

EZOFAGEALNI, GASTRIČNI, KOLOREKTALNI, PANKREATIČNI, HEPATOCELULARNI KARCINOMI I HOLANGIOKARCINOMI U SEVERNOJ MAKEDONIJI: SERIJA PACIJENATA LEČENIH NA UNIVERZITETSKOJ KLINICI, IZMEĐU 2015. I 2019. GODINE

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ORIGINAL ARTICLE

ESOPHAGEAL, GASTRIC, COLORECTAL, PANCREATIC, HEPATOCELLULAR CARCINOMAS AND CHOLANGIOCARCINOMAS IN NORTHERN MACEDONIA: A SERIES OF PATIENTS TREATED AT THE UNIVERSITY CLINIC, BETWEEN 2015 AND 2019

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SAŽETAK

Uvod: Globalno opterećenje društva gastrointestinalnim kancerom (GIK) raste. Tumori želuca, debelog creva i jetre su među pet najčešćih gastrointestinalnih karcinoma kod muškaraca i žena širom sveta. Incidenca GIK-a pokazuje značajne varijacije u Evropi i Severnoj Americi. Ovaj rad razmatra znake konvergencije bolničkog morbiditeta u Severnoj Makedoniji ka procenjenim vrednostima globalnog morbiditeta.

Cilj: Cilj rada je da opiše bolnički morbiditet od gastrointestinalnih kancera na Univerzitetškoj klinici u Severnoj Makedoniji.

Materijal i metode: Retrospektivna longitudinalna analiza obuhvatila je seriju slučajeva sa GIK-om, na najvećoj, Univerzitetškoj klinici za gastroenterohepatologiju (UKG) u Skoplju, tokom perioda 2015 – 2019. Deskriptivnim metodama statistike opisan je bolnički morbiditet od GIK-a i distribucija prema starosti, polu i lokalizaciji kancera.

Rezultati: U petogodišnjem periodu, na Univerzitetškoj klinici za gastroenterohepatologiju je lečen ukupno 2.831 pacijent sa GIK-om, od čega je 1.484 pacijenta imalo kolorektalni kancer, 763 pacijenta rak želuca i 88 pacijenata rak jednjaka. Iako su kanceri jetre bili manje zastupljeni, čak osmina takvih pacijenata (355 ili 13%) imala je nespecifični malignitet jetre. Većina pacijenata je bila u starosnoj grupi 60 – 69 godina, sa izuzetkom raka jednjaka. Primećen je porast incidence raka pankreasa, skoro podjednak kada se razmatra distribucija po polu, i uglavnom u starosnim grupama 60 – 69 i 70 – 79 godina.

Zaključak: Bolnički morbiditet od GIK-a u severnoj Makedoniji pokazuje trend porasta, stoga je važno utvrditi koliko je skrining doprineo ranom otkrivanju ovih kancera, i osigurati pristup i dostupnost terapije za B i C hepatitis.

Ključne reči: gastrointestinalni karcinom, rak želuca, rak pankreasa, hepatocelularni kancer, rak jednjaka, kolorektalni kancer

ABSTRACT

Introduction: The global burden of gastrointestinal cancer (GIC) is growing. Stomach, colon and liver are among the five most common sites for GIC in men and women worldwide. The incidence of GIC shows significant variation in Europe and North America.

Aim: The aim of this paper is to describe hospital morbidity from GI cancer at the University Clinic in Northern Macedonia.

Material and methods: A retrospective longitudinal analysis included a series of cases with GIC, at the University Clinic of Gastroenterohepatology (UCG) in Skopje, in the period 2015–2019. Descriptive statistical methods were used to describe hospital morbidity from GIC, and its distribution by age, sex, and cancer site.

Results: In a five-year period, a total of 2,831 patients with GIC were treated at the UCG, of which 1,484 patients had colorectal cancer, 763 patients had gastric cancer and 88 patients had esophageal cancer. Although liver cancers were less common, as many as one eighth of such patients (355 or 13%) had nonspecific liver malignancy. Most patients were in the 60 – 69 age group, with the exception of esophageal cancer. An increase in the incidence of pancreatic cancer was observed, almost equal, when considering the distribution by sex, and mainly in the age groups 60 –69 and 70–79 years.

Conclusion: Hospital morbidity due to GIC in North Macedonia shows an increasing trend, so it is important to determine how much screening has contributed to the early detection of these cancers and to ensure access to and availability of therapy for hepatitis B and C.

Key words: gastrointestinal carcinoma, gastric cancer, pancreatic cancer, hepatocellular cancer, esophageal cancer, colorectal cancer

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UVOD

Globalno opterećenje društva gastrointestinalnim kancerima (GIK) raste. Želudac, debelo crevo i jetra su među pet najčešćih lokalizacija gastrointestinalnih karcinoma kod muškaraca i žena širom sveta [1,2,3]. Incidenca GIK-a pokazuje značajne geografske varijacije, pri čemu je incidenca kolorektalnog kancera viša u Zapadnoj Evropi i Severnoj Americi, a incidenca kancera želuca i jetre je viša u Aziji i Africi. Prema Globalnoj opservatoriji za rak (GLOBOCAN) [4], stope incidence i mortaliteta u Severnoj Makedoniji slične su onim koje su zabeležene u zemljama Zapadne Evrope. U 2020. godini, incidenca kolorektalnog kancera u Zapadnoj Makedoniji bila je 10,9 i 14,4 na 100.000 stanovnika, za muškarce i za žene, naspram 9,9% i 10%, respektivno, u Zapadnoj Evropi [4].

Prema podacima Direkcije za e-zdravlje (interni podaci), u 2018. godini, najviša incidenca u Makedoniji je zabeležena za GIK. Ovi podaci ukazuju na to da su više od jedne trećine svih kolorektalnih i gastričnih karcinoma novi slučajevi, naspram slučajeva hepatičnih i karcinoma pankreasa, gde su dve trećine svih slučajeva novi slučajevi. Na primer, 74% (304 od ukupno 402 slučaja) hepatičnih i karcinoma žučnih puteva (C22 u Međunarodnoj klasifikaciji bolesti X (MKB-X)), i 70% (338 od ukupno 486 slučajeva) karcinoma pankreasa (MKB-X: C25), naspram 35% (747 od ukupno 2.121 slučaja) karcinoma debelog creva (MKB-X: C18), 33% (486 od ukupno 1.486 slučajeva) rektalnih karcinoma (MKB-X: C20), i 36% (403 od ukupno 1.129 slučajeva) karcinoma rektosigmoidnog spoja (MKB-X: C19), i 49% (516 od ukupno 1.045 slučajeva) gastričnih karcinoma (MKB-X: C16). Slično ovim podacima, incidenca raka jetre i pankreasa ima agresivan trend, uprkos tome što su, prema podacima o prevalenci, ovi karcinomi rangirani ispod karcinoma debelog creva, rektuma i želuca.

Otkriće gastričnog patogena iz prve grupe karcinogena [5], *Helicobacter pylori* (*H. pylori*), značajno je izmenilo lečenje i shvatanje ove bolesti, u smislu infektivne bolesti, koja je predvidiva i koja se može sprečiti [6-8].

Na osnovu procena GLOBOCAN-a iz 2018. godine, rak pankreasa je rangiran kao jedanaesti kancer po učestalosti u svetu, uzrokujući 4,5% svih smrti nastalih usled kancera u 2018. godini, dok je u Sjedinjenim Američkim Državama to treći najčešći kancer [9]. Do sada je poznato da, u svetu, incidenca i mortalitet od raka pankreasa koreliraju sa većom starošću i muškim polom [10,11].

Među različitim vrstama primarnih kancera jetre, peti kancer po učestalosti na svetskom nivou [12,13], hepatocelularni karcinom (HCK), kao i intrahepatični holangiokarcinom (IHK), su najčešći, čineći oko 70% i 15% slučajeva, respektivno [14-16].

Imajući u vidu značajne varijacije incidence GIK-a u Evropi i Severnoj Americi, ovaj rad se bavi znacima

INTRODUCTION

The global burden of gastrointestinal cancers (GIC) is growing. The stomach, colon, and liver are among the five most common sites for GIC, in men and women worldwide [1,2,3]. The incidence of GIC shows significant geographic variation, with colorectal cancer incidence being higher in Western Europe and North America, and gastric and liver cancer incidence being higher in Asia and Africa. Based on the Global Cancer Observatory (GLOBOCAN) [4], the incidence and mortality rates in North Macedonia are similar to those of Western European countries. In 2020, the incidence of colorectal cancer in North Macedonia was 10.9 and 14.4 per 100,000 population, for men and women, as compared to 9.9% and 10%, respectively, in Western Europe [4].

According to the E-health Directorate (internal data), in 2018, the highest incidence in North Macedonia was observed for GIC. These data suggest that more than one third of all colorectal and gastric carcinoma cases are new cases, as opposed to liver and pancreatic cases where two thirds of all cases are new cases. For example, 74% (304 of a total of 402 cases) of liver and bile duct carcinomas (C22 of the International Classification of Diseases version X (ICD-X)), and 70% (338 of a total of 486 cases) of pancreatic carcinoma (ICD-X: C25), as opposed to 35% (747 of a total of 2,121 cases) of colon carcinoma (ICD-X: C18), 33% (486 of a total of 1,486 cases) of rectal carcinoma (ICD-X: C20), and 36% (403 of a total of 1,129 cases) of carcinoma at the recto-sigmoid junction (ICD-X: C19), and 49% (516 of a total of 1,045 cases) of gastric carcinoma (ICD-X: C16). Similarly to these data, the worldwide incidence of pancreatic and liver cancer has an aggressive trend, despite being ranked, according to prevalence data, below colon, rectal and gastric carcinoma.

The discovery of the group 1 carcinogen gastric pathogen [5], *Helicobacter pylori* (*H. pylori*), has considerably altered the treatment and concept of the disease towards an infectious disease, which is predictable and preventable [6-8].

Based on GLOBOCAN 2018 estimates, pancreatic cancer has ranked the 11th most common cancer in the world, making up 4.5% of all deaths caused by cancer in 2018, while it is the third most common cancer in the United States [9]. To date, it is known that incidence and mortality of pancreatic cancer correlate with increasing age and the male sex, worldwide [10,11].

Among the various types of primary liver cancers, the fifth most common cancer globally [12,13], hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most common, accounting for roughly 70% and 15% of cases, respectively [14-16].

Given the significant variation of incidence of GIC in Europe and North America, this paper discusses the

konvergencije bolničkog morbiditeta u Severnoj Makedoniji prema morbiditetu na globalnom nivou. Cilj ovog rada jeste da opiše bolnički morbiditet od GIK-a na Univerzitetskoj klinici u Severnoj Makedoniji.

MATERIJALI I METODE

Retrospektivna longitudinalna analiza uključivala je seriju slučajeva GIK-a na Univerzitetskoj klinici za gastroenterohepatologiju (UKG) u Skoplju, u periodu između 2015. i 2019. godine.

Primenili smo deskriptivne statističke metode prikazivanja bolničkog morbiditeta, u odnosu na distribuciju GIK-a, u odnosu na starost, na pol, kao i u odnosu na lokalizaciju kancera, u petogodišnjem periodu, od 1. januara 2015. godine do 31. decembra 2019. godine.

Izvorni skup podataka je očišćen od duplikata i filtriran po jedinstvenim pacijentima. Podaci su analizirani u programu MS Excel za macOS (Microsoft Corporation, Redmond, Washington, US).

REZULTATI

Najnoviji podaci GLOBOCAN-a [4] pokazuju da su ukupna stopa incidence standardizovane prema godinama

signs of convergence of hospital morbidity in North Macedonia towards the global morbidity. The aim of this paper is to describe hospital morbidity from GI cancer at the University clinic in Northern Macedonia.

MATERIAL AND METHODS

A retrospective longitudinal analysis included a series of GIC cases at the University Clinic of Gastroenterohepatology (UCG) in Skopje, during the period between 2015 and 2019.

We applied descriptive statistical methods to present hospital morbidity, by GIC distribution, by age, by sex, and by cancer site, for a five-year period, from January 1, 2015 to December 31, 2019.

The original dataset was cleaned from duplicates and filtered by unique patients. Data was analyzed in MS Excel software for macOS (Microsoft Corporation, Redmond, Washington, US).

RESULTS

The latest GLOBOCAN data [4] shows that the overall age-standardized incidence rate and the risk of developing cancer have decreased between 2018 and

Tabela 1a. Indikatori kancera, Severna Makedonija, 2018. i 2020. godina

	2018. godina / 2018. year			2020. godina / 2020. year		
	Muškarci Males	Žene Females	Oba pola Both sexes	Muškarci Males	Žene Females	Oba pola Both sexes
Populacija, br. Population, n	1,042,282	1,042,774	2,085,056	1,042,282	1,042,774	2,085,056
Novi slučajevi raka, br. New cancer cases, n	4,258	3,549	7,807	4,247	3,385	7,632
Stopa incidence standardizovana prema godinama starosti (svet) / Age-standardized incidence rate (world)	260.1	208.2	230.8	253.8	193.8	220.4
Rizik za dobijanje raka pre 75. godine života (%) Risk of developing cancer before the age of 75 years (%)	27.1	21.2	24.0	26.2	19.7	22.7
Smrti uzrokovane rakom, br. Cancer deaths, n	2,532	1,584	4,116	2,584	1,640	4,224
Stopa smrtnosti standardizovana prema godinama starosti (svet) Age-standardized mortality rate (world)	149.4	83.4	113.9	148.1	84.1	113.6
Rizik za umiranje od raka pre 75. godine života (%) Risk of dying from cancer before the age of 75 years (%)	16.3	9.3	12.7	16.1	9.4	12.6
Slučajevi sa petogodišnjom prevalencom, br. 5-year prevalent cases, n	8,252	9,154	17,406	9,581	9,265	18,846
Prvih 5 najčešćih kancera, sa izuzetkom kancera kože koji nisu melanomi (rangirano po slučajevima)	Pl / L P / P KR / CR	D / Br KR / CR CoU / CoU	Pl / L D / Br KR / CR	Pl / L P / P KR / CR	D / Br KR / CR CoU / CoU	Pl / L D / Br KR / CR
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	B / B1 Ž / S	Pl / L CeU / CeU	P / P CoU / CoU	B / B1 Ž / S	Pl / L CeU / CeU	P / P CoU / CoU

Table 1a. Cancer indicators, North Macedonia, 2018 and 2020

Izvor: Globalna opservatorija za rak [4]; Pl – pluća; P – prostata; KR – kolon-rektum; B – bešika; Ž – želudac; CeU – cervix uteri; CoU – corpus uteri; D – dojka; M – melanom

Source: Global Cancer Observatory [4]; L – lung; P – prostate; CR – colorectum; BI – bladder; S – stomach; CeU – cervix uteri; CoU – corpus uteri; Br – breast

Tabela 1b. Indikatori kancera Evropske regije SZO u 2018. i Zapadne Evrope u 2020. godini

Table 1b. Cancer key indicators, WHO European Region in 2018 and Western Europe in 2020

	2018, godina / 2018, year			2020, godina / 2020, year		
	Muškarci Males	Žene Females	Oba pola Both sexes	Muškarci Males	Žene Females	Oba pola Both sexes
Populacija, br, Population, n	447,845,844	447,986,637	2,085,056	96,374,578	99,771,743	196,146,321
Stopa incidence standardizovana prema godinama starosti (svet) / Age-standardized incidence rate (world)	311.3	239.8	268.6	365.3	294.3	325.0
Rizik za dobijanje raka pre 75, godine života (%) Risk of developing cancer before the age of 75 years (%)	31.1	23.6	27.0	34.9	27.9	31.2
Stopa smrtnosti standardizovana prema godinama starosti (svet) Age-standardized mortality rate (world)	144.4	85.9	111.0	127.1	83.9	103.3
Rizik za umiranje od raka pre 75, godine života (%) Risk of dying from cancer before the age of 75 years (%)	15.1	9.1	11.9	13.0	8.8	10.8
Prvih 5 najčešćih kancera, sa izuzetkom kancera kože koji nisu melanomi (rangirano po slučajevima)	P / P PI / L KR / CR	D / Br KR / CR PI / L	D / Br KR / CR KPI / L	P / P PI / L KR / CR	D / Br KR / CR PI / L	P / P D / Br PI / L
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	B / B1 Ž / S	CoU / CoU M / M	P / P B / B1	B / B1 M / M	M / M CoU / CoU	KR / CR B / B1

Izvor: Globalna opservatorija za rak [4]; PI – pluća; P – prostata; KR – kolon-rektum; B – bešika; Ž – želudac; CeU - cervix uteri; CoU - corpus uteri; D – dojka; M – melanom

Source: Global Cancer Observatory [4]; L – lung; P – prostate; CR – colorectum; BI – bladder; S – stomach; CeU - cervix uteri; CoU - corpus uteri; Br – breast

starosti kao i rizik od oboljevanja od kancera opali između 2018. i 2020. godine, zajedno sa indikatorima mortaliteta u Severnoj Makedoniji (Tabela 1a). Dok je stopa incidence niža, stopa smrtnosti je viša nego u zemljama Evropske regije SZO i zemljama Zapadne Evrope (Tabela 1b).

Tokom petogodišnjeg perioda, ukupno 2.831 pacijent sa GIK-om je lečen na UKG-u, od kojih je 1.484 (53%) imalo kolorektalni kancer, 763 (27%) pacijenata je imalo rak želuca, a 88 (3%) pacijenata je imalo rak jednjaka. Iako su kanceri jetre bili manje zastupljeni, čak preko jedne osmine takvih pacijenata (355 ili 13%) imalo je nespecifični malignitet jetre. Rak jednjaka je dijagnostikovao kod 88 pacijenata, od kojih 73 muškog i 15 ženskog pola, u rasponu starosnih grupa. Sledeći rezultati predstavljaju serije pacijenata na UKG-u, prema lokalizaciji karcinoma, starosti i polu, tokom posmatranog vremenskog perioda (Tabela 2).

2020, along with the mortality indicators in North Macedonia (Table 1a). While the incidence rate is lower, the mortality rate is higher than in the countries of the WHO European Region and Western Europe (Table 1b).

During a 5-year period, a total of 2,831 patients with GIC were treated at the UCG, of which 1,484 (53%) patients had colorectal cancer, 763 (27%) patients had gastric cancer and 88 (3%) patients had esophageal cancer. Although liver cancers were less common, as many as over one eighth of such patients (355 or 13%) had nonspecific liver malignancy. Esophageal cancer was diagnosed in 88 patients, of which 73 male and 15 female, in a range of age groups. The following results present series of patients at the UCG, by carcinoma site, age, and sex, over the observed period (Table 2).

Tabela 2. Broj pacijenata sa rakom jednjaka dijagnostikovanih i lečenih na UKG-u, prikazani prema polu, 2015 – 2019.

Table 2. Number of diagnosed and treated patients with esophageal cancer at the UCG, by sex, 2015 – 2019

Godina Year	Br. pacijenata No. of patients	Muški pacijenti, br. (%) Male patients, N (%)	Ženski pacijenti, br. (%) Female patients, N (%)
2015.	20	17 (85%)	3 (15%)
2016.	14	10 (71%)	4 (29%)
2017.	16	12 (75%)	4 (25%)
2018.	19	16 (84%)	3 (16%)
2019.	19	18 (95%)	1 (05%)
Ukupno / Total	88	73 (83%)	15 (17%)

Tabela 3. Pacijenti sa rakom želuca dijagnostikovani i lečeni na UKG-u, prikazani prema polu, 2015 – 2019, (br., %).

Godina Year	Br. pacijenata No. of patients	Muški pacijenti, br. (%) Male patients, N (%)	Ženski pacijenti, br. (%) Female patients, N (%)
2015.	164	109 (66%)	55 (34%)
2016.	182	132 (73%)	50 (27%)
2017.	142	93 (65%)	49 (35%)
2018.	141	102 (72%)	39 (28%)
2019.	134	96 (72%)	38 (28%)
Ukupno / Total	763	532 (70%)	231 (30%)

Evidentno je da je rak jednjaka bio daleko više zastupljen kod muškaraca (85% ukupnog broja slučajeva, raspon: 71 – 95%) nego kod žena (15% ukupnog broja slučajeva, raspon: 5 – 29%). Tokom posmatranog perioda, broj slučajeva sa rakom jednjaka imao je stabilni trend, uz padove u 2016. i 2017. godini.

Tokom analiziranog perioda, na UKG-u je rak želuca otkriven kod 763 pacijenta, od kojih 532 muška pacijenta i 231 ženski pacijent, sa većom distribucijom u starosnoj grupi 60 – 69 godina. Podaci o postojanju ili eradikaciji *Helicobacter pylori*, ili drugi faktori rizika, nisu bili dostupni (Tabela 3).

Podaci o raku želuca otkrivaju da je, i za ovaj tip kancera, broj slučajeva među muškim pacijentima (70% ukupnog broja slučajeva, raspon: 65 – 73%) bio daleko veći nego među ženskim pacijentima (30% ukupnog broja slučajeva, raspon: 27 – 35%). Tokom posmatranog perioda, broj slučajeva raka želuca imao je stabilan trend, sa povećanjem u 2018. godini.

Tokom analiziranog perioda, na UKG je kolorektalni karcinom otkriven kod 1.484 pacijenata, od kojih je 827 bilo muških, a 657 ženskih pacijenata, u starosnoj grupi 60 – 69 godina (Tabela 4). Broj slučajeva sa kolorektalnim karcinomom je imao promenljivi trend tokom posmatranog perioda.

Uočen je trend porasta broja slučajeva karcinoma pankreasa na UKG, tokom analiziranog perioda (Tabela 5). Kod ukupno 528 pacijenata je dijagnostikovano rak pankreasa, od toga 287 muških pacijenata i 241 ženski

Table 3. Diagnosed and treated patients with gastric cancer at the UCG, by sex, 2015 – 2019, (n, %)

It is evident that esophageal carcinoma was far more dominant in men (85% of total cases, range: 71 – 95%) compared to women (15% of total cases, range: 5 – 29%). Over the observed period, the number of cases with esophageal carcinoma had a stable trend with decreases in years 2016 and 2017.

During the analyzed period, at the UCG, gastric cancer was detected in 763 patients, of which 532 male and 231 female, with a higher distribution in the 60 – 69 age group. Data of the existence or eradication of *Helicobacter pylori*, or other risk factors, were not available (Table 3).

The data on gastric cancer reveal that, for this type of cancer, as well, the number of cases in male patients (70% of total cases, range: 65 – 73%) was much higher than in female patients (30% of total cases, range: 27 – 35%). Over the observed period, the number of gastric cancer cases had a stable trend, with an increase in 2018.

During the analyzed period, at the UCG, colorectal carcinoma was detected in 1,484 patients, of which 827 male and 657 female, mainly in the 60 – 69 age group (Table 4). The number of cases with colorectal carcinoma had a variable trend over the observed period.

There was an observed increasing trend of the number of cases with pancreatic carcinoma at the UCG, in the analyzed period (Table 5). A total of 528 patients were diagnosed with pancreatic cancer, of whom 287 male and 241 female, mostly in the 60 – 69

Tabela 4. Pacijenti sa kolorektalnim kancerom dijagnostikovani i lečeni na UKG, prikazani prema polu, 2015 – 2019, (br., %)

Godina Year	Br. pacijenata No. of patients	Muški pacijenti, br. (%) Male patients, N (%)	Ženski pacijenti, br. (%) Female patients, N (%)
2015.	303	196 (65%)	107 (35%)
2016.	298	119 (40%)	179 (60%)
2017.	280	175 (63%)	105 (38%)
2018.	313	181 (58%)	132 (42%)
2019.	290	156 (54%)	134 (46%)
Ukupno / Total	1.484	827 (56%)	657 (44%)

Table 4. Diagnosed and treated patients with colorectal cancer at the UCG, by sex, 2015 – 2019, (n, %)

Tabela 5. Pacijenti sa rakom pankreasa dijagnostikovani i lečeni na UKG, prikazani prema polu, 2015 – 2019, (br.,%)

Godina Year	Br. pacijenata No. of patients	Muški pacijenti, br. (%) Male patients, N (%)	Ženski pacijenti, br. (%) Female patients, N (%)
2015.	89	48 (54%)	41(46%)
2016.	112	64 (57%)	48 (43%)
2017.	81	40 (49%)	41 (51%)
2018.	105	68 (65%)	37 (35%)
2019.	141	67 (48%)	74 (52%)
Ukupno / Total	528	287 (54%)	241 (46%)

Table 5. Diagnosed and treated patients with pancreatic cancer at the UCG, by sex, 2015 – 2019, (n, %)

pacijent, uglavnom starosti između 60 i 69 godina, odnosno 70 i 79 godina. Kod samo dvoje od tih pacijenata (jedan muškog a drugi ženskog pola) je dijagnostikovano *pan-NET*. Podaci o njihovim navikama i drugim faktorima rizika nisu bili dostupni (Tabela 5).

Analizirani podaci sa UKG-a su pokazali da je hepatocelularni karcinom dijagnostikovano kod 48 pacijenata, holangiokarcinom kod 34 pacijenata, a karcinom ekstrahepatičnih žučnih puteva kod 59 pacijenata. Nespecifični malignitet jetre dijagnostikovano je kod 355 pacijenata (Tabela 6). Postojao je značajan trend porasta broja karcinoma sa lokalizacijom na jetri na UKG-u, tokom analiziranog perioda (Tabela 6).

and 70 – 79 age groups. Only two of them were diagnosed with *pan-NET* (one male and one female). Data on their habits or other risk factors were not available (Table 5).

The analyzed data from the UCG showed that hepatocellular carcinoma was diagnosed in 48 patients, cholangiocarcinoma in 34 patients, and carcinoma of extrahepatic bile ducts in 59 patients. Nonspecific liver malignancy was diagnosed in 355 patients (Table 6). There was a significant increasing trend of the number of liver site carcinoma cases at the UCG, in the analyzed period (Table 6).

Tabela 6. Pacijenti sa kancerima jetre dijagnostikovani i lečeni na UKG, prikazani prema tipu, 2015 – 2019, (br., %)

Godina Year	Hepatocelularni karcinom Hepatocellular carcinoma	Holangiokarcinom Cholangiocarcinoma	Hepatoblastom Hepatoblastoma	Angioblastom Angioblastoma	Karcinom jetre (nespecifični) Liver carcinoma (nonspecific)
2015.	7	8	/	/	92
2016.	2	5	/	1	68
2017.	12	8	/	1	45
2018.	11	3	1	/	69
2019.	16	10	/	/	81
Ukupno / Total	48	34	1	2	355

Table 6. Diagnosed and treated patients with liver cancers at the UCG, by type, 2015 – 2019, (n, %)

DISKUSIJA

Tokom analiziranog perioda, u seriji pacijenata sa GIK-om koji su lečeni na UKG-u, uočen je značajan trend porasta broja slučajeva karcinoma sa lokalitetom na jetri i pankreasu; broj slučajeva karcinoma želuca i karcinoma jednjaka je imao stabilan trend, dok je broj slučajeva sa kolorektalnim karcinomom imao promenljivi trend. Ovi trendovi približavaju se trendovima podataka o globalnoj incidenciji GIK-a. Incidenca i mortalitet od hepatocelularnog karcinoma su u porastu u Severnoj Americi i Evropi [17], a kada su u pitanju kanceri pankreasa, i stope incidence i stope smrtnosti, u zemljama sa visokim prihodima, pokazale su ili stabilan trend ili blagi porast [18]. Kanceri želuca su pokazali ujednačen pad

DISCUSSION

In the analyzed period, among a series of patients with GIC, treated at the UCG, a considerably increasing trend of the number of carcinoma cases at the site of the liver and the pancreas was observed; the number of cases with gastric and esophageal carcinoma had a stable trend, while the number of cases with colorectal carcinoma had a variable trend. These trends converge towards the trends of GIC global incidence data. The incidence and mortality of hepatocellular carcinoma have been increasing in North America and Europe [17], and, for pancreatic cancers, both incidence and mortality rates in high-income economies have been either stable or slightly increasing [18]. Gastric cancers

u incidenci tokom proteklih decenija, što se pripisuje boljim praksama u čuvanju hrane [18].

Kada je u pitanju histološki tip, na svetskom nivou, skvamozni karcinom je i dalje najčešći tip karcinoma jednaka, mada je, u zapadnim zemljama, to adenokarcinom. Veruje se da je porast broja slučajeva podtipa adenokarcinoma u vezi sa porastom incidence gojaznosti, gastroezofagealnog refluksa i Barrettovog jednjaka, a da zavisi od genomske nestabilnosti, rase i pola pacijenta [19].

Razvojem dijagnostičkih procedura i antibiotika za lečenje *H. pylori* došlo je do unapređenja u lečenju peptičkih ulkusa [20-22] i pacijenata sa povećanim rizikom od raka želuca [23-27]. Iako eradikacija *H. pylori* može da smanji broj slučajeva raka želuca, broj slučajeva lečenja terapijom eradikacije se povećava [28-32]. Pregledni rad, koji su objavili Satoki Šičijo i Jošihiro Hirata, potvrdio je da postoji potreba za uspostavljanjem programa praćenja pacijenata nakon uspešne eradikacije *H. Pylori*, prema stratifikaciji rizika, odnosno, na osnovu karakteristika i prediktora gastričnog kancera [33].

Kolorektalni kancer je najčešći tip GIK-a u Evropi, sa 342.137 novih slučajeva (14,3% svih kancera) [26,34-41]. Ista incidenca je zabeležena i u Severnoj Makedoniji, što je evidentno iz podataka Direkcije za e-zdravlje i potvrđeno analizom podataka UKG-a. Literatura ukazuje na to da su ishrana i gojaznost među glavnim faktorima rizika za kolorektalni kancer [42]. U Severnoj Makedoniji, nezdrave navike u ishrani su veoma zastupljene, sa prosečnim dnevnim unosom masti od 34,1% (u poređenju sa preporučenim unosom od < 30%), izuzetno visokim unosom natrijuma od 7.883 mg (u poređenju sa preporučenom vrednosti od 500 – 2500 mg), i visokim unosom soli, što su sve posledice visokog stepena konzumacije prerađene hrane [43].

Uprkos napretku u saznanjima o potencijalnim faktorima rizika koji uzrokuju rak pankreasa, kao i novim dostupnim alatima za rano dijagnostikovanje, procenjuje se da će doći do porasta incidence ove vrste kancera. Iako je uzrok raka pankreasa složen i multifaktorski, pušenje cigareta [10] i porodična istorija su dominantni faktori [11]. Rak pankreasa se uglavnom deli na dva tipa: adenokarcinom pankreasa, koji je najčešći (85% slučajeva) i koji nastaje u egzokrinim žlezdama pankreasa, i neuroendokrini tumor pankreasa (*Pan-NET*), koji je ređi (manje od 5%) i nastaje u endokrinom tkivu pankreasa [44]. Adenokarcinom pankreasa ima veoma lošu prognozu, obično, nakon uspostavljanja dijagnoze, 24% pacijenata ima jednogodišnje, a 9% petogodišnje preživljavanje [44].

Hepatocelularni karcinomi čine 90% primarnih kancera jetre i predstavljaju veliki zdravstveni problem na svetskom nivou. Postoji niz glavnih infektivnih,

have shown a uniform decline in incidence over the decades, which has been attributed to better food preservation practices [18].

With regard to the histological type, globally, squamous cell carcinoma remains the most common type of esophageal carcinoma, although in Western countries, it is adenocarcinoma. It is believed that the rise of the number of adenocarcinoma subtype cases corresponds to a rise in the incidence of obesity, gastro-esophageal reflux disease, and Barrett's esophagus, and depends on the genomic instability, race, and gender of the patient [19].

The development of diagnostic procedures and antibiotics for *H. pylori* have improved the treatment of peptic ulcers [20-22] and patients with increased risk of gastric cancer [23-27]. Even though eradication of *H. pylori* can reduce the number of gastric cancer cases, the number of cases treated with eradication therapy is increasing [28-32]. A review by Satoki Shichijo and Yoshihiro Hirata confirmed the need for the establishment of a surveillance program of patients after a successful *H. Pylori* eradication, according to risk stratification i.e., the characteristics and predictors of gastric cancer [33].

Colorectal cancer is the most common type of GIC in Europe, with 342,137 new cases (14.3% of all cancers) [26,34-41]. The same incidence is in North Macedonia, as evident in data from the Directorate for E-health and confirmed with the analysis of the UCG data. Literature suggests that diet and obesity are among the main risk factors for colorectal cancer [42]. In North Macedonia, unhealthy dietary habits are very prevalent, with average daily intake of fats of 34.1% (compared with < 30% recommended intake), exceptionally high sodium intake of 7,883 mg (compared with the recommended value of 500 – 2500 mg), and high salt intake, which are all the result of a high consumption of processed foods [43].

Despite advancement in the knowledge of potential risk factors that cause pancreatic cancer, as well as newly available tools for early diagnosis, its incidence is estimated to increase. Although the cause of pancreatic cancer is complex and multifactorial, cigarette smoking [10] and family history are dominant [11]. Pancreatic cancer is mainly divided into two types: pancreatic adenocarcinoma, which is the most common (85% of cases) arising in the exocrine glands of the pancreas, and pancreatic neuroendocrine tumor (*Pan-NET*), which is less common (less than 5%) and occurs in the endocrine tissue of the pancreas [44].

Pancreatic adenocarcinoma has a very poor prognosis, typically after diagnosis, only 24% of people survive 1 year, and 9% live for 5 years [44].

Hepatocellular carcinoma represents about 90% of primary liver cancers and constitutes a major global

metaboličkih i naslednih faktora rizika, kao i faktora rizika vezanih za način života, i kada je u pitanju HCK i kada je u pitanju ICK. Neki od ovih faktora rizika se ili potencijalno mogu sprečiti (na primer, upotreba alkohola i duvana), ili se, u ovom trenutku, mogu lečiti (npr. infektivni hepatitis). U većini slučajeva, molekularni put ili mehanizam putem kojeg ovi etiološki faktori izazivaju primarni kancer jetre, nije dobro definisan [45].

Holangiokarcinom je drugi po učestalosti kancer jetre sa klinički tihim nastankom i napredovanjem i sa rastućom incidencom na svetskom nivou [46]. Naši rezultati pokazuju da i Severna Makedonija ima sličnu incidencu i rastući trend. Usled nedostataka markera za rano dijagnostikovanje ovog kancera, većina pacijenata sa holangiokarcinomom bude identifikovana u podmaklom stadijumu i umire od metastaza [46].

U našem uzorku uočen je vrlo visok broj slučajeva nespecifičnog karcinoma jetre. U većini ovih slučajeva obavljena je histopatološka analiza, ali su rezultati bili nedovoljni da bi obezbedili definitivniju dijagnozu koja bi omogućila jasniju diferencijaciju. Ovo može potencijalno da onemogućiti izbor adekvatne terapije i obezbeđivanje boljeg ishoda za pacijente [47].

Za preciznu analizu gastrointestinalnih karcinoma, potrebni su detaljniji podaci za celu zemlju, uključujući tu i faktore rizika, lokalizaciju i stadijume. Takođe, ustanovljen je veliki broj slučajeva karcinoma jetre, i, mada je izvestan nivo dijagnostike sproveden, evidentno je da postoji potreba za više dijagnostičkih resursa i alata, kako bi se omogućilo precizno utvrđivanje dijagnoze. Ovo će potencijalno pomoći u utvrđivanju najadekvatnije terapije i lečenja, te će obezbediti bolji kvalitet nege i bolje ishode za pacijente.

Preventiva, međutim, ostaje jedna od najisplativijih intervencija. Kako bi se smanjila incidenca kancera gastrointestinalnog trakta, važno je da postoje dobro organizovani nacionalni programi skrininga, u svrhu prevencije i ranog otkrivanja ovih bolesti, a naročito kolorektalnog kancera. Takođe, pristup terapiji za hepatitis B i C je važan za prevenciju karcinoma jetre.

Na kraju, ali ne i najmanje važno, dugoročna prevencija kancera gastrointestinalnog trakta u velikoj meri zavisi od postojanja i implementacije zdravstvene politike za prevenciju glavnih faktora rizika, kao što su: gojaznost, pušenje, nezdrava ishrana, i fizička neaktivnost. Ovo bi trebalo, između ostalog, da uključuje i promovisanje zdravih životnih navika, kao i smanjenje pristupa nezdravim izborima.

ZAKLJUČAK

Podaci UKG-a ukazuju na trend porasta broja slučajeva gastrointestinalnih kancera, posebno kod muškaraca, pri čemu preovlađuju kolorektalni, i kanceri pankreasa

health problem. There are a number of major infectious, lifestyle, metabolic, and hereditary risk factors for both HCC and ICC. Some of these risk factors are either potentially preventable (e.g., alcohol and tobacco use) or are currently treatable (e.g., hepatitis infection). In most cases, the molecular pathway or mechanism by which these etiological factors cause primary liver cancer, has not been well delineated [45].

Cholangiocarcinoma is the second most common liver cancer with a clinically silent development and an increasing global incidence [46]. Our results show that North Macedonia has a similar incidence and an increasing trend. Due to the absence of early markers for its diagnosis, most cholangiocarcinoma patients are identified at an advanced stage and die of metastases [46].

A very large number of non-specific liver carcinoma cases was observed in our sample. In most of these cases histopathological examination was performed, but the results were insufficient to give a definitive and more differentiating diagnosis. This can potentially impede choosing the appropriate treatment and ensuring a better patient outcome [47].

For a precise analysis of gastrointestinal carcinomas, more detailed data for the entire country are needed, including risk factors, localization, and staging. In addition, a large number of non-specific liver carcinoma cases was observed, and, while some level of diagnostics was performed, it is evident that there is a need for more diagnostic resources and tools, in order to enable a precise determination of the diagnosis. This will potentially assist in determining the most appropriate therapy and treatment and enable better quality of care and patient outcome.

Prevention, however, remains one of the most cost-effective interventions. To decrease the incidence of GI cancers, it is important to have well-organized national screening programs for prevention and early detection, especially of colorectal cancer. In addition, access to therapy for hepatitis B and C is important in the prevention of liver carcinoma.

Last but not the least, prevention of GI cancers in the long term largely depends on having and implementing policies for the prevention of major risk factors, such as obesity, smoking, unhealthy diet and physical inactivity. This should include, among other things, promoting healthy lifestyles and reducing access to unhealthy choices.

CONCLUSION

The UCG data show an increasing trend of the number of GIC cases, especially in men, with a predominance of colorectal, pancreatic and liver cancer. The establishing

i jetre. Uspostavljanje programa praćenja pacijenata sa GIK-om, stratifikovanih prema riziku, nakon lečenja, moglo bi da pomogne u razumevanju načina da se preokrene napredak bolesti. Podaci UKG pokazuju konvergenciju trenda ka globalnim procenama incidence i prevalence GIK-a. U budućnosti je važno utvrditi u kojoj meri je skrining doprineo ranom otkrivanju ovih kancera, ali i obezbediti pristup terapiji, kao i dostupnost terapije, za hepatitis B i C.

Sukob interesa: Nije prijavljen.

of a surveillance program of risk stratified patients with GIC, after treatment, could help in understanding the ways to reverse the progress of disease. The UCG data show a convergence trend toward global estimates of GIC incidence and prevalence. In future, it is important to determine how much screening has contributed to the early detection of these cancers and to ensure access to and availability of therapy for hepatitis B and C.

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LITERATURA / REFERENCES

1. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin.* 2014 Jul-Aug;64(4):252-71.
2. Rustgi AK, El-serag HB. Esophageal carcinoma. *N Engl J Med* 2014; 371:2499-509.
3. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut.* 2015 Mar;64(3):381-7.
4. Ferlay J, Lam F, Colombet M, Mery L, Pineros M, Znaor A, et al. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer, dostupno na: <https://gco.iarc.fr/today>, pristupljeno: 20. januar 2021.
5. Shichijo S, Hirata Y. Characteristics and predictors of gastric cancer after H. pylori eradication; *World J Gastroenterol* 2018; 24(20): 2163-72.
6. Hsu PI, Lai KH, Hsu PN, Lo GH, Yu HC, Chen WC, et al. Helicobacter pylori infection and the risk of gastric malignancy. *Am J Gastroenterol* 2007; 102:725-30.
7. Shichijo S, Hirata Y, Niikura R, Hayakawa Y, Yamada A, Koike K. Association between gastric cancer and the Kyoto classification of gastritis. *J Gastroenterol Hepatol* 2017; 32: 1581-6.
8. Handa Y, Saitoh T, Kawaguchi M, Misaka R, Ohno H, Tsai CR, et al. Association of Helicobacter pylori and diffuse type gastric cancer. *J Gastroenterol* 1996; 31 Suppl 9: 29-32.
9. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res.* 2004; 64(7):2634-8.
10. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Lohr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. *Pancreatol.* 2015; 15(1):8-18.
11. Wild C. World cancer report 2014. Wild CP, Stewart BW, editors. Geneva, Switzerland: World Health Organization; 2014.
12. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology.* 2010; 51(5):1820-32.
13. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011; 34(3):274-85.
14. Nouredin M, Rinella ME. Nonalcoholic Fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. *Clin Liver Dis* 2015; 19: 361-79.
15. Satapathy SK, Sanyal AJ. Epidemiology and Natural History of Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; 35: 221-35.
16. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; 365: 1118-1127.
17. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology.* 2019 Jan 1;156(2):477-91.
18. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global burden of 5 major types of gastrointestinal cancer. *Gastroenterology.* 2020 Jul 1;159(1):335-49.
19. Lepage C, Drouillard A, Jouve JL, Faivre J. Epidemiology and risk factors for oesophageal adenocarcinoma. *Dig Liver Dis.* 2013 Aug;45(8):625-9.
20. Wang C, Yuan Y, Hunt RH. The association between Helicobacter pylori infection and early gastric cancer: a meta-analysis. *Am J Gastroenterol* 2007; 102: 1789-98.
21. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Japan Gast StudyGroup. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008; 372: 392-7.
22. Hanaoka N, Uedo N, Shiotani A, Inoue T, Takeuchi Y, Higashino K, et al. Auto-fluorescence imaging for predicting development of metachronous gastric cancer after Helicobacter pylori eradication. *J Gastroenterol Hepatol* 2010; 25: 1844-9.
23. Mori G, Nakajima T, Asada K, Shimazu T, Yamamichi N, Maekita T, et al. Incidence of and risk factors for metachronous gastric cancer after endoscopic resection and successful Helicobacter pylori eradication: results of a large-scale, multicenter cohort study in Japan. *Gastric Cancer* 2016; 19: 911-8.
24. Sugimoto T, Yamaji Y, Sakitani K, Isomura Y, Yoshida S, Yamada A, et al. Neutrophil infiltration and the distribution of intestinal metaplasia is associated with metachronous gastric cancer following endoscopic submucosal dissection. *Can J Gastroenterol Hepatol* 2015; 29: 321-5.
25. Maeda M, Nakajima T, Oda I, Shimazu T, Yamamichi N, Maekita T, et al. High impact of methylation accumulation on metachronous gastric cancer: 5-year follow-up of a multicentre prospective cohort study. *Gut* 2017; 66: 1721-3.
26. Shiotani A, Haruma K, Graham DY. Metachronous gastric cancer after successful Helicobacter pylori eradication. *World J Gastroenterol* 2014; 20: 11552-9.
27. Kobayashi M, Sato Y, Terai S. Endoscopic surveillance of gastric cancers after Helicobacter pylori eradication. *World J Gastroenterol* 2015; 21:10553-62.
28. Ohba R, Iijima K. Pathogenesis and risk factors for gastric cancer after Helicobacter pylori eradication. *World J Gastrointest Oncol* 2016; 8: 663-72.
29. Kamada T, Hata J, Sugiu K, Kusunoki H, Ito M, Tanaka S, et al. Clinical features of gastric cancer discovered after successful eradication of Helicobacter pylori: results from a 9-year prospective follow-up study in Japan. *Aliment Pharmacol Ther* 2005; 21: 1121-6.
30. Maehata Y, Nakamura S, Esaki M, Ikeda F, Moriyama T, Hida R, et al. Characteristics of Primary and Metachronous Gastric Cancers Discovered after Helicobacter pylori Eradication: A Multicenter Propensity Score-Matched Study. *Gut Liver* 2017; 11: 628-34.

31. Nishizawa T, Suzuki H, Arano T, Yoshida S, Yamashita H, Hata K, et al. Characteristics of gastric cancer detected within 1 year after successful eradication of *Helicobacter pylori*. *J Clin Biochem Nutr* 2016; 59: 226-30.
32. Matsuo T, Ito M, Tatsugami M, Boda T, Takata S, Tanaka S, et al. Gastric cancer development after *Helicobacter pylori* eradication therapy: a new form of gastric neoplasia. *Digestion* 2012; 85: 61-7.
33. Yamamoto K, Kato M, Takahashi M, Haneda M, Shinada K, Nishida U, et al. Clinicopathological analysis of early-stage gastric cancers detected after successful eradication of *Helicobacter pylori*. *Helicobacter* 2011; 16: 210-6.
34. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018; 68(6):394- 424.
35. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, Knudsen AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. *Ann Intern Med*. 2014 Jul 15;161(2):104-12.
36. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Expected long-term impact of the German screening colonoscopy programme on colorectal cancer prevention: analyses based on 4,407,971 screening colonoscopies. *Eur J Cancer*. 2015 Jul;51(10):1346-53.
37. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Prevention, early detection, and overdiagnosis of colorectal cancer within 10 years of screening colonoscopy in Germany. *Clin Gastroenterol Hepatol*. 2015 Apr;13(4):717-23.
38. Brenner H, Kretschmann J, Stock C, Hoffmeister M. Expected long-term impact of screening endoscopy on colorectal cancer incidence: a modelling study. *Oncotarget*. 2016 Jul 26;7(30):48168-79.
39. Chen C, Stock C, Hoffmeister M, Brenner H. How long does it take until the effects of endoscopic screening on colorectal cancer mortality are fully disclosed?: a Markov model study. *Int J Cancer*. 2018 Dec 1;143(11):2718-24.
40. Cottet V, Jooste V, Fournel I, Bouvier AM, Faivre J, Bonithon-Kopp C. Long-term risk of colorectal cancer after adenoma removal: a population-based cohort study. *Gut*. 2012 Aug;61(8):1180-6.
41. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol*. 2012; 23(7):1880-8.
42. Alsherdah N, Akhtar S. Diet, obesity and colorectal carcinoma risk: results from a national cancer registry-based middle-eastern study. *BMC Cancer*. 2018;18(1):1-1227.
43. Milevska Kostova N, Chichevalieva S, Ponce NA, van Ginneken E, Winkelmann J. The fYR of Macedonia: Health System Review. *Health Systems in Transition*. 2017;19(3):1-160.
44. Adams LA, Lindor KD. Nonalcoholic fatty liver disease. *Ann Epidemiol*. 2007;17(11):863-9.
45. Margini C, Dufour JF. The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. *Liver Int*. 2016 Mar;36(3):317-24.
46. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver International*. 2019;39:19-31.
47. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *Journal of hepatology*. 2018 Jul 1;69(1):182-236.