SAŽETAK

Uvod: Globalno opterećenje društva gastrointestinalnim kancerom (GIK) raste. Tu- mori želuca, debeleg creva i jetre su među pet najčešćih gastrointestinalnih karcino-
ma kod muškaraca i žena širom sveta. Incidencija GIK-a pokazuje značajne varijacije
u Europi i Severnoj Americi. Ovaj rad razmatra znake konvergencije bolničkog mor-
bideta u Severnom Makedoniji ka procenjenim vrednostima globalnog morbiditeta.

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

Materijal i metode: Retrospektivna longitudinalna analiza obuhvatila je seriju
slučajeva sa GIK-om, na najvećoj, Univerzitetskoj klinici za gastroenterohepato-
logiju (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 Univerzitetskoj klinici za gastroentero-
hepatologiju 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 incidencije
liver malignancy. Most patients were in the 60 – 69 age group, with the excep-
tion 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.

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

Ključne reči: gastrointestinalni karcinom, rak želuca, rak pankreasa, hepatoce-
lularni 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.

Materials and methods: A retrospective longitudinal analysis included a series of cases with GIC, at the University Clinic of Gastroenterology Hepatology (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 hepatocellular 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 excep-
tion of hepatocellular 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 increas-
ing 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, hepato-
cellular cancer, esophageal cancer, colorectal cancer

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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 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 11h 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...
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.

MATERIALS 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 2020.

| Tabela 1a. Indikatori kancera, Severna Makedonija, 2018. i 2020. godina |
|------------------|------------------|------------------|------------------|------------------|------------------|
|                  | Muškarci | Žene | Oba pola | Muškarci | Žene | Oba pola |
|------------------|-----------|------|----------|-----------|------|----------|
| Populacija, br.  | 1,042,282 | 1,042,774 | 2,085,056 | 1,042,282 | 1,042,774 | 2,085,056 |
| Novi slučajevi raka, br. | 4,258 | 3,549 | 7,807 | 4,247 | 3,385 | 7,632 |
| Stopa incidencije 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 umiranja 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 prevalencijom, br. / 5-year prevalent cases, n | 8,252 | 9,154 | 17,406 | 9,581 | 9,265 | 18,846 |
| Prvih 5 najčešćih kanceria, izuzetkom kanceria kože koji nisu melanomi (rangirano po slučajevima) / Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases) | PI / L | D / Br | PI / L | PI / L | D / Br | PI / L |
| | P / / | KR / CR | P / / | P / | KR / CR | D / Br |
| | KR / CR | CoU / CoU | KR / CR | KR / CR | CoU / CoU | KR / CR |
| | Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases) / Source: Global Cancer Observatory [4]; L – lung; P – prostate; CR – colorectum; Bl – bladder; S – stomach; CoU – corpus uteri; CoU – corpus uteri; D – dujka; M – melanom | B / B1 | PI / L | P / P | B / B1 | PI / L | P / P |
| | Ž / S | CoU / CoU | CoU / CoU | Ž / S | CoU / CoU | CoU / CoU |
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Tabela 1b. Indikatori kancerova Evropske regije SZO u 2018. i Zapadne Evrope u 2020. godini

|                        | 2018, godina / 2018, year | 2020, godina / 2020, year |
|------------------------|---------------------------|---------------------------|
|                        | Males         | Females    | Both sexes | Males         | Females    | Both sexes |
| Population, n          | 447,845,844 | 447,986,637 | 2,085,056   | 96,374,578    | 99,771,743 | 196,146,321 |
| Stopa incidencije standardizovana prema godinama starosti (svet) / Age-standardized incidence rate (world) | 311.3        | 239.8      | 268.6       | 365.3        | 294.3      | 325.0       |
| Risk 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       | 27.9        |
| Stopa smrtnosti standardizovana prema godinama starosti (svet) / Age-standardized mortality rate (world) | 144.4        | 85.9       | 111.0       | 127.1        | 83.9       | 103.3       |
| Risk za umiranja 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 kancerova koje nisu melanom (rangirano po slučajevima) / Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases) | P / P         | D / Br     | D / Br      | P / P         | D / Br     | P / P        |
|                        | P / L         | KR / CR    | KR / CR     | P / L         | KR / CR    | P / L       |
| Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases) / Source: Global Cancer Observatory \[4\]; L – lung; P – prostate; CR – colorectum; Bl – bladder; St – stomach; CeU – cervix uteri; CoU – corpus uteri; D – dojka; M – melanom | 1. Pl / L     | KPI / L    | KR / CR      | PI / L       | KR / CR  | P / L        |
|                        | Z / S         | CoU / CoU  | P / P        | Z / S         | CoU / CoU  | M / M       |

Izvor: Globalna opservatorija za rak \[4\]; Pluća; Želudac; Čejtrak; Června veziva; Dojka; Melanomi (rangirano po slučajevima).

starosti kao i rizik od bolovanja od kancerova opali između 2018. i 2020. godine, zajedno sa indikatorima mortaliteta u Severnoj Makedoniji (Tabela I.1). Dok je stopa incidencije niža, stopa smrtnosti je viša nego u zemljama Evropske regije SZO i zemljama Zapadne Evrope (Tabela I.2).

Tokom petogodišnjeg perioda, ukupno 2,831 pacijent sa GSK-om je lečen na UKG-u, od kojih je 1.484 (53%) imalo kolorektalni kancer, 763 (27%) pacijentana je imalo rak želuca, a 88 (3%) pacijentana je imalo rak jednjaka. Iako su kanceri jetre bili manje zastupljeni, čak i 15% pacijenata je imalo rak jednjaka. Rak jednjaka je dijagnostikovan kod 88 pacijenata, od kojih 73 muškog i 15 ženskog pola, u rasponu starosnih grupa. Slučajevi pacijenata, vraćeno, kancerima, starosti i polu, tokom posmatranog vremenskog perioda (Tabela 2).

Tabela 2. Broj pacijenata sa rakom jednjaka dijagnostikovanih i lečenih na UKG-u, između 2015. i 2019. godine

| Godina | Br. pacijenata | Muški pacijenti, br. (%) | Ženski pacijenti, br. (%) |
|--------|----------------|--------------------------|--------------------------|
|        | No. of patients | Male patients, N (%)     | 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%)                  |
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. 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 age group.

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

| Year | No. of patients | Male patients, N (%) | 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%)               |
| Total| 763             | 532 (70%)            | 231 (30%)              |

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

| Year | No. of patients | Male patients, N (%) | 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%)              |
| Total| 1,484           | 827 (56%)            | 657 (44%)              |
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**DISKUŠIJA**

Tokom analiziranog perioda, u seriji pacijenata sa GIK-a kojima je lečeno na UKG-u, uočen je značajan trend porasta broja slučajeva karcinoma sa lokalizacijom 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. Incidencija i mortalitet od hepatocelularnog karcinoma su u porastu u Severnoj Americi i Evropi [17], a kada su u pitanju kanceri pankreas, šećera i stope smrtnosti, u zemljama sa visokim prihodima, pokazale su i stabilan trend ili banji porast [18]. Kanceri šećera 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 incidencije 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 jednokrakog, mada je, u zapadnim zemljama, to adenokarcinom. Veruje se da je porast broja slučajeva podtipa adenokarcinoma u vezi sa porastom incidencije gojaznosti, gastroezofagealnog refluka i Baretovog jednja-ko-gus, i depends on the genomic instability, race, and gender of the patient [19].

Razvojem dijagnostičkih procedura i antibiotika za lečenje H. pylori došlo je do unapređenja u lečenju pep-tičkih ulkuza [20-22] i pacijenata sa povećanim rizikom od raka želuća [23-27]. Iako eradijacija H. pylori može da smanji broj slučajeva raka želuća, broj slučajeva lečenja terapijom eradijacije se povećava [28-32]. Pregledni rad, koji su objavili Satokı Şičijo i Jošihiro Hirata, potvrdio je da postoji potreba za uspostavljanjem programa praćenja pacijenata nakon uspešne eradijacije H. Pylori, prema stratifikaciji rizika, odnosno, na osnovu karakteristika i prediktora gastričnog kancer [33].

Kolorektalni kancer je najčešći tip GIK-a u Evropi, sa 342.137 novih slučajeva (14,3% svih kancer) [26,34-41]. Ista incidencija je zabeležena i u Severnoj Makedoniji, što je evidentno iz podataka Direkcije za e-zdravlje i po-

324.137 novih slučajeva (14,3% svih kancer) [26,34-41]. Ista incidencija je zabeležena i u Severnoj Makedoniji, što je evidentno iz podataka Direkcije za e-zdravlje i po-

drenoju sa preporučenim unosom od < 30%), izuzetno visokim unosom natrijuma od 7.883 mg (u poređenju sa preporučenim unosom od < 30%), izuzetno visokim unosom natrijuma od 7.883 mg (u poređenju sa preporučenim unosom od < 30%), i visokim unosom soli, što su sve posledice visokog stepena konzumacije preradene hrane [43].

Uprkos napretku u saznanjima o potencijalnim faktorima rizika koji uzrokuju rak pankreasa, kao i novim dostupnim alatima za rano dijagnostikovanje, proce-
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A SERIES OF PATIENTS TREATED AT THE UNIVERSITY CLINIC, BETWEEN 2015 AND 2019

Metabolic and related factors play a role in the development of liver cancer, and the factors that are usually associated with liver cancer are obesity, smoking, unhealthy diet and high alcohol consumption. The presence of these factors can lead to liver injury and cancer development. Therefore, it is important to reduce the incidence of liver cancer by promoting healthy lifestyles and reducing access to unhealthy choices. 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 diagnostic examination was performed, the results were insufficient to give a definitive and differentiating diagnosis. This can potentially improve the appropriate treatment and ensuring a better 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 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 GI 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 UCG pokazuju konvergenciju trenda ka globalnim procenama incidencije i prevalencije GIK-a. U budućnosti je važno utvrditi u kojoj meri je skrining doprinio ranom otkrivanju ovih kanceri, ali i obezbediti pristup terapiji, kao i dostupnost terapije, za hepatitis B i C.

**Sukob interesa:** Nije prijavljen.

### 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, Soejomotaram 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, Merry L, Pinneros 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 eradiation; 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. Characteristics and predictors of gastric cancer after H. pylori eradication; World J Gastroenterol 2018; 24(20): 2163-72.

10. Hidalgo M, Cescato RM, Benedito MC, Neoptolemos J, Paterson JC, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res. 2004; 64(7):2634-8.

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. Nourreddin M, Rinella ME. Nonalcoholic fatty liver disease, diabetes, obesity, and hepatocellular carcinoma. Clin Liver Dis 2015; 19: 361-79.

15. Satapathy SK, Sanayi 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, Douilloud 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. Kusaka 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, Shiokami A, Inoue T, Takeuchi Y, Higashino K, et al. Auto-fluorescence imaging for predicting development of metachronous gastric cancer after Helicobacter pylori eradiation. J Gastroenterol Hepatol 2010; 25: 1844-9.

23. Mori G, Nakajima T, Asaka K, Shimazu T, Yamamichi N, Maekita T, et al. Incidence and risk factors for metachronous gastric cancer after endoscopic resection and successful Helicobacter pylori eradiation: results of a large-scale, multicenter cohort study in Japan. Gastric Cancer 2016; 19: 911-8.

24. Sugimoto T, Yamaji Y, Sakatani 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. Shiozaki H, Saruta K, Harauma 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 eradiation. 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 PharmacolTher;2005; 21: 1211-6.

30. Maehata Y, Nakamura S, Eskai 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 BiochemNutr2016; 59: 226-30.

32. Matsuo T, Ito M, Tatsuogami 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. Alsheridah 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.