs normothermia, relative risk for POCD at 1 wk after surgery = 0.77, *P* = .048. | RCT | 160 |
| | Hypothermia vs normothermia, relative risk for POCD at 5 y after surgery = 0.66, *P* = .16. | RCT | 161 |

*Abbreviations:* CI, confidence interval; CPB, cardiopulmonary bypass; EEG, electroencephalogram; MMSE, Mini-Mental State Examination; NS, not significant; OR, odds ratio; POCD, postoperative cognitive dysfunction; RCT, randomized controlled trial; RR, relative risk.

[a] Partially modifiable risk factor.

[b] Delirium during hospital stay.

**Table 3**
**Nonmodifiable risk factors for POCD**

| Risk Factor | POCD vs No POCD | Study Design | Reference |
|---|---|---|---|
| Age | Multivariate OR 1.04 (1.01–1.08), *P* = .01 | RCT | 51 |
| | Multivariate OR 1.03 (0.99–1.06), *P* = .1 | Prospective observational study | 11 |
| | Age of patients with POCD 51.9 ± 17.3 vs no POCD 49.4 ± 16.5, measured at discharge *P* = .027 | Prospective cohort study | 20 |
| | OR 1.03 (1.01–1.06), *P* = .013 | Prospective cohort study | 67 |
| | OR 1.151 (1.030–1.285), *P* = .003 | Prospective cohort study | 104 |
| | Multivariate OR 1.34 (1.01–1.78), *P* = .043 | Prospective cohort study | 147 |
| | Multivariate OR 0.95 (0.71–1.26), *P* = .70 | RCT | 146 |
| | Multivariate linear regression parameter estimate (for continuous cognitive change score) −0.009 (−0.012 to −0.005), *P*<.001 | RCT | 66 |
| Educational level | Multivariate OR 0.98 (0.91–1.07), *P* = .67 | Prospective cohort study | 11 |
| | Multivariate OR 0.84 (0.76–0.93) at 3 mo *P* = .0031 | Prospective cohort study | 20 |
| | OR 0.9 (0.83–0.98), *P* = .021 | Prospective cohort study | 67 |
| | Multivariable linear regression model, parameter estimate: 0.012 (−0.002–0.027), *P* = .098 | RCT | 66 |
| Type of surgery | Minimally invasive<br>4% vs 34%, intra-abdominal/thoracic 21% vs 14%, orthopedic<br>11% vs 16% at discharge *P* = .001 | Prospective cohort study | 20 |
| | Congenital disease<br>10 vs 42<br>Valvular disease<br>32% vs 54%<br>Aorta disease<br>14% vs 20%<br>Tumor<br>2% vs 2%; *P* = .051 overall | Prospective cohort study | 147 |
| | NS | Prospective cohort study | 23 |
| Genetic risk alleles | *CRP* 1059G/C SNP<br>OR 0.37 (0.16–0.78), *P* = .013<br>*SELP* 1087G/A SNP<br>OR 0.51 (0.30–0.85), *P* = .011 | Prospective cohort study | 67 |
| Left hippocampal volume | POCD vs no POCD<br>2.26 ± 0.21 vs 2.45 ± 0.15, *P*<.01 | Prospective cohort study | 162 |
| Right hippocampal volume | POCD vs no POCD<br>2.49 ± 0.11 vs 2.62 ± 0.20, *P*<.05 | Prospective cohort study | 162 |
| MCA velocity | Left MCA POCD vs no POCD 42.5 ± 5.5 vs 54.3 ± 4.4, *P*<.1<br>Left vs Right MCA POCD 42.5 ± 5.5 vs 56.3 ± 4.5, *P*<.05[a] | Prospective cohort study | 163 |
| Preoperative renal insufficiency | Multivariate OR 0.18 (0.04–0.75), *P* = .019 | RCT | 146 |
| Previous stroke | Multivariate OR 0.30 (0.11–0.84), *P* = .02 | RCT | 144 |

*Abbreviations:* CRP, C-reactive protein; MCA, middle cerebral artery; NS, not significant; OR, odds ratio; POCD, postoperative cognitive dysfunction; RCT, randomized controlled trial; SELP, P-selectin; SNP, single nucleotide polymorphism.

[a] Values estimated from the bar graph in Fig. 1.

**PATIENTS AND METHODS**

A total of 35 patients undergoing elective knee or hip arthroplasty under spinal or general anesthesia from August to November 2025 were included. The average patient age was 65 ± 15 years.

Inclusion Criteria

Diagnosis of knee or hip osteoarthritis appropriate for arthroplasty

Age > 65 years

Exclusion Criteria

Liver or renal insufficiency

Active malignancy

Autoimmune disease

Connective tissue disorders

**Diagnostic Criteria**

POCD diagnosis required reduced environmental awareness and impaired concentration or attention, along with at least two of the following: perceptual disturbances, incoherent speech, sleep–wake cycle disruption, or changes in motor activity. Symptoms typically fluctuated over hours to days.

Cognitive Assessment

Mini-Mental State Examination (MMSE)

The MMSE (maximum score 30) was used to assess global cognitive status. Dementia thresholds were adjusted for education: <20 for primary school education and <24 for middle school education.

Montreal Cognitive Assessment (MoCA)

The MoCA (maximum score 30) evaluated visuospatial skills, naming, memory, attention, language, abstraction, delayed recall, and orientation. Scores <26 indicated cognitive impairment. Patients with fewer than 12 years of education received 1 additional point.

**Anesthetic Techniques**

According to the surgical requirements, the type of the surgery and overall health of our patients,previous illnesses having in mind, as an Anesthesiologist I opt between spinal block and general anesthesia.

Pre-operative therapy was given according to the preexisting health condition of the patients, and amp. Diazepam 10mg i.m was given as premedication. In spinal blocks we used Bupivacaine 0,5% izobaric ,doses were according to the age and height of the patients, often with 0.01 mg Fentanyl as adjuvance in the spinal for increasing the time of the block and with that managing the pain in the first couple of hours after surgery .

IntraoperativeKetamin in lower doses 20-30 mg combined with Midazolam 1-3 mg was given in agitated and non-cooperative patients.

In general anesthesia we used Propofol and Rucuronium as induction agents, and Remifentanyl for managing the pain, for maintaining anesthesia we gave Izofluran as gas agent , primary for cardio circulatory stability, or propofol given continuously with the pump. Intra operative were often given vazopresors maintaining MAP between 100 and 120 .

Pain managment

In spinal block pain management is far superior to general anesthesia, intra and few hours postoperative. After that period pain was managed with Methamizole and Tramadol or Acetaminophen.

In general anesthesia pain was managed with Remifentanyl intra op and Methamizole and Tramadol post op, preemptive analgesia was given MgSO4 10ml + Comboval(Acetaminofen+Ibuprofen)I.

How Long Does Postoperative Cognitive Dysfunction Last?

Aside from this disagreement over how POCD diagnosis is defined, it is also unclearhow long it may last. This issue is difficult to address for several reasons.

1. it is ethically unreasonable and practically impossible to randomize patients to surgery andanesthesia (vs placebo treatment). Without a nonsurgical control group, though, it isunclear how much of the cognitive dysfunction in surgical patients is truly due to anesthesia, surgery, and perioperative care.

2. The initial rapid drop in cognition seen inpatients with POCD occurs much more rapidly than normal age-related cognitive decline.

3.Matched cohort study designs can attempt to provide nonsurgical control groupsfor comparison, but such study designs are nonrandomized and thus potentiallyconfounded by the fact that surgical patients may be intrinsically different from nonsurgical controls.

## RESULTS

Preoperative Cognitive Status

MMSE scores ranged from 22 to 26, indicating mild cognitive impairment influenced by age and educational level. MoCA findings paralleled MMSE results.

Postoperative Findings

Within several days following surgery: - 17 of 35 patients exhibited POCD, with MMSE scores of 18–22. - Cardiovascular comorbidities were associated with higher POCD incidence. - MoCA revealed significant declines in visuospatial function, attention, language, abstraction, and orientation. - Several patients required psychotropic medications such as haloperidol or risperidone, tapered after the first postoperative week.

## DISCUSSION

POCD is influenced by numerous factors, including patient age, education level, surgical type, anesthetic strategy, and preexisting comorbidities. Orthopedic procedures pose particular risk due to surgical complexity. Neurocognitive testing remains essential for early identification of POCD. Ongoing research continues to clarify the role of inflammation, tau dysregulation, mitochondrial dysfunction, and neuronal injury in POCD pathogenesis.

Prevention

Strategies to reduce POCD include: - Minimally invasive surgical techniques - Shorter operative times when feasible - Optimization of hemodynamic stability - Use of short-acting, rapidly metabolized anesthetics - Reduction of perioperative sedative exposure in elderly patients - Early mobilization and multimodal analgesia

A larger meta-analysis (2,365 patients) found no difference in the incidence of POCD after regional or general anaesthesia.The analysis recognised the variance in testing and categorised neurological deterioration between cortical functions (e.g. decline in memory, concentration and visual and spatial skills) for separate interrogation, demonstrating one method of drawing together conclusions from research that utilises varying measurements of cognitive decline.

## CONCLUSION

Postoperative cognitive dysfunction is a significant postoperative complication among elderly patients undergoing orthopedic surgery. Although progress has been made in understanding its mechanisms, further research is needed to establish standardized diagnostic tools and effective prevention strategies. Continual advancements in perioperative care hold promise for reducing POCD incidence and improving postoperative recovery. 1 in 10 elderly patients will suffer with POCD at 3 months postoperatively, and for some, this reduced quality of life outweighs the benefits of surgery.

Until there is routine preoperative neuropsychometricassessment of patients over 65 years, there is an absence of appropriate preoperative counselling or recognition of cognitive decline post-intervention. The implementation of testing and consent is best placed in preoperative clinics, a valuable opportunity to discuss cognitive decline after surgery with both the patients and their families, who will often play a significant role in recognising cognitive decline and advocating for the patients.Recent advances in the study of POCD include the working group offering a quantified measure of decline for diagnosis of POCD.

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Profesional paper

# АНТИГЕНСКА СРОДНОСТ И ВАКЦИНАЛНИ ИМПЛИКАЦИИ НА INFLUENZA A(H3N2) J.2.4.1 (K SUBCLADE) И INFLUENZA A/ CROATIA/10136RV/2023 (H3N2): ЕПИДЕМИОЛОШКИ ПРОЕКЦИИ ЗА СЕЗОНАТА 2025/26 ВО РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА И СОСЕДНИТЕ ЗЕМЈИ

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## АПСТРАКТ

Вирусите на инфлуенца A(H3N2) се карактеризираат со изразена генетска варијабилност и динамична еволуција преку процесот на антигенски дрифт. Во текот на 2025 година беше идентификувана нова подкласа J.2.4.1 (K subclade), која покажува значајни генетски и антигенски разлики во однос на вакциналниот сој Influenza A/Croatia/10136RV/2023 (H3N2), вклучен во сезонската вакцина за 2025/26. Овој труд има за цел да ја анализира антигенската сродност помеѓу овие вируси, да ја процени вакциналната ефикасност и да изврши епидемиолошка проекција за ширењето на вирусот во Република Северна Македонија и регионот на Југоисточна Европа. Анализата е базирана на филогенетски пристап, антигенска картографија и математички модели. Резултатите укажуваат на намалена антигенска преклопеност и потенцијално намалена ефикасност на вакцината, со ризик од доминација на K субкладата во претстојната сезона.

Клучни зборови: инфлуенца A(H3N2), антигенски дрифт, вакцинална ефикасност, субклада K, филогенетска анализа, епидемиолошко моделирање

## ВОВЕД

Инфлуенцата A(H3N2) претставува еден од најважните респираторни патогени со значајно влијание врз јавното здравје, особено кај постарата популација и хронично болните пациенти. Неговата способност за континуирана еволуција преку антигенски дрифт доведува до честа појава на нови варијанти кои можат да ја намалат ефективноста на постојните вакцини. Во 2025 година, идентификувана е нова подкласа J.2.4.1 (K subclade), која се разликува од вакциналниот сој A/Croatia/10136RV/2023 со најмалку седум значајни аминокиселински мутации во HA генот. Овие мутации се локализирани во антигенските епитопи, што потенцијално влијае врз имунолошкото препознавање. Ова истражување се фокусира на проценка на антигенската дистанца, вакциналната заштита и можните епидемиолошки сценарија во регионот.

## ЦЕЛ НА ИСТРАЖУВАЊЕТО

Целта на овој труд е да се анализира антигенската сродност помеѓу Influenza A(H3N2) J.2.4.1 (K subclade) и вакциналниот сој Influenza A/Croatia/10136RV/2023, да се процени нивното влијание врз вакциналната ефикасност и да се моделира потенцијалното ширење на вирусот во сезоната 2025/26 во Република Северна Македонија и соседните земји.

## МАТЕРИЈАЛ И МЕТОДИ

Истражувањето е дизајнирано како интегративна молекуларно-епидемиолошка анализа со комбинирање на филогенетски, антигенски и математички пристапи. Геномските податоци за вирусите на инфлуенца A(H3N2) беа прибрани од јавно достапни бази на податоци, со фокус на секвенци добиени во текот на 2025 година од Европа и особено од регионот на Југоисточна Европа. Секвенците беа порамнети и анализирани со примена на современи биоинформатички алатки за реконструкција на филогенетски дрва, со цел утврдување на еволутивните односи и кластеризацијата на субкладите. Антигенската карактеризација беше извршена преку анализа на податоци од тестови за хемаглутинациска инхибиција, при што беше конструирана антигенска карта за проценка на растојанието помеѓу циркулирачките вируси и вакциналниот сој. Овие растојанија беа интерпретирани како индикатор за степенот на антигенска сродност и потенцијалната ефикасност на вакцината. Истражувањето се базира на интегриран пристап кој вклучува молекуларна, антигенска и епидемиолошка анализа. Филогенетската реконструкција е извршена врз основа на HA генот со користење на секвенци достапни од глобални бази на податоци. Антигенската сродност е проценета преку антигенска картографија и анализа на епитопските промени. Математичките модели на ширење се базираат на SEIR модели адаптирани за сезонски грип, со вклучување на параметри како мобилност на населението, вакцинална покриеност и контактни мрежи. Дополнително, направена е компаративна анализа со податоци од претходната сезона. Епидемиолошката компонента се базираше на моделирање на трансмисијата користејќи детерминистички пристапи, при што беа вклучени параметри како основен репродукциски број, стапка на контакт и сезонска варијабилност. Податоците за циркулација на вирусите беа синтетизирани од регионални извештаи за надзор, со цел да се изгради реалистична проекција за сезоната 2025/26.

## РЕЗУЛТАТИ

Филогенетската анализа на секвенците на вирусите на инфлуенца A(H3N2) циркулирачки во текот на 2025 година покажа јасна кластеризација на изолатите во рамките на новоидентификуваната субклада J.2.4.1 (K субклада), која доминира во однос на претходно циркулирачките J.2.3 и J.2.4 линии. Генетската дистанца помеѓу анализираните изолати и вакциналниот сој Influenza A/Croatia/10136RV/2023 (H3N2) укажува на акумулација на повеќекратни аминокиселински супституции во клучните антигенски епитопи на хемаглутининот, особено во регионите A и B, кои се од суштинско значење за врзување на неутрализирачки антитела.Антигенската картографија дополнително потврди дека вирусите од K субкладата се позиционирани на значително растојание од вакциналниот сој, што укажува на намалена антигенска сродност. Оваа дистанца, изразена преку антигенски единици, е конзистентна со намалена серолошка реактивност во моделите на хемаглутинациска инхибиција, што имплицира потенцијално намалена способност на постоечката вакцина да индуцира заштитен имунолошки одговор. Епидемиолошката анализа покажа дека во Република Северна Македонија и соседните земји постои изразена доминација на K субкладата, со учество кое во повеќето случаи надминува 70–85% од сите детектирани вируси на инфлуенца A. Ко-циркулацијата на A(H1N1)pdm09 е забележана, но со значително пониско учество, што укажува на релативна епидемиолошка супресија од страна на доминантниот H3N2 сој.

| Држава | Доминантен субтип | Главна субклада | Учество (%) | Ко-циркулирачки субклади | Проценето учество | Епидемиолошка интерпретација |
|---|---|---|---|---|---|---|
| Северна Македонија | A(H3N2) | K (J.2.4.1) | 75–90% | H1N1pdm09; J.2.4 | 10–25% | Висока доминација на нова варијанта |
| Србија | A(H3N2) | K (J.2.4.1) | 80–90% | H1N1pdm09 | 10–20% | Рано започната и интензивна сезона |
| Бугарија | A(H3N2) | K (J.2.4.1) | 70–85% | H1N1pdm09; J.2.3 | 15–30% | Типичен ЕУ/ЕЕА модел |
| Грција | A(H3N2) | K (J.2.4.1) | 70–85% | H1N1pdm09 | 15–30% | Пик во зимски бран |
| Албанија | A(H3N2) | K (J.2.4.1) | 75–90% | H1N1pdm09 | 10–25% | Регионална конзистентност |
| Косово | A(H3N2) | K (J.2.4.1) | 75–90% | H1N1pdm09 | 10–25% | Епидемиолошки идентично со соседните земји |

Табела бр.1 Циркулација на субклади на инфлуенца А (сезона 2025/2026)

Математичките модели за пренос и ширење на инфекцијата предвидуваат дека, во услови на намалена вакцинална ефикасност и висока трансмисибилност на К субкладата, сезоната 2025/26 ќе се карактеризира со рано започнување и зголемен интензитет на епидемискиот бран. Проекциите укажуваат на потенцијално зголемување на инциденцата, особено кај повозрасната популација и ризичните групи, што е во согласност со познатата патогеност на H3N2 вирусите. Интеграцијата на филогенетските, антигенските и епидемиолошките податоци сугерира дека К субкладата поседува селективна предност, најверојатно поврзана со имуноевзивни механизми и подобрена адаптација кон човечката популација. Овие наоди ја нагласуваат потребата од континуирано геномско следење и ревизија на вакциналните состави со цел подобро усогласување со циркулирачките соеви. Антигенската картографија потврдува постоење на значителна дистанца помеѓу вакциналниот сој и К субкладата, што укажува на ограничена имунолошка преклопеност. Ова директно имплицира намалена способност на постоечката вакцина да обезбеди заштита од инфекција.


Антигенска карта

A/Croatia/10136RV/2023

- 
  - K subclade viruses
- 
- 

Поголемата дистанца укажува на намалена вкрстена реактивност на антителата.

Антигенска карта добиена со симулацијата на Smith моделот, која ја прикажува позицијата на вакциналниот сој A/Croatia/10136RV/2023 во однос на вирусите од J.2.4.1 (K субклада). Просторната оддалеченост и кластеризацијата на К варијантите укажуваат на значајна антигенска дивергенција, што имплицира намалена вкрстена реактивност на антителата и потенцијален пад на вакциналната ефикасност доколку J.2.4.1 (K субклада) влезе во циркулација како доминатен сој. Моделите на ширење покажуваат дека К субкладата има висок потенцијал за доминација, особено во услови на зголемена мобилност на населението и релативно умерена вакцинална покриеност.

## ДИСКУСИЈА

Антигенската дистанца помеѓу J.2.4.1 (K subclade) и вакциналниот сој претставува клучен фактор кој ја намалува вакциналната ефикасност. Иако вакцината може да обезбеди одреден степен на заштита од тешки форми на болеста, нејзината способност за спречување на инфекција е значително компромитирана.Седумте мутации во HA протеинот ја менуваат конформацијата

на антигенските детерминанти, што резултира со намалена неутрализација од постоечките антитела. Овој феномен е типичен пример на антигенски дрифт со клинички и епидемиолошки последици. Во контекст на Република Северна Македонија и Балканскиот регион, дополнителен ризик претставува високата сезонска мобилност, туристичкиот транзит и регионалната поврзаност. Овие фактори овозможуваат брзо ширење на новите варијанти. Добиените резултати јасно укажуваат дека еволутивната динамика на вирусите на инфлуенца A(H3N2) во текот на 2025 година е обележана со доминација на новата субклада J.2.4.1 (K субклада), која демонстрира значајни генетски и антигенски отстапувања од вакциналниот сој Influenza A/Croatia/10136RV/2023 (H3N2). Оваа појава е во согласност со познатиот механизам на антигенски дрифт, кој претставува клучен двигател на континуираната еволуција на вирусите на инфлуенца и нивната способност да го избегнат имунолошкиот одговор на популацијата. Акумулацијата на аминокиселински супституции во антигенските детерминанти на хемаглутининот, особено во имунодоминантните региони, укажува на селективен притисок кој фаворизира варијанти со намалена препознатливост од страна на неутрализирачките антитела. Антигенската картографија дополнително ја потврдува оваа констатација, прикажувајќи значајна антигенска дистанца помеѓу циркулирачките K варијанти и вакциналниот сој (Influenza A/Croatia/10136RV/2023 (H3N2). Оваа дистанца има директни импликации врз вакциналната ефикасност, особено во услови кога имунитетот стекнат преку вакцинација или претходна инфекција не обезбедува доволна заштита.Епидемиолошките податоци од Република Северна Македонија и поширокиот регион на Југоисточна Европа укажуваат на висок степен на синхронизација во циркулацијата на вирусите, со доминација на една генетска линија. Оваа хомогеност сугерира интензивна регионална трансмисија и можност за брзо ширење на доминантната варијанта. Воедно, забележаната ко-циркулација на A(H1N1) pdm09, иако со пониско учество, укажува на комплексноста на вирусната екологија и потенцијалот за интерференција помеѓу различни субтипови. Проекциите добиени преку математичките модели укажуваат дека намалената вакцинална ефикасност, во комбинација со високата трансмисивност на K субкладата, може да резултира со поинтензивна и порано започната сезона на грипот. Ова е особено значајно за здравствените системи, бидејќи H3N2 вирусите традиционално се поврзуваат со потешка клиничка слика и поголем товар врз болничките капацитети. Моделите укажуваат дека постои висок ризик од: доминација на K субкладата во сезоната 2025/26 година, појава на поран пик на активноста на сезонскиот грип и зголемен број на инфекции кај вакцинирани лица (breakthrough инфекции). Во Република Северна Македонија, особено во јужните региони како Гевгелија, се очекува засилен внес на вирусот поради граничната циркулација со Грција и туристичкиот сообраќај. Врз основа на антигенската сродност, проценетата вакцинална ефикасност против инфекција е умерено намалена. Сепак, вакцината сè уште обезбедува значајна заштита од: хоспитализација, развивање на тешка клиничка форма на болеста и намалена смртност. Намалената ефикасност е директна последица на антигенската дивергенција помеѓу вакциналниот сој и циркулирачката K субкласа. Во контекст на глобалната циркулација, овие наоди се конзистентни со трендовите забележани во Европа и пошироко, што дополнително ја нагласува потребата од интегриран пристап кој вклучува геномски надзор, антигенска карактеризација и континуирана ревизија на вакциналните соеви. Ограничувањата на студијата се однесуваат на потенцијалната нерамномерна достапност на секвенциони податоци и варијациите во системите за надзор помеѓу различните земји.

## ЗАКЛУЧОК

Новата подкласа Influenza A(H3N2) J.2.4.1 (K subclade) претставува значајна еволутивна варијанта со потенцијал за доминација во сезоната 2025/26. Значајната антигенска дистанца во однос на вакциналниот сој Influenza A/Croatia/10136RV/2023 укажува на намалена вакцинална ефикасност против инфекција, но задржана заштита од тешки форми на болеста. Епидемиолошките модели предвидуваат засилена циркулација во регионот, што бара засилен надзор и адаптација на јавно-здравствените стратегии. Ова истражување покажува дека субкладата J.2.4.1 (K субклада) на вирусот на инфлуенца A(H3N2) претставува доминантна генетска и антигенска варијанта во сезоната 2025/26 во Република Северна Македонија и регионот на Југоисточна Европа. Намалената антигенска сродност со вакциналниот сој Influenza A/Croatia/10136RV/2023 (H3N2) укажува на потенцијално намалена вакцинална ефикасност и зголемен ризик

од ширење на инфекцијата, но сепак со доволен потенцијал за заштита од развој на тешки форми на болеста. . Епидемиолошките проекции сугерираат рано започнување и зголемен интензитет на сезоната, што бара засилени мерки за јавно здравје, вклучувајќи подобрен надзор, рана детекција и адаптација на вакциналните стратегии. Континуираното следење на генетската и антигенската еволуција на вирусите останува клучен предуслов за ефективна контрола на инфлуенцата и намалување на нејзиниот јавно-здравствен товар.

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Profesional paper

# ASSESSMENT OF ERYTHROCYTE CONCENTRATE UTILIZATION AND THE NEED FOR PATIENT BLOOD MANAGEMENT IMPLEMENTATION

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## ABSTRACT

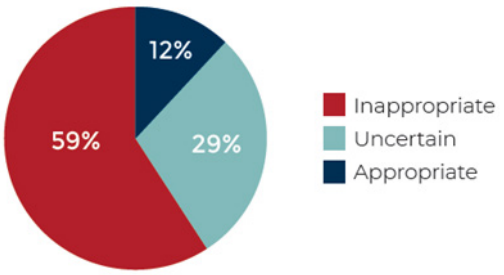
Blood transfusion services play a critical role in supporting surgical and medical care, yet a substantial proportion of erythrocyte concentrate transfusions worldwide remain inappropriate. Patient Blood Management (PBM) has emerged as an essential strategy to improve patient outcomes, reduce unnecessary transfusions, and ensure the responsible use of this limited resource. This study presents blood donations collected at the Center for Transfusion Medicine Shtip from 2022–2024 and analyzes erythrocyte concentrate utilization in the Clinical Hospital Shtip across medical specialties. The findings underscore the need for continuous internal audits, adherence to evidence-based transfusion guidelines, and broader implementation of PBM principles to optimize clinical practice and safeguard blood supplies.

Keywords: Blood transfusion, Erythrocyte concentrate, Patient Blood Management (PBM), Transfusion practices, Hemoglobin threshold, Transfusion appropriateness.

## INTRODUCTION

Blood transfusion services have an essential role in the resuscitation and management of patients undergoing elective surgeries and are an integral part of the healthcare system all over the world. Transfusion of Erythrocyte concentrates is a complex process involving multiple steps and people, from the moment the blood is collected from the donor, to the moment it is given to the patient. As healthcare professionals involved in the "transfusion chain", we have a dual responsibility, to the patient who is receiving the blood and to the person who donated it. Therefore, we must use it wisely and safely. The Regional Center for Transfusion Medicine Shtip is responsible for the supply and distribution of blood between hospitals in the eastern region, and for the needs of the Clinical Hospital Shtip, but the indication for transfusion of Erythrocyte concentrates is the responsibility of the clinician.

Published studies show that between 40% to 60% of transfusions are inappropriate, suggesting no benefit or worse–harm to patients. A study evaluated 494 publications using an expert panel to systematically assess transfusion appropriateness, defined as the likelihood of improving health outcomes. The panel concluded that only 12% of transfusions were considered to be appropriate to improve outcomes; 88% either resulted in harm or showed no benefit.




Most Guidelines recommend transfusion triggers at hemoglobin of 6–7 g/dl for the majority of patients, with a possibly higher threshold at hemoglobin of 7–10 g/dl for patients considered to be high-risk. The debate on the appropriate haemoglobin threshold for transfusion continues to this day. Whenever possible, physiological tissue oxygen and ischaemia indicators should be used to guide the decision to transfuse blood products. However, blood transfusions come with risks, including acute hemolytic reactions, allergic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and septic reactions. The World Health Organization (WHO) issued a policy in 2021 urging countries to adopt Patient Blood Management (PBM) to minimize reliance on transfusions. PBM is a patient-centered, evidence-based approach that aims to improve outcomes by preserving patients' own blood and enhancing patient safety. PBM is structured around three pillar – Table 1 :

1 screening and treating anemia,

2 minimizing blood loss during surgery, and

3 supporting patients while appropriate treatment is initiated.

TABLE 1. Three pillars of patient blood management (adapted and modified)[11-14]

| | Pillar one: Optimise red blood cell mass | Pillar two: Minimise blood loss | Pillar three: Manage anaemia |
|---|---|---|---|
| Preoperative | Detect/treat anaemia and iron deficiency<br>Treat underlying causes<br>Optimise haemoglobin<br>Cease medications | Identify, manage, and treat bleeding/ bleeding risk<br>Minimise phlebotomy<br>Plan/rehearse procedure | Assess patients' bleeding history and develop management plan<br>Estimate patients' tolerance for blood loss<br>Optimise cardiopulmonary function |
| Intra-operative | Time surgery with optimisation of erythropoiesis and red blood cell mass | Meticulous haemostatic/surgical/ anaesthetic techniques<br>Cell salvage techniques<br>Avoid coagulopathy<br>Patient positioning/warming<br>Pharmacological agents | Optimise cardiopulmonary function<br>Optimise ventilation and oxygenation<br>Restrictive transfusion strategies |
| Postoperative | Manage anaemia and iron deficiency<br>Manage medications and potential interactions | Monitor and manage postoperative bleeding<br>Keep patient warm<br>Minimise phlebotomy<br>Awareness of drug interactions and adverse events<br>Treat infections promptly | Maximise oxygen delivery<br>Minimise oxygen use<br>Treat infections promptly<br>Tolerance of anaemia<br>Restrictive transfusion strategies |

These strategies form the foundation of bloodless surgery, which seeks to provide quality surgical care without the use of allogeneic blood transfusions, thereby improving clinical outcomes and respecting patient autonomy. By assembling multidisciplinary teams, establishing clear protocols, and focusing on PBM, these programs aim to enhance patient care.

## AIM

To present the donations in the Center for Transfusion Medicine Shtip, that were collected in the period 2022–2025 and to determine the number of transfusions of blood components (Erythrocyte concentrates) in Clinical Hospital Shtip, their distribution according to different medical specialties.

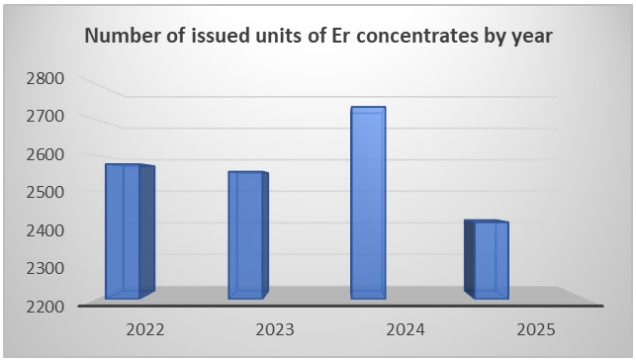
## METHODS

Transfusion records were prospectively collected and analyzed. The data was found from the E-delphin program and patient files in the Moj termin program.

Results: In 2022, 2576 units of erythrocyte concentrate were issued, in 2023 that number is almost the same, 2555, in 2024 we have a total of 2735 units issued erythrocyte concentrate and 2414 units in 2025. Internal department was the department with the highest number of transfused patients (45,4%). Then follow the orthopedic department (32,2%), as indication intraoperative blood loss, surgical department (17%), gynecology and obstetrics (11,3%) and the rest. Overall anaemia was the most common indication for Er concentrate utilization and the mean haemoglobin level at transfusion was 8 g/dL . Approximately 84% of departments administered transfusions to patients at a median Hb level greater than 7 g/dL. In our study, requests for female patients were more and they also utilized more blood components than males. Five units were received back after 30 minutes and were not taken into the inventory but were discarded. The largest percentage of patients (64,6%) have received 1 unit of Erythrocyte concentrate.

Additionally, the number of blood donors increased steadily during the observed period. In 2022, there were 4625 donors, rising to 4803 in 2023, 5054 in 2024 ,and reaching 5517 in 2025 – the highest number in the 4-year span. This number of blood donors refers to donations at the Center for Transfusion Medicine Shtip as well as in the field in our region. Total donations in the Center are 2146 in 2021, 2464 in 2022, 2606 in 2024 and 2728 in 2025, the rest are blood units collected in the field.

Chart 1 Number of issued units of Er concentrates



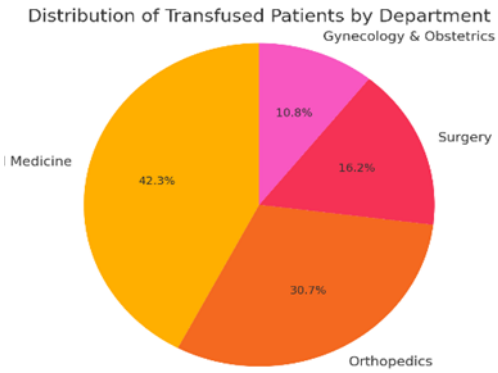
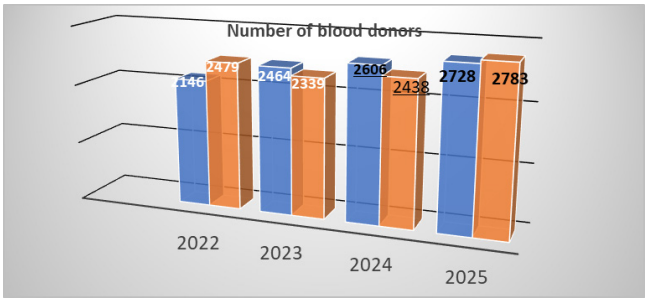




Chart 2 Number of blood donors




## CONCLUSION

The extended four-year analysis (2022–2025) of Er concentrate utilization in Clinical Hospital Shtip provides important insights into transfusion practices, resource consumption, and donor activity trends.

Over the observed period, Er concentrate utilization showed an overall fluctuating but concerning pattern. A slight decrease was observed in 2023 compared to 2022 (2576 vs. 2555 units), followed by a peak in 2024 (2735 units), and a notable reduction in 2025 (2414 units). This final decrease may reflect either improved transfusion stewardship, changes in clinical activity, or increased awareness of restrictive transfusion strategies; however, it still requires further investigation to determine causality.

Despite these fluctuations in utilization, donor activity demonstrated a continuous and consistent upward trend, increasing from 4625 donors in 2022 to 5517 donors in 2025. Similarly, both institutional and field-based donations showed sustained growth, confirming successful donor mobilization strategies and improved community engagement. This growing gap between donation capacity and utilization emphasizes the importance of rational and evidence-based blood use to

ensure sustainability of the system.

The distribution of transfusions across departments remained relatively stable, with Internal medicine continuing to represent the highest proportion of transfused patients (45.4%), followed by Orthopedics (32.2%), Surgical departments (17%), and Gynecology and obstetrics (11.3%). This pattern reflects the persistent clinical burden of anemia, trauma, and perioperative blood loss in these specialties and identifies key areas for targeted Patient Blood Management (PBM) interventions.

A critical and consistent finding throughout the study period is that the mean hemoglobin level at transfusion remained approximately 8 g/dL, with around 84% of transfusions performed at hemoglobin levels above the recommended restrictive threshold of 7 g/dL. This indicates continued reliance on relatively liberal transfusion practices, suggesting that further efforts are needed to align clinical decision-making with current evidence-based guidelines.

Additionally, the predominance of single-unit transfusions (64,6%) is in line with modern transfusion recommendations and represents a positive practice trend toward minimizing unnecessary exposure to blood products. However, isolated findings such as the return and subsequent discard of five units highlight the need for improved logistics and stricter handling protocols to minimize wastage.

Overall, the study underscores a persistent gap between increasing donor availability and the optimization of clinical transfusion practices. While donor recruitment efforts have been highly successful, the clinical utilization patterns suggest that further standardization is required to ensure appropriate use of this valuable resource.

In conclusion, these findings strongly support the need for comprehensive implementation of Patient Blood Management (PBM) programs in Clinical Hospital Shtip. Such programs should focus on stricter adherence to transfusion thresholds, regular internal audits, clinician education, and development of standardized transfusion protocols. Strengthening PBM strategies will not only improve patient safety and clinical outcomes but also ensure sustainable and efficient use of blood resources in the long term.

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Profesional paper

# HISTOPATHOLOGICAL AND ONCOLOGICAL OUTCOMES AFTER NEOADJUVANT THERAPY IN RECTAL CANCER: A NARRATIVE REVIEW AND COMPARISON WITH SURGERY ALONE

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## ABSTRACT

Background: Rectal cancer remains a major oncological challenge. Historically, surgery alone was associated with high local recurrence rates and suboptimal survival. The introduction of neoadjuvant chemoradiotherapy (CRT) and, more recently, total neoadjuvant therapy (TNT) has significantly improved oncological and histopathological outcomes(1).

Aim: To summarize and compare the histopathological and oncological outcomes of neoadjuvant treatment strategies (CRT and TNT) versus surgery alone in locally advanced rectal cancer.

Methods: A narrative review of landmark randomized controlled trials and meta-analyses published up to 2025 was performed. Major trials including CAO/ARO/AIO-94, CAO/ARO/AIO-04, FOWARC, RAPIDO, PRODIGE 23, and PROSPECT were analyzed. Outcomes of interest included pathological complete response (pCR), R0 resection rate, local recurrence (LR), disease-free survival (DFS), and overall survival (OS).

Results: Neoadjuvant therapy consistently outperformed surgery alone. pCR rates ranged from approximately 8% with standard CRT to nearly 28% with TNT. R0 resection rates exceeded 90% in neoadjuvant-treated patients compared with 75–80% in surgery-alone cohorts(2). Local recurrence decreased from 15–20% to below 10%. DFS improved from approximately 55–60% to 75–82%, while OS reached up to 88% in TNT-treated cohorts.

Conclusion: Neoadjuvant CRT and TNT represent the current standard of care for locally advanced rectal cancer(3). TNT, in particular, provides superior tumor response and improved oncological outcomes compared with surgery alone and may facilitate personalized and organ-preserving treatment strategies.

Keywords: Rectal cancer, neoadjuvant therapy, chemoradiotherapy, total neoadjuvant therapy, pathological complete response, oncological outcomes.

## INTRODUCTION

Rectal cancer remains one of the most common malignancies of the gastrointestinal tract and continues to represent a major oncological challenge worldwide. Historically, surgery alone was considered the standard treatment; however, local recurrence rates were high (15–20%), and five-year overall survival rarely exceeded 60–65%. These unsatisfactory outcomes emphasized the need for multimodal therapeutic strategies(1,2).

The introduction of preoperative chemoradiotherapy (CRT) significantly reduced local recurrence rates to below 10% and improved the quality of surgical resection, establishing CRT as a cornerstone in the management of locally advanced rectal cancer (LARC). More recently,

total neoadjuvant therapy (TNT)(3), which incorporates systemic chemotherapy and radiotherapy entirely in the preoperative setting, has demonstrated additional benefits, including higher rates of pathological complete response (pCR), improved disease-free survival (DFS), and a potential for organ-preserving strategies(4).

Several landmark randomized trials, including CAO/ARO/AIO-94, RAPIDO, PRODIGE 23, and PROSPECT, have confirmed the oncological superiority of neoadjuvant treatment compared with surgery alone. Current international guidelines (ESMO, NCCN) endorse CRT and TNT as standards of care in LARC. This narrative review summarizes and critically discusses the available evidence up to 2025, focusing on histopathological and oncological outcomes of neoadjuvant strategies compared with surgery alone(5,6).

## AIM OF THE REVIEW

The aim of this narrative review is to summarize and compare the histopathological and oncological outcomes of neoadjuvant treatment strategies (CRT and TNT) versus surgery alone in patients with locally advanced rectal cancer.

## MATERIALS AND METHODS

This study was designed as a narrative review of the literature. A comprehensive search of major medical databases (PubMed, Scopus, and Google Scholar) was performed to identify relevant randomized controlled trials, meta-analyses, and high-quality reviews published up to 2025.

The search strategy included combinations of the following keywords: “rectal cancer,” “neoadjuvant therapy,” “chemoradiotherapy,” “total neoadjuvant therapy,” “pathological complete response,” “R0 resection,” “local recurrence,” “disease-free survival,” and “overall survival.”

Priority was given to landmark phase III trials that have shaped current clinical practice, including CAO/ARO/AIO-94, CAO/ARO/AIO-04, FOWARC, RAPIDO, PRODIGE 23, and PROSPECT. The results of these studies were qualitatively summarized and compared with historical outcomes of surgery-alone treatment strategies. No formal meta-analytic statistical pooling was performed, in keeping with the narrative design of the review.

## RESULTS

Pathological Complete Response and Tumor Regression: Pathological complete response has emerged as an important surrogate marker of long-term oncological outcomes. In the CAO/ARO/AIO-94 and similar CRT-based trials, pCR rates were approximately 7–10%. With the introduction of TNT strategies, pCR rates increased substantially, reaching approximately 25–28% in trials such as RAPIDO and PRODIGE 23. This enhanced tumor regression reflects the biological effectiveness of delivering full systemic and local therapy in the preoperative setting.

Quality of Surgical Resection (R0 Resection): Surgery alone historically achieved R0 resection rates of approximately 75–80%. In contrast, neoadjuvant treatment strategies consistently improved resection quality, with R0 rates exceeding 90% in most modern CRT and TNT series.

Local Recurrence:

Local recurrence was a major limitation of surgery-alone treatment, with rates ranging from 15% to 20%. The introduction of CRT reduced local recurrence to below 10%, and TNT strategies have further decreased this risk to approximately 5–8% in contemporary trials.

Disease-Free Survival:

Disease-free survival improved substantially with the adoption of neoadjuvant strategies. While surgery alone achieved DFS rates of approximately 55–60%, modern CRT protocols increased DFS to around 70–75%, and TNT regimens further improved DFS to approximately 80–82% in selected trials.

Overall Survival:

Overall survival followed a similar trend. Surgery alone historically achieved five-year OS rates of approximately 60–65%. With CRT, OS increased to approximately 70–75%, while TNT strategies demonstrated the most favorable outcomes, with reported OS rates approaching 85–88% in some trial populations.

## DISCUSSION

This narrative review confirms that neoadjuvant therapy has fundamentally changed the management of locally advanced rectal cancer. Both CRT and TNT significantly improve local control, tumor regression, and the oncological quality of surgical resection compared with

surgery alone.

Pathological complete response has gained increasing importance as a surrogate marker of favorable long-term outcomes, with multiple studies demonstrating superior DFS and OS in patients achieving pCR. By delivering systemic chemotherapy preoperatively, TNT not only enhances local tumor control but also addresses micrometastatic disease earlier, improves treatment compliance, and creates opportunities for organ-preserving strategies, such as non-operative management in carefully selected complete responders.

Nevertheless, treatment intensification is not without challenges. Increased toxicity and patient burden must be considered, and careful patient selection remains crucial. Future research should focus on identifying predictive biomarkers, optimizing treatment intensity, and refining risk-adapted strategies to maximize benefit while minimizing harm.

## CONCLUSION

Neoadjuvant CRT and TNT represent the standard of care for locally advanced rectal cancer, offering clear advantages over surgery alone in terms of tumor response, local control, and long-term oncological outcomes. TNT, in particular, provides the most favorable results and may facilitate a more personalized and organ-preserving treatment approach. Ongoing research will continue to refine multimodal strategies and improve patient selection to further enhance survival and quality of life.

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Review

# EVALUATION OF VITAMIN A LEVELS IN THE BODY AND ITS IMPACT ON PUBLIC HEALTH USING BIOANALYTICAL METHODS

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## ABSTRACT

Vitamin A is a fat-soluble micronutrient that plays an important role in various biological processes, including vision, cell growth and differentiation, as well as immune system function. Maintaining the proper balance of this vitamin in the body is essential for human health, as both deficiency and excess can lead to serious metabolic and clinical disorders.

Hypovitaminosis A is a notable public health concern, particularly in developing nations, and is linked to visual impairment, a compromised immune system, and a higher susceptibility to infections. Conversely, hypervitaminosis A is often the result of excessive supplementation and may result in liver toxicity, neurological issues, and skeletal complications.

This paper aims to provide a review of the literature regarding the biological significance of vitamin A, the effects of hypovitaminosis and hypervitaminosis, and the bioanalytical techniques employed to measure its levels in the body.

Bioanalytical methods assess vitamin A status in the body by identifying and quantifying retinol and its metabolites in serum or plasma using laboratory techniques. HPLC, LC-MS and UHPLC-MS are the most commonly used method for measuring vitamin A, recognized for its sensitivity, seletivity and precision in analysis.

The ionization technique in mass spectrometry is important, as atmospheric pressure chemical ionization generates fewer matrix interferences than electrospray ionization. Additionally, sample preparation, which involves extraction with organic solvents and cleanup using solid-phase extraction, is crucial because it directly affects the accuracy of the results.

Timely diagnosis and assessment of vitamin A levels through laboratory analysis are important for preventing health issues.

Keywords: hypovitaminosis, hypervitaminosis, bioalanalytical methods, human health

## INTRODUCTION

Vitamins are commonly taken to promote health and wellbeing, as they play a crucial role in regulating biological and metabolic functions in the human body. They are categorized into two main groups based on their solubility: Fat-soluble vitamins, which include Vitamins A, D, E, and K, are absorbed along with dietary fats and are stored in the body's fat tissues and liver. Although they are essential for various functions, excessive amounts can accumulate and may lead to toxicity.

Water-soluble vitamins include Vitamin C and the B-complex group. Unlike fat-soluble vitamins, they are not stored in large amounts in the body and are excreted through urine, necessitating consistent dietary

consumption (Gropper, & Smith, 2020; Alija et al. 2024).

Vitamin A is a general term that denotes compounds with the biological activity of retinol. Dietary vitamin A is consumed in two primary forms: preformed vitamin A (which includes retinyl esters and retinol) and provitamin A carotenoids (such as beta-carotene, alpha-carotene, and beta-cryptoxanthin). The amount of vitamin A derived from each of these forms can differ significantly across animal species and individual human diets.

These precursors act as substrates for the synthesis of two important metabolites of vitamin A: 11-cis-retinal, which is necessary for vision, and all-trans-retinoic acid, which is important for cell differentiation and the regulation of gene transcription in almost all tissues (Sofia et al. 2008; Albalat, 2009)

Vitamin A is a fat-soluble vitamin that encompasses a group of biologically active compounds, including retinol, retinal, and retinoic acid, which are involved in various physiological processes, as well as plays a key role in the differentiation of T cell subsets, the migration of T cells into tissues, and the proper development of T cell–dependent antibody responses (Ross, 2010).

Vitamin A is obtained from animal-based foods such as dairy products, fish, and meats, particularly liver. The primary provitamin A carotenoid is beta-carotene, while other provitamin A carotenoids include alpha-carotene and beta-cryptoxanthin. Beta-carotene is predominantly found in green leafy vegetables, sweet potatoes, and carrots.

Vitamin A form animal sources or supplements is preformed, making it more prone to causing toxicity compared to provitamin A form plant sources. Both forms need to be metabolized within cells to retinal and retinoic acid, the active forms of vitamin A, to fulfill the essential biological functions of the vitamin (Ahmed et al. 2021).

Vitamin A plays a crucial role in maintaining normal vision by contributing to the formation of the visual pigment rhodopsin in the retina. It is also significant in regulating cell differentiation, embryonic development, and immune system function (Sommer & Vyas, 2012).

Vitamin A metabolism is a complex process that includes the transport of fatty acids, specific storage in the liver, and chemical conversion to activate genetic and visual functions.

Intake and Absorption - Vitamin A is obtained from the diet in two primary forms:

Preformed Vitamin A (Retinoids): This form is present in animal products such as liver, eggs, and dairy as retinyl esters. Provitamin A (Carotenoids): An example is Beta-carotene, which is found in plant sources like carrots and spinach. In the small intestine, these forms are emulsified by bile salts and assembled into micromicelles. In intestinal cells (enterocytes), beta-carotene can be divided to produce retinol, while retinyl esters are digested and subsequently re-esterified for packaging into chylomicrons.

Transport and Storage - Chylomicrons move through the lymphatic system into the bloodstream and ultimately reach the liver. The liver acts as the primary storage location for the body. Vitamin A is stored in the stellate cells of the liver as retinyl esters. When needed, the liver releases retinol, which is bound to a transport protein known as RBP (Retinol Binding Protein) and Transthyretin. This preserves the fat-soluble vitamin, allowing it to move through the watery environment of the blood without being harmed.

Cellular Activation - Upon arriving at the target cell, retinol undergoes two significant oxidative changes: Retinol is converted to Retinal, which is crucial for the visual cycle in the retina. Retinal is then transformed into Retinoic Acid, marking the final and irreversible stage. Retinoic acid functions like a hormone, entering the cell nucleus, binding to receptors (RAR and RXR), and activating or inhibiting genes that regulate cell growth, immunity, and skin development.

Vision Cycle (In the Retina) - This process is unique as vitamin A functions not by influencing genes but as a structural component of the photoreceptor. Retinol is absorbed by the cells of the retinal pigment epithelium (RPE) and is converted into 11-cis-retinal. This compound then binds to the protein opsin to create rhodopsin. When light enters the eye, 11-cis-retinal transforms into all-trans-retinal, resulting in the transmission of an electrical signal to the brain, which is when vision occurs.

Excretion - occurs when the body has a surplus of substances, which are then further oxidized into water-soluble forms, such as glucuronic acid, and removed from the body through feces and urine (figure 5).

The authors Nelson, D. L., & Cox, M. M. (2021) in their study explained the chemical structure and how retinoic acid acts as a hormone in the cell nucleus through RAR receptors. While the authors Hall, J. E., & Hall, M. E.

(2020) in their study explained on the Vision Cycle (Wald Cycle), the conversion of 11-cis-retinal to rhodopsin.

Lindsay et all. (2020) offers a thorough examination of Vitamin A metabolism, highlighting its absorption, storage, and transport mechanisms in the body. The review discusses important metabolic processes such as the uptake of retinyl esters, the functions of cellular transport proteins, and the regulation of vitamin A levels in circulation.

Clinically, the failure of vitamin A homeostasis presents in two forms: deficiency (Hypovitaminosis A) and toxicity (hypervitaminosis). In contrast to water-soluble vitamins, the kinetics of vitamin A are controlled by binding proteins (RBPs), and any disruption in this balance can lead to direct cellular damage.

a)Xerophthalmia: Impact on the Ocular System

The progression of this condition is outlined by the WHO:

Hemeralopia (Night Blindness): This occurs due to the lack of 11-cis-retinal needed to synthesize Rhodopsin in rod cells. It is the initial functional sign.

Squamous Metaplasia: In the absence of retinoic acid (RA), the conjunctival epithelium loses its goblet cells, which are responsible for mucus production. This change leads to pathological keratinization of the epithelium.

Bitot's spots: These consist of keratin deposits and bacterial debris, specifically from Corynebacterium xerosis, resulting in the formation of white plaques on the eye's surface.

Keratomalacia: A final stage characterized by softening of the cornea due to proteolysis. Collagenase enzymes break down the corneal stroma, resulting in perforation and complete blindness.

b) Keratinizing Metaplasia (Skin and Lung) occurs due to insufficient RAR/RXR signaling, leading to improper differentiation of epithelial stem cells.

In the case of follicular hyperkeratosis, keratin builds up in hair follicles, resulting in a condition characterized by skin "peaks."

Respiratory infections may arise from a deficiency of mucus and cilia in the bronchi, which allows for easier bacterial colonization. Vitamin A is referred to as the "anti-infective vitamin" for this reason

The pathogenesis of hypervitaminosis A (figure 7) involves toxicity that arises when the Retinol Binding Protein (RBP) reaches its limit in binding retinol. When retinol is free and unconjugated, it functions like a surfactant, disrupting the lipid membranes of cells and organelles, including lysosomes (Sommer, 2008)

Acute Toxicity and Intracranial Pressure

Doses exceeding 100 times the recommended daily allowance can lead to Pseudotumor cerebri. Free retinoids influence the redistribution of cerebrospinal fluid, resulting in increased intracranial pressure, which may cause papilledema and severe headaches (Penniston et all. 2006)

Chronic Toxicity and Bone

High levels of vitamin A negatively affect vitamin D and increase the activity of osteoclasts.

Mechanism: The expression of the RANKL gene is heightened, which encourages the breakdown of bone. This results in elevated calcium levels, bone discomfort, and unexpected fractures.

Hepatotoxicity: Stellate cells accumulate excess retinyl esters, enlarge, and promote collagen production, which can result in liver fibrosis and high blood pressure in the portal vein (Ross, S. A., et al. (2000)).

Teratogenesis: Disruption of HOX Genes

Retinoic Acid (RA) serves as an important morphogen that defines the anterior-posterior axis of the embryo.

Mechanism: Elevated external levels of RA, such as those caused by medications like Isotretinoin, disrupt the natural RA gradients in the embryo. This misalignment affects the HOX genes, which play a crucial role in body organization.

Outcome: Fetal Retinoid Syndrome may result, characterized by microtia, anomalies of the aortic arch, and defects in the thymus and craniofacial structures (Clagett-Dame, et all. 2011)

Bioanalytical methods for determining vitamin A

Analytical methods are used to assess vitamin A status in the body by identifying and quantifying retinol and its metabolites in serum or plasma through laboratory techniques.

The most commonly utilized technique for measuring vitamin A is high-performance liquid chromatography (HPLC), known for its sensitivity and precision in analysis (Burtis et al., 2012).

Additional methods comprise:

- spectrophotometry

- gas chromatography (GC)

- liquid chromatography coupled with mass spectrometry (LC-MS)

These techniques are commonly utilized in clinical and research laboratories to evaluate vitamin A status and to identify deficiencies or excess levels in the body (Skoog et al., 2014).

Mass Spectrometry (MS/MS) has revolutionized the field. The use of sub-μm particle columns allows the separation of all isomers of retinol and retinoic acid in a very short time. LC-MS/MS is now the preferred method for assessing vitamin A status in the population, as it can accurately measure minor metabolites that HPLC-UV cannot detect. (Wang et al. 2018; Fanali et al. 2017)

## METHODOLOGY

This paper is based on a review of current scientific literature, including articles from indexed journals and databases. Studies that focus on bioanalytical methods for measuring vitamin A and its functional biomarkers, along with their application in clinical assessment and public health, were examined.

## DISCUSSION

Maintaining an appropriate balance of vitamin, A is crucial for normal bodily functions. Both insufficient and excessive levels can lead to serious health issues. Hypovitaminosis A continues to be a notable public health concern in various countries and necessitates interventions through enhanced nutrition and supplementation initiatives.

Uncontrolled use of supplements can lead to an increased risk of hypervitaminosis A. Therefore, monitoring vitamin A levels in a laboratory setting is important for diagnosing and managing these conditions.

Bioanalytical methods for analyzing vitamin A (retinol) are important for evaluating nutritional status and diagnosing its deficiency or excess in the body. The most commonly used and reliable method is high-performance liquid chromatography (HPLC), which enables the separation and precise quantification of retinol and carotenoids in serum, plasma, or food, and can be paired with different detectors, such as ultraviolet-visible (UV-Vis), diode array detection (DAD), fluorescence, or mass spectrometry (MS).

MS exhibits high selectivity and sensitivity, as demonstrated by studies that show enhanced quantification of vitamins using HPLC-tandem MS. Furthermore, the ionization technique in MS is significant, with atmospheric pressure chemical ionization (APCI) producing fewer matrix interferences compared to electrospray ionization (ESI).

Sample preparation, including extraction with organic solvents and cleanup with solid-phase extraction (SPE), is significant as it directly influences the accuracy of the results.

LC-MS (liquid chromatography combined with mass spectrometry) and UHPLC-MS (Ultra high performance liquid chromatography-mass spectrometry) are utilized for more advanced analyses, providing high sensitivity and specificity, particularly at low concentrations. Simpler methods like spectrophotometry are used less frequently due to their lower specificity (Lindsay et al. 2020).

The authors Sportiello et al. (2025) discusses a study in which natural hydrophobic solvents (NaHDES) were utilized to extract β-carotene from pumpkin skins, considered agro-industrial waste. The findings indicate that a specific combination of menthol and lactic acid was the most effective, reaching yields comparable to those achieved with traditional solvents like acetone, while being safer and more environmentally friendly. Also, the optimal extraction conditions were determined using statistical methods, achieving maximum efficiency with lower energy consumption and lower costs.

Devi-Nair G. R. et al. (2022) describe the creation of a laboratory method for the simultaneous determination of retinol (vitamin A) and two carotenoids (lutein and β-carotene) in food products.

This method utilizes high-performance liquid chromatography (HPLC) and allows for analysis of these components within 45 minutes, demonstrating good accuracy and repeatability. The findings indicate high sensitivity with a low detection limit, favorable linearity, and satisfactory recovery during the extraction process. Also, the use of an improved sample preparation system (SPE) helps in better cleanup and increases the quality of the analysis. This method is considered reliable and efficient for the routine analysis of these components in foods and can also be used for similar analyses in other products. The study shows that these natural solvents are

a sustainable and effective alternative for the utilization of food waste and for the extraction of valuable components such as carotenoids.

A study by Katsa et al. (2021) and colleagues reported on the determination of fat-soluble vitamins in rice cereal baby foods using HPLC–DAD and UHPLC-APCI-MS/MS techniques. Three methods were conducted and compared in this study. The fundamental principle of all three methods involved enzymatic hydrolysis, hot saponification, and liquid–liquid extraction. Among the three methods, one method was preferred since it could detect all three vitamins (A, D3, E) simultaneously and is deemed faster, ecofriendly as well as cheaper for routine analysis. However, the presented method reported higher detection limits compared to previous studies; that was presumed to be in relation to the matrix effect.

## CONCLUSION

Vitamin A is a crucial micronutrient necessary for various biological processes within the body. Both hypovitaminosis and hypervitaminosis A are conditions that can lead to significant health issues. Timely diagnosis and evaluation of vitamin A status through laboratory analysis are vital for preventing and addressing these conditions. Nutritional education and the appropriate use of supplements are key strategies for maintaining optimal levels of this vitamin in the body.

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Review

# НЕВИДЛИВИТЕ РАНИ НА МУЛТИПЛЕКС СКЛЕРОЗАТА: ДЕЛ ОД НЕЗАДОВОЛЕНИТЕ ПОТРЕБИ НА ПАЦИЕНТИТЕ

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## АПСТРАКТ

Авторите сметаат дека овој труд има клучно значење како за пациентите, така и за здравствените работници кои се грижат за лица со мултипна склероза. Целта ни беше да прикажеме реален увид во моменталната состојба на овие пациенти, истакнувајќи ги предизвиците и недостатоците во односот помеѓу здравствените авторитети, лекарите, медицинскиот персонал и пациентите. Со тоа сакаме да поттикнеме преземање на соодветни мерки кои ќе придонесат за подобрување на квалитетот на животот на пациентите. Нашата визија е овој труд да претставува основа за бројни идни истражувања, кои ќе ја зголемат користа за пациентите и ќе ја надградат стручноста на медицинскиот персонал.

Клучни зборови: мултиплекс склероза, пациенти, незадоволени, медицински потреби

Мултипната склероза (МС) преставува инфламаторно заболување на централниот нервен систем (ЦНС). Се должи на мултифакториелно условена, автоимуна реакција која води до демиелинизација како резултат на лимфоцитна инфилтрација на масната миелинска обвивка околу аксоните во ЦНС (1). Овој процес ја нарушува спроводливоста на сигналите што резултира со нарушување на комуникацијата помеѓу нервните клетки. Патоанатмски, се карактеризира со дифузно воспаление, демиелинизација, глиоза и аксонална повреда на мозочното ткиво (2). Релапсите се клинички израз на акутниот воспалителен процес. Релапсно-ремитентната форма (РРМС) е најчеста форма (85-90% од пациентите на почетокот на болеста). Прогресијата се должи на хронично-дифузна аксонална и невронска дегенерација (3).

МС е водечка медицинска причина за попреченост поради невролошко заболување, која обично започнува во третата и четвртата деценија од животот. Со зголемувањето на видовите на имуномодулаторна терапија станува предизвик изборот на вистинската терапија за секој пациент (4, 5). Со оглед на фактот дека МС ги засега пациентите, а со тоа и заедницата, безбедното и успешно менаџирање на истата претставува есенцијален општествено-медицински проблем.

Мултиплата склероза настанува како последица на комплексна интеракција помеѓу генетските фактори и факторите од животната средина (6). Претставува едно од најраспространетите невролошки заболувања во светот и во многу земји претставува водечка причина за нетрауматско невролошко оштетување кај младите луѓе. Болеста најчесто започнува помеѓу 20 и 40 години, но може да се манифестира на било која

возраст (7). Речиси 10% од случаите се дијагностицираат пред 18-годишна возраст. Во Европа, преваленцата на МС се проценува на околу еден случај на 1000 луѓе (6).

Незадовлени медицински потреби

Терминот „незадоволени медицински потреби“ се користи за да опише „ситуација во која поединци или групи не успеваат да добијат бенефиции од различни причини, иако тие би можеле да ги добијат преку интервенции или обезбедување здравствени услуги“. Основната природа на неисполнетите потреби е далеку од статична, бидејќи таа може да претрпи значајни промени во зависност од здравствениот систем и поддршката која е достапна во секоја земја (8). Преваленцата и перцепцијата на неисполнетите потреби кај поединци со хронични болести, како што е МС, зависат од разликите во пристапот до услуги, здравствените политики и распределбата на ресурси во различни земји (9).

Луѓето со МС можат да имаат различни потреби во зависност од нивната инвалидност, индивидуалните животни искуства, личните карактеристики и тежината на болеста. Кога овие потреби остануваат неадресирани, пациентите се оставени сами на себе да се борат со потешкотиите кои произлегуваат од нивната болест. Справувањето со неисполнетите потреби на овие пациенти треба да поттикне подобро разбирање и зголемена свест за перспективата на пациентите. Всушност, истражувањето на неисполнетите потреби од перспективата на пациентите може да биде корисно за справување со дневните потешкотии и за оптимизација на негата. Крајната цел треба да биде имплементацијата на интегриран, ориентиран пристап кон секој пациент поединечно.

Обезбедувањето соодветна и постојана нега (10) претставува голем предизвик поради варијабилноста на клиничките карактеристики при почетокот на болеста и нејзиното понатамошно развивање. Оттука произлегува и значењето на здравствениот систем во управувањето со хронични болести, како што е МС. Најизразената категорија на неисполнети потреби е поврзана со потешкотии при пристапот до нега од социјален аспект и со потребата за помош во секојдневниот живот. Ограниченият пристап до здравствени услуги претставува значаен предизвик за остварување на правото на нега, што често бара дополнителни трошоци за пациентите. Постарите луѓе, пониското ниво на образование, подолгото траење на болеста и повисоките нивоа на инвалидитет се клучни детерминанти за намален квалитет на живот и почести неисполнети потреби. Многу е важно да се адресираат потенцијалните нееднаквости во негата за пациентите со потешки состојби (10). Лекарите играат клучна улога во пополнувањето на оваа празнина преку имплементирање на персонализирани стратегии за третман и обезбедување сеопфатни услуги за поддршка.

Пристапот до информации (11) претставува вид на незадоволена потреба насочена кон подобрување на комуникацијата меѓу лекарот и пациентот, со цел да се овозможи целосна информираност и активно вклучување во одлуките за здравствената нега, како и зголемување на свесноста за симптомите, со што се воспоставува пристап ориентиран кон пациентот. Ова може да се постигне преку вложување поголеми напори во информирањето на пациентите, организирање лични или онлајн состаноци, како и преку соодветно советување за правилно користење на достапните онлајн ресурси. Овој пристап ќе овозможи подлабоко разбирање на специфичните потреби на секој поединец, овозможувајќи ефективен и персонализиран пристап за нивно адресирање и подобрување на вкупниот квалитет на живот.

Одложување на прогресијата на болеста и подобрување на третманите за прогресивниот тип на мултипна склероза

Потребата за нови терапии кои ја забавуваат невролошката прогресија и го подобруваат квалитетот на животот на пациентите е од големо значење (12). Новите истражувања се фокусираат на развој на лекови насочени кон спречување на конкретни молекуларни патеки кои ја поттикнуваат напредната фаза на болеста (12). Унапредувањето на терапиите би овозможило намалување на инвалидитетот и зголемување на самостојноста кај пациентите. Оваа незадоволена медицинска потреба стимулира развој на нови терапевтски пристапи и клинички испитувања.

Одложување или избегнување на инвалидноста

Речиси 80% од возрасните лица со мултипна склероза престанале да работат уште во првите пет години по дијагнозата, најчесто како резултат на инвалидноста (13). Ова претставува значителна загриженост, особено со напредувањето на пациентите низ различните стадиуми на инвалидност, кои вклучуваат ограничена мобилност и целосна зависност при секојдневните

активности. Инвалидноста поврзана со МС може да се категоризира како физичка или психолошка, вклучувајќи и когнитивни нарушувања.

Психолошка инвалидност

Иако психолошката инвалидност често се наведува како голема незадоволена потреба од страна на здравствените работници и пациентите, бројните физички нарушувања влијаат на менталното здравје по напредувањето на болеста (14). Ерозивните ефекти на долгорочниот емоционален стрес се подмолни, но пациентите со МС генерално не разговараат за емоционалниот стрес со здравствените работници (14). Од друга страна, негувателите на пациентите со МС често се нарекуваат „скриени пациенти“, бидејќи тие обезбедуваат години посветена грижа, особено при појава на рецидиви (15). Потребите за нега се уште поголеми кај пациенти со прогресивна болест и тешки симптоми. Во текот на болеста, когнитивните проблеми се јавуваат кај приближно 50% од пациентите. Овие дефицити може да влијаат на краткотрајната меморија, концентрацијата, визуо-просторните функции, извршните функции и обработката на информации.

Физичка инвалидност

Покрај намалената мобилност, која претставува најчест и најочигледен физички симптом кај МС, други проблеми кои се јавуваат со напредувањето на болеста вклучуваат дисфагија, нарушувања во говорот и видот (16). Незадоволените здравствени потреби на пациентите се поврзани со стадиумот на болеста и степенот на инвалидност, додека социјалните потреби се под влијание на клинички и социодемографски фактори. Нарушувањето на видот претставува водечка причина за инвалидност кај пациентите со МС.

Идентификување на корисни алатки и биомаркери

Најчесто користената алатка за поставување на дијагноза на МС и проценка на прогресијата на болеста е магнетната резонанца (МРИ). Сепак, вредноста на МРИ како биомаркер за било што друго освен оптоварувањето со лезии или воспалението може да биде ограничена (17). Постојат и многу други можни алатки и биомаркери за дијагностицирање на МС и следење на текот на болеста, вклучувајќи имуногенетски и лабораториски биомаркери. Сепак, нивната примена е ограничена поради недостиг на специфичност, високи трошоци и практични предизвици за секојдневна употреба (18). Цереброспиналната течност (CSF) претставува интересна цел за истражување на биомаркери кај МС (17). Дополнително, напорите за воспоставување соодветни биомаркери за ризик, дијагноза и прогресија на МС се ограничени поради недоволно разбирање на етиологијата на болеста.

Добивање подобри мерки за функционален исход

Бидејќи МС влијае на повеќе области на физичката и невролошката функција, ниту една единствена мерка не е доволна за проценка на подобрување или влошување на симптомите. Клиничарите кои третираат пациенти со МС се свесни за ограничувањата на невролошкиот преглед. Дополнително, моменталното ниво на перформанси или функционалност на пациентот може да варира и можеби не го одразува директно патолошкиот процес на болеста (19).

Рехабилитацијата е клучна за долгорочна поддршка на лица со мултипла склероза, особено во прогресивните фази на болеста. Мултидисциплинарните тимови, кои ги вклучуваат невролозите, физиотерапевтите, логопедите и психолозите, ја подобруваат функционалноста, активностите и учеството на пациентите во секојдневниот живот (20). Во последните 15 години, третманите за релапсно-ремитентна МС значително напреднаа, поместувајќи го фокусот од спречување на рецидивите кон намалување на инвалидитетот и подобрување на квалитетот на живот. Современите терапии ги намалуваат рецидивите, ја забавуваат прогресијата на болеста и минимизираат несакани ефекти (21). Персонализираниот и мултидисциплинарен пристап овозможува континуирана поддршка за пациентите и нивните семејства, со цел максимално подобрување на нивниот животен стандард.

Заклучок

Решавањето на незадоволените потреби на пациентите со мултипна склероза има значителен потенцијал да го подобри нивниот квалитет на живот. И покрај напредокот во истражувањата и терапиите во последните години, многу аспекти остануваат недоволно адресирани, вклучувајќи ги терапевтските можности, превенцијата на инвалидност и мерките за функционален исход. Потребен е континуиран напредок, не само во основната наука и откривањето на генетски и биолошки фактори, туку и во разбирањето на приоритетите на самите пациенти, за да се оптимизира нивната самостојност, продуктивност и долгорочен квалитет на живот. Исто така, потребно е да се посвети внимание на управувањето со трошоците

поврзани со третманот, како би се обезбедила одржлива и достапна грижа за сите пациенти.

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Review

# ANTERIOR LUMBAR INTERBODY FUSION (ALIF): A NOVEL AND ESSENTIAL APPROACH TO THE MYSTERY OF L5-S1 DEGENERATIVE DISEASE. SURGICAL TECHNIQUE AND EARLY EXPERIENCE IN NORTH MACEDONIA

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## ABSTRACT

Degenerative disease at the L5-S1 level is one of the most challenging spinal surgical pathologies due to its specific biomechanical demand, complex pathophysiology, and historically confusing algorithms. Prior posterior approaches (PLIF/TLIF) have limited success in restoring normal disc height, lordosis, and foraminal dimension(s). These approaches require substantial neural element retraction and profound disruption of paraspinal muscles. Anterior lumbar interbody fusion (ALIF) offers several important advantages to patients, including direct ventral access to the disk,superior sagittal balance restoration, and avoidance of posterior muscle disruption.

The first documented series of the ALIF technique for the treatment of L5-S1 degenerative diseases in North Macedonia is presented. Since its adoption in 2022 at the University Clinic of Traumatology in Skopje, the senior author has performed 9 self-standing or combined ALIF procedures over a 1.5-year period. Technical nuances and clinical results are discussed. The procedure itself, complications, and results are described with clinical experience examples. Authors stress the importance of knowing this technique as part of the armamentarium for L5-S1 treatment pathology, in addition to classical posterior approaches. Finally, the authors stress the importance of accurate assessment of preoperative vascular and visceral anatomy to avoid major complications.

By venturing out of the posterior "comfort zone", ALIF provides the spine surgeon with a powerful tool to deal with the L5-S1 mystery. Our initial series from North Macedonia confirms that ALIF is an optimal first-line approach for isolated L5-S1 degeneration.

Keywords: ALIF, L5-S1 degeneration, anterior lumbar fusion, spondylolisthesis, first experience North Macedonia, sagittal balance

## INTRODUCTION

The lumbosacral junction (L5-S1) is the most mobile and load-bearing segment of the spine. It is therefore most prone to degenerative change. Pathological changes at this level commonly include disc collapse and loss of lordosis. There may also be foraminal stenosis or even low-grade spondylolisthesis, creating a constellation of situations that has historically confused surgeons regarding optimal surgical strategy. This "mystery" presented to the surgeons stems from several factors. The same pathogenic mechanism can result in different final pathomorphological changes and a variable clinical presentation.

Posterior interbody fusion techniques such as PLIF and TLIF have long been the standard approach, largely due to their familiarity and logistical convenience for

surgical teams. However, reliance on these methods has delayed the broader adoption of anterior approaches, despite evidence of biomechanical superiority at L5-S1(1). Our previous experience with posterior techniques for degenerative lumbar spondylolisthesis further highlights the limitations of posterior-only approaches and the potential value of anterior alternatives(2).

Anterior lumbar interbody fusion (ALIF) allows direct access to the ventral disc space for complete discectomy under direct visualization and placement of a large interbody fusion cage. A major benefit of the ALIF approach is the large interbody fusion surface created to encourage bone fusion. Restoration of lumbar disc space height and lordosis can be achieved without retracting the neural elements(3).

**The History of Anterior Lumbar Interbody Fusion (ALIF)**

The technique of performing surgery on the lumbar spine from the anterior, used to treat patients who have lumbar degenerative disease, has existed for about 70 years. Over time, with the accumulation of vast experience and growing understanding of surgical principles, the original technique of an anterior approach was refined and is now applied in spine surgery for fusion of the lumbar spine for a range of disorders. Anterior spine surgery was not invented for operations on degenerative disk disease; rather, it originated in the late 19th century in attempts to treat infections (e.g., Pott's disease) of the spine, deformities, or instability of the spine.

The first documented attempt at an anterior approach to the lumbar spine was made in 1906 by Müller, who performed a transperitoneal debridement for a patient with lumbar tuberculosis(4).

Royle, in the early 1920s, used a retroperitoneal approach to resect a congenital hemivertebra in the lumbar spine(5). One year later, MacLennon became the first surgeon to treat scoliosis in children by an anterior retroperitoneal approach. In the 1930s, Chaklin performed an anterior retroperitoneal osteotomy of the lumbar spine. Theoretically and experimentally, the foundation was laid for the method of an anterior lumbar fusion. In 1932, Capener proposed the "ideal operation" for such a bone grafting, and the first such "ideal operation" was performed in 1933 using a tibial peg. Autografts as interbody spacers were first reported in 1936.

Burns is credited with being the first surgeon to perform an anterior spinal fusion of the lumbar spine. He used bone grafts to treat patients with lumar spondylolisthesis, operating through a transperitoneal approach(6). In 1944, Iwahara published a landmark article on the anterior interbody lumbar fusion for degenerative disease of the lumbar spine, using a retroperitoneal approach that is the basis of the technique for the modern ALIF surgery that is so popular today.

Lane and Moore, in 1948, were the first to use the approach for anterior lumbar interbody fusion for lumbar disc disease and reported a 94% "Good or Excellent" result in 22 patients (though fusion rates with early allogenic bone grafts were lower, around 54%)(7). Their grafts consisted of bone grafts, either autograft or allograft, without the benefit of special instrumentation or interbody cages. Anterior lumbar interbody fusion (ALIF) techniques have evolved over the past several decades. Use of interbody cages, self-standing cages, supplement fixation (anterior plates and/or posterior instrumentation), and minimally invasive approaches has all been combined to improve fusion rates, to enhance disc space height and lordosis, and to reduce complications.

Although initially there were concerns regarding vascular and visceral structures, with increasing experience, the procedure has become safer and more predictable. Often, an access surgeon is utilized to open and retract the anterior abdominal wall.

What started out as heroic surgery for TB and congenital deformities in the early 1900's has evolved into a modern, evidence-based surgical procedure that allows for the treatment and cure of chronic lumbar back and leg pain, and enables patients to return to active lifestyles. Thanks for painting such a great historical picture of where surgery for spondylolisthesis started and where we have gone from there.

This manuscript presents the surgical technique of anterior lumbar interbody fusion (ALIF) at the L5-S1 level as performed at the University Clinic of Traumatology in Skopje, North Macedonia. In 2022, our team, led by the senior author of this paper, introduced this approach for treating degenerative diseases of the lumbosacral junction, marking the first time ALIF was used in the country. This technique and its application to clinical cases clearly demonstrate the technical, safety, and efficacy aspects of the method described. This article also represents an important step forward in the field of treatment of degenerative spinal pathology in North Macedonia.

**Advantages of ALIF Over Posterior Approaches**

When it comes to fusing the L5-S1 segment, the anterior lumbar interbody fusion (ALIF) approach brings several clear biomechanical and clinical advantages compared to traditional posterior techniques.

Rather than dissecting through the back muscles, ALIF allows direct access to the disc space from the front. This spares the paraspinal muscles from extensive trauma, which translates into less postoperative pain and avoids the iatrogenic muscle trauma and denervation, atrophy, and fatty degeneration that often occur with posterior approaches, associated with postoperative back pain(8). Because the surgeon never has to retract the nerves, the risk of nerve-root injury and epidural scarring—common concerns with PLIF and TLIF—is significantly reduced(9).

Another major benefit is the ability to place much larger interbody cages. These cages do an excellent job of restoring disc height (even a modest 2 mm increase can reliably open up the foramina), correcting the local disc angle, and helping rebuild the natural lumbar lordosis. The anterior route also makes it possible to perform a more complete discectomy, creating a larger surface area for solid bone fusion(10).

The literature consistently supports these advantages: ALIF tends to achieve better restoration of sagittal balance and foraminal height than TLIF(11). In contrast, posterior approaches often fall short, leaving patients with under-corrected lordosis and lingering foraminal stenosis—two important limitations when dealing with L5-S1 pathology.

**Surgical Technique – Step-by-Step ALIF at L5-S1**

All cases in this series were performed using a standard mini-open retroperitoneal or transperitoneal approach under general anesthesia, with a vascular surgeon on standby.

The patient is positioned supine with slight lumbar spine extension to facilitate access to the lumbosacral disc. The incision is planned preoperatively along the projected line of the L5-S1 disc space, as marked on a lateral fluoroscopic radiograph. Its exact location and length depend heavily on the patient's sacral slope and pelvic tilt(12).

A midline, paramedian, or Pfannenstiel incision is typically made, starting at or slightly below the umbilicus and extending toward the pubic bone. The Pfannenstiel incision is frequently preferred for its superior cosmetic outcome and practical exposure. After entering the retroperitoneal space with careful paraperitoneal dissection, key anatomical landmarks are identified. The pecten ossis pubis acts as a reliable guide, directing the dissection toward the sacral promontory.

At the beginning of the procedure, the initial dissection plane (plan de clivage) is very similar to that used in the anterior intrapelvic approach(13). We most commonly use a left-sided approach, as it is more ergonomic for a right-handed senior surgeon, although there is no fundamental anatomical difference between sides. The choice of side is mainly guided by the patient's surgical history: we eschew any side with previous lower abdominal or pelvic operations (such as inguinal hernia repair or appendectomy). In general, a history of prior surgery in this region is considered a relative contraindication for ALIF.

Although the initial dissection plane closely resembles the anterior intrapelvic approach used for pelvic and acetabular fractures(13), the two techniques diverge in their deeper orientation. In ALIF, the blood vessels are left inferiorly, and the working corridor is oriented more laterally and superiorly toward the disc space. In contrast, the anterior intrapelvic approach is directed more inferiorly, beneath the external iliac vessels, as it primarily targets the pelvic brim and acetabulum.

Special attention is paid to the identification and gentle mobilization of the great vessels, including the common iliac arteries and veins, as well as the delicate sacral venous plexus. The left ureter is usually identified early in the procedure; to facilitate its location and protection, a double-J stent can be placed in the left ureter before surgery. Once the vessels and ureter are safely retracted, a self-retaining retractor system (SynFrame®)(14) is positioned to keep a stable and unobstructed working corridor to the L5-S1 disc space (Figure 1).

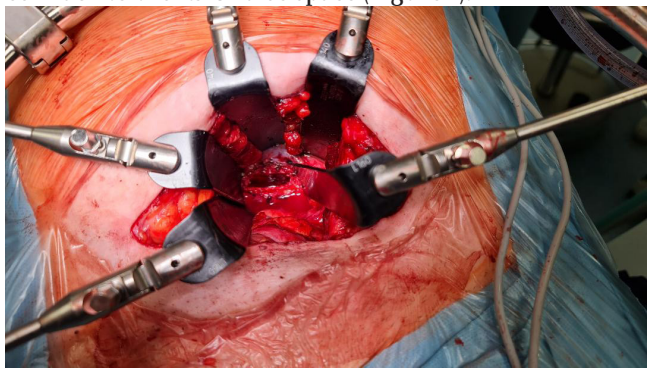


Figure 1: Retractor system positioning during ALIF exposure

Next, a transverse annulotomy is performed, followed

by a thorough discectomy under direct vision. All disc material is precisely removed while preserving the posterior longitudinal ligament whenever possible to protect the neural elements.

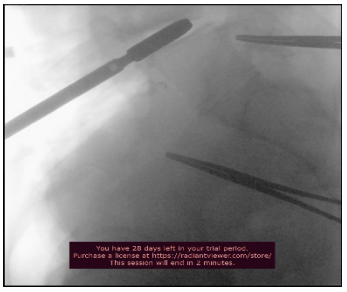



Figure 2. Intraprocedural fluoroscopy image showing the removal of the disc material

Sometimes, with loupes and a headlight, or eventually with an operative microscope, it is possible to perform anterior central/foraminal decompression via the disc space(1), using rongeurs, curettes or Kerrison rongeurs.

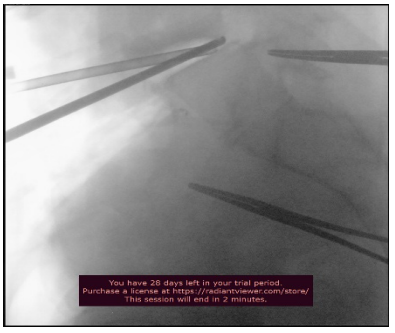



Figure 3

The endplates are then carefully prepared using curettes and rasps to create a bleeding subchondral surface without excessive weakening of the underlying bony structure. Sequential trials are inserted to determine the optimal cage height, width, and lordotic angle that best restores disc height and segmental alignment.

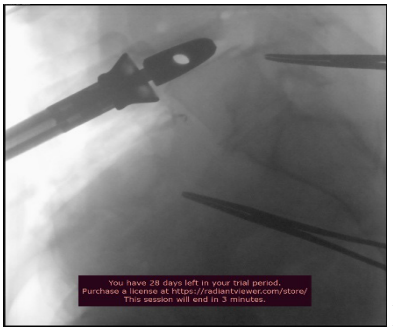
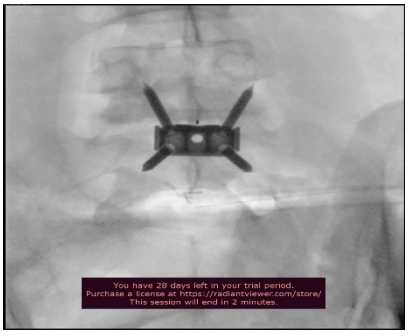



Figure.4.

Finally, a lordotic interbody cage—made of either PEEK or titanium—is filled with autograft bone or synthetic bone substitute and carefully inserted under fluoroscopic guidance into the prepared intervertebral space, and as it is a standalone construct, we secure it with screws to the vertebral bodies. Intraoperative fluoroscopy confirms proper cage placement and restoration of disc height.



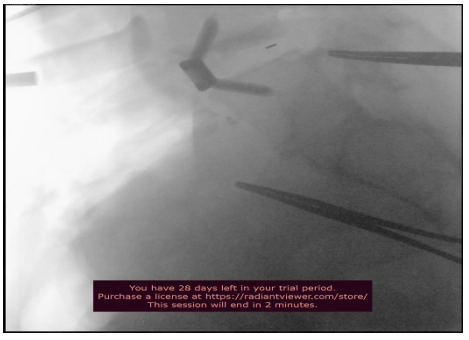




Figure.5 and 6

In several cases with instability or high-grade spondylolisthesis, we add percutaneous posterior transpedicular screws to create a hybrid construct(15).

**Clinical Experience**

First ALIF Series in North Macedonia Between January 2022 and April 2023, nine ALIF procedures were performed exclusively at L5-S1 by the senior author—the first such operations in North Macedonia. All patients presented with refractory radiculopathy, mechanical low-back pain, or neurogenic claudication secondary to localized symptomatic degenerative disc disease (DDD), primary foraminal stenosis or low-grade isthmic or degenerative spondylolisthesis with or without spondylolysis

**Typical Case Illustration**

A representative 52-year-old female with grade I L5-S1 spondylolisthesis and severe bilateral foraminal stenosis underwent ALIF procedure plus posterior fusion. Preoperative radiographs demonstrated disc collapse and 25 % slip.

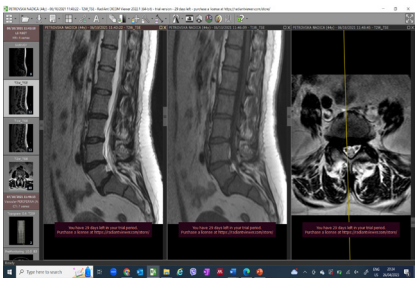


Figure.7

As in every other case, we perform ACT as part of preoperative preparation.

Figure.8

Postoperative imaging confirmed complete slip reduction, disc height restoration, and segmental lordosis gain (Figures 5–8). The patient reported immediate resolution of leg pain and returned to work within short period of time.

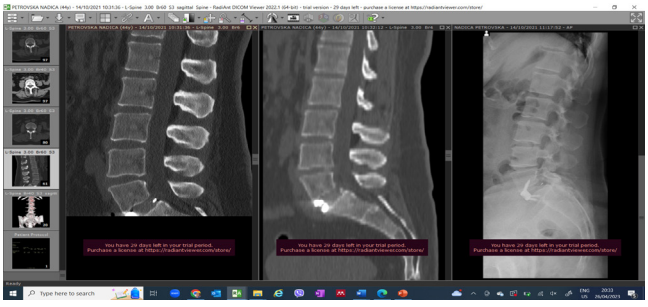


Figure .9.

At the beginning, we have always performed posterior stabilization to enhance stability and fusion, and make the procedure safer.

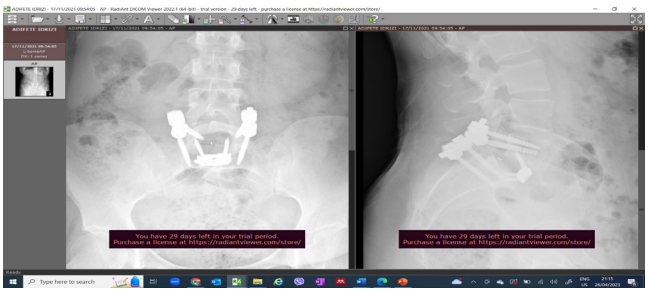


Figure .10.

Successful anterior lumbar interbody fusion (ALIF) requires careful preoperative planning and an appreciation of potential risks associated with the surgical approach. Although the anterior retroperitoneal approach provides excellent disc space exposure and solid interbody fusion, the technique necessitates proper patient selection and an understanding of the potential technical challenges, particularly at the lumbosacral junction.

**Preoperative Planning** must include:

- Detailed history of any prior abdominal surgery (laparoscopic or open/laparotomic), as adhesions or scar tissue can significantly complicate retroperitoneal dissection and increase the risk of visceral or peritoneal injury.
- Comprehensive assessment of lumbosacral anatomy, including evaluation of the L5 slippage angle in cases of spondylolisthesis, as well as identification of transitional anomalies such as lumbarization of S1 or sacralization of L5, which can alter the surgical corridor and vascular relationships.
- Selective vascular imaging (e.g., CT angiography or MR angiography) when indicated by abnormal vascular anatomy on standard MRI, high-grade slippage, multilevel procedures, to delineate the position and course of the great vessels (aorta, vena cava, and iliac vessels) and minimize vascular complications.

**Potential Complications**, though infrequent in our experience, are inherent to the anterior approach due to its proximity to major vascular, visceral, and neural structures. In our series of nine cases, no major neurovascular events occurred. However, the following complications were discussed with all patients as part of the informed consent process: peritoneal injury or tear, dynamic ileus, iliac vein or sacral plexus laceration/injury, ureteral injury, bowel injury, lymphatic disruption (with potential for lymphocele or chylous ascites), retrograde

ejaculation (rare, primarily in males at the L5-S1 level due to sympathetic chain or superior hypogastric plexus injury)

While these complications are rare with experienced surgeons and proper surgical technique, the tissue must be handled gently, vascular structures adequately mobilized, and assistance of a vascular surgeon obtained as necessary. Early detection and management are key to further avoiding catastrophic events. While all of our patients were made aware of these potential risks, the overall safety of the procedure was not compromised, with no permanent major complications.

This section highlights that while ALIF offers distinct biomechanical and clinical advantages, a disciplined, patient-specific approach to preoperative evaluation and intraoperative caution remains essential for optimal outcomes.

## DISCUSSION

The posterior comfort zone—shared by surgeons, anesthesiologists, nurses, residents, and industry—has consistently limited ALIF adoption regardless of clear biomechanical advantages at L5-S1(1)(16). The cervical spine community embraced anterior surgery decades ago; the lumbar community must now follow. As Wallace Stevens noted, "A change of style is a change of meaning." A different ventral perspective on the same pathology provides surgeons with a more strong tool.

Biomechanically, ALIF (anterior lumbar interbody fusion) at L5-S1 provides advantages in height restoration, correction of lordosis, and restoration of the foraminal opening, and is superior when compared to posterior approaches(10). Its main challenge is the anterior retroperitoneal approach, which places at risk major vessels, visceral organs, autonomic chains, and lymphatic chains(17). The overall rate of complications is relatively low, around 10–15%(18)(19), yet it differentiates from those encountered with posterior approaches (PLIF/TLIF). One of the aims of this article is to present meta-analyses and systematic reviews on this topic, including specific approach-related complications, potential risk factors, preventive measures, and management strategies. The information will be used to discuss the indications for the ALIF approach in the treatment of degenerative L5-S1 discopathy and to present the initial experiences with the application of ALIF in North Macedonia.

This approach is also supported by studies in comparative literature and Evidence-Based Multiple North American studies. Fras et al. from the Institute for Spinal Surgery and Research, Haverford, USA found 81% patient satisfaction after ALIF versus 72% after PLIF on VAS pain scores. Similarly, Ledonio, Hendricks, and Santos from the University of Minnesota showed that greater disc material removal and larger graft-bearing surface, as performed in ALIF versus TLIF, are both associated with higher fusion rates(20).

Guyer et al., Shellock et al., and Hisey et al. (Texas Back Institute) evaluated patients with spondylolisthesis treated with a combined approach of anterior lumbar interbody fusion (ALIF) combined with minimally invasive pedicle screw fixation. 85.4% solid fusion, significant slip reduction, and improvement in ODI and VAS scores were achieved in this challenging patient population with zero subsidence noted at the latest follow-up. ALIF in this combination appears to be the preferred approach to sagittal restoration.

The overall complication profile for anterior lumbar surgery has been systematically reviewed and meta-analyzed. A 2024 systematic review and meta-analysis of 54 studies including 8,066 patients who underwent anterior lumbar surgery reported that 13.1% of patients had 1 or more complications, including intraoperative (3.8%), postoperative (7.4%), infection (1.5%), and reoperation (1.7%) rates. There was no significant difference between open and mini-open approaches for overall complications, but patients who underwent mini-open approaches had lower rates of reoperation. The use of an access surgeon decreased rates of reoperation. In contrast, patients undergoing surgery after preoperative CTA had higher intraoperative complication rates (possibly because of the inherent challenge posed by complex anatomy that is selected for surgical approach in these cases)(18).

Vascular Complications (Most Frequent and Potentially Serious) Vascular injuries represent the signature risk of ALIF, occurring in 1–24% of cases depending on the series definition (major vs. minor) and level. Venous injuries predominate (80–90%), primarily left common iliac vein lacerations or avulsions during mobilization/retraction at L4-L5 and L5-S1. Arterial injuries are rarer (0.45–1.5%), typically iliac artery thrombosis or (exceptionally) aortic laceration(21). One single-center series of 212 ALIF cases reported 6.1% vascular injuries (5 major: 4 venous requiring multi-suture repair, 1 arterial requiring thrombectomy/stent); another modern series of 337 patients (508 levels) documented 1.7% venous injuries

(no arterial events, mean EBL 126 cc, one transfusion)(22). L5-S1 accounts for the majority of events due to the iliac vessel bifurcation and the iliolumbar vein's proximity.

Risk factors include older age (>60 years), coronary artery disease, prior lumbar surgery, multilevel fusion, male gender, and higher BMI (correlates with EBL). Anatomical variants (e.g., high iliac bifurcation, large iliolumbar vein) are critical at L5-S1(21).

Prevention relies on preoperative 3D CTA to map vessel anatomy as well as bifurcation. Intraoperative strategies include gentle medial vessel mobilization, self-retaining retractors with periodic release to prevent thrombosis, avoidance of threaded cages that increase shear forces, and vascular access surgeon assistance in complex cases. In the Skopje series, vascular standby was routine with no injuries.

Management involves immediate compression, Trendelenburg positioning, venorrhaphy or primary suture repair, and topical hemostatics (e.g., thrombin, sponges). Postoperative duplex US, MR venography, or IVC filter consideration applies if thrombosis is suspected. Mortality is rare (<0.5%) but documented in aortic injuries. Compared with posterior approaches, ALIF carries a higher visceral/vascular risk but lower transfusion requirements and neural retraction injuries.

Visceral and Peritoneal Complications Peritoneal injury or opening occurs during retroperitoneal dissection and can lead to dynamic (postoperative) ileus—the most common early GI event. Ileus rates vary but account for a significant part to the 7.4% postoperative complication pool; prolonged ileus (>3–7 days) prolongs hospitalization and increases aspiration/pulmonary risks(18). Direct bowel injury is uncommon (<0.5–1%) but reported (e.g., serosal tears or, rarely, perforation). Ureteral injury is rare (<<1%) yet possible during lateral retraction or if anatomy is distorted by prior abdominal surgery—preoperative awareness (as noted in the original presentation) is essential(18).

Preventative measures and treatment incorporate blunt retroperitoneal dissection, complete closure of any perforated peritoneum, and minimal manipulation of the bowel. The management of postoperative ileus is generally supportive, employing a regime of NG tube decompression, early mobilization, prokinetics and restricted fluid intake.

Autonomic/Neurological and Sexual Dysfunction Sympathetic chain injury near the superior hypogastric plexus at L5-S1 can cause retrograde ejaculation (RE) and, rarely, dryness or bladder dysfunction. Systematic reviews report RE rates of 0.1–3.2% with retroperitoneal ALIF (higher, 3–6% with transperitoneal)(17). Overall neurological complications (nerve root or plexus injury) range 4.1–7.7%, higher at L5-S1 or in deformity cases (up to 38% in some subgroups) due to traction or facet subluxation. Risk factors include transperitoneal approach, aggressive plexus retraction, electrocautery near sympathetic fibers, rhBMP-2 use, and male patients with prostatic disease(23).

Management of RE is often expectant (many resolve spontaneously within 3–6 months); β-agonists or urologic referral for persistent cases.

Lymphatic and Other Approach-Related Issues Lymphatic disruption (e.g., chylous leak or lymphocele) is infrequent but documented after iliac vessel mobilization; it may present as retroperitoneal collection or ileus exacerbation. Management is typically conservative or percutaneous; laparoscopic fenestration is rarely required. Wound complications (infection, hernia) are low (1–2%) with mini-open techniques(24).

Implant- and Fusion-Related Complications These are not approach-specific but relevant: subsidence (minimized by large ALIF cages), pseudarthrosis (lower with thorough discectomy and large graft area per Minnesota studies), and adjacent segment disease. Hybrid constructs containing posterior screws reduce these dangers without adding major morbidity(25).

ALIF vs. Posterior Approaches: Comparative Safety Meta-analyses show comparable efficacy and fusion rates, but ALIF has higher severe complications (mortality, DVT, GI events) offset by lower blood loss, neural injury, and better sagittal correction(26). Posterior techniques (PLIF/TLIF) carry more dural tears, epidural scarring, and paraspinal muscle damage. In the original presentation's cited American studies, ALIF demonstrated superior patient satisfaction (81% vs. 72% PLIF) and fusion metrics(20).

Our initial nine-case series, the first ALIF experience in North Macedonia, confirms technical reproducibility, safety, and usefulness in a resource-limited setting. Radiographic restoration of disc height, lordosis, and foraminal patency translated into rapid clinical improvement, in line with international benchmarks. Long-term follow-up (ongoing) will further validate fusion rates and durability.

Limitations encompass small sample size and short-term

data; however, the novelty of introducing this technique nationally justifies early reporting. Future studies will compare ALIF versus TLIF head-to-head within our population.

## CONCLUSION

ALIF is a good option for isolated L5-S1 degenerative disease, with or without supplemental posterior fixation. For L4-L5 pathology, TLIF remains the first choice unless significant lordosis restoration is required. By introducing ALIF in 2022, North Macedonia has joined the international community of centers utilizing this powerful anterior corridor.

The L5-S1 mystery is best solved not by doing "as much as we can" posteriorly, but by choosing the anatomically logical anterior route. As Tim Burton observed, "One person's craziness is another person's reality." What in the past seemed radical is now evidence-based standard care.

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# ГОНИОСКОПИЈАТА КАКО ЗЛАТЕН СТАНДАРД ВО ИСПИТУВАЊЕТО НА ИРИДОКОРНЕАЛНИОТ АГОЛ – ПРЕГЛЕД НА ЛИТЕРАТУРА

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## АБСТРАКТ

Гониоскопијата преставува важна офталмолошка дијагностичка метода која се употребува за евалуација и дијагностицирање на заболувањата на иридокорнеалнот агол. Таа е инвазивна метода која се изведува со помош на различни окуларни леќи и нивна директна апликација во око и со помош на биомикроскопот се добива реална слика од структурите на ИКА. И покрај откривање на нови не инвазивни и софистицирани имицинг методи за испитување на ИКА гониоскопијата се уште е златен этандард и најчесто користена метода за преглед на структурите што ја сочиниуват самиот иридокорнеален агол и други структури на окото. Ова метода е динамична и се добива реална слика во тек на испитувањето.

Целта на овој труд беше да се докаже важноста на ова дијагностичка метода со сите предности и недостатоци во секојдневната офталмолошка пракса.

Клучни зборови: Гониоскопија, иридокорнеален агол, глауком.

## ВОВЕД

Гониоскопијата претставува клиничка офталмолошка дијагностичка метода за испитување на иридокорнеалниот агол и неговите структури. Иридокорнеалниот агол претставува клучна анатомска и функционална структура во предниот сегмент на окото.

Тоа е местото каде што се среќаваат ирисот и рожницата и игра значајна улога во одведувањето на очната водичка преку трабекуларниот мрежест систем и каналот на Шлем.

Пред 1900г идирокорнеалниот агол бил познат како ,,Viriditas'' - Зелена нијанса на зеницата без можност да се видат структурите. Во 1930 Леон Кепе – амерички познат офталмолог ја изуми Кепе ленсот со што ја овозможи директната гониоскопија додека во1950 Ханс Голдман – познат австриско-шфајцарски офталмолог и научник ја изуми Голдмановата лупа со 3 огледала и со тоа ја основа индиректната офталмоскопија која се користи и денес.

## МАТЕРИЈАЛ И МЕТОДИ

За материјали и методи, користевме различни извори за да собереме материјали што ги анализиравме и обработивме. Пребарувањето на објавените студии

беше спроведено во научни бази на податоци како што се Google Scholar, PubMed и Scopus.

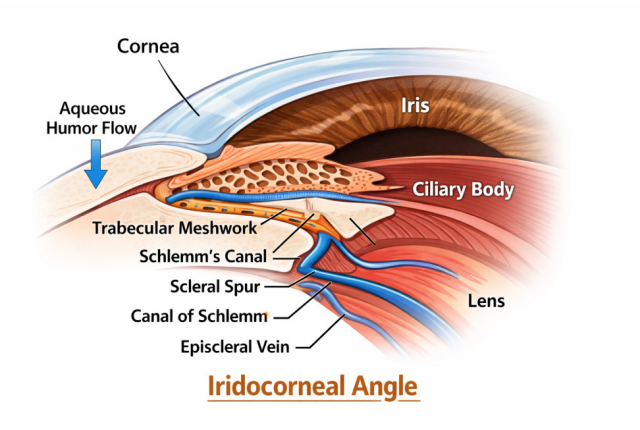
Во анализата беа вклучени и студии кои беа објавени во периодот од последните 10 години, на англиски јазик, кои директно се однесуваат на темата на студијата. Студиите без целосен текст и оние што не ги исполнуваа критериумите за научен квалитет беа исклучени.

Процесот на селекција вклучуваше преглед на насловите, апстрактите и целосната содржина на статиите. Вкупно беа анализирани 11 објавени тудови.

**Анатомија на иридокорнеалниот агол**

Во овој агол се наоѓаат неколку клучни структури:

Трабекуларен мрежест систем (Trabecular meshwork), шлемов канал (Canal of Schlemm), склерален гребен (Scleral spur), цилијарно тело (Ciliary body), швалбе-ова линија (Schwalbe's line).(1,2,3)




Слика бр. 1 Шематски приказ на иридокорнеалниот агол

**Методи за евалуација на иридокорнеалниот агол**

Прецизното проценување на иридокорнеалниот агол е од суштинско значење во офталмолошката дијагностика, особено при процена на ризикот од развој на глауком. Постојат различни дијагностички методи кои овозможуваат директно или индиректно визуелизирање и мерење на структурите во аголот.

**Гониоскопија**

Гониоскопијата е сеуште златен стандард за клиничка евалуација на иридокорнеалниот агол. И покрај откривање на нови методи за евалузција гониоскопијата се уште останува најважна и нај аплицирана метода за евалуација на ИКА во офталмолошката клиничка пракса.(2,4)

**Важност на гониоскопијата во клиничката пракса:**

Глаукомот не е единствената патологија што треба да ве насочи кон испитување на аголот на комората со гониоскопија. Постојат многу други патологии кои ја менуваат конфигурацијата на делови од аголот, како што се тумори и други инфламаторни заболувања коии ги зафаќат токму структурите на ИКА. (5,6,7)

**Техника на изведување:**

Се користи гониоскопска леќа за визуелизација на аголот. Пациентот е под локална анестезија, и се оценуваат видливите структури: Швалбеовата линија, трабекуларен мрежест систем, Шлемов канал, склерален гребен и корен на ирисот. (7,8,9)

Најчесто користени гониоскопски леќи се:

**Goldmann three-mirror lens**

Има 3 огледала под различни агли, овозможува преглед на: Аголот на предната комора, периферија на ретина и макулата. Потребен е контакт гел и се користи со процепна лампа.

**Goldmann single-mirror lens**

Едно огледало, специјално за преглед на аголот, потребен е контакт медиум.

**Zeiss four-mirror lens**

Има 4 огледала, не бара ротирање на леќата, обично не е потребен гел и овозможува динамичка (indentation) гониоскопија

**Sussman four-mirror lens**

Слична на Zeiss, рачна верзија и практична за брз преглед

**Posner four-mirror lens**

Мала контактна површина, лесна за манипулација и добра за динамичка гониоскопија.(8,9,10,11)

Гониоскопијата треба да се изведува во релативно темна просторија. Во спротивно, консензуалната пупиларна реакција ќе ја стесни зеницата на испитуваното око. Затоа, се препорачува просторија со ниско ниво на светлина. (11,12)

Слика бр.2 Гониоскопски призми

**Системи за градирање на иридокорнеалниот агол**

**1. Shaffer систем**

Најчесто користен систем. Се базира на ширината на аголот во степени.

Grade 4 (35–45°) – широк агол, нема ризик од затворање

Grade 3 (25–35°) – отворен агол

Grade 2 (20°) – умерено тесен, можен ризик

Grade 1 (10°) – многу тесен, висок ризик

Grade 0 (0°) – затворен агол

-Колку е помал степенот, толку е поголем ризикот од акутен глауком со затворање на агол.

**2. Spaeth систем**

Подетален систем. Го опишува:

Нивото на инсерција на ирисот

Ширината на аголот

Конфигурацијата на ирисот

Пигментацијата

-Попрецизен е, но покомплексен и повеќе се користи во специјалистичка пракса.

**3. Scheie систем**

Се базира на тоа кои структури се видливи при гониоскопија.

Grade I – видлив е цилијарен бодил

Grade II – не се гледа цилијарен бодил

Grade III – не се гледа склералниот шпор

Grade IV – не се гледа трабекуларната мрежа

-Колку е поголем бројот, толку е потесен аголот (обратно од Shaffer).(14,15,16,18)

**Предности на гониоскопијата**

Прецизна проценка на аголот

Овозможува директен увид во ширината и структурата на иридокорнеалниот агол, што е клучно за разликување на глауком со отворен и затворен агол.

Рана дијагностика на глауком

Особено е важна во откривање на ризик за затворање на аголот и превенција на акутен напад на глауком.

Откривање на анатомски абнормалности
Може да се забележат синехии, неоваскуларизација, пигментација или трауми во аголот.

Помош при избор на терапија

Наодот од гониоскопијата помага во одлуката дали е потребна медикаментозна терапија, ласерска иридотомија или хируршка интервенција.

Релативно брза и достапна метода

Постапката трае кратко и се изведува во амбулантски услови.

**Недостатоци на гониоскопијата**

Контактен преглед

Се изведува со поставување на специјална леќа на окото, што може да предизвика непријатност кај пациентот.

Зависност од искуството на офталмологот
Точноста на интерпретацијата зависи од стручноста и искуството на лекарот.

Можност за субјективност

Проценката на ширината на аголот може да варира помеѓу различни испитувачи.

Не дава квантитативни мерења

За разлика од современи методи како оптичка кохерентна томографија (OCT), гониоскопијата најчесто обезбедува квалитативна, а не прецизна нумеричка анализа.

Ризик од минимални компликации

Ретко може да се јави иритација на рожницата или инфекција ако не се почитуваат(17,18,19)

## ЗАКЛУЧОК

Гониоскопијата претставува основна и многу важна метода во офталмологијата, особено во дијагностиката и следењето на глауком. И покрај одредени недостатоци, нејзината дијагностичка вредност е голема и често незаменлива во клиничката пракса. И покрај новите методи имицинг методи на испитување кои се побрзи и неивазивни методи како на пример предната оптичка кохерентна томографија(OCT-as), Ултразвучната биомикроскопија(UBM) и најново гонокамерата сепак во сите офталмолошки центри гониоскопијата е незаменлива поради горенаведените причини.

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Case report

# ПЛЕОМОРФЕН АДЕНОМ НА МАЛИ ПЛУНКОВНИ ЖЛЕЗДИ-ЕКСТРАОРАЛНА ЛОКАЛИЗАЦИЈА

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## АБСТРАКТ

Плеоморфниот аденом е најзастапениот бениген тумор, како кај големите, така и кај малите плунковни жлезди. Кога станува збор за малите плунковни жлезди, плеоморфниот аденом почесто се јавува кај женскиот пол, помеѓу четвртата и шеста декада од животот. Клиничката манифестација речиси секогаш оди во прилог на бениген карактер на промената, затоа што се работи за споро растечка, тврда и безболна на палпација туморска формација. Во овој случај, 20 годишен пациент се јавува на преглед заради безболна и лесно подвижна промена на кожата, во проекција на премоларите на долната вилица, од левата страна, која што пациентот за прв пат ја забележал пред шест месеци. Промената е ексцидирана со локална анестезија. Наодот од патохистолошката анализа констатираше плеоморфен аденом на малите плунковни жлезди.

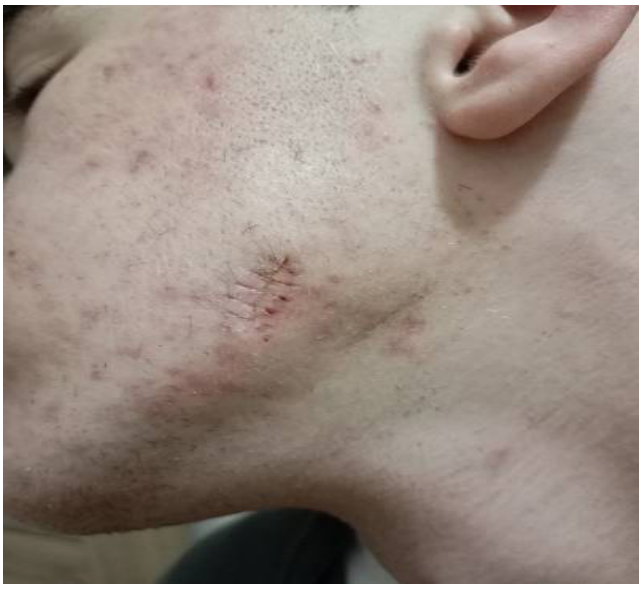

Клучни зборови: Плеоморфен аденом, мали плунковни жлезди, бениген тумор.

## ПРИКАЗ НА СЛУЧАЈ

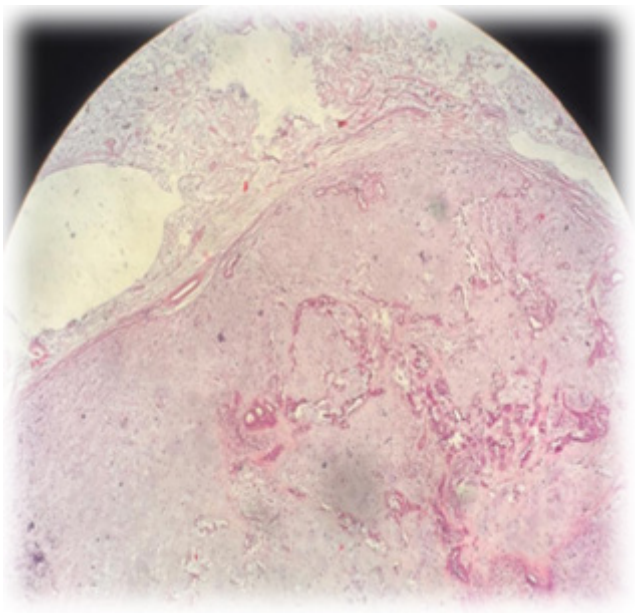
Пациент на дваесет годишна возраст се јавува на нашата клиника заради туморска промена на кожата на лицето, во проекција на долниот раб на мандибулата, 3cm латерално од комисурата на усната, на левата страна. На клинички преглед може да се забележи дека пациентот има проблематична кожа на лицето, со мноштво акни и фурункули. Промената перзистира шест месеци и не бележи промена во дијаметарот откако пациентот за првпат ја забележал. Истата на палпација е безболна, лесно подвижна, со големина на орев и со нерамна површина. Интраорално прегледот без особености. Пациентот е со интактно забало, уредна хигиена и нормално пребоена мукоза. Пациентот е со добра здравствена состојба, непушач и не конзумира алкохол. Што се однесува до фамилијарната анамнеза, негира болести од интерес.

Промената е екстирпирана во локална анестезија, дефектот сутуриран во слоеви и материјалот е испратен на патохистолошка анализа. Истата покажа дека се работи за Adenoma pleomorhe - Tumor mixtus на малите плунковни жлезди.

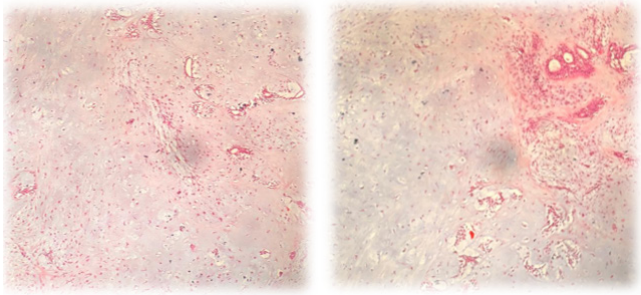
Слика 1. Плеоморфен аденом на мали плунковни жлезди (екстраорална локализација )



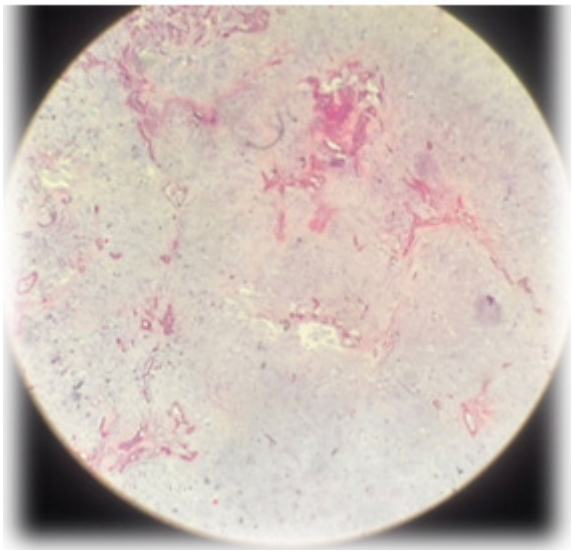
Слика 2. Непосредно по вадење на сутури



Слика 3 . Микроскопски преглед периферијата каде се гледа со сврзно ткивна капсула, ХеЕо х100



Слика 4,5. Микроскопски преглед на плеоморфен кон аденом, боење по ХеЕо, х100 јасно ограничена неоплазма



Слика 6. Микроскопски преглед на плеоморфен аденом, боење по ХеЕо, х100

**Патохистолошки наод:**

Доставен е јасно ограничен солидна туморска формација со димензии 1,8 x 1,7 x 1 см. На пресек се гледа солидно беличесто ткаење со еластично жилава конзистенција. Материјалот за ХПА е вклапен во 2 парафински блока.

Микроскопската анализа на примероците покажа туморско ткиво со бифазична морфологија. Неоплазмата доминантно е градена од епителни клетки кои што се вклопени во мукоиден, миксоиден и хондроиден матрикс. Епителните и миоепителните клетки се во тубуларен и лентовиден аранжман градени од кубични до цилиндрични клетки со бенигни карактеристики (слика 4,5,6). На периферијата се гледа сврзно-ткивна капсула (слика 3).

## ДИСКУСИЈА

Туморите на плунковните жлезди сочинуваат околу 6% од сите тумори во регијата на глава и врат, при што 80% се локализирани во паротидната жлезда, од кои 75% се бенигни, а 25% малигни (1). Дијагностиката и третманот се комплексни поради варијабилната хистологија и анатомската сложеност (2).

Плеоморфниот аденом е најчестата неоплазма на саливарните жлезди (45–75%), со инциденца од 2–3,5/100.000 жители годишно. Најчесто се јавува кај лица од третата до шестата декада, почесто кај женскиот пол (1:3–1:4) (3). Клинички се манифестира како безболна, споро растечка, иницијално подвижна формација, додека рекурентните форми се мултинодуларни и фиксирани (3).

Најчеста локализација е паротидната жлезда (70–80%), потоа субмандибуларната (10%) и ретко сублингвалната жлезда (1,3%). Малите плунковни жлезди се зафатени во 5–10%, најчесто на палатумот (4).

Хистолошки, плеоморфниот аденом е бифазичен тумор составен од епителна, миоепителна и стромална компонента, поради што е познат и како бениген микстен тумор (5–7). Се класифицира во миксоиден, клеточен и микстен тип (8). Честа е појавата на псевдоподи и дисконтинуитет на капсулата (>50%), како и сателитски нодули (10–15%), без индикација за малигнитет (9–11).

Хистогенезата е поврзана со резервните клетки на интеркалатните дуктуси, што ја објаснува морфолошката хетерогеност (12). Третманот е хируршка ексцизија, со ризик од малигна трансформација од 4,5%, кој расте со возраста и траењето на туморот. Малигнизираниот плеоморфен аденом има лоша прогноза, со 5-годишно преживување од 25–65% и висока стапка на метастазирање (4,13).

Како ризик фактори се наведуваат изложеност на радијација, генетска предиспозиција, хормонални и хемиски фактори, SV40 вирус и хромозомски аберации (8q12, 12q15), како и пушење и алкохол (14–16).

Туморите на малите плунковни жлезди се ретки, хистолошки хетерогени и најчесто локализирани на палатумот (50%) (17,18). Почести се кај жени, со поголема инциденца на малигнитет во повисока возраст (19). Плеоморфниот аденом е најчестиот бениген тумор во оваа група, најчесто кај жени во четвртата и петтата декада, што не корелира со нашиот случај (машки пол, 20 години) (20–22).Клинички, се манифестира како асимптоматска, јасно ограничена, подвижна нодуларна формација со интактна мукоза. Екстраорална локализација, како во нашиот случај, е ретка и може да биде поврзана со механичка траума, при што диференцијално дијагностички доаѓаат предвид неурилемом, липом и неурофибром (27,28). Бенигниот карактер се сугерира со бавен раст и отсуство на болка, улцерација и аденопатија, за разлика од малигните неоплазми кои се брзо растечки и симптоматски. Дијагнозата се базира на клинички преглед, радиолошка дијагностика и тенкоиглена биопсија, а се потврдува хистопатолошки (29).

Бенигните тумори на малите саливарни жлезди бележат поголема фреквенција од малигните неоплазми (30,31,32,33).

Некои пак истражувања даваат податок дека малигните неоплазми се среќаваат почесто за разлика од бенигните (34,35,36).

Третманот на тумори на малите плунковни жлезди се базира на нивна комплетна хируршка ексцизија. Плеоморфниот аденом особено е неопходно да се ексцидира со адекватни маргини. Според патохистолошкиот наод во нашиот случај (карактеристичен за плеоморфен аденом), ексцизијата е направена со маргини во здраво, односно промената е екстирпирана со интактна капсула. Непотполна ексцизија претставува причина за рецидив на промената, а последователно на тоа и покомплексна оперативна.

Третманот пак на малигните тумори може да вклучува

палатектомија за лезии на палатумот, ексцизија на букалниот мускул за лезии на образната мукоза, односно ресекција на мандибулата или максилата ако се инволвирани (37).

Комплетна хируршка ексцизија на туморот со околното здраво ткиво и сочувана капсула претставува третман на избор за овој вид на тумори, чија што навремена дијагноза е од големо значење, како заради тоа што претставува редок ентитет, така и заради можната негова трансформација во малигна неоплазма, односно carcinoma ex pleomorphic adenoma (38).

Заклучок

Како што може да се заклучи од горе наведеното туморите на малите плунковни жлезди, иако многу ретко, бележат и екстраорална локализација. Диференцијално дијагностички претставуваат предизвик (особено во нашиот случај заради возраста и проблематичната кожа на пациентот) и нивната клиничка манифестација е речиси идентична со поголем број на бенигни кожни, односно тумори на кожните аднекси. Ова може да биде причина да се направи превид во дијагностиката, односно последователни консеквенци од истиот. Во овој случај, екцизијата на туморот во здраво ткиво и неговата последователна патохистолошка евалуација беа клучни за решавање на дијагностичката дилема.

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Case report

# ACUTE INTRAPARTUM COMPLETE UTERINE INVERSION MANAGED SUCCESSFULLY WITH MANUAL REPOSITIONING

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## ABSTRACT

Introduction: Uterine inversion during delivery is rare but lifethreatening complication in which the uterine corpus is completely or partially prolapsed through the cervix. Uterine inversion can occur after the third stage of labor and is characterized by postpartum hemorrhage and severe shock.

Case report: 25yearold primigravida at 40+4 gestational weeks had complete uterine inversion immediately following cord traction 20 minutes postdelivery. The unusual appearance of a mass at the vaginal introitus prompted urgent intervention. Obstetric and anesthesiology teams were immediately mobilized. Under intravenous general anesthesia, we performed manual repositioning within 5-6 minutes, followed by uterotonics and blood transfusion. The patient recovered without major consequences within 48 hours.

Conclusion: Early recognition, avoidance of premature cord traction, hemodynamic stabilization, and prompt repositioning are critical for successful management. In our case, prompt recognition of the uterine inversion and its immediate reposition under general anaesthesia was a key for successful management.

Keywords: uterine inversion, obstetric emergency, manual repositioning

## INTRODUCTION

Puerperal inversion of the uterus is rare, but serious, life-threating obstetric complication in which the uterine corpus is completely or partially prolapsed through the cervix. Uterine inversion can occur after the third stage of labor and is characterized by postpartum hemorrhage and severe shock. If not treated properly, it can lead to maternal death. [1]. The frequency of this complication is approximately 1 in 2000 to 1 in 23,000 deliveries. It occurs most often in “low-risk” deliveries. The incidence of this complication has been reduced fourfold with the introduction of active management of the third stage of labor [2].

The most common causes of inversion are excessive traction on the umbilical cord in order to remove the placenta, when its insertion is at the fundus of the uterus and the pressure on the fundus in condition of a relaxed uterus. Other risk factors include: short umbilical cord, manual removal of the placenta, rapid delivery, invasive placentation, fetal macrosomia, use of uterine relaxants, nulliparity, connective tissue diseases and history of uterine inversion during a previous delivery. In the most of the cases, no risk factors for this complication have been identified [2-4].

Depending on when the inversion occurred after childbirth, it can be acute (within the first 24 hours),

subacute (24 hours-4 weeks), and chronic (more than 4 weeks after childbirth) [6]. We present a successfully treated case of an acute intrapartum uterine inversion, at the Specialized Hospital for Gynecology and Obstetrics "Mother Teresa" in Skopje, Republic of North Macedonia.

## CASE REPORT

We present a case of the 25 years old primigravid women, at 40+4 gestational weeks of pregnancy. She had a spontaneous labor of male infant weighting 3800g. Approximately 20 minutes after delivery of the baby, placental delivery was attempted with controlled cord traction and a mass appeared at the vaginal introitus (placenta attached to the uterus). This was a complete intrapartal inversion of the uterus.

Obstetric and anesthesiology teams were immediately mobilized. The patient had lower abdominal pain and hypotension (70/44mmHg). Two large-bore intravenous lines were secured and intravenous crystalloid administration started promptly. We performed the manual uterine repositioning under general anesthesia (Johnson maneuver) 5-6 minutes after the event. Placenta was removed after the repositioning of the uterus. During this complication, massive hemorrhage occured. Uterotonics were administered immediately after repositioning: oxytocin, methylergometrine and misoprostol.

We started with administration of the substitution therapy 25 minutes after the event and this continued in the next 24 hours postpartum: 4 units of erythrocyte concentrate (4x350ml), 4 units of fresh frozen plasma (4x220ml) and 5 units of human albumin (100ml, 20% concentrate). The levels of hemoglobin and hematocrite 25 minutes after the inversion were: hemoglobin - 64g/L (121g/L antepartum), hematocrite - 0.17 (0.33 antepartum). Approximately 72 hours after the event the values of hemoglobin and hematocrite were back to normal. No further hemorrhage occured, vital signs were stabile and the patient was discharged at the 4th day after delivery.

## DISCUSSION

Uterine inversion is defined as the turning inside out of the fundus into the uterine cavity. It's incidence is ~1:2,000–1:23,000 deliveries [2]. Our experience at the Specialized hospital for gynecology and obstetrics "Mother Teresa" corresponds with the lower incidence – this is the only reported case in the past decade (~ 25,000 spontaneous deliveries).

The classification of acute puerperal inversion is based on the level reached by the uterine fundus during its introflexion. There are four degrees depending of the severity of the problem: I degree (incomplete inversion) - the inverted fundus extends within the uterine cavity but not through the cervix (introflexion of the uterine fundus is still within the uterine body), II degree (incomplete inversion) - the inverted part extends inside the cervical canal, III degree (complete inversion) - the completely inverted uterine fundus goes beyond the cervix and extends into the vagina), IV degree (complete inversion) - the entire uterus and vagina are inverted and exit the genitals [5,6].

The diagnosis of complete inversion is not difficult. The fleshy and bloody mass is visualised outside the vulva [7]. Treatment of the puerperal uterine inversion is urgent. It is based on a medical correction of shock and a trial of manual reposition [5,6]. The first approach is to attempt a manual repositioning [8], proposed by Dr. Johnson in the mid-1900s and still valid today [Figure 1]. Maximal relaxation of the uterus is important during the reposition and neuromuscular relaxant drugs are recommended, but if they fail, general anesthesia is indicated [9]. Once the fundus is repositioned in its correct location, it is necessary to hold it in a place for a few minutes and administer an oxitocine to prevent the occurence of reinversion. After the reposition,the broad spectrum of antibiotics should be administered [10].

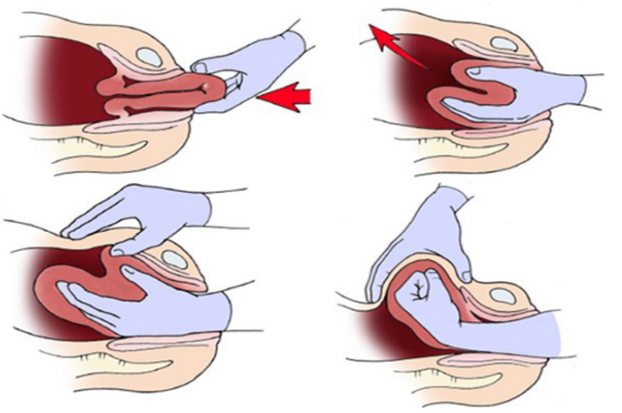

Figure 1. Johnson's maneuver for manual repositioning of the inverted uterus [8]

In our case , we performed the manual uterine repositioning under general anesthesia (Johnson maneuver) 5-6 minutes after the event. Placenta was removed after the repositioning of the uterus. During this

complication, massive hemorrhage occured. Uterotonics were administered immediately after repositioning: oxytocin, methylergometrine and misoprostol. We started with administration of the substitution therapy 25 minutes after the event and this continued in the next 24 hours postpartum: 4 units of erythrocyte concentrate (4x350ml), 4 units of fresh frozen plasma (4x220ml) and 5 units of human albumin (100ml, 20% concentrate). The levels of hemoglobin and hematocrite 25 minutes after the inversion were: hemoglobin - 64g/L (121g/L antepartum), hematocrite - 0.17 (0.33 antepartum). Approximately 72 hours after the event the values of hemoglobin and hematocrite were back to normal. No further hemorrhage occured, vital signs were stabile and the patient was discharged at the 4th day after delivery. Whenever the attempt for manual reduction fails, the surgical approach becomes imperative with the various surgical techniques suggested [6].

In our case, the risk factor was the pronounced excessive traction of the umbilical cord in order to deliver the placenta more quickly, which was inserted into the fundus of the uterus. It must be emphasized that this should not be done in order to prevent the occurrence of this complication, which is frightening and life-threatening for the patient. It is also very important to monitor the patient in the third stage of labor, in order to detect this complication in time, which is accompanied by intense uterine hemorrhage and is frightening for the obstetric team. Their rapid and appropriate cooperation with each other, as well as the urgent engagement of the anesthesia team, is of crucial importance. The goal is to perform manual repositioning of the prolapsed uterus as quickly as possible, under general anesthesia, and to prescribe appropriate therapy, as well as appropriate resuscitation procedures with blood and blood product substitution.

## CONCLUSION

The puerperal uterine inversion is a rare but severe condition. Its diagnosis is clinical and the treatment must be immediate. Early recognition, avoidance of premature cord traction, hemodynamic stabilization, and prompt repositioning are critical for successful management. In our case, prompt recognition of the uterine inversion and its immediate reposition under general anaesthesia was a key for successful management.

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# FETAL MALFORMATIONS - ANENCEPHALY AND SPINA BIFIDA, AS AN INDICATION FOR PREGNANCY TERMINATION IN THE SECOND TRIMESTER

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## ABSTRACT

Introduction: Anencephaly is the most severe malformation of the central nervous system. It is common type of neural tube defect and is characterized by the complete or partial absence of the calvaria and brain. It is a fatal disease and newborns born with this anomaly usually live less than a day. It's incidence is 1-5/1000 births. The occurrence of neural tube defects is due to a combination of genetic and environmental factors.

Case report: A 31-year-old patient with a third pregnancy., at 15+4 weeks of gestation. She reported smoking 20 cigarettes per day and taking folic acid supplements starting at 6 gestational weeks. On ultrasound examination, there was a fetus with a positive cardiac action, abdominal circumference and femur length corresponding to 15 weeks of gestation. Biparietal diameter and head circumference could not be measured due to protrusion of brain tissue through a calvarial defect. We performed labor induction with oxytocin and after expulsion of the fetus and placenta, an instrumental revision of the uterine cavity was performed under general anesthesia. According to the autopsy report, the fetus had low-set auricles, a stocky neck, protrusion of the eyeballs and a frog-like appearance. External inspection showed a congenital malformation of the central nervous system represented by the absence of the bones of calvaria and absence of brain tissue with the presence of an area cerebrovasculosa measuring 2x1.7 cm and a cleft of the vertebral arches in the lumbar region measuring 0.5cm covered with skin and soft tissues (spina bifida occulta).

Conclusion: The simplest way to reduce the incidence of neural tube defects is to advise women of reproductive age to take folic acid supplements. Fetal ultrasonography is the gold standard for detecting neural tube defects. Anencephaly should be detected as early as possible, in order to perform a timely termination of pregnancy.

Key words: anencephaly, neural tube defects, folic acid suplementation, ultrasound

## INTRODUCTION

Anencephaly is the most severe malformation of the central nervous system. It is common type of neural tube defect and is characterized by the complete or partial absence of the calvaria and absent brain. The brainstem, diencephalon and cerebellum are commonly present [1]. As the central nervous system develops in embrio, the neural plate folds and fuses, forming the neural tube. Any disruption of the neural tube closure process can result in structural abnormalities that are called neural tube defects. Anencephaly results from the failure of the neural tube to close at its rostral end during

fetal development [2]. It is a fatal disease and newborns born with this anomaly usually live less than a day. It's incidence is 1-5 per 1000 births [3]. The other neural tube defect is spina bifida caused by failure of closure of the caudal (spinal) part of the neural tube in the 4th week of gestation [4]. Spina bifida has two forms: occulta and aperta. Spina bifida occulta is a closed form where the lesion is covered with skin and the spinal cord is not exposed [5]. In the cases of spina bifida aperta, the spinal cord is exposed to the surrounding environment, without skin covering [4,6]. Severity ranges from asymptomatic spina bifida occulta to severe forms - spina bifida aperta (meningomyelocele), with spinal cord exposure and neurological dysfunctions: mobility problems, bowel and bladder dysfunction, hydrocephalus [7]

The occurrence of neural tube defects is due to a combination of genetic and environmental factors [8] After the birth of one child with this malformation, there is a 4% risk that a subsequent child will be affected [9]. Insufficient intake of folic acid in the diet (or as a supplement) before and during the first trimester of pregnancy plays an important role [8]. Other risk factors are: some epilepsy medications (valproic acid, phenytoin, carbamazepin), obesity and poorly controlled diabetes. [9]. Some studies suggest that neural tube defects and spontaneous abortions are more common in pregnant women who experience high temperatures (hot tub, sauna, having a fever) during the first 4-6 gestational weeks [8,10].

## CASE REPORT

We present a case of a 31-year-old female patient with a third pregnancy, who was referred to our hospital for an ultrasound examination at 15+4 weeks of gestation. The previous two pregnancies were normal, ending with spontaneous delivery. In this pregnancy, she reported smoking 20 cigarettes per day and receiving folic acid suplementation starting at 6 weeks of gestation. The history of past illnesses and allergies was negative. PRISCA 1 was not performed, and microbiological tests were negative. On ultrasound examination, a fetus with a positive cardiac action was detected, with abdominal circumference and femur length corresponding to 15 weeks of gestation, but biparietal diameter and head circumference could not be measured due to protrusion of brain tissue through a calvarial defect [Figure 1]. The patient was hospitalized with suspicion of encephalocele. With the patient's prior consent, we performed labor induction with oxytocin and after expulsion of the fetus and placenta, an instrumental revision of the uterine cavity was performed under general intravenous anesthesia. Anesthesia and intervention underwere without complications. Uterotonic and antibiotic therapy were administered.

We submited the fetus and placenta to autopsy and histopathological analysis, with the following findings: a female fetus with a body weight of 51 grams and a body length of 11 cm. The fetus had low-set auricles, a stocky neck, protrusion of the eyeballs and a frog-like appearance. External inspection showed a congenital malformation of the central nervous system represented by the absence of the bones of the calvaria and the absence of brain tissue with the presence of an area cerebrovasculosa measuring 2x1.7 cm and a cleft of the vertebral arches in the lumbar region measuring 0.5 cm covered with skin and soft tissues, which was consistent with spina bifida occulta. After opening the chest and abdominal cavity, the visceral organs were neatly placed in the appropriate anatomical positions, properly formed without the presence of developmental malformations. A placenta measuring 8x4x3 cm and weighing 70 g had a regular structure. The amniotic membranes were smooth and shiny. The umbilical cord was paracentrally inserted, 12 cm long, and 3 blood vessels were visible on the cross-section. Microscopically, the cross-sections of the area cerebrovasculosa showed remnants of primitive neural tissue surrounded by edematous connective tissue with embedded proliferated blood vessels. The lungs had fetal atelectasis, and the remaining visceral organs were immature, appropriate for gestational age. Placental samples showed regular placental tissue and amniotic membranes without pathological substrate.

Figure 1. Ultrasonography that shows the apsance of brain hemisferes, normal lateral ventricles

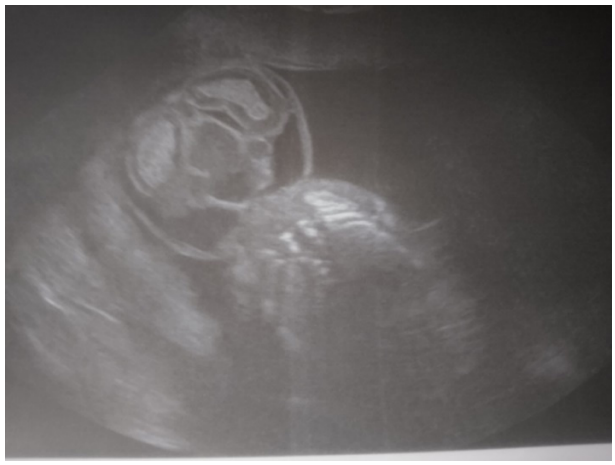
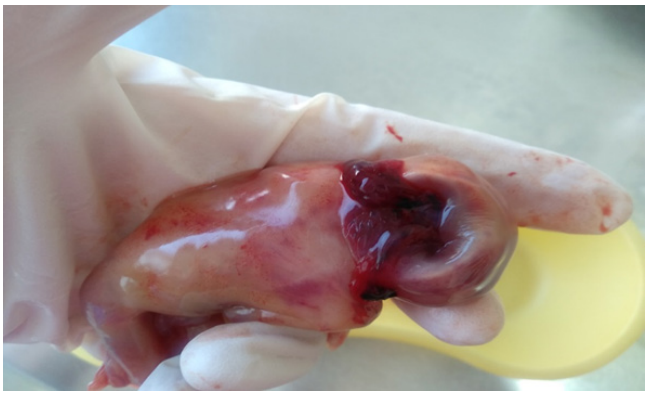


Figure 2. The aborted fetus with a large cranial defect



## DISCUSSION

Anencephaly is one of the most common anomalies resulting from a defect in the development of the neural tube and there is an absent part of the calvaria or the entire calvaria, with an absent brain. The incidence is 1-5/1000 births and mortality is 100%, intrauterine or in the first hours after birth. The cause of this malformation is unknown, but there are several risk factors such as genetic mutations and polymorphisms of certain genes, maternal diabetes, obesity, exposure to certain drugs or toxins, as well as a positive family history of neural tube defects (for example, a previous pregnancy with a fetus with anencephaly or spina bifida). The most important nutritional risk factor is folic acid deficiency, due to insufficient intake or due to polymorphisms of the gene encoding the enzyme involved in folic acid metabolism (methyltetrahydrofolate reductase - MTHFR). Some polymorphisms of this gene cause thermolability of the enzyme and its reduced enzymatic activity and these individuals need to have higher levels of folic acid in plasma to meet their needs (higher intake through food or supplements) [11].

The diagnosis of this condition is made by ultrasonography. The presence of anencephaly can be detected even in the first trimester. An important factor for an accurate ultrasound diagnosis of is gestational age. Calcification of the skull is complete by 10 weeks of gestation, and the diagnosis may be missed if the ultrasound examination is performed at a gestational age of less than 11 weeks. In ultrasound imaging, there is an absence of the upper part of the cranium and absence of brain tissue in place of the cerebral hemispheres [12]. Also, in ~ 90 % of cases of anencephaly, serum alpha-fetoprotein levels are increaed in maternal blood and also in the amniotic fluid [13].

In the second trimester of pregnancy, the “frog eyes” sign is detected by ultrasound due to the absence of the brain above the orbits. In 30-50% of cases of anencephaly, polyhydramnion is also present, due to intraamniotic leakage of cerebrospinal fluid, impaired fetal swallowing and increased urine production due to a lack of antidiuretic hormone.

Anencephaly is a lethal anomaly, so ultrasound diagnosis is essential to perform timely termination of pregnancy. Prevention of neural tube defects is also important, and most American, British and Canadian organizations recommend taking 0.4-0.8 mg/day of folic acid, and if the woman has had a previous pregnancy with this type of anomaly, the recommended dose is 4 mg/day [14].

According to the recommendations of the World Health Organization, it is necessary to take 0.4 mg of folic acid daily as a supplement to prevent the occurrence of neural tube defects, preferably one month before conception and during the first three months of pregnancy. If folic acid supplementation is started after the first trimester, it will not be effective, because the neural tube has already been formed [15]. In our case, the patient suplemented 0.4 mg of folic acid daily starting from the sixth week of gestation, which was probably late, because the critical period for the development of anencephaly and spina bifida is earlier, in the fourth week of gestation. Women with polymorphisms of genes encoding enzymes involved in folate metabolism have higher folic acid needs than other women. By enriching food with folic acid, optimal levels of folic acid in plasma cannot be achieved. Therefore, supplementation in the preconception period and in the first trimester of pregnancy is the best way to improve folic acid levels [16]. Because of the high prevalence of MTHFR genetic polymorphisms in the general population, there is a concern about reduced enzymatic activity. Newer research has focused on supplementation with L-methylfolate, as a biologicaly active form, rather than folic acid [18].

The other problem is that ~50% of pregnancies are unplanned. If women has unplanned pregnancy and not used supplements, this preventive method is inefective. At the time of the absence of menstrual cycle and pregnancy test, which is ~15 days after conception, the neural tube is preparing for closure. Food fortification with folic acid is implemented in the United States, but has not yet been introduced in European countries [16-18].

## CONCLUSION

Anencephaly is incompatible with life. The most important aspect is the prevention of its occurrence. The simplest way to reduce the incidence of anencephaly and other neural tube defects is to advise women of reproductive age to take folic acid supplements. It is important to avoid valproic acid in women with epilepsy. Fetal ultrasonography is the gold standard for detecting neural tube defects. Anencephaly should be detected as early as possible, in order to perform a timely termination of pregnancy.

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# COMBINATION OF ECHINOCOCCAL CYSTS IN THE LIVER AND SPLEEN: CASE REPORT

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## ABSTRACT

Introduction : Hydatid disease is a zoonotic parasitic infection caused by Echinococcus granulosus or Echinococcus multilocularis. It primarily affects the liver, followed by the lungs. Splenic involvement is rare, and the simultaneous presence of cysts in both the liver and spleen is exceptionally uncommon. This report describes the clinical presentation, diagnostic process, and surgical treatment of a 68-year-old woman with hydatid cysts in the liver and spleen.

Case Presentation: The patient complained of upper abdominal pain and nausea. Serological tests (ELISA) showed a high antibody titer of 1:2560, and imaging confirmed hydatid cysts in the right lobe of the liver (8x8 cm and 10x4 cm) and the spleen (7x6 cm). The patient underwent a medial laparotomy, during which cyst evacuation, pericystectomy, and cholecystectomy were performed. Postoperatively, the patient recovered well and received albendazole therapy to minimize the risk of recurrence.

Conclusion: This case highlights the importance of early recognition and a multidisciplinary approach in managing rare presentations of hydatid disease involving multiple abdominal organs.

Keywords: echinococcal cyst, liver, spleen, evacuation.

## INTRODUCTION

Hydatid disease, also known as cystic echinococcosis (CE), is a parasitic infection caused by the larval stage of Echinococcus granulosus. Humans are accidental intermediate hosts, infected by ingesting eggs shed by definitive hosts (usually dogs). The ingested eggs hatch into larvae, which penetrate the intestinal mucosa and travel through the portal circulation to the liver, the most commonly affected organ (70–80% of cases). The lungs (10–20%) are the second most frequently involved (1) while splenic involvement is extremely rare, occurring in less than 10% of cases. (2)

Simultaneous hydatid cysts in the liver and spleen represent a rare clinical condition. While hepatic cysts are usually primary due to the liver's role as the first filter for parasites, splenic cysts are often secondary due to systemic dissemination or retrograde flow through the splenic artery. This report describes the diagnostic and therapeutic challenges in managing combined hepatic and splenic echinococcosis, emphasizing the need for a multidisciplinary approach.

## CASE PRESENTATION

Patient Information

A 68-year-old woman presented to our department with a six-month history of upper abdominal pain and intermittent nausea. She denied fever, jaundice, weight loss, or changes in appetite. The patient had a previous surgical intervention (left-sided mastectomy) six years ago and had received chemotherapy and radiotherapy afterward.

Clinical Findings

On physical examination, the patient appeared well but reported mild discomfort upon palpation of the right upper quadrant. There were no palpable masses or organomegaly. The rest of the systemic examination was unremarkable.

Investigations

Laboratory Tests

Complete blood count: Within normal limits, no eosinophilia.

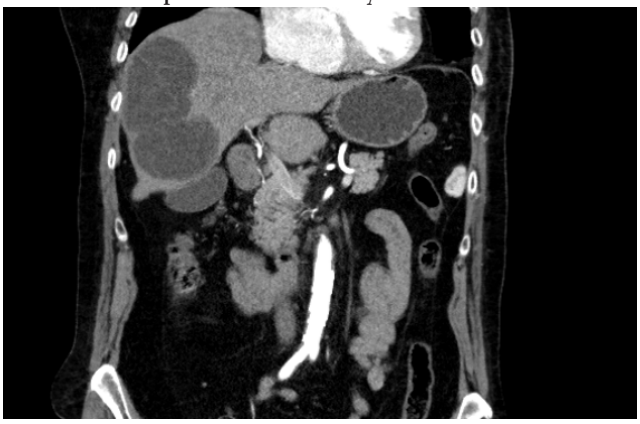
Liver function tests: Normal.

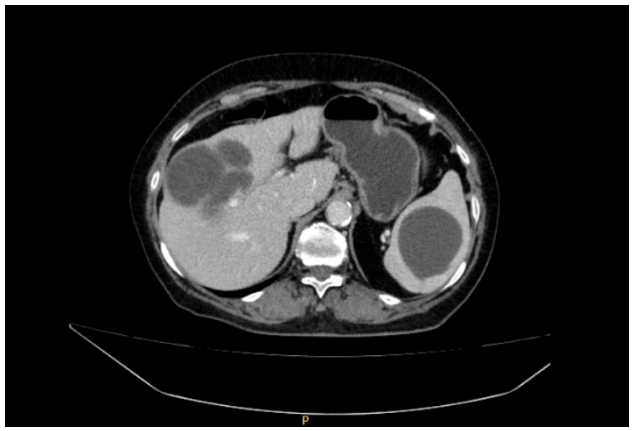
Serology: ELISA for Echinococcus antibodies was strongly positive (1:2560), supporting the diagnosis of hydatid disease.

Imaging

Ultrasound: Two hypoechoic, well-defined cystic lesions were detected in the right lobe of the liver, measuring 8x8 cm and 10x4 cm, with internal septa and "daughter cysts." A single cystic lesion of 7x6 cm was identified in the spleen.

CT scan: Confirmed the ultrasound findings and revealed thick-walled, well-encapsulated cysts with the characteristic "water lily" sign in the liver and spleen. No evidence of rupture or secondary infection.





Picture no. 1 and 2 - CT scans of the abdomen showing hydatid disease in both liver and spleen

Diagnosis

Based on clinical, serological, and imaging findings, a diagnosis of combined hepatic and splenic hydatid disease was made. Surgical intervention was indicated.

Treatment

Preoperative Preparation

Routine preoperative blood tests, including coagulation profile and renal function tests, were unremarkable.

Surgical Procedure

The patient underwent elective laparotomy with a medial incision under general anesthesia. The following steps were performed:

Cyst Evacuation:

The hepatic cysts were carefully punctured and aspirated. A 20% hypertonic saline solution was injected into the cavities to inactivate protoscoleces and then re-aspirated. The splenic cyst was treated in the same manner.

Pericystectomy:

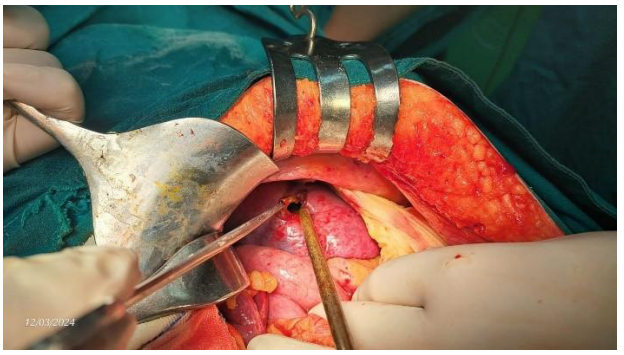
The cyst walls were excised as extensively as possible (ad maximum) while preserving vital structures.

Cholecystectomy:

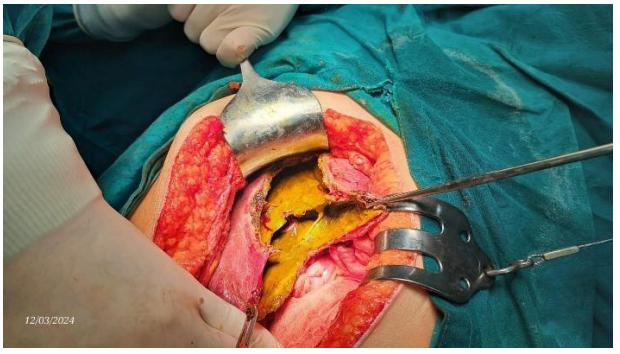
The gallbladder was removed due to incidental findings of chronic cholecystitis.

Drain Placement:

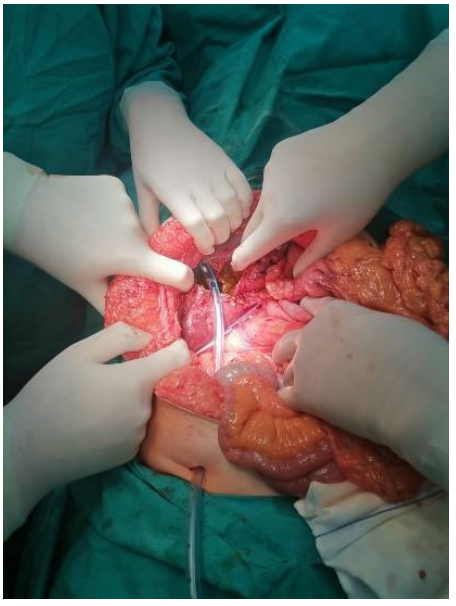
Drains were placed in the liver and splenic regions to monitor postoperative serous discharge and prevent fluid collections.



Pic no. 3 - Puncture of the hepatic cysts



Pic no. 4 – Excision ad maximum of the cyst walls



Pic no. 5 – Drain placement

Postoperative Course

The patient had an uneventful recovery:

No signs of infection or bile leakage.

Drains were removed on the fifth postoperative day after minimal discharge.

The patient was discharged on the seventh day with instructions to continue albendazole therapy for three cycles.

## DISCUSSION

Epidemiology: Hydatid disease is endemic in many parts of the world, including the Mediterranean, the Middle East, Africa, and South America. Dual involvement of the liver and spleen is uncommon, occurring in less than 5% of reported cases. (3) A study by Moro and Schantz (2009) confirmed the global distribution of Echinococcus, highlighting that liver involvement is predominant, while splenic involvement remains rare. Recent epidemiological reviews indicate that co-infection rates may be underestimated due to asymptomatic cases (McManus et al., 2012).

Pathophysiology: The liver, as the first organ in the portal circulation, acts as the primary filter for Echinococcus larvae. Splenic cysts result from secondary dissemination, either hematogenously or through retrograde arterial flow. The rarity of splenic cysts can be attributed to the spleen's dense reticuloendothelial barrier. (4) Studies such as those by Zhang et al. (2014) suggest that alternative pathways, including lymphatic spread, might play a role in rare splenic involvement, though evidence remains inconclusive compared to hepatic dissemination mechanisms.

Clinical Presentation: Patients with hepatic hydatid disease often present with non-specific symptoms such as abdominal pain, nausea, and bloating. Splenic cysts are usually asymptomatic until they become large enough to cause mass effects, including splenomegaly or pressure symptoms. (5) A comparative study by Pedrosa et al. (2000) found that hepatic hydatid cysts tend to be diagnosed earlier due to their more overt clinical manifestations, whereas splenic involvement is often incidental, the same goes for our case, where the splenic involvement was an incidental finding while doing imaging for the hepatic hydatid disease.

Diagnostic Approach: Hydatid disease is diagnosed through a combination of serological tests and imaging studies.

Serology: ELISA has a sensitivity of 85–98% for hepatic hydatid disease. However, cross-reactivity with other parasitic infections can yield false-positive results. (6) A study by Wen et al. (2019) found that immunoblotting techniques offer improved specificity over conventional ELISA in endemic regions, as we can also see in our patient, the high ELISA count was very specific.

Imaging:Ultrasound is the initial modality of choice, with characteristic findings of cystic lesions containing "daughter cysts" and hydatid sand. (7) CT and MRI are superior for assessing cyst size, wall calcification, and complications such as rupture or superinfection. Comparative imaging studies (Brunetti et al., 2010) suggest MRI provides better soft-tissue differentiation, whereas CT is more effective in detecting calcifications. In our study also CT was used, but with no calcifications found, which was also confirmed intraoperatively.

Management Strategies: Treatment depends on cyst location, size, and complications

Medical Therapy: Albendazole is effective as an adjunctive therapy but is rarely sufficient as monotherapy for large cysts. (8)A meta-analysis by Horton (2003) found that albendazole has an 80% efficacy rate in reducing cyst viability but is inferior to surgical removal in larger or complicated cysts.

Surgical Intervention: Surgery remains the mainstay for large, symptomatic, or complicated cysts. Options include cystectomy, pericystectomy, or PAIR (Puncture, Aspiration, Injection of scolicidal agent, and Reaspiration). (9) A randomized study by Giorgio et al. (2013) compared PAIR with open surgery and found that while PAIR is less invasive, it has a higher recurrence rate in liver hydatid disease. That is why we also decided on open surgery. Splenic cysts often require splenectomy due to anatomical constraints. According to Darwish et al. (2015), partial splenectomy may be a viable option to preserve splenic function, though long-term data on recurrence rates are limited.

Prognosis and Follow-up: Patients with properly managed hydatid disease have excellent outcomes, with a recurrence rate below 10% when albendazole therapy is combined with complete cyst excision. A systematic review by Eckert and Deplazes (2017) supports the importance of long-term follow-up, recommending regular imaging for at least two years post-treatment to monitor for recurrence. (10) Comparative studies indicate that combination therapy (surgery plus albendazole), which was also combined in our case, significantly reduces recurrence compared to monotherapy approaches. However, recent trials (El-On et al., 2020) suggest newer scolicidal agents may improve long-term outcomes, necessitating further research.

## CONCLUSION

Simultaneous involvement of the liver and spleen in hydatid disease is uncommon but clinically significant. Early diagnosis and surgical intervention are crucial for preventing complications such as rupture, secondary infection, or anaphylaxis. This case emphasizes the importance of a multidisciplinary approach in managing rare presentations of hydatid disease, involving infectious disease specialists, surgeons, and radiologists.

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Case report

# EMERGENCY SURGICAL MANAGEMENT OF AN INCARCERATED MORGAGNI HERNIA IN AN 85-YEAR-OLD FEMALE: A CASE REPORT

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## ABSTRACT

Morgagni hernia (MH) is an exceedingly rare form of congenital diaphragmatic hernia, often remaining asymptomatic until later in life when it may present as a surgical emergency due to incarceration or strangulation of abdominal viscera. We report the case of an 85-year-old female who presented with acute abdominal pain and vomiting. After being evaluated at multiple regional facilities without a definitive diagnosis, she was referred to our tertiary center. Computed Tomography (CT) revealed a right-sided parasternal diaphragmatic defect containing an incarcerated transverse colon. Emergency laparotomy was performed; the colon was found to be viable and was repositioned, followed by primary suture repair of the diaphragmatic defect. The patient's postoperative course was uneventful. This case highlights the importance of clinical suspicion and the gold-standard role of CT imaging in diagnosing this rare thoracoabdominal emergency in the elderly.

Keywords: Morgagni hernia, Transverse Colon Incarceration, Space of Larrey, Acute Bowel Obstruction

## INTRODUCTION

Morgagni hernia, first described in 1769 by Giovanni Battista Morgagni, is a congenital diaphragmatic defect resulting from the failure of fusion between the transverse septum of the diaphragm and the costal arches [1,2]. This defect occurs at the sternocostal hiatus, also known as the foramen of Morgagni or the space of Larrey [2,3]. While congenital diaphragmatic hernias (CDH) are relatively common in neonates, the Morgagni type accounts for only 2–5% of all CDH cases [4,5].

In adults, Morgagni hernias are frequently asymptomatic and are often discovered incidentally during imaging for unrelated conditions [1,6]. However, as patients age, increased intra-abdominal pressure—due to factors such as obesity, chronic cough, or constipation—can facilitate the herniation of abdominal organs (most commonly omentum, transverse colon, and stomach) into the thoracic cavity [3,7]. When symptomatic, patients may present with vague gastrointestinal or respiratory complaints, but acute incarceration or strangulation represents a life-threatening complication requiring immediate surgical intervention [8,9].

Diagnosing Morgagni hernia in the elderly is particularly challenging as symptoms often mimic more common conditions like pneumonia, hiatal hernia, or Chilaiditi syndrome [10]. This report details the diagnosis and emergency surgical management of a symptomatic, incarcerated Morgagni hernia in an 85-year-old patient who had previously undergone several inconclusive evaluations.

## CASE PRESENTATION

Patient History and Clinical Findings

An 85-year-old female (born in 1940) presented to the Emergency Department with a five-day history of progressively worsening epigastric pain, nausea, and persistent vomiting. The patient reported a lack of bowel movements and flatulence for 48 hours. Her medical history was notable for hypertension and chronic cardiovascular management but was otherwise unremarkable for prior abdominal trauma or surgeries.

Before her arrival at our clinic, the patient had been examined at several regional hospitals. An abdominal ultrasound (performed on April 14, 2025) noted diffuse intestinal distention and a cortical cyst on the lower pole of the kidney, but no definitive cause for the obstruction was identified. She was subsequently transferred for further diagnostic workup.

Upon admission to our facility, the patient was hemodynamically stable but appeared distressed and moderately dehydrated. Physical examination revealed a distended abdomen with significant tenderness in the epigastrium and right upper quadrant. Bowel sounds were hyperactive. Respiratory auscultation noted slightly diminished breath sounds in the right lower lung field.

Diagnostic Assessment

Initial laboratory investigations (April 16, 2025) revealed a White Blood Cell (WBC) count of 9.50 \times 10^9/L, with a slight elevation in granulocytes (73.80%). Hemoglobin was 115 g/L, and biochemistry showed a glucose level of 2.75 mmol/L and total proteins of 56 g/L, indicating mild malnutrition or acute metabolic stress.

Computed Tomography (CT) was the definitive diagnostic tool. The CT of the thorax and abdomen (April 16, 2025) revealed:

Diaphragmatic Defect: A right-sided parasternal (Morgagni) hernia.

Hernia Contents: Incarceration of the transverse colon within the right thoracic cavity, accompanied by reactive changes in the surrounding fatty tissue and a small amount of free fluid.

Secondary Findings: A concomitant hiatal hernia and chronic peribronchitic changes.

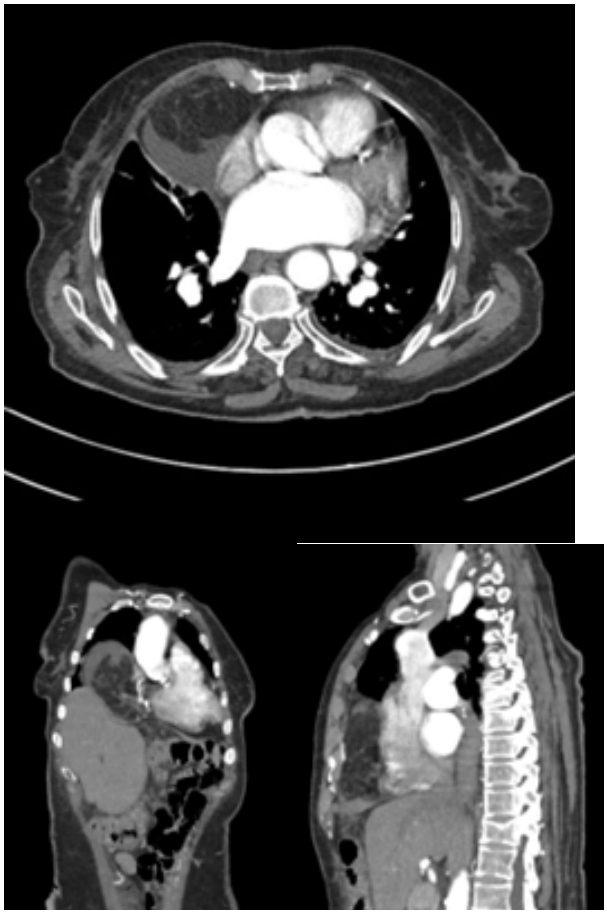

Figure 1: CT Scan (Axial, Sagittal, and Coronal projections) showing the right-sided parasternal diaphragmatic defect with incarcerated transverse colon.

The CT findings confirmed an incarcerated Morgagni hernia with secondary signs of intestinal obstruction. Given the age of the patient and the duration of symptoms, the risk of bowel ischemia was high, and the decision for emergency surgical intervention was made.

Surgical Intervention

The patient underwent an emergency exploratory midline laparotomy. Upon entering the abdominal cavity, the hernia was localized to the right parasternal region. The hernia sac contained a segment of the transverse colon that was tightly incarcerated within the diaphragmatic defect.

Intraoperative Findings:

The incarcerated transverse colon was carefully reduced back into the abdominal cavity.

The bowel tissue was edematous and congested but showed immediate improvement in color and peristalsis upon release.

Following warm saline application and observation, the tissue was deemed viable; therefore, no bowel resection was required.

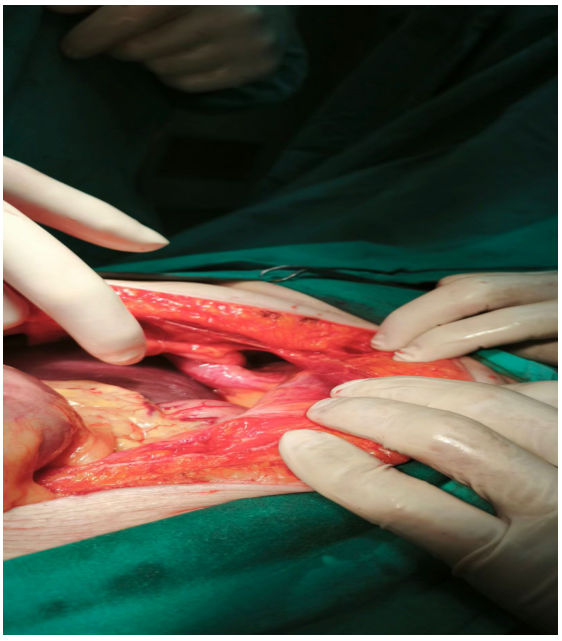

Figure 2: Intraoperative image showing the diaphragmatic sac before reduction and repair.

Defect Repair: The diaphragmatic defect (foramen of Morgagni) was repaired using primary interrupted non-absorbable sutures. No prosthetic mesh was utilized due to the emergency nature of the case and the adequate quality of the diaphragmatic tissue for primary closure.

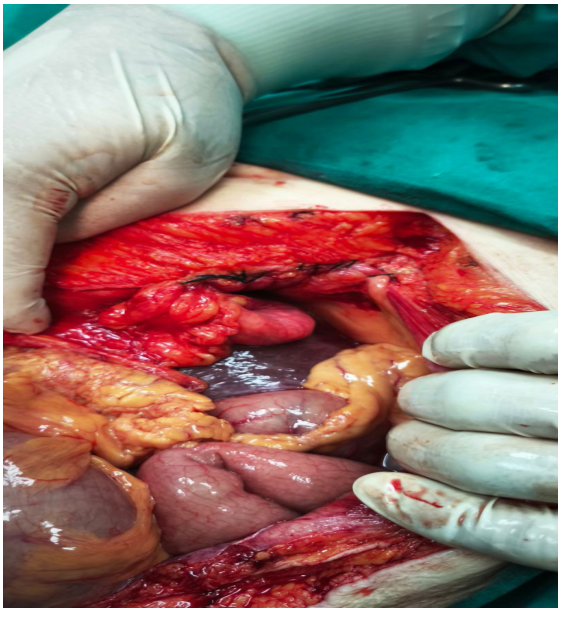

Figure 3: Intraoperative image showing the diaphragmatic defect after successful suture repair.

A didactic appendectomy was performed as per clinical protocol in this specific operative context. The abdominal cavity was lavaged, and the operative wound was closed in layers.

Postoperative Course and Outcome

The patient's postoperative recovery was stable and uneventful. She received prophylactic anticoagulant therapy (Clexane 40mg) and analgesia (Tramadol/Paracetamol). She was started on a gradual oral diet, which she tolerated well. The patient was discharged on the sixth postoperative day (April 22, 2025) with instructions for a hygiene-dietary regimen and follow-up consultation.

## DISCUSSION

Pathophysiology and Epidemiology

Morgagni hernias occur through the "space of Larrey," a triangular area of weakness between the sternal and costal attachments of the diaphragm [1,11]. While 90% of these hernias occur on the right side—likely because the liver provides a mechanical barrier on the right while the heart and pericardium protect the left—bilateral or left-sided cases (Larrey hernias) are occasionally reported [12,13].

The rarity of this condition in adults often leads to diagnostic delay. In our patient's case, she had visited multiple facilities without a precise diagnosis, highlighting that Morgagni Hernia is rarely considered as a primary differential for acute abdomen in the elderly [14].

Diagnosis

While plain chest X-rays can sometimes suggest the diagnosis by showing air-fluid levels in the mediastinum, CT is considered the gold standard [15,16]. In the acute setting, CT accurately identifies the site of the defect, the specific organs herniated, and signs of complication such as incarceration, volvulus, or strangulation [1,15]. In our case, CT was instrumental in differentiating the condition from Chilaiditi syndrome and standard hiatal hernias [10,17].

Surgical Management

Surgical repair is mandatory for all diagnosed Morgagni hernias, even in asymptomatic patients, due to the persistent risk of bowel incarceration [12,18]. The transabdominal approach is generally preferred in emergency settings as it allows for easier reduction of the

contents and direct assessment of bowel viability [1,19].

While many surgeons now favor laparoscopic repair for elective cases, open laparotomy remains the standard approach in emergency situations with suspected bowel compromise [9,20]. In this patient, primary suture repair provided a secure closure without the need for prosthetic mesh, which is often avoided in emergency or potentially contaminated fields [21,22].

## CONCLUSION

Morgagni hernia represents a significant diagnostic challenge in the geriatric population, where clinical symptoms are often vague or attributed to more frequent cardiopulmonary and gastrointestinal conditions. This case illustrates the "diagnostic trap" of Morgagni hernia, as the patient underwent multiple evaluations at regional facilities without a definitive diagnosis until reaching a tertiary center.

Several key conclusions can be drawn from this clinical experience:

The Diagnostic Role of MDCT: In an era of advanced imaging, multi-detector computed tomography (MDCT) with multiplanar reconstructions remains the gold standard. It is indispensable for differentiating Morgagni hernia from Chilaiditi syndrome or pleuropericardial cysts, and for identifying signs of incarceration that mandate immediate surgical intervention.

Emergency Management vs. Elective Approach: While laparoscopic repair is the preferred choice for elective cases, this case confirms that open midline laparotomy remains a safe and effective approach in the emergency setting. It provides the necessary exposure to evaluate bowel viability and perform primary repair without the inherent risks of increased intra-abdominal pressure associated with pneumoperitoneum in a potentially compromised elderly patient.

Primary Suture Repair: In emergency repairs involving incarcerated bowel, primary interrupted suture closure is a viable alternative to prosthetic mesh, particularly when the diaphragmatic edges are healthy and the risk of infection or tissue edema is present.

In summary, a high index of clinical suspicion followed by prompt radiological verification and timely surgical intervention are the cornerstones of successful management. Despite the patient's advanced age of 85, the excellent postoperative outcome emphasizes that emergency surgery for Morgagni hernia is well-tolerated and life-saving when performed before the onset of irreversible bowel necrosis.

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Case report

# POSTERIOR MYOCARDIAL INFARCTION, EARLY DIAGNOSIS AND APPROPRIATE TREATMENT. A CASE REPORT

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## ABSTRACT

Introduction Posterior myocardial infarction (PMI) is often misjudged (one of the most frequently missed) and this can lead to inadequate treatment. The clinical presentation of PMI is not different from other myocardial infarctions, but the absence of "traditional" electrocardiographic signs of infarction, such as ST-segment elevation, can lead to errors or delays in diagnosis.

Case Report: A 68-year-old man was admitted to our clinic with chest pain that began 8 hours before admission and increased in intensity over the last 2 hours. He reported a history of hypertension but was not taking regular antihypertensive medication. Family history was positive for coronary artery disease; his father had an acute myocardial infarction. The patient was a former smoker who quit 10 years earlier. Based on ECG changes and the clinical picture, coronary angiography was performed and a stent was placed in the circumflex artery. The patient was discharged home in overall improved condition.

Conclusion: Transmural infarction of the posterior wall is the most commonly misdiagnosed condition when interpreting a 12-lead electrocardiogram. This case report therefore emphasizes the importance of posterior leads in diagnosing acute posterior myocardial infarction and the value of early reperfusion in STEMI patients, thereby reducing adverse outcomes in these patients.

Keywords: Posterior myocardial infarction; posterior ecg leads; coronary revascularisation; STEMI

## INTRODUCTION

Acute posterior myocardial infarction (PMI) is a rare but clinically significant presentation of acute coronary syndrome in which ischemia or infarction primarily affects the posterior (inferobasal) wall of the left ventricle, typically due to occlusion of a dominant right coronary artery or a circumflex branch. Because normal 12-lead electrocardiography (ECG) is less sensitive for posterior wall injury, PMI is frequently misdiagnosed or detected late, delaying reperfusion therapy and worsening outcomes. Awareness of its unusual ECG symptoms and quick use of supplementary diagnostic techniques are thus critical. [1,2]

Clinically, patients with posterior MI may present with chest pain similar to other STEMI presentations, but they may also have atypical symptoms and subtle ECG changes, most notably horizontal ST depression and tall R waves in anterior leads (V1-V3) that are the mirror

image of posterior ST elevation. To detect posterior wall motion anomalies, diagnostic confirmation typically requires posterior leads (V7-V9), additional leads, serial ECGs, cardiac biomarkers, and, in many cases, imaging (echocardiography or cardiac MRI). Rapid detection informs immediate reperfusion methods (primary PCI or thrombolysis when PCI is unavailable), as well as customized secondary prophylaxis. [2,3]

Individual instances with acute PMI are nonetheless worth reporting since clinical detection can be difficult, presentation might vary, and therapy decisions are based on sophisticated interpretation of ECG and supplementary tests. Case studies help to medical education by displaying diagnostic errors, demonstrating the utility of posterior leads and imaging, and emphasizing the consequences of early versus delayed reperfusion. The purpose of this case report is to describe the clinical presentation, diagnostic method, therapy, and outcome of a patient with acute posterior MI, as well as to address lessons gained for improved recognition and treatment in future practice. [4,5,6,7]

## CASE REPORT

A 68-year-old male presented to our clinic with chest and back pain. The symptoms began 8 hours before admission and intensified over the last 2 hours. He reported a history of hypertension but was not taking regular antihypertensive therapy. Family history was positive for coronary artery disease; his father had an acute myocardial infarction. The patient was a former smoker who quit 10 years ago. Review of systems was unremarkable except for hypertension with blood pressure 170/100 mmHg. A 12-lead ECG was performed immediately, showing ST-segment depressions in V1–V4 (Figure 1).

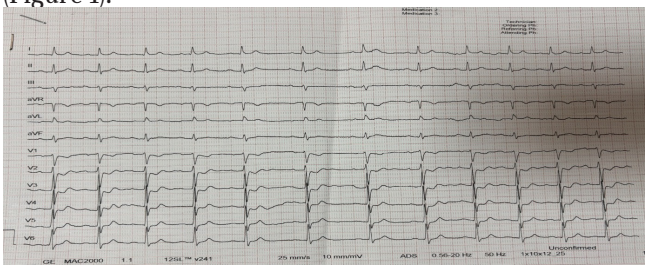

Figure 1. ST-segment depressions in V1–V4

The patient was hospitalized in the emergency cardiology unit and an interventional cardiologist was consulted because of the ECG changes and chest pain. On the interventional cardiologist's recommendation, a control ECG with posterior leads V7–V9 was performed, which showed ST-segment elevation in V7–V9 (Figure 2).

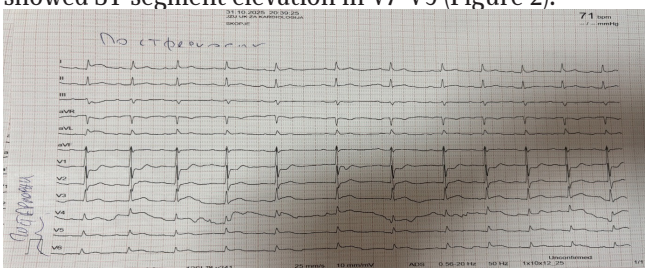

Figure 2. ST-segment elevation in posterior leads V7–V9

The patient was given 300 mg aspirin, 60 mg prasugrel, rosuvastatin 40 mg, and a 7,500 IU IV bolus of unfractionated heparin. The need for coronary angiography was explained and the patient provided informed consent. He was immediately taken to the cardiac catheterization laboratory; coronary angiography showed 100% occlusion of the mid-circumflex artery. A stent was placed in the corresponding coronary artery (Figures 3–5).

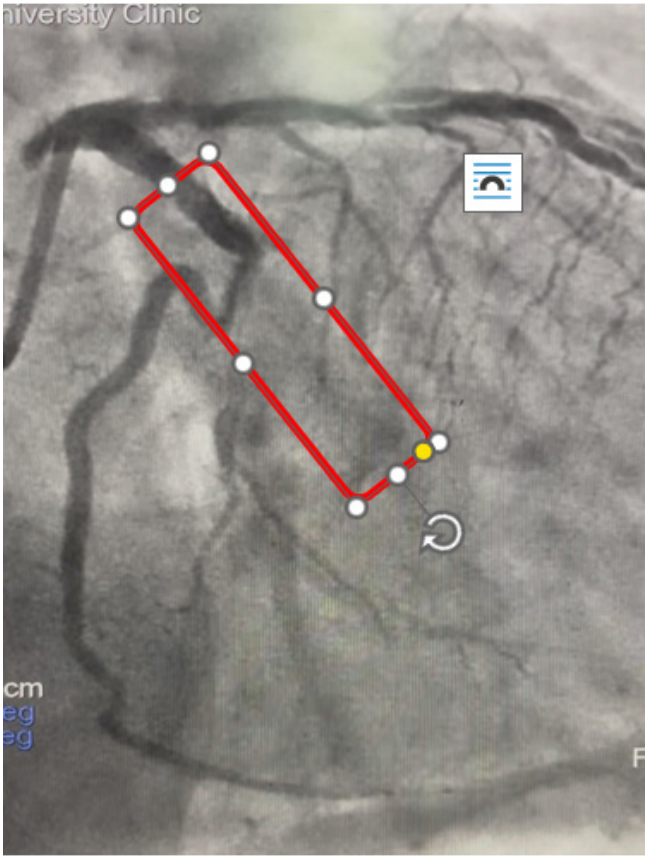


Figure 3. Total occlusion of Om1 artery 100%

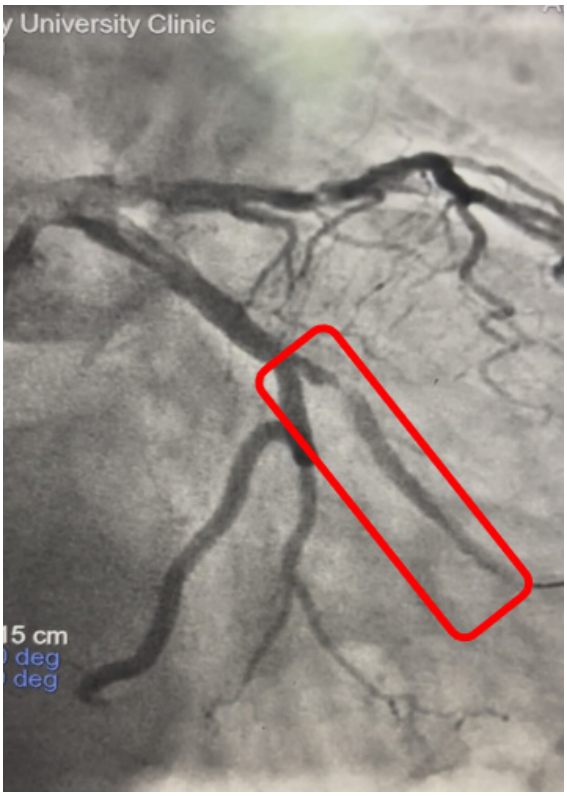


Figure 4 After wiring the artery

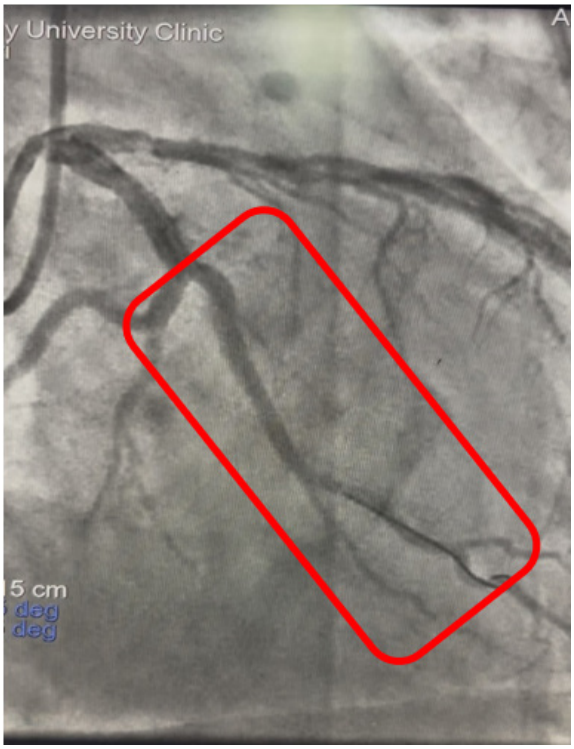


Figure 5. After stenting OM1 (timi 3 flow)

During hospitalization blood tests were taken several times; only troponins were elevated. Echocardiography showed hypokinesis of the apex of the left ventricle and the infero-posterior wall with an ejection fraction of 46%.

The patient was discharged home in overall good condition and hemodynamically stable on the following medications:

- Acetylsalicylic acid (aspirin) 100 mg once daily
- Prasugrel 10 mg once daily
- Rosuvastatin 40 mg once daily
- Perindopril 4 mg once daily
- Spironolactone 25 mg once daily
- Dapagliflozin 10 mg once daily

## DISCUSSION

Acute posterior myocardial infarction (PMI) remains a diagnostic and therapeutic challenge because its classic findings are not well represented on the standard 12-lead electrocardiogram (ECG). The case described illustrates several typical features and pitfalls: non-specific anterior ST-segment depression and tall R waves in V1–V3 that represent the mirror image of posterior ST elevation. These findings underscore why PMI can be missed or misclassified as ischemia of the anterior wall or as non-ST-elevation acute coronary syndrome, potentially delaying reperfusion.

Electrocardiographic recognition is critical to rapid diagnosis. Horizontal ST depression and significant R waves in the right precordial leads should urge quick investigation into posterior involvement and the acquisition of real posterior leads (V7-V9). Posterior leads improve sensitivity for detecting ST-elevation equivalents and can convert ambiguous ECGs into unequivocal STEMI diagnosis, leading an urgent reperfusion approach. Serial 12-lead ECGs are helpful for detecting changes over time. PMI outcomes are determined by the extent of the infarct, the timing of reperfusion, and the existence of comorbidities such as arrhythmia, heart failure, or mechanical defects. Delayed or delayed diagnosis might lead to an increase in infarct size and affect short and long term results. Early detection with posterior leads, rapid reperfusion, and optimum secondary prophylaxis (antiplatelet therapy, statin, beta blocker, ACE inhibitor/ARB, lifestyle adjustment) can improve recovery and reduce adverse effects. Amit Agarwal et al. (1999) provided early evidence

supporting the importance of posterior leads, demonstrating that the addition of posterior chest leads significantly improves diagnostic sensitivity for myocardial infarction in patients with ischemic symptoms and nondiagnostic 12-lead ECG findings. Their findings revealed that many individuals with posterior infarction exhibit ST-segment depression in the anterior leads rather than conventional ST elevation. [4]

Subsequent studies further emphasized the diagnostic value of posterior leads. CheukKit Wong (2011) showed that ST-segment elevation in leads V7, V8, and V9 is particularly useful in identifying isolated posterior myocardial infarction. In that study, ≥0.5 mm ST-segment elevation in posterior leads significantly improved detection of posterior STEMI, underscoring that posterior infarction may remain undetected if only standard leads are recorded. [5]

More recent clinical observations also support routine use of an extended ECG. A case series by Mochamad Yusuf Alsagaff et al. (2022) demonstrated that isolated posterior STEMI can present with a nondiagnostic 12-lead ECG and may only become apparent when posterior leads are recorded. Their findings reinforce the concept that a 15-lead ECG (12 standard leads plus V7–V9) should be considered in patients with persistent ischemic symptoms and inconclusive ECG findings. [8]

Additional insights into ECG patterns suggestive of posterior coronary occlusion have been described by H. Pendell Meyers et al. (2021) in the Journal of the American Heart Association. Their study demonstrated that ischemic ST-segment depression maximal in leads V1–V4, rather than V5–V6, is highly specific for occlusion myocardial infarction rather than non-occlusive ischemia. This pattern represents the reciprocal manifestation of posterior wall injury and should be recognized as a potential STEMI equivalent requiring urgent reperfusion therapy. [9]

## CONCLUSION

Posterior myocardial infarction is often missed on a typical 12-lead ECG, potentially delaying diagnosis and treatment. This instance highlights the necessity of recording posterior leads (V7-V9) in patients with ischemia symptoms and nondiagnostic ECG abnormalities, as they can indicate ST-segment elevation, indicating a STEMI equivalent. Early detection enabled fast activation of the catheterization laboratory and immediate PCI, resulting in successful reperfusion. This case highlights the importance of systematic use of posterior leads and rapid reperfusion in avoiding treatment delays and improving clinical outcomes in posterior myocardial infarction, which is consistent with the European Society of Cardiology's 2023 ESC Guidelines for the management of acute coronary syndrome.

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# CLINICAL PRESENTATION AND MANAGEMENT OF AMYOPATHIC DERMATOMYOSITIS WITH POLYRADICULONEUROPATHY: A RARE CASE REPORT

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## ABSTRACT

Amyopathic Dermatomyositis (ADM) is a rare (10-20%) subtype of dermatomyositis, an inflammatory disease primarily affecting the skin and muscles. Women are more affected than men (2:1). Polyradiculoneuropathy (PRN) is a condition that affects the nerve roots and peripheral nerves, causing weakness, loss of reflexes, sensory disturbances, and pain, with an incidence of 1-2 cases/100,000 people annually.

The patient, a 62-y/o female, reported several months ago the onset of weakness, pronounced fatigue, and the appearance of redness in the facial area, chest, spine and extremities. Upon admission, erythematous and livid plaques, infiltrated in the aforementioned regions. Laboratory analysis revealed increased sedimentation, reduced erythrocytes and hemoglobin, with all other findings, including tumor markers and thyroid status, within normal reference values. Immunological tests showed the following results: RF-3.5, CRP-7.5, Anti-CCPNegative, Anti-dsDNA-Negative, Anti-SSA/Ro-Negative, Anti-SSB/La-Negative, Antiproteinase (PPP3)-Negative, Anti-Scl70-Negative, Anti-Centromere B-Negative.

Electromyography (EMG) indicated generalized lesions of the peripheral motor neuron of mild axonal type. A computed tomography (CT) scan of the chest and abdomen showed findings of mediastinal and hilar lymphadenopathy, with all other results within normal findings. A skin biopsy was performed, which supported the presence of cutaneous changes associated with systemic disease, including dermatomyositis.

The patient was treated with corticosteroid therapy (methylprednisolone 120 mg for 10 days, followed by 100 mg for 4 days), vitamin therapy (Amp. Vit B1, Vit B6, Vit C), and gastroprotective therapy (Tbl. Pantoprazole 40 mg), improvement in the dermatological status was noted, and the patient was transferred to the Neurology Clinic for further treatment.

Key words: Amyopathic Dermatomyositis, Polyradiculoneuropathy, Inflammatory Disease, Muscle Weakness and Corticosteroid Therapy

## INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) represent a complex spectrum of systemic, immune-mediated disorders with potential multi-organ impact, extending beyond skeletal muscles to affect organs such as the skin [1]. Within this category, amyopathic dermatomyositis is characterized by hallmark cutaneous manifestations—such as Gottron's papules, heliotrope rash, and poikiloderma—occurring in the absence of muscular involvement [2,3]. Although rare, with an incidence

estimated at two cases per million individuals, amyopathic dermatomyositis constitutes between 2% and 21% of dermatomyositis cases [4]. This condition can exhibit systemic involvement, with interstitial lung disease (ILD) developing in approximately 13% to 65% of patients, often progressing rapidly and severely [5]. Notably, cases of rapid ILD progression are associated with the presence of serum antibodies against melanoma differentiation-associated protein 5 (MDA5) [6, 11]. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) criteria provide the only validated classification system for IIMs, including amyopathic dermatomyositis [10, 12].

Reports also document occurrences of dermatomyositis alongside polyneuropathy, a presentation termed "neuromyositis"[7]. However, in numerous cases, neuropathic symptoms were undetectable during the patient's life, with diagnosis only confirmed post-mortem, which limits prospective clinical insights into such syndromes. Thus, the interplay between peripheral neuropathy and inflammatory muscle diseases remains insufficiently elucidated.

First-line treatment for DM typically involves corticosteroids, often in combination with intravenous immunoglobulin (IVIG), methotrexate, azathioprine, or mycophenolate mofetil [5]. The pathophysiology of the disease is multifactorial and involves autoantibodies, genetic factors, and environmental influences [4].

Autoantibodies play a central role in DM pathogenesis, with two main categories: myositisspecific antibodies (MSAs) specific to myositis and myositis-associated antibodies (MAAs) found in various connective tissue disorders [6]. MSAs are increasingly being recognized for their prognostic value because of their correlation with distinct clinical phenotypes [4]. One such MSA is anti-transcriptional intermediary factor 1 gamma (TIF1-γ), which has been associated with an elevated risk of malignancy [7].

In this study, we report the case of a patient with ADM with concurrent peripheral neuropathy who was positive for anti-TIF1-γ antibodies without malignancy. In addition, we present a systematic review of the clinical characteristics of DM patients with anti-TIF1 antibodies.

## CASE PRESENTATION

We present here a 62-y/o female, reported several months ago the onset of weakness, pronounced fatigue, and the appearance of redness in the facial area, chest, spine and extremities. Upon admission, erythematous and livid plaques, infiltrated in the aforementioned regions. The patient reports the onset of fatigue and pronounced tiredness a few months prior. The condition progressed with severe itching all over the body and difficulty breathing. A biopsy (No. 23323) was taken on 20.03.2024, revealing findings indicative of cutaneous changes associated with systemic diseases, including Dermatomyositis. Hospital admission for further treatment was indicated. Upon admission, the patient was afebrile, conscious, communicative, oriented in space, time, and person, with a normal status across organs and systems.

- Dermatologic Status: Upon admission, erythematous plaques, some infiltrated, were noted on the limbs, upper back, neck, and chest, with more pronounced presence around the elbows, knees, and the backs of the hands (Gottron's sign). Facial erythema was present.
- Routine and extended laboratory tests were performed with the following results: Blood counts from 07.05.2024 to 14.05.2024 showed SE 49-41, Er 3.93-3.97, Leu 4.3-3.18, Hgb 117-119, Hct 0.344-0.353, MCV 87-88, MCH 29.9-30, MCHC 34.2-33.7, Plt 239-248. Differential blood counts included Neu 78-68%, Lym 17-16%. Glucose levels (Gluc) were 10-5.1. Additional analyses showed normal urea (4.2-4.9), creatinine (49-50), total bilirubin (3.8-4.3), direct bilirubin (2.3-2.4), indirect bilirubin (1.5-1.9), protein status (Alb 35-36, TP 64-66, Glob 29-30), enzyme status (AST 40-32, ALT 22-16, LDH 246-236, CK-MB 17-18, CK 163-222), and immunological markers (CRP 10.35-3.43). Lipid status: Trig 1.12, Chol 4.9, HDL 1.52, LDL 2.8. Electrolyte status: Fe 16.6-14.3. Tumor markers: Ca 125 13, Ca 19-9 14.96, CEA 0.218, AFP 2.75, Homocysteine 10.45. Anemia markers: B12 284.2. Hormonal status: ATG 1.9, T4 107.6, T3 1.42, TSH 2.20, a-TPO <28.
- Immunological Tests at the Rheumatology Clinic: RF 3.5, CRP 7.5, Anti-CCP negative, Anti-dsDNA negative, Anti-SSA/Ro negative, Anti-SSB/La negative, Anti-proteinase-PR3 (ANCA) negative, Anti-Scl 70 negative, Anti-centromere B (CENP-B) negative.
- Consultation at Rheumatology Clinic: Neurological exam, EMG, potential muscle biopsy, colonoscopy, gynecological exam, and CT of the lungs and abdomen were indicated to rule out paraneoplastic syndrome.
- Neurological Exam: Cranial nerves intact. Reflex

responses were normal. Muscle tone intact. No asymmetry noted when placing limbs in position. Gowers sign could not be tested (the patient was cooperative).

- EMG with Neurography: Normal neurographic findings. No spontaneous denervation activity observed. Mild neuropathic changes were noted in the amplitude of all examined muscles, with slight reduction in the innervation sample. No convincing signs of myopathic changes in the amplitude were observed. The findings suggest a generalized mild axonal peripheral motor neuron lesion. Further tests (pulmonary X-ray, cardiology exam, and paraneoplastic syndrome panel) are indicated.
- Pulmonary X-ray: No convincing signs of fresh consolidation in the lung parenchyma.
- Sinuses clear. Heart size within normal limits on X-ray.
- Cardiology Exam: Patient is hemodynamically and rhythmically stable. Blood pressure 170/100, ECG shows sinus rhythm, frequency 100/min, with a left-axis deviation. Old progression of the R wave observed in anterior leads, with a normal ST segment and T wave.
- Hematology Consultation: Blood count with differential smear, revealed no indication (lymph nodes) for puncture at the moment.
- CT of Thorax: Visualized lung parenchyma with normal attenuation and architecture bilaterally. No signs of alveolar opacities, collapse, consolidation, or lung mass. Thickened costal pleura and residual adhesive changes laterobasally in DLL. Trachea and bifurcation appear normal. Bronchi not thickened, and no bronchiectasis noted. Heart shows normal size and shape. No pleural or pericardial effusion. Thoracic aorta without focal aneurysmal dilation or dissection. Pulmonary arteries of normal caliber without intraluminal filling defects. Morphologically altered and reactive lymph nodes up to 10 mm in the short axis, prevascular, bilaterally paratracheal, aortopulmonary, subcarinal, and bilaterally hilar. Soft tissues and bones unremarkable. Impression: 1. Mediastinal and hilar lymphadenopathy. 2. No active parenchymal condition.
- CT of Abdomen: Liver without defects, spleen and pancreas normal. Adrenals clear. Kidneys with preserved parenchyma, with a left parapelvic cyst measuring 35 mm. Urovesical region without endomasses. Uterus with calcified myoma. No free fluid or enlarged lymph nodes in the abdomen or pelvis. Aorta and iliac arteries show some atheromatous plaques. Skeleton with moderate degenerative changes.

The patient received parenteral corticosteroid therapy (amp. Lemod solu 120 mg) for 10 days, followed by amp. Lemod solu 100 mg for 4 days, as well as gastroprotective and vitamin therapy.

The patient was transferred to the Neurology Clinic for further treatment.

## DISCUSION

The patient's initial presentation and course during hospitalization suggest a complex, systemic disease with dermatologic and potential rheumatologic involvement. Her symptoms began with fatigue and progressed to widespread erythematous plaques, notably on the face, upper back, neck, and limbs, which is characteristic of dermatomyositis. Additionally, Gottron's papules, a diagnostic sign, were present, strengthening the suspicion of this inflammatory myopathy. Findings necessitates ongoing surveillance, as dermatomyositis can sometimes coexist with or indicate an underlying malignancy.

A thorough immunological assessment at the Rheumatology Clinic revealed no evidence of specific autoantibodies like Anti-dsDNA, Anti-SSA/Ro, and Anti-CCP, which are often elevated in other autoimmune conditions. The negative results help narrow down the differential diagnoses, making a primary diagnosis of dermatomyositis more likely. However, ongoing monitoring for signs of paraneoplastic syndrome is prudent, given her age and systemic manifestations.

Patients with dermatomyositis are more likely to develop cancer if they are positive for antitranscriptional intermediary factor 1 (TIF1) antibodies than if they are negative (HR 3.4 (95% CI 2.2–5.4)), according to the results of a UK study of 263 patients [8]. During a 10-year follow-up period, cancer occurred exclusively within a 3-year window either side of diagnosis in anti-TIF1 antibody-positive patients and was most common in patients over the age of 39. Patients with anti-TIF1 antibodies also had a higher risk of ovarian cancer than those without (19% of cancers versus 2% of cancers, respectively; $P < 0.05$) [9].

Neurological assessment, including EMG and

neurography, indicated mild neuropathic changes but did not reveal significant myopathic features, which are sometimes expected in dermatomyositis. This atypical finding, along with the lack of spontaneous denervation, suggests either an early or mild form of the disease or a mixed presentation involving peripheral neuropathy [13].

Cardiological evaluation highlighted elevated blood pressure and a sinus rhythm with a leftaxis deviation on ECG, which may be unrelated to her primary illness but warrants management and observation, as cardiac involvement can sometimes accompany dermatomyositis [14, 15]. The patient's corticosteroid therapy led to symptomatic improvement, which further supports an inflammatory etiology. However, given her broad range of symptoms and atypical findings, a multidisciplinary approach—including neurology, rheumatology, dermatology, and oncology consultations—remains essential for comprehensive management. Continued monitoring for potential malignancy, as well as adjustment of immunosuppressive therapy, will be critical to her long-term care plan.

## CONCLUSION

In conclusion, the patient presents with a likely diagnosis of dermatomyositis, as suggested by her characteristic dermatologic symptoms, including Gottron's sign, systemic inflammation, and improvement with corticosteroid therapy. Although specific autoantibodies were not detected, her presentation aligns with an inflammatory myopathy. The presence of mediastinal and hilar lymphadenopathy without evidence of malignancy raises the possibility of paraneoplastic syndrome, necessitating continued surveillance.

Neurological evaluation revealed mild peripheral neuropathy, while cardiological findings, including hypertension and left-axis deviation, require ongoing management. Given the complexity and systemic nature of her condition, a multidisciplinary approach is essential, with further immunosuppressive therapy and close monitoring for potential underlying malignancy forming key components of her care.

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# PROGRESSIVE HEARING LOSS IN PATIENT WITH VESTIBULAR SCHWANNOMA: A CASE REPORT

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## ABSTRACT

Vestibular schwannoma (acoustic neuroma) is a benign, slow-growing tumor arising from the Schwann cells of the vestibular division of the vestibulocochlear nerve and is the most common neoplasm of the cerebellopontine angle. Treatment options include observation with serial magnetic resonance imaging (MRI) and audiological monitoring, microsurgery, and stereotactic radiosurgery.

We present the case of a 32-year-old female patient with vestibular schwannoma who chose conservative management using a "wait-and-scan" approach with serial MRI and audiological follow-up. Initial contrast-enhanced MRI revealed an 8 × 3 mm mass in the internal auditory canal. During the 3-year follow-up period, despite stable tumor size on MRI, the patient experienced progressive hearing deterioration, ultimately reaching profound hearing loss. This case highlights the potential discordance between radiological stability and functional outcomes. Treatment decisions should therefore be made very carefully, taking into account the risks and potential complications of microsurgery and Gamma Knife radiosurgery.

Keywords: vestibular schwannoma, acoustic neuroma, hearing loss, magnetic resonance imaging

## INTRODUCTION

Vestibular schwannoma (VS), or acoustic neuroma as it was formerly known, is a benign tumor that develops from the Schwann cells of the vestibular division of the vestibulocochlear nerve. It accounts for 8% of all intracranial tumors and is the most common neoplasm of the cerebellopontine angle in adults [1]. The annual incidence of VS ranges from approximately 3.0 to 5.2 per 100.000 [2]. The natural history of VS growth is enigmatic. The tumor may grow continuously or only to a certain size, followed by stagnation or even shrinkage. Progressive growth in the cerebellopontine angle will eventually lead to compression of the brain stem and/or the cerebellum, occlusion of the fourth ventricle, and subsequently incarceration [3]. The typical clinical presentation includes unilateral sensorineural hearing loss, tinnitus, and balance disturbances. Tumor growth is associated with deterioration in hearing and speech

discrimination and tumor volume had a greater effect on these audiometric measures when initial auditory function was worse [4]. However, there is evidence of deterioration in hearing thresholds and speech recognition scores irrespective of tumor growth [5]. Treatment options include observation with serial magnetic resonance imaging (MRI) scanning and audiological monitoring, microsurgery, and stereotactic radiosurgery. Hearing preservation is prioritized in select cases using middle cranial fossa or retrosigmoid approaches, while translabyrinthine surgery is preferred for larger tumors or disabling dizziness. Stereotactic radiosurgery offers a non-invasive alternative but has variable long term hearing outcomes and potential tumor regrowth [6].

This report describes a rare case of vestibular schwannoma in young patient who chose "wait and scan" strategy and exhibited progressive hearing loss despite stable tumor size. The protocol number of Ethical approval is 1257/2026.

## CASE PRESENTATION

A 32-year-old female patient presented with sudden hearing loss in the left ear and tinnitus. She also reported transient weakness on the left side of the face during the four weeks prior to admission. The initial audiological evaluation included pure tone audiometry, tympanometry, distortion product otoacoustic emissions, and speech audiometry. Pure tone audiometry demonstrated severe sensorineural hearing loss in the left ear and normal hearing in the right ear. Additional findings in the left ear included a type A tympanogram, present otoacoustic emissions (Figure 1), and a rollover phenomenon on speech audiometry. The word recognition score (WRS) decreased as the intensity of the speech stimuli increased, suggesting retrocochlear pathology; however, accurate determination of the maximum WRS was not possible because the upper intensity limit of the speech stimuli had been reached.

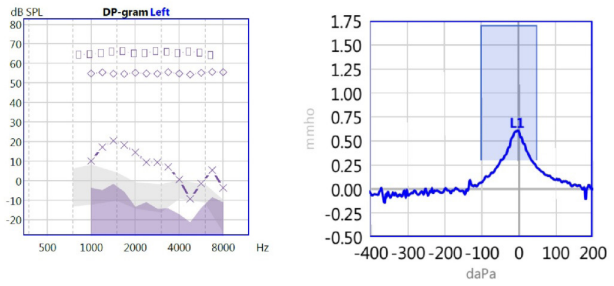


Figure 1. Left ear DP-gram and tympanogram

Enhanced cranial MRI with gadolinium-based contrast revealed an 8 × 3 mm mass within the internal auditory canal, suggestive of a vestibular schwannoma. The tumor was intracanalicular, without extension into the cerebellopontine angle, corresponding to Koos grade I. MRI scans obtained 2 and 3 years after diagnosis demonstrated an unchanged tumor size of 8 mm, measured by the largest diameter (Figure 2).

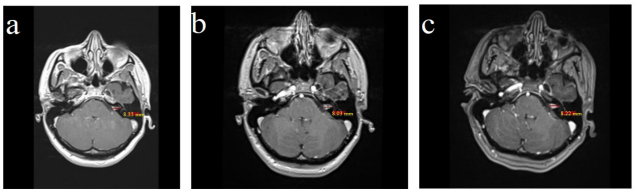


Figure 2. MRI scan: a) initial, b) 2 years after diagnosis, c) 3 years after diagnosis

Despite stable tumor size on serial MRI, the patient exhibited progressive hearing deterioration, eventually reaching profound hearing loss (Figure 3). During the initial audiological assessment, the pure tone average (PTA), calculated at 500, 1000, 2000, and 4000 Hz, was 86 dB HL. Although the hearing threshold corresponded to non-serviceable hearing by standard criteria, residual functional hearing persisted, as reflected by relatively preserved speech discrimination. After 6 months, the PTA worsened to 100 dB HL, and 3 years after diagnosis, hearing further deteriorated to 108 dB HL.

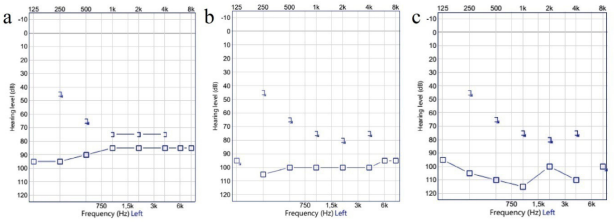


Figure 3. Audiograms: a) first examination, b) after 6 months, c) 3 years after diagnosis

The patient chose a "wait-and-scan" strategy instead of active treatment. She was informed about the available treatment options, including stereotactic radiosurgery and microsurgery, as well as the possible complications associated with these interventions.

## DISCUSSION

Vestibular schwannoma is a slow-growing benign tumor typically presenting with unilateral sensorineural hearing loss, tinnitus, and occasionally vestibular symptoms. Although hearing impairment has traditionally been linked to tumor size and growth, this relationship is inconsistent. The present case demonstrates progressive hearing deterioration despite stable tumor size, highlighting a discordance between radiological stability and functional deterioration.

Management strategies have increasingly shifted toward a conservative "wait-and-scan" approach in selected patients, supported by current European Association of Neuro-Oncology recommendations. MRI with gadolinium contrast-enhanced T1-weighted scans is the gold standard for the initial evaluation [7]. This approach involves serial MRI scans and audiological monitoring, given that many tumors show little or no growth over time. However, tumor growth remains unpredictable, with reported rates ranging from 30% to 70% [7]. Approximately 21% of the intrameatal tumors have grown 5 years after diagnosis, whereas 37% of the extrameatal tumors have exhibited growth. Ten years after diagnosis the rates are 25% and 42%, respectively [8]. Larger tumor volume is generally associated with poorer baseline hearing and increased risk of non-serviceable hearing, yet hearing decline may occur independently of measurable growth, and even in cases of tumor regression [9].

This case underscores important diagnostic considerations in sudden unilateral sensorineural hearing loss. While often considered idiopathic, a small proportion of cases may involve retrocochlear pathology, including VS. A recent study determined a prevalence of VS 2.2% among patients with sudden hearing loss [10]. Early imaging may fail to detect subtle lesions, or tumors may appear stable despite clinical progression. Therefore, comprehensive audiological evaluation is essential. In particular, speech recognition testing can reveal disproportionate deficits suggestive of retrocochlear involvement. A multidisciplinary approach is necessary, as stable MRI findings do not guarantee stable auditory function.

## CONCLUSION

This case demonstrates that vestibular schwannoma may lead to progressive hearing deterioration without detectable tumor growth on MRI, highlighting the multifactorial nature of auditory dysfunction in these patients. Every presentation of unilateral sudden sensorineural hearing loss should be approached with a high level of clinical suspicion, even at the initial stage when retrocochlear pathology has not yet been identified.

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Case report

# INGUINAL LYMPH NODE PRESENTING AS DELAYED SITE OF METASTASIS IN EARLY STAGE OF ENDOMETRIAL CARCINOMA- INTRANODAL ULTRASOUND GUIDED METHYLENE BLUE LYMPHADENECTOMY AS THERAPEUTIC OPTION.

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## ABSTRACT

INTRODUCTION: Inguinal lymph nodes are common sites of metastasis for various malignancies. However, metastasis to inguinal lymph nodes from endometrial carcinoma is uncommon due its typical patterns of spread, although it remains possible manifestation.

CASE PRESENTATION: We present a case of 70 years old female patient previously treated for FIGO II stage endometrial carcinoma, the patient underwent total abdominal hysterectomy with Wertheim-Meigs procedure with bilateral salpingo-oophorectomy with bilateral pelvic lymphadenectomy. Four years post-treatment, follow up CT scan revealed ventral hernia and enlarged right inguinal lymph nodes. A combined surgical procedure was performed, including hernia repair and methylene blue guided lymphadenectomy. Ultrasound guided injection of methylene blue enabled accurate localization and precise excision of the affected lymph nodes.

CONCLUSION: This case demonstrates a rare presentation of inguinal lymph nodes metastasis from early staged endometrial carcinoma, potentially caused by previous surgical disruption and lympho-vascular invasion. Methylene-blue lymphadenectomy appeared to be safe, cost-effective technique that optimized surgical precision and diagnostic specificity, making it valuable tool in the management of atypical metastatic patterns.

## INTRODUCTION

Inguinal lymph nodes are common sites of metastasis for malignant melanoma and squamous cell carcinoma over low extremities and trunk, squamous cell carcinoma of anal canal, vulva and penis and malignant lymphoma. Endometrial carcinoma can spread through various routes including direct extension, lymphatic and hematogenous dissemination and retrograde spread. Locally, endometrial carcinoma can directly invade nearby organs like ovaries and fallopian tubes. Cancer cells can enter lymphatic vessels and usually spread to pelvic and para-aortic lymph nodes. In some case also cancer cells can move backwards through fallopian tubes into peritoneal cavity. Hematogenous spread results in distant metastasis in lungs, liver, bones and brain. Unusual metastasis sites for endometrial carcinoma are abdominal wall, spleen, central nervous system, adrenals, pancreas, appendix and extra abdominal

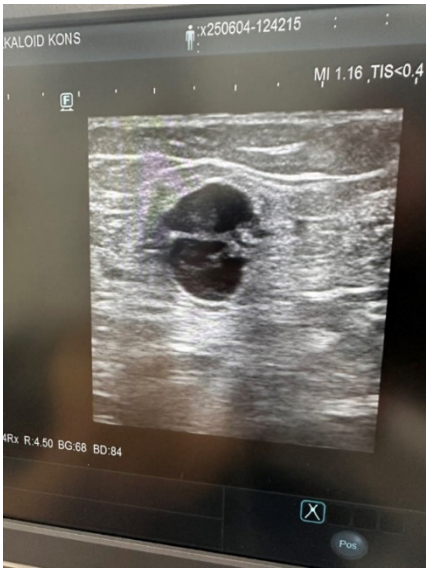
lymph nodes such as inguinal lymph nodes. Endometrial carcinoma is less likely to spread to superficial or deep inguinal lymph nodes, because only round ligament of uterus during its course through the inguinal canal can drain to superficial inguinal lymph nodes, this drainage pathway is minor one.

Intranodal ultrasound guided methylene blue application is used to mark the lymph nodes that need to be removed during a lymphadenectomy. This technique helps to increase the accuracy of identifying and locating the lymph nodes.

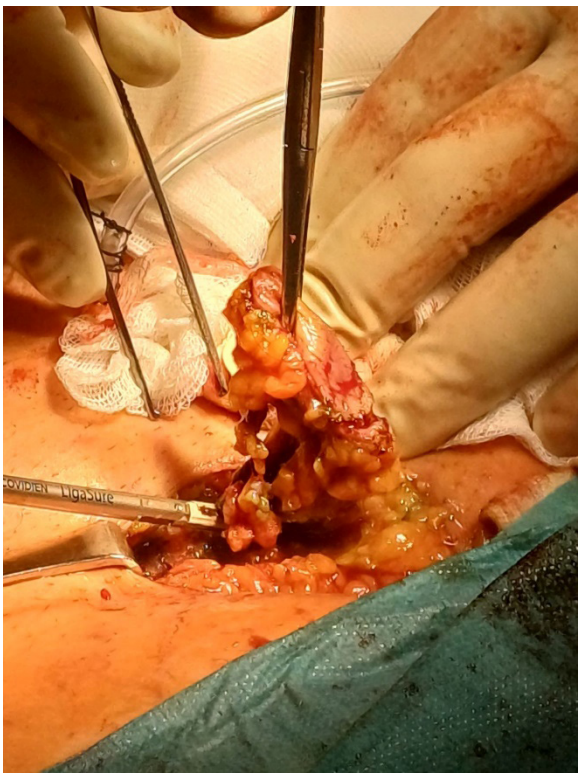
We present a case report of 70 years old female patient, who presents in our tertiary care hospital, following a recent CT scan preformed as a follow up for endometrial carcinoma diagnosed four years ago. The scan revealed ventral hernia and enlarged right inguinal lymph nodes, prompting further evaluation. On physical evaluation, the right inguinal lymph nodes were enlarged and palpable and visible ventral hernia was noted. The patient was advised to undergo surgical intervention.

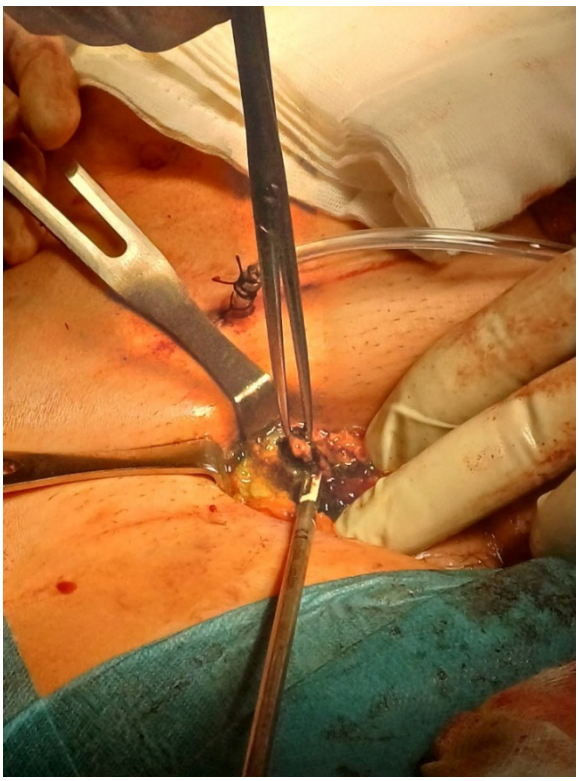
## CASE REPORT

A 70 years old female patient was diagnosed with endometrial carcinoma in 2021. She underwent total abdominal hysterectomy with Wertheim -Meigs procedure and bilateral salpingo-oophorectomy with pelvic lymph node dissection. Histopathology revealed endometrial adenocarcinoma invading the cervical stroma but has not extended beyond uterus. The tumor is poorly differentiated. No regional lymph node metastasis was found in surgically removed lymph nodes. Lymphatic invasion was present, increasing the risk of spread. Vascular invasion was also present. She was staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system as FIGO II. After surgery, the patient was referred to the oncology department for further evaluation and adjuvant therapy. In February 2025, the patient underwent a follow-up CT scan after completing surgery, chemotherapy and radiotherapy for endometrial carcinoma. A ventral hernia was noted on anterior abdominal wall with a hernial neck measuring 45mm with no radiological evidence of incarceration. In the right inguinal region were noted enlarged lymph nodes, largest measured 18mm in diameter. The patient was referred to the University Clinic for digestive surgery for further evaluation and management. On physical evaluation, the right inguinal lymph nodes were enlarged and palpable and visible ventral hernia was noted. Core needle biopsy was indicated. Core biopsy revealed infiltration by a malignant epithelial neoplasm. Immunohistochemistry demonstrated that the tumor cells were positive for p63 and PAX6, supporting an epithelial origin. The patient underwent a combined surgical procedure consisting of ventral hernia repair and lymphadenectomy. Under real-time ultrasound guidance, methylene blue dye was injected directly into the target lymph node. The needle was carefully advanced into lymph node cortex under aseptic conditions to ensure accurate intranodal deposition of the dye. Following the injection of methylene blue the overlying skin was externally marked to correlate with the stained lymph node beneath. The skin marking serves as surgical landmark. The methylene blue not only stains the lymph node internally but may also create mild subcutaneous discoloration, further enhancing visual guidance. During surgery, the skin excision was made directly over the pre -marked site. Careful dissection was preformed along tissue planes to expose the blue-stained lymph nodes which were readily identifiable due to its distinct coloration. The nodes were meticulously excised en bloc to preserve its architecture for histopathological evaluation. The excision was made carefully to prevent extravasation of dye which could make identifying or locating other lymph nodes more difficult. Following lymphadenectomy, the ventral hernia was repaired using standard hernioplasty procedure. The postoperative course was uneventful. Histopathological examination of the excised lymph nodes confirmed the presence of malignancy.

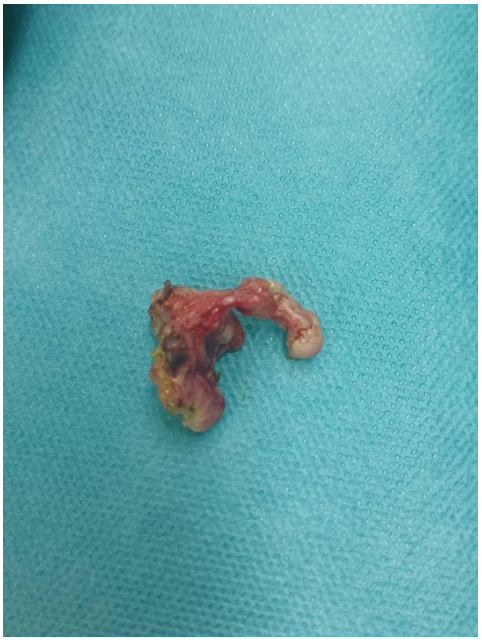


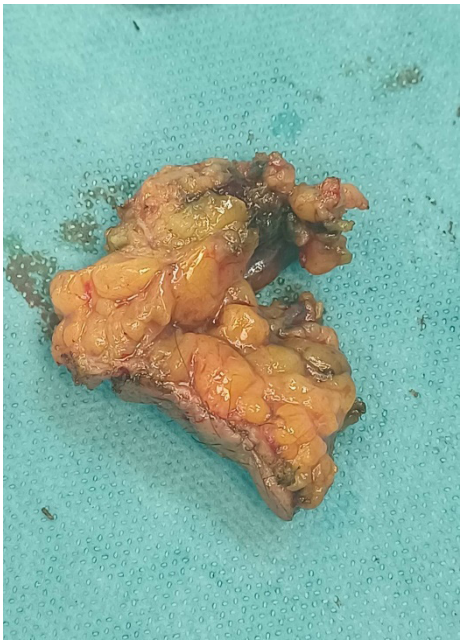

Picture1: Ultrasound image of an enlarged lymph node in the moment of injecting methylene blue dye.



Picture 2 and 3: Excision of methylene blue-marked lymph nodes.





Picture 4 and 5: Surgically excised lymph nodes following lymphadenectomy

## DISCUSSION

Metastatic involvement of inguinal lymph nodes in early staged endometrial carcinoma is extremely rare manifestation. There is multiple hypothesis for inguinal lymph node metastasis in FIGO stage II endometrial carcinoma including aberrant lymphatic drainage via superficial pathways, tumor cells may access superficial lymphatic channels of the lower abdominal wall along the inferior epigastric vessels, eventually draining inguinal

lymph nodes, this can be facilitated by previous surgical incisions or scars, which disrupt normal lymphatic flow and create alternate pathways. Also, surgical trauma may lead to the formation of new lymphatic or vascular channels between the tumor bed and inguinal region, providing a route for metastatic spread. This hypothesis is especially relevant in patients underwent radical surgery. In certain cases, micro-metastatic disease exists prior to detection, underscoring the limitations of current imaging and diagnostic techniques. The presence of lympho-vascular space invasion may facilitate atypical lymphatic dissemination, predisposing to metastasis at non-regional sites such as the inguinal lymph nodes . Methylene blue intranodal-guided lymphadenectomy offers several distinct advantages over conventional lymphadenectomy techniques contributing to better surgical precision and improved oncological outcomes. Ultrasound guided intranodal injection of methylene blue enhances anatomical precision in the identification of metastatic lymph nodes, allowing for more accurate and targeted lymphadenectomy. Targeted lymphadenectomy significantly limits the extent of tissue dissection, thereby reducing operative time, intraoperative blood loss and the incidence of procedure-related complications. Methylene blue is a low-cost, widely available dye with favorable safety profile, making this technique advantageous in resource-limited settings where advanced imaging or radioactive tracers may not be readily accessible. Methylene blue guided lymphadenectomy facilitates more individualized treatment planning, which may contribute to improved long-term disease control and overall survival rate.

## CONCLUSION

Methylene blue intranodal-guided lymphadenectomy enhances the precision of lymph node dissection, reduces surgical morbidity and improves diagnostic accuracy, all of which contribute to better clinical outcomes. Its simplicity, effectiveness and safety profile support its integration into surgical oncology practice, especially in gynecologic malignancies requiring meticulous nodal assessment.

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# ПОЛИПЕКТОМИЈА КАЈ ПАЦИЕНТ СО ПОЗИТИВНА ФАМИЛЈАРНА АНАМНЕЗА - КОЛОРЕКТАЛЕН КАРЦИНОМ

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## АБСТРАКТ

Вовед: Полип претставува секое испакнување на слузницата на дебелото црево препокриена со епител, Полипите се делат на две групи хистолошки првата ненеоплатстични како хамартоми, јувенилнии хиперпластични и неопластични најчесто аденоми кои малигнизираат во висок процент.

Полипите се ситни под 10 мм и крупни над 10 мм со зголемен ризик од малигнизација со димензии над 40мм почесто кај сесилните од пендуларните аденоми повеќето вилозни по состав. Клиничката презентација е болка во стомакот и крварење но најчесто се асимптоматски.

Цел: да се евалуират наодите и клиничкото значење на скрининг колоноскопија кај пациентите со позитвна фамилјарна анамнеза за КРК

Материјали и методи: Пациент на 51 годишна возраст беше подложен на скрининг колоноскопија поради семејна историја на КРК (мајката дијагностицирана на 60 годишна возраст). Постапката беше извршена под свесна седација ,користејќи стандарден адултен колоноскоп .се направи илеоколоноскопија ,Терминален илеум со уреден наод цревото прочистено ,цекум и валвула уредни на ниво на 90 цм аб –ано се виде семи пендуларен полип со дијаметар околу 8 мм ,пред цекум се виде уште еден минутен полип ,ректосигма уште еден друг минутен полип ,од ректум до терминален илеум без други макропатолошки промени. Хистопатолошкиот наод: тубуларен аденом со подрачја на лесна дисплазија на епителот.

Заклулок Овој случај ја потенцира важноста на раната скрининг колоноскопија кај лица со позитивна семејна историја на КРК ,Дури и во одсуство на симптоми,детекцијата и и отстранувањето на преканцерозни лезии претставува значајна можност за превенција на карцином.Придржувањето до актуелните скрининг-препораки за високо ризични групи е од суштинско значењеза и намалување на инциденцата и морталитетот од КРК.

Клулни зборови: КОЛОРЕКТАЛЕН карцином,колоноскопија,аденоматозен полип,полипектомија ,нискостепена дисплазија.

## ВОВЕД

Карциномот на дебелото црево, често именуван како колоректаленканцер(КРК),енајчестозастапенамалигна болест на гастроинтестиналниот тракт. Развојот на овој тип канцер претставува мултифакторијален процес со етиологија која е условена од генетски чинители и експозиција на фактори од средината, вклучувајќи ги и исхраната и различни инфламаторни состојби на дигестивниот систем. Колоректалниот канцер претставува комплексна болест каде што генетските алтерации често се асоцирани со развој и прогресија од премалигни лезии (аденоми) во инвазивен аденокарцином

Во светски рамки во 2020 год., регистрирани се околу 2 милиони нови случаи со колоректален канцер (10% од сите канцери). Постојат големи географски варијации во инциденцата, највисоки пресметани во земјите од Јужна Европа (40.6 за мажи, 24,5 за жени на 100

000 жители). Колоректалниот карцином е причина за околу 1 милион смртни случаи во светски рамки во 2020 година, со највисоки стапки на морталитет во земјите од Централна и Источна Европа каде што припаѓа и нашата држава. Се забележува благ пад на инциденцата и морталитетот во последните неколку години во развиените земји, на пример, во САД е регистриран годишен пад од 2.4% на инциденцата и пад на морбидитетот од 2.2% за периодот 2008-2017 год. што најверојатно се должи на добро осмислени и спроведени национални програми за превенција и скрининг на колоректалниот карцином. Сепак, колоректалниот канцер останува трета најчесто застапена малигна болест, со стапки што се во пораст кај помладата популација (помеѓу 30 и 50 години). „Карциномот на дебелото црево сега често се детектира уште пред да почне клинички да пројавува симптоми, како резултат од спроведените скрининг-стратегии. Просечната стапка на 5-годишно преживување за пациенти со дијагностициран колоректален канцер е околу 64%, каде што преживувањето е обратнопропорционално со стадиумот на болеста во моментот на негово дијагностицирање, и тоа:

локализирана болест 90%,

регионална болест 71% и

дисеминирана болест 14%.

Во случаите кога болеста е понапредната, клиничката презентација вклучува: сидеропенична анемија, појава на ректално крвавење, абдоминална болка, промена на конзистенцијата и зачестеноста на цревните празнења и поретко интестинална опструкција и перфорација. Десностраните лезии се почесто асоцирани со помлада возраст, анемија, крвавење и/или дијареја. Туморите на левиот колон почесто се презентираат со цревна опструкција и се јавуваат кај постара популација. Поради фактот дека дебелоцревниот карцином во раните фази на неговиот развој е претежно асимптоматски, скринингот игра клучна улога во навремената дијагноза, а со тоа и во неговото излекување, како и во детекцијата и третманот на преканцерозните лезии (аденоматозните дебелоцревни полипи и мукозни рани неоплазии). „Препораките на сите релевантни светски асоцијации за скрининг на колоректален карцином препорачуваат спроведување на неколку теста и процедури за детекција на аденоматозни полипи или примарна детекција на канцер.“ За пациенти што одбиваат или кај кои не може да се спроведат ендоскопски процедури се препорачува:

иригографија секоја на 5 години или

КТ-колонографија секоја на 5 години

Определената возраст за отпочнување на споменатите процедури за скрининг е 50 години, базирајќи се на препораките на поголемиот дел од светските гастроентеролошки здруженија, со тоа што препораките на американските здруженија (Американско друштво за рак, US-Society Task Force on Colorectal Cancer, AGA...) оваа возрасна граница ја поместуваат и ја спуштаат на 45 години. Тестови што се користат за скрининг на општата популација вклучуваат:

• годишно, фекален тест на окултно крвавење (FOBT)

• годишно, фекален имунохистохемиски тест (FIT)

• годишно, фекален ДНК-тест.

Дијагностички процедури што се препорачуваат за скрининг на КРК се:

• флексибилна сигмоидоскопија секоја 5. година

• колоноскопија секоја 10. година.

Во случај на детекција на суспектни промени во текот на ендоскопските процедури (сигмоидоскопија и колоноскопија), тие се биопсираат и хистопатолошки се анализираат. Доколку се детектираат преканцерозни лезии како аденоматозни полипи или рани мукозни неоплазми, тие ендоскопски се ресецираат со техники на полипектомија или ендоскопска мукозна ресекција (EMR), интервенции што успешно се изведуваат од страна на тимот на гастроентерохепатолози во гастроентерохепатолошкиот оддел во Клиничка болница Тетово. Скринингот за КРК треба да започне во уште порана возраст и тој треба да биде уште пофреквентен и построг за пациенти што имаат висок ризик за развој на КРК. Тука спаѓаат пациенти со една од следниве состојби: пациенти со минатата историја за полипи на дебелото црево, пациенти со минатата историја за КРК, пациенти со позитивна фамилијарна анамнеза за КРК и пациенти со докажана инфламаторна цревна болест. Пациенти дијагностицирани или суспектни за хередитарни фамилијарни синдроми како што се хередитарен неполипозен колон канцер синдром (HNPCC) или фамилијарна аденоматозна полипоза (FAP) треба, исто така, да бидат третирани како пациенти со висок ризик за развој на КРК и кај нив треба да се

спроведе поинтензивен протокол на следење. Доколку КРК се дијагностицира во фаза додека е сè уште локализиран, без хематогено далечни дисеминирани метастази (стадиум I-III), тој треба хируршки да се третира. Хируршката ресекција е најдобриот терапевтски модалитет кој претставува потенцијално куративна опција, дури и за пациенти со лимитирана метастатска болест на црниот дроб. Адјувантната хемотерапија најчесто се применува за пациенти што се стеџирани во стадиум III, додека хемотерапијата е стандарден тераписки пристап за метастатски колоректален карцином. Улогата на радиотерапијата е најчесто лимитирана само за палијативни цели

Консултацијата со гастроентерохепатолог е од критично значење за соодветен скрининг и навремено дијагностицирање на КРК, каде што ендоскопската евалуација (колоноскопијата) има централна улога. Ова е од особена важност за делот на популацијата што спаѓа во групите со висок ризик за развој на КРК каде што покрај гореспоменатите групи со зголемен ризик, спаѓаат и пациенти со присутни таканаречени „алармни симптоми“ (неразјаснета сидеропенична анемија, неинтенциска загуба на телесна тежина, долнодигестивно гастроинтестинално крвавење). Ова уште повеќе добива на значење ако се знае дека колоректалниот канцер претставува потенцијално курабилна болест доколку се детектира и третира во рана фаза на неговиот развој со правилен пристап кон пациентите и користење на процедури, методи и интервенции кои ни стојат на располагање и веќе нашироко се применуваат.

Повеќето колоректални карциноми започнуваат како аденоматозни полипи, кои се мали израстоци на внатрешната обвивка на дебелото црево. Овие полипи се обично безопасни, но некои можат постепено да се претворат во рак во текот на многу години. Овој бавен напредок е всушност добра вест бидејќи им дава на лекарите можност да ги најдат и отстранат полипите пред да станат проблематични

Термините «колоректален карцином» и «колоректален карцином» често се користат заменливо. Колоректалниот карцином ги вклучува и карциномот на дебелото црево и карциномот на ректумот, бидејќи имаат слични карактеристики и третмани.

Раното скринирање кај високо ризични популаци е клучно за навремено откривање и превенција.

Симптомите на КРК зависат од локализацијата на туморот во цревото и од тоа дали има метастази. Повеќето од симптомите се препокриваат со другите болести на колонот и затоа раната дијагноза е скоро невозможна. Симптомите се на локални, конституционални (општи) и предизвикани од метастази

Локални симптоми: Локалните симптоми се поизразени доколку локализацијата на туморот е поблиску до анусот. Тогаш како симптом се јавува промена на нормалната ,работа на цревата (новопојавена дијареја или констипација без видлива друга причина) и појава на чувство за недовршена дефекација (тенезми) и редукција на дијаметарот на столицата; Крварења од долниот интестинален тракт;

Мелена (темна столица, почеста при крварења од горен интестинален тракт –

дуоденален улкус) при локализација на почетните делови на колонот

Ако туморот е доволно голем за да го исполни целиот лумен на колонот, може да предизвика цревна опструкција со следните симптоми (констипација, абдоминална болка и повраќање). Како компликации на цревната опструкција може да се јави перфорација на цревата и перитонитис.

Конституционални (општи) симптоми

Органи во кои најчесто метастазира КРК.

КРК најчесто метастазира во хепарот. Во некои случаи тоа е безсимптомно, но може да се појави иктерус (жолтица) и абдоминална болка (поради растегање ,на капсулата на хепарот). Ако метастазите прават опструкција на жолчните патишта, иктерусот може да биде придружен и со други симптоми на билијарна опструкција, како што е стеатореа (масти во столицата).

ДИЈАГНОЗА / СКРИНИНГ ТЕСТОВИ –

ректално туширање - хемокулт тест (за крв во столицата) - ендоскопија со биопсија (сигмоидоскопија и колоноскопија)

Други методи за скрининг - двојно контрастна бариумска енема под рендген (бариумска каша преку уста – воздух преку ректум) - виртуелна колоноскопија - Компјутерска аксијална томографија - Лабораториско испитување на крв за CEA (carcino-embryonic antigen).

Неговото висока концентрација индицира на метастази од аденокарцином, меѓутоа често се лажно

– позитивни или лажно негативни. - Генетски тестови / испитување (за FAP, HNPCC) - ПЕТ скенер - Висок С - реактивен протеин.

Постојат 3 главни скрининг – тестови, и тоа: тест за крв во столица, флексибилна сигмоидоскопија и колоноскопија. Од трите избројани, сигмоидоскопијата не може да ја испита десната страна на колонот, каде 42% од малигнитетите се локализирани. Виртуална колоноскопија преку КТ скен се чини дека е добра исто како и класичната колоноскопија, но е многу скапа, асоцирана е со изложување на радијација и не може да ги оттргне детектираните абнормални маси, како што може класичната колоноскопија.

Нов скрининг метод претставува М2-РК тестот. Ензимскиот биомаркер М2-РК е идентификиран како главен ензим при КРК и полипи на дебело црево. М2-РК не зависи од крв во изметот и е специфично асоциран со промените во метаболизмот на туморот. При позитивен наод на М2-РК, пациентите се подложени на колоноскопија.

Тестот на крв во столица е прави на секои 2 години кај пациенти со ризик за

појава на КРК. Обично се асоцира со сигмоидоскопија или колоноскопија.

## ЦЕЛ

Да се евалуират наодите и клиничкото значење на скрининг колоноскопија кај пациентите со позитвна фамилјарна анамнеза за КРК.

## ПРИКАЗ НА СЛУЧАЈ

Пациент на 51 годишна возраст беше подложен на скрининг колоноскопија поради семејна историја на КРК (мајката дијагностицирана на 60 годишна возраст). Постапката беше извршена под седација, користејќи стандарден адултен колоноскоп. Се направи илеоколоноскопија ,Терминален илеум со уреден наод цревото прочистено ,цекум и валвула уредни на ниво на 90 цм аб–ано се виде семи пендуларен полип со дијаметар околу 8 мм, пред цекум се виде уште еден минутен полип, ректосигма уште еден друг минутен полип, од ректум до терминален илеум без други макропатолошки промени.

Се индицира полипектомија.

Резултати-Во горниот дел на асцендентен колон беше пронајден солитарен сесилен полип.

Хистопатолошкиот наод - ADENOMA TUBULARE COLONIS CUM DYSPLASIA EPITHELII GRADUS LEVIS.

Заклучок-наодот одговара за тубуларен аденом со подрачја на лесна дисплазија на епителот.

Стадиум на Колоректален Карцином

Стадиумот е клучен бидејќи ги води одлуките за третман и помага во предвидувањето на прогнозата. Стадиумот им помага на лекарите да одлучат дали само операцијата е доволна или дали треба да се користи хемотерапија, зрачење или напредни терапии.

Кои се опциите за третман на колоректален карцином?

Третманот зависи од стадиумот, локацијата и видот на ракот, како и од целокупното здравје.

Хирургија:

Полипектомија и ендоскопска мукозна ресекција (EMP): За многу мали карциноми содржани во полипи, овие минимално инвазивни процедури можат да го отстранат целиот канцероген полип за време на колоноскопија.

Лапароскопска хирургија: Минимално инвазивен пристап кој користи мали засеци за отстранување на полипи или тумори, честопати вклучувајќи ги и блиските лимфни јазли.

Ресекција на дебелото црево: Отстранување на канцерогениот дел од дебелото црево или ректумот заедно со дел од околното здраво ткиво и лимфни јазли. Може да се изврши колостомија или илеостомија (отвор кон надворешноста на телото за столицата), што може да биде привремено.

Медицински третмани:

Хемотерапија: Користи моќни лекови за убивање на клетките на ракот, често по операција.

Таргетирана терапија: Блокира специфични протеини или гени кои го поттикнуваат растот на ракот (на пр., бевацизумаб, цетуксимаб).

Имунотерапија: Го зајакнува имунолошкиот систем за борба против ракот, ефикасна во некои напредни случаи. Терапија со зрачење:

Се користи особено кај ректален карцином за намалување на туморите пред операција или уништување на преостанатите клетки на ракот потоа.

Каква е прогнозата за колоректален карцином?

Прогнозата за колоректален карцином зависи од стадиумот, возраста, општата здравствена состојба и тоа колку добро ракот реагира на третманот.

5-годишни стапки на преживување (податоци од САД):

Сцена I: за 90%

Втора фаза: околу 70-80%

Фаза III: околу 50-70%

Фаза IV: за 15%

Раното откривање значително го подобрува преживувањето. Напредокот во хирургијата, целната терапија и имунотерапијата продолжуваат да ги подобруваат исходите.

Скрининг и превенција на колоректален карцином

Скринингот е еден од најефикасните начини за превенција на колоректален карцином.

Упатства (Американско здружение за рак):

Започнете со редовен скрининг на 45-годишна возраст за луѓе со просечен ризик.

Продолжете барем до 75-годишна возраст.

Методи на скрининг: колоноскопија (на секои 10 години), тестови на столицата (FIT, FOBT), сигмоидоскопија или КТ колонографија.

Луѓето со поголем ризик (семејна историја, генетски состојби, воспалително заболување на цревата) може да имаат потреба од скрининг порано и почесто.

Замислете ја колоноскопијата како „превентивна поправка“. Таа може да ги отстрани полипите пред да се претворат во рак, па затоа е толку моќна алатка.

## ЗАКЛУЧОК

Овој случај ја потенцира важноста на раната скрининг колоноскопија кај лица со позитивна семејна историја на КРК, Дури и во одсуство на симптоми,детекцијата и и отстранувањето на преканцерозни лезии претставува значајна можност за превенција на карцином. Придржувањето до актуелните скрининг-препораки за високо ризични групи е од суштинско значењеза и намалување на инциденцата и морталитетот од КРК.

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Case report

# ASSOCIATION BETWEEN HYPERPARATHYROIDISM AND MOBITZ TYPE II ATRIOVENTRICULAR BLOCK

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## ABSTRACT

According to the World Health Organisation (WHO) and American College of Cardiology (ACC) Mobitz type II Atrioventricular Block is defined as the occurrence of a single non-conducted P wave associated with constant PR intervals before and after the blocked impulse, provided that the sinus rate or the P–P interval is constant (no slowing) and there are at least two consecutive conducted P waves (i.e., 3:2 AV block) to reveal the behavior of the PR interval (1). It is typically associated with structural heart disease, including coronary artery disease, myocardial infarction, cardiomyopathy, and degenerative conduction disorders such as Lev syndrome and Lenègre disease. Additional causes include medications, electrolyte imbalances, inflammatory conditions, and infiltrative diseases such as Amyloidosis. This case presents the importance of electrolite imbalances as a cause of atrioventricular blocks due to hormonal diseases. Calcium plays a key role in this situation. Elevated serum calcium levels reduces myocardial excitability and shortens action potential duration, increasing refractoriness and impairing AV nodal and His–Purkinje conduction. Implantable cardiac pacemakers constitute a definitive, life-saving therapy for patients with clinically significant bradyarrhythmias and advanced conduction system disease.

Keywords: Mobitz Type II Atrioventricular Block, Hyperparathyroidism, Calcium, Cardiac Pacemaker

## INTRODUCTION

Atrioventricular (AV) block is a conduction disorder characterized by impaired transmission of electrical impulses from the atria to the ventricles. Mobitz type II AV block is a clinically significant form with a high risk of progression to complete heart block and is commonly associated with structural and degenerative conditions such as Lev syndrome and Lenègre disease. Reversible causes, including electrolyte imbalances, should also be considered. Hypercalcemia, often due to hyperparathyroidism, can impair cardiac conduction by altering myocardial excitability and increasing refractoriness. This report highlights a case of Mobitz type II AV block secondary to hypercalcemia, emphasizing the importance of identifying reversible causes.

## CASE PRESENTATION

A 79 years old woman patient presented to the emergency department with three days symptoms of dizziness and nausea. She stated history of hypertension disease with no other chronic diseases. No family history, no herbal agents or honey use were reported. Vital signs of the

patients were as follows, 36.4 celsius temperature, 120/75 mmHg blood pressure, but 50 beats per minute. She was hemodynamically stable. Electrocardiography was performed to the patient. The ECG showed signs of mobitz type II atrioventricular block. After the first medical contact she was admitted to the coronary intensive care unit for the continuous monitoring. The second ECG record confirmed the diagnosis of Mobitz

Type II Atrioventricular block (Figure 1). Routine blood tests conducted to the patient. The thyroid panel tests were all in normal range which excludes the hypo/hyperthyroidism, as one of the main causes of atrioventricular blocks.

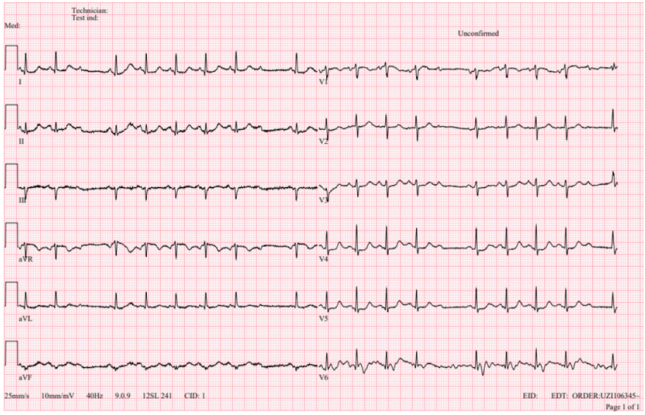

Figure 1 ECG shows the absence of a single QRS wave after P wave. P-R distance is stable and not prolonged as the difference from mobitz type 1

Elevated serum parathyroid hormone (PTH) levels were a key finding in this case. Electrolyte evaluation revealed abnormalities consistent with hyperparathyroidism, including elevated serum calcium levels and decreased serum phosphate levels. However, serum potassium, magnesium, and sodium levels were within normal ranges. No vitamin D deficiency was detected, which excluded the most common cause of secondary hyperparathyroidism. A transthoracic echocardiogram showed a normal ejection fraction and normal left ventricular contractility. No significant valvular pathologies such as dysfunction or calcification were observed, although mild valvular insufficiencies were noted, mainly involving the aortic valve.

## MECHANISM

Chronic hypercalcemia, resulting from Hyperparathyroidism, can lead to atrioventricular block through its effects on cardiac electrophysiology. Elevated serum calcium levels reduce myocardial excitability (Figure 2). Additionally, the action potential duration may be shortened, impairing impulse conduction within the atrioventricular node and the His–Purkinje system by increasing conduction refractoriness (4). Prolonged exposure to high parathyroid hormone levels may also lead to myocardial fibrosis and calcinosis, which can result in irreversible conduction abnormalities. High calcium levels may further cause dissociation between contraction and relaxation in cardiac muscle (4). These mechanisms may contribute to underlying conduction system disease and could explain the rare but clinically significant association between hypercalcemia caused by hyperparathyroidism and atrioventricular block.

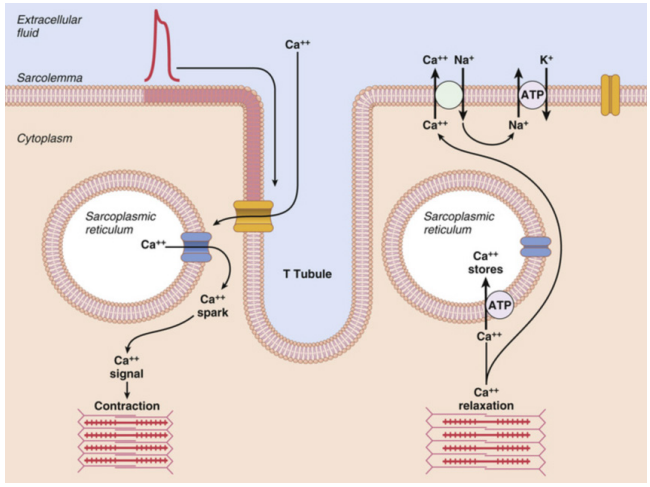


Figure 2 The role of Calcium in the mechanisms of excitation-contraction coupling and relaxation in cardiac muscle. ATP, adenosine triphosphate. Guyton AC, Hall JE. Textbook of Medical Physiology.

## MANAGEMENT AND OUTCOME

The first step in the management of atrioventricular block is accurate diagnosis. The diagnosis requires a stable sinus rate (2). However, Mobitz type II AV block, like other conduction disturbances within the His–Purkinje system, may be tachycardia-dependent, meaning it can become apparent when the sinus rate increases, such as during exercise (2). Mobitz type II atrioventricular block can be potentially life-threatening. In a cohort study of 214 patients with chronic second-degree AV block (types I and II), the 5-year survival rate was 61% for Mobitz II, similar to other advanced conduction blocks. Patients who received pacemakers had significantly better survival (75% at 5 years) compared with patients without pacing (41%) (6). Mobitz type II block is also more likely to progress to complete heart block (7). When

hemodynamic instability occurs, urgent treatment is required. Administration of intravenous atropine may be lifesaving in acute situations. However, the definitive long-term treatment is implantation of a dual-chamber (DDR) pacemaker. Coronary artery disease may be an underlying cause of high-degree atrioventricular block in approximately 40% of patients (5). Acute AV block also frequently occurs in patients with myocardial infarction (7). In our case, coronary angiography was performed to exclude ischemic causes of the conduction abnormality. After a detailed medical history and diagnostic evaluation, no other etiological factors explaining the AV block were identified. During monitoring, the patient's heart rate dropped to 30 beats per minute, and symptoms of hemodynamic instability developed. Therefore, a permanent pacemaker was urgently implanted. Following pacemaker implantation, the paced rhythm was confirmed on ECG monitoring. The final step was to evaluate for possible procedural complications, such as pneumothorax, using a chest X-ray.

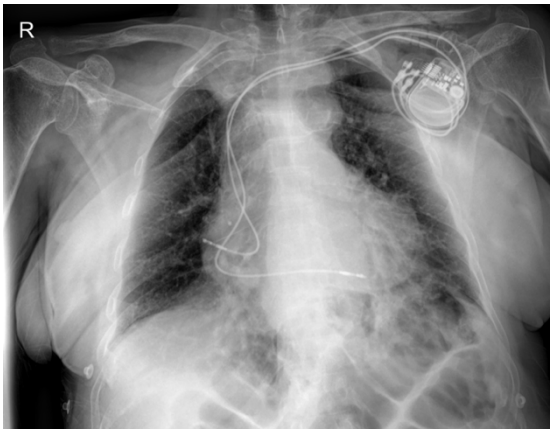


Figure 3 The absence of pneumothorax signs in lung x-ray. PM is seen in the left upper chest region.

## CONCLUSION

Mobitz type II atrioventricular (AV) block remains one of the most frequently misdiagnosed bradyarrhythmias, partly due to inconsistencies in diagnostic criteria. Accurate and timely recognition is essential, as this condition carries a significant risk of progression to complete AV block and adverse clinical outcomes. In the presence of haemodynamic instability or clinically significant symptoms, urgent management is required. Permanent pacemaker implantation represents the definitive treatment; however, systematic evaluation for potentially reversible causes should always be undertaken. Correctable aetiologies, including electrolyte disturbances (particularly potassium, calcium, and magnesium abnormalities), should be promptly identified and managed. Thyroid dysfunction should also be excluded and treated appropriately when present, as both hypo- and hyperthyroidism may contribute to conduction abnormalities. Electrocardiography remains the cornerstone of diagnosis and should be performed without delay in patients presenting with syncope, presyncope, dizziness, or incidental bradyarrhythmias. Early recognition and comprehensive management are crucial to improving clinical outcomes in patients with AV conduction disease.

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With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an abstract of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five key words or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in PubMed which have proven their significance. The style of references required by Medicus is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

The international generic names should be used for all drugs. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

## Informacione plotësuese për autorët

I. Faqja e parë – ballina: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – abstrakti dhe fjalët kyqe: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – teksti i plotë i artikullit: Teksti i plotë i artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë (trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

## Additional Information for Authors

I. First page - front page: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - abstract and keywords: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – full text of the article: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e dorëshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjëqë do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vrojtimit gjatë realizimit të studimeve të verbuara. Definoni termet statistikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përmbledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e probabilitetit (p) dhe të tregoni se është shprehës (sinjifikant në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

Interval – CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë mendon për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin "Vancouver", referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Një punim mund të ketë më së shumti një autor dhe 4 koautor. Koautori i fundit duhet të jetë mentori ose koautori më i afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text. Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

One article can have one author and 4 co-author. Last co-author is the mentor of the article or closest co-author of the paper." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics. The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; Udhërrëfyes i shkurtër i ShoqatësShqiptaretëKardiologjisëpërparandalimineSëmundjes AterosklerotikeKardiovaskulareënëpraktikënklinike,Tiranë,2006
7. Azemi M, Shala M, dhe bp. Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papublikuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bërjen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për ilustrimet (figurat): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for illustrations (figures): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).