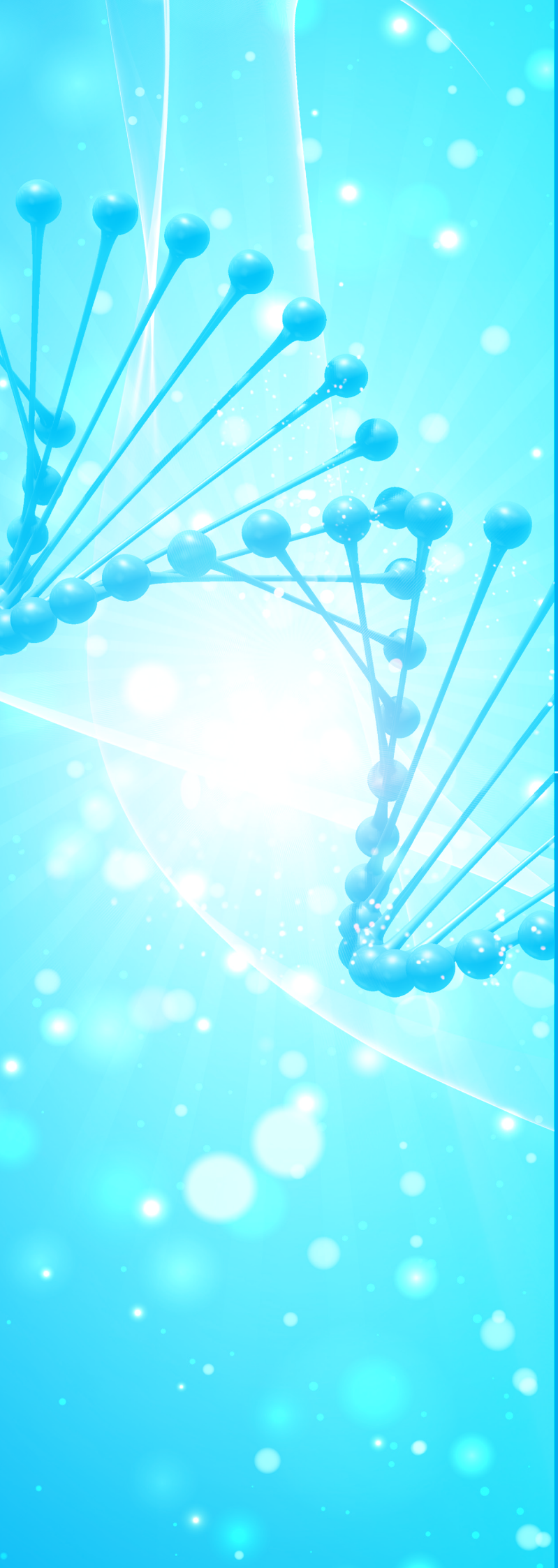

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FORENZIČKI ASPEKTI KOMPLIKOVANIH SAMOUBISTAVA

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SAŽETAK

Uvod/Cilj: Komplikovana samoubistva (KS) su ona do kojih dolazi nakon što osoba počini jedno ili više ubistava. Ovaj društveni fenomen se javlja u kontekstu porodičnih tragedija. Učestalost je niska, ali se zbog tragičnog ishoda i posledica koje ostavlja na društvo javlja potreba istraživača širom sveta da obrađuju ovu temu. Cilj ove studije je analiza forenzičkih aspekata KS sa posebnim osvrtom na demografske karakteristike izvršilaca, način izvršenja ubistva i samoubistva i međusobni odnos žrtava i počinilaca KS, a kako bi se razumele okolnosti pod kojima nastaje, ali i rizik od pojave ovog društvenog fenomena.
Metode: Ovo je retrospektivna deskriptivna studija koja je obuhvatila osmogodišnji period (2015-2022). U studiju su uključeni svi pojedinci koji su izvršili samoubistvo nakon što su počinili jedno ili više ubistava. Podaci su dobijeni iz obdukcionih zapisnika i policijskih izveštaja osoba obdukovanih na Institutu za sudsku medicinu u Beogradu. Analizirane su demografske karakteristike, poreklo smrti, broj i lokalizacija rana, okolnosti slučaja, heteroanamnestički podaci, izjave svedoka, relacije između žrtava i ubica, motivi i toksikološke analize.
Rezultati: Izdvojeno je 19 KS i ukupno 39 nastradalih osoba. Žrtve su većinski bile ženskog (80%), a ubice muškog pola (89,5%). Ubice su od žrtava u proseku bile starije pet godina. Najveći broj ubica nije bio visoko obrazovan (84,2%), a veliki deo je imao neku psihijatrijsku dijagnozu (47,4%). Za obe komponente KS najčešće je korišćeno vatreno oružje (70-73,7%). Najviše se radilo o porodičnim odnosima (90%), najčešće partnerskim (60%). Vodeći motiv je bila ljubomora (45%), a potom loša finansijska i porodična situacija (25%) i milosrđe (15%).
Zaključak: KS nastaju u okviru porodice, najčešće vatrenim oružjem od strane muškaraca iz nižeg ili srednjeg društvenog sloja, koji su prethodno pokazali kritično ponašanje. Razlozi koji dovode do KS su ljubomora, svađe i bolest. Identifikovanjem komponenti KS moguće je sprečiti njihovu pojavu.

Ključne reči: komplikovano samoubistvo, vatreno oružje, psihijatrijsko oboljenje, ljubomora,sudska medicina

Uvod

Komplikovana samoubistva (KS) su ona samoubistva koja nastaju kada pojedinac neposredno nakon zadesnog ili, što je i češće, namernog ubistva jedne ili više drugih osoba, ubije sebe (1,2). Različiti autori na osnovu vremenske distance između ubistva i samoubistva kao dve osnovne komponente ovog fenomena drugačije definišu KS (3). Jedni priznaju samo ubistva praćena samoubistvima počinjenim u prva 24 sata, a drugi podrazumevaju duži protok vremena, od nekoliko dana, do toga da se u nekim studijama ne koristi vremensko ograničenje (4–6). U novije vreme većina autora za vremeski okvir između ova dva događaja uzima period do 72 sata, odnosno do sedam dana, što podrazumeva da su u tom periodu nastale samoubilačke povrede, a sama smrt se može dogoditi i nakon definisanog perioda. Mada je učestalost pojave ovih događaja relativno retka u poređenju sa drugim zločinima koji imaju tragičan ishod, a što potvrđuju različite studije, oni ipak privlače pažnju, kako istraživača, tako i javnosti (7). Razlog za to je što se KS javljaju u kontekstu

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FORENSIC ASPECTS OF HOMICIDE-SUICIDE PHENOMENA

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SUMMARY

Introduction/Aim: Homicide-suicides (H-S) are those suicides that occur after a person commits one or more murders. This social phenomenon occurs in the context of family tragedies. The frequency is low, but due to the tragic outcome, there is a need for researchers worldwide to address this topic. The aim of this study was to analyze the forensic aspects of H-S with special reference to the demographic characteristics of the perpetrator, the way of committing murder and suicide, and the mutual relationship between the victim and the perpetrator of H-S, in order to understand the circumstances under which it occurs, as well as the risk of this social phenomena.
Methods: This retrospective descriptive study covered an eight-year (2015-2022) period. The study included individuals who committed suicide after committing one or more homicides. Data were obtained from autopsy and police reports from the Institute of Forensic Medicine in Belgrade. Demographic characteristics, circumstances of the case, number and localization of wounds, hetero-amnestic data, relationships between victims and killers, motives, and toxicological analysis were analyzed.
Results: 19 cases of H-S and 39 victims were observed. The majority of victims were female (80%), and the killers were male (89.5%). The killers were 4.9 years older than the victims. The highest percentage of murderers were not been highly educated (84.2%), and a lot of them had a psychiatric diagnosis (47.4%). For both components of H-S, firearms were most often used (70-73.7%). Most of them were in the family (90%), specifically in emotional relationships (60%). The leading motives were jealousy (45%), family and financial problems (25%), and mercy (15%).
Conclusion: H-S occurs within the family, most often using firearms by men from the lower social class, who have previously shown critical behavior. The reasons that lead to H-S are jealousy, quarrels, and illness. By identifying some of the components of H-S, it is possible to prevent their occurrence.

Keywords: homicide-suicide, firearms, mental illness, jealousy, forensic medicine

Introduction

Homicides-suicides (H-S) are those suicides that occur when a person, immediately after the accidental, or more frequently, the intentional murder of one or more persons, kills himself (1,2). Different authors, according to the time distance between the murder and suicide as two basic components of this phenomenon, define H-S in different ways (3). Some recognize only those murders which are followed by suicides committed in the first 24 hours, while others include a longer period of time lasting up to several days, while in some studies, there are no time limitations (4,6). Recently, most authors have considered the time frame between these two events to be 72 hours, that is, up to seven days, which means that suicidal injuries occurred during that period, while death itself could happen after the defined period. Although the frequency of occurrence of these events is relatively rare in comparison to other crimes that have a tragic outcome, which is confirmed in various studies, they attract the attention of researchers, and public, as well (7). The reason for that lies in the fact that H-S occurs in the context of family tragedies, which entails numerous

porodičnih tragedija, što sa sobom povlači brojna moralna, etička, psihijatrijska i sudskomedicinska pitanja. Okolnosti i način dešavanja ovog društvenog fenomena ostavljaju posledice na preživele pojedince, ali i na društvo u celini (8).

Važnost ovog fenomena leži i u činjenici da različiti autori na drugačiji način sagledavaju ovaj tragični događaj. Prvi je taj da se radi o tipičnom ubistvu na koje se nadovezuje samoubistvo usled osećanja kajanja ili straha od predstojeće kazne, drugo je to da se radi o dvostepenom samoubistvu (usled intimne povezanosti žrtve i počinioca), a neki drugi autori ga smatraju izolovanim fenomenom koji se razlikuje od tipičnih ubistava i samoubistava po svojim karakteristikama i okolnostima pod kojima se dešava (8–10).

Uzimajući u obzir nisku učestalost ove pojave, istraživanja su malobrojna i najčešće su u pitanju studije deskriptivnog tipa. Prve studije, ali i najveći broj istih je sproveden u Sjedinjenim Američkim Državama (1,11,12). U Republici Srbiji, kao i u mnogim zemljama širom sveta, ne postoji registar KS, koji bi mogao da služi kao izvor informacija istraživačima koji su zainteresovani da obrađuju ovu temu i koji bi omogućio praćenje stope javljanja i menjanje karakteristika KS kroz vreme (7).

Cilj ove studije je analiza forenzičkih aspekata KS sa posebnim osvrtom na demografske karakteristike izvršilaca, način izvršenja ubistva i samoubistva i međusobni odnos žrtava i počinilaca KS, a kako bi se razumele okolnosti pod kojima nastaje, ali i rizik od pojave ovog društvenog fenomena.

Metode

Kao izvor podataka korišćenih u svrhe ove deskriptivne retrospektivne studije analizirani su obdukcioni zapisnici, policijski izveštaji kao i heteroanamnestički podaci dobijeni od osoba najbližih preminulima, a koji se tiču okolnosti slučajeva samoubistava i ubistava osoba koje su obdukovane na Institutu za sudsku medicinu Medicinskog fakulteta u Beogradu, u periodu 2015-2022. godine.

Imajući u vidu činjenicu da se u ovoj studiji analizira redak fenomen, kao i prethodno pomenute različite literaturne podatke koji se tiču vremenske diskrepance između počinjenja ubistava i samoubistva (3–6), u našu studiju su uključeni svi oni slučajevi osoba koje su izvršile samoubistvo, nakon što su u prethodnih sedam dana počinile jedno ili više ubistava. Pored obdukcionih zapisnika počinilaca, analizirani su i obdukcioni zapisnici žrtava.

Razmatrane su opšte demografske karakteristike pojedinaca koji su bili izvršioci kao što su pol, uzrast, obrazovanje, bračni status i slično. Prikupljeni su i podaci o polu i uzrastu žrtava, kao i relaciji sa počiniocima. Iz policijskih izveštaja prikupljene su, a kasnije i analizirane, okolnosti o slučaju koje se tiču mesta događaja, oružja samoubistava i oružja ubistava. Iz obdukcionih zapisnika prikupljeni su podaci o broju i lokalizaciji rana, kao i prirodi, tj. poreklu smrti, kako ubica, tako i žrtava. Prikupljeni su i podaci koji se tiču prethodne osuđivanosti ubica, ali i podaci koji govore o tome da li je oružje kojim je izvršeno KS bilo u posedu ubice, pa samim tim i lako dostupno. U obzir i razmatranje su uzete sve izjave svedoka, ukoliko ih je bilo za dati slučaj. Iz heteroanamnestičkih podataka dobijenih tokom razgovora obducenata sa članovima uže porodice žrtava prikupljeni su podaci o slučaju, okolnosti koje se tiču potencijalnih motiva, ali i informacije o tome da li su izvršioci bolovali od neke somatske ili psihijatrijske bolesti, da li su konzumirali narkotike i alkohol tokom života, kao i sve atipično klasifikovane informacije koje su istraživači smatrali potencijalno korisnim za svrhe ove studije. Podaci o prisustvu narkotika u krvi u trenutku smrti, kao i alkoholemiji, dobijeni su hemijsko-toksikološkim analizama urađenim u Hemijsko-toksikološkoj laboratoriji Instituta za sudsku medicinu Medicinskog fakulteta Univerziteta u Beogradu.

Svi dobijeni podaci su obrađeni programom SPSS 26.0. Obrada rezultata izvršena je primenom deskriptivnih statističkih metoda. Svi podaci izraženi su u obliku aposlutnih i procentualnih učestalosti.

Rezultati

U analiziranom osmogodišnjem periodu, na Institutu za sudsku medicinu Medicinskog fakulteta Univerziteta u Beogradu, je zabeleženo 19 komplikovanih samoubistava, od čega je u 18 stradala po jedna osoba pre samoubistva, a u jednom slučaju dve. To nam govori o ukupnom broju od 39 tragično nastradalih osoba, tj. 19 ubica i 20 žrtava. Najviše KS se dogodilo u 2015. (n=5) i 2017. (n=6) godini (tabela 1).

Žrtve KS su većinski bile ženskog pola i to 16 od 20 osoba (80%). Raspon njihovih godina je bio od 4 do 91, sa prosečnim uzrastom od 49,2±20,3

moral, ethical, psychiatric and forensic issues. The circumstances and ways of occurrence of this social phenomenon leave consequences for those who survived, and also for society as a whole (8).

The importance of this phenomenon also lies in the fact that different authors perceive this tragic event in a different way. The first refers to a typical murder followed by suicide due to feelings of remorse or fear of impending punishment, the second refers to the two-step suicide (due to the intimate relationship between the victim and the perpetrator), while some other authors consider it to be an isolated phenomenon that differs from typical murders and suicides in terms of its characteristics and circumstances under which it occurs (8,10).

Taking into consideration the low frequency of this phenomenon, there are few research studies and most often they are descriptive studies. The first studies, and also the largest number of them were conducted in the United States of America (1,11,12). In the Republic of Serbia, as well as in many countries around the world, there is no registry of H-S, which could be the source of information for researchers, who are interested in analyzing this topic and which would allow monitoring of the rate of occurrence and the change of the characteristics of H-S over time (7).

The aim of this study is to analyze the forensic aspects of H-S with a special insight into the demographic characteristics of perpetrators, ways of committing murder and suicide, and the relationship between the victims and perpetrators of H-S, in order to understand the circumstances under which it occurs, as well as the risk of occurrence of this social phenomenon

Methods

Autopsy reports, police reports, as well as hetero-anamnestic data, were obtained from persons who were most closely related to the deceased, and which related the circumstances of suicides and murders of persons who were autopsied at the Institute of Forensic Medicine of the Faculty of Medicine in Belgrade in the period 2015-2022, were analyzed as the source of data used for the purpose of this descriptive retrospective study.

Considering the fact that a rare phenomenon is analyzed in this study, as well as the above-mentioned literature data related to the time discrepancy between the murder and suicide (3-6), all cases of persons who committed suicide after having committed one or more murders in the previous seven days were included in our study. In addition to the autopsy records of perpetrators, the autopsy records of victims were also analyzed.

General demographic characteristics of perpetrators were analyzed, including sex, age, education, marital status, etc. Data on victims' sex and age were also collected, as well as data on the relationship with the perpetrators. The circumstances of the case related to the place, and weapons used in suicides and murders were collected from police reports and later analyzed. Data on the number and localization of wounds, as well as the nature, that is, the cause of death of both murderers and victims, were collected from autopsy reports. Data regarding the previous convictions of murderers were also collected, as well as data regarding the weapon with which the H-S was committed, including the fact whether it was in the possession of the murderer, and therefore, easily accessible. All witness statements for the given case, if there were any, were taken into consideration and analyzed. From the hetero-anamnestic data, which were obtained during the conversation between the coroner and the members of the closest family of victims, data on the case were collected, as well as on circumstances in terms of potential motives, and information on whether the perpetrators suffered from any somatic or psychiatric illness, whether they consumed narcotics and alcohol during their lifetime, and any atypically classified information that the researchers considered to be potentially useful for the purpose of this study. Data on the presence of narcotics in blood at the time of death, as well as alcoholemia, were obtained by chemical-toxicological analyses carried out at the Chemical-Toxicological Laboratory of the Institute of Forensic Medicine of the Faculty of Medicine, University of Belgrade.

All the obtained data were analyzed with the help of the SPSS 26.0 program. The analysis of results was conducted using descriptive statistical methods. All data were presented in the form of absolute and percentage frequencies.

Tabela 1. Učestalost javljanja KS u ispitivanom periodu

Godine	Slučajevi (N)	Ukupan broj žrtava (N)
2015	5	5
2016	1	1
2017	6	7
2018	1	1
2019	2	2
2020	2	2
2021	2	2
2022	1	1
Ukupno	19	20
Prosečno za period 2015-2022.	2,4	2,5

Tabela 2. Pol, bračni status i stepen obrazovanja ubica

Karakteristike	N	%
Pol		
Muškarci	17	89,5
Žene	2	10,5
Bračni status		
Oženjen/udata	8	42,1
Razveden/a	6	31,6
Razveden/a	2	10,5
Neoženjen/neudata	3	15,8
Stepen obrazovanja		
Osnovno obrazovanje	4	21,1
Srednje obrazovanje	12	63,1
Visoko obrazovanje	3	15,8
Ukupno	19	100

godine, što ih čini u proseku oko pola decenije (4,9 godina) mlađim od ubica (grafikon 1). Žrtve su najčešće bile bivši ili sadašnji emotivni partneri počiniocu (60%), u 15% slučajeva roditelji, u 15% dete, a u 10% nadređena osoba.

Počinioci su predominantno bili muškog pola (89,5%) (tabela 2). Najmlađi počinilac je bio star 31, a najstariji 75 godina, dok je prosečan uzrast bio 54,1±10,7 godine, oko pet godina više od prosečnog uzrasta žrtava (grafikon 1). U bračnoj ili vanbračnoj zajednici je bilo 8 (42,1%) ubica, 31,6% (6) su bili razvedeni, 10,5% (2) udovci/ce, a 15,8% (3) nisu nikada stupali u brak ili vanbračnu zajednicu (tabela 2). Ubice su ređe imale završeno visoko obrazovanje (15,8%) i osnovno obrazovanje (21,1%), a najčešće završeno obrazovanje srednjeg stepena (63,1%) (tabela 2).

Kada govorimo o somatskim bolestima, šest (31,6%) ubica je imalo dijagnozu nekog oboljenja iz spektra kardiovaskularnih bolesti, a sledeća najčešća dijagnoza je bila šećerna bolest tipa 2 (15,8%). Od psihijatrijskih poremećaja ubice su imale depresiju (n=1), agresivnost (n=1), hronični moždani sindrom (n=1), neuračunljivost (n=1), šizofreniju (n=1), alkoholizam (n=1). Nedefinisane psihijatrijske dijagnoze su bile prisutne kod dve osobe (10,5%), za

Grafikon 1. Raspodela ubica i žrtava po uzrastu pojedinačno za svako komplikovano samoubistvo

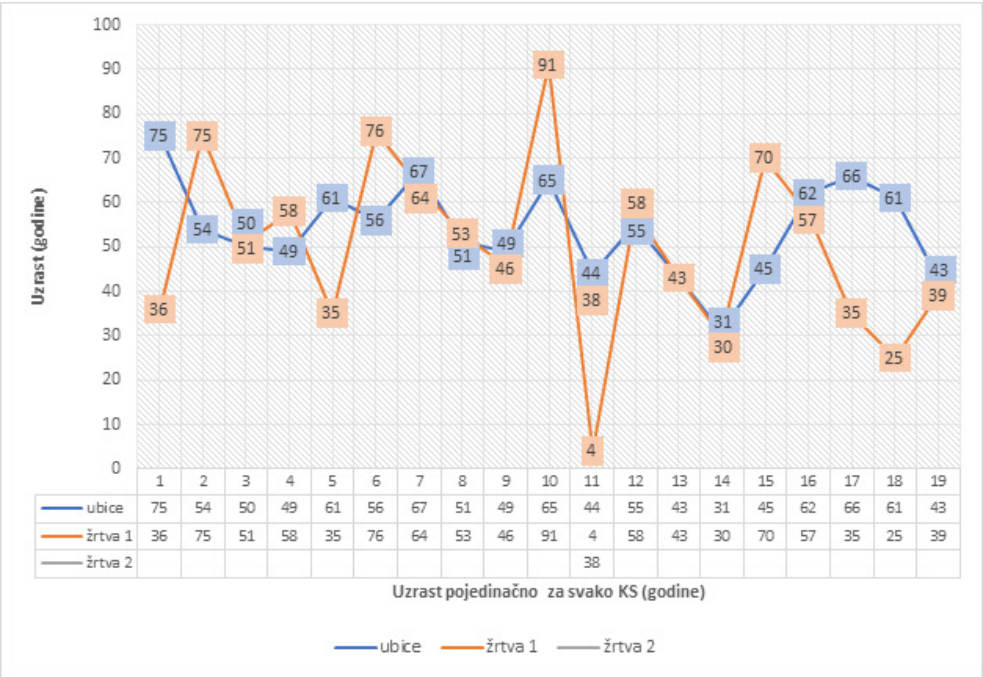

Table 1. Frequency of occurrence of homicide-suicide phenomena in the observed period

Years	Cases (N)	Total number of victims (N)
2015	5	5
2016	1	1
2017	6	7
2018	1	1
2019	2	2
2020	2	2
2021	2	2
2022	1	1
Total	19	20
Average for the period 2015-2022	2.4	2.5

Table 2. Gender, marital status and level of education of murderers

Characteristcs	N	%
Gender		
Male	17	89.5
Female	2	10.5
Marital status		
Married	8	42.1
Divorced	6	31.6
Widowed	2	10.5
Single	3	15.8
Level of education		
Elementary school	4	21.1
Midle school	12	63.1
Higher education	3	15.8
Total	19	100

Results

In the observed eight-year period, 19 complicated suicides were recorded at the Institute of Forensic Medicine of the Faculty of Medicine, University of Belgrade, while in 18 cases, one person died before the suicide, and in one case two persons died. This means that the total number of tragic deaths was 39, that is, 19 murderers and 20 victims. The largest number of H-S was in 2015 (n=5) and in 2017 (n=6) (Table 1).

The majority of victims were women, more precisely 16 out of 20 persons (80%). Their age ranged between 4 and 91 years, while the average age was 49.2±20.3 years, which means that they were on average 4.9 years younger than murderers (Figure 1). The victims were most often former or current emotional partners of perpetrators (60%), parents in 15% of cases, children in 15% of cases, and superiors in 10%.

The perpetrators were predominantly male (89.5%) (Table 2). The youngest perpetrator was 31 years old, while the oldest was 75, and the average age was 54.1±10.7, which is about five years more in comparison to the victims' average age (Figure 1). There were 8 murderers (42.1%) who were married or lived in an illegitimate union, 31.6% (6)

Figure 1. Distribution of murderers and victims by age for each homicide-suicide case (H-S)

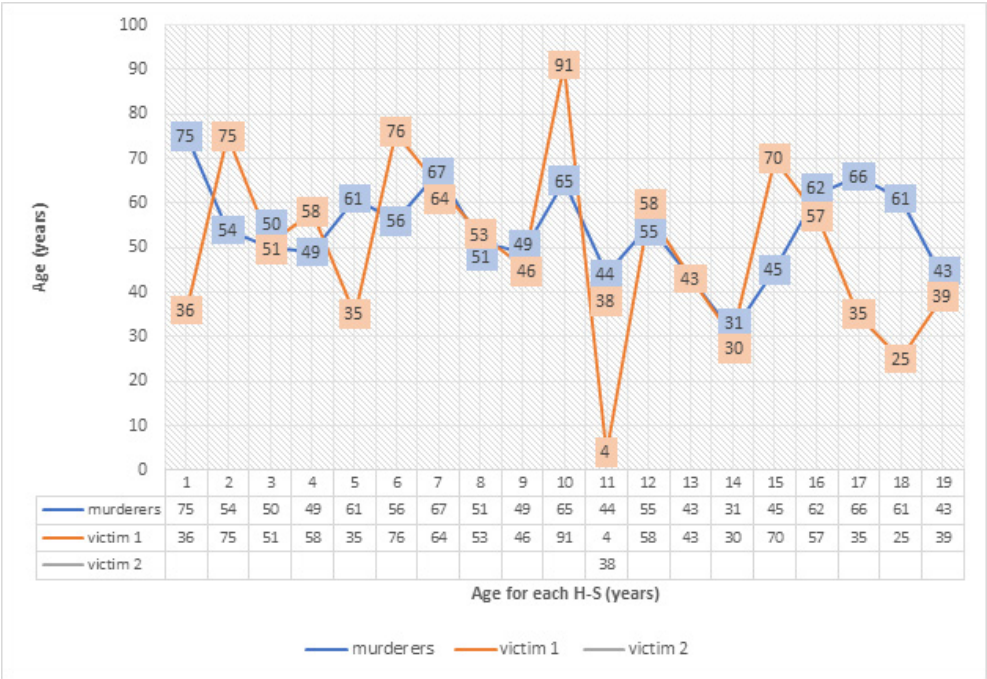

Tabela 3. Vrsta oružja korišćena za ubistva i samoubistva

	Ubistvo N (%)	Samoubistvo N (%)
Vatreno oružje	14 (70,0)	14 (73,3)
Hladno oružje-oštrica	5 (25,0)	3 (15,8)
Ruke-zagušenje	1 (5,0)	0
Kanap	0	1 (5,25)
Nasilno gladovanje	0	1 (5,25)
Ukupno	20 (100,0)	19 (100,0)

tri osobe (15,8%) nisu bili dostupni jasni podaci, a bez dijagnoze je bilo devet (47,4%) ubica.

Hetereoanamstički podaci govore o tome da je ukupno 9 (47,4%) od 19 ubica imalo barem jedan susret sa psihijatrom za života, kao i to da nijedan počinilac nije pio psihijatrijsku terapiju u trenutku izvršenja KS, bez obzira na dijagnozu koju je imao.

Niko od počinilaca nije zloupotrebljavao narkotike tokom života, dok je osam (42,1%) njih zloupotrebljavalo alkohol. U trenutku smrti nijedan počinilac nije imao narkotike u krvi, a alkohol je bio prisutan kod tri osobe i to u sledećim koncentracijama: 1,72‰, 0,65‰ i 0,17‰.

Prethodno krivično osuđivanih lica je bilo 26,3% (n=5), neosuđivanih 52,6% (n=10), dok su za 21,1% (n=4) podaci bili nepoznati. Osam od četrnaest ubica koji su počinili KS vatrenim oružjem je imalo dozvolu za korišćenje i bilo je vlasnik tog oružja. Pet osoba (26,3%) nije koristilo vatreno oružje za izvršenje KS, pa nisu ni mogle da budu vlasnici istog.

Ubistva su se većinski dogodila u urbanoj sredini 70% (n=14) u odnosu na ruralnu 30% (n=6). Predominantno je korišćeno vatreno oružje, kako za izvršenje ubistava 70% (n=14), tako i za izvršenje samoubistava 73,7% (n=14). Sledeće po učestalosti je bilo hladno oružje-oštrica i to za pet (25%) ubistava i tri (15,8%) samoubistva. Ruke počinioca su korišćene za izvršenje jednog (5%) ubistva zagušenjem. Korišćeni su i kanap za vešanje (5,25%) i nasilno gladovanje (5,25%) kao način da se izvrši po jedno samoubistvo (tabela 3). Žrtve su u 45% (n=9) slučajeva iskrvarile na smrt, a u 40% (n=8) je smrt nastupila usled višestrukih povreda glave. Usled politraume je preminulo 10% (n=2) žrtava, a 5% (n=1) usled zagušenja. Višestruke povrede glave nastale dejstvom projektila su bile vodeći uzrok smrti počinilaca 68,4% (n=13), a potom sa opadajućom učestalošću iskrvarenje kod četiri (21,1%), ugušenje kod jedne (5,25%) i jakostepena pothranjenost kod jedne osobe (5,25%). Povrede na telu žrtava su najčešće bile u predelu glave i to kod osam osoba (40%), zatim u više regiona tela kod šest osoba (30%), na grudima pet (25%) i na vratu jedne žrtve (5%). Ubice su žrtvama najčešće nanosile više od jedne povrede što je registrovano na 12 tela (60%), a u jednom ekstremnom slučaju, ubica je naneo žrtvi preko 80 povreda oštricom.

Žrtve i ubice su se u svakom slučaju (100%) poznavale, nije bilo nasumičnih tragičnih događaja. U sedam (35%) slučajeva počinilac je bio trenutni partner počiniocu, u pet (25%) bivši partner, u tri (15%) roditelj, u tri (15%) dete, a u dva (10%) zaposleno lice. Kao vodeći motivi za izvršenje KS izdvajaju se ljubomora, raskid i neuzvraćena ljubav u devet (45%), potom loša finansijska situacija i porodični problemi i nesuglasice u pet (25%), kao i patnja koju prolaze bližnji usled bolesti člana porodice u tri slučaja (15%). Jedno ubistvo praćeno samoubistvom je bilo pokrenuto pozitivnim simpotima u okviru kliničke slike šizofrenije (5%), a u dva slučaja motivi su ostali nepoznati (10%).

Diskusija

Kako su KS retka pojava i registri ovih događaja u RS ne postoje ni na državnom, ni na lokalnim nivoima, nije moguće napraviti poređenje kroz prethodne godine i uvideti da li se njihova stopa javljanja povećava, smanjuje ili ostaje nepromenjena. Situacija je slična i u mnogim drugim zemljama (7).

Slično kao i u ostalim studijama, naši rezultati su pokazali da su ubice većinski bile muškog (89,1%), a žrtve ženskog pola (80%) (13,14). Raspon godina uzrasta napadača je bio od 31 do 74 godine, a najveći broj njih je bio u 5. ili 6. deceniji života. Žrtve su u proseku bile okopet godina mlađe, pri čemu je najmlađa žrtva imala 4, a najstarija 91 godinu. Gotovo svaki počinilac je pre nego što je usmrtio sebe, usmrtio jednu osobu, a u jednom slučaju to su bile dve osobe. Američke studije kojih ima najviše i koje su prve sprovedene, ali i evropski podaci, govore o tome da je situacija približno ista i u drugim centrima (15,16). U Italiji, Britaniji, ali i našim istraživanjem, pokazano je da su počinioci najređe bili visoko obrazovani i da su najčešće pripadali niskoj do srednjoj društvenoj klasi (1,9,17). Među najizazovnijim podacima za prikupljanje i tumačenje bili su oni koji se tiču psihijatrijske di-

Table 3. Means of execution of murders and suicides

	Homicide N (%)	Suicide N (%)
Firearm	14 (70.0)	14 (73.3)
Cold weapon	5 (25.0)	3 (15.8)
Hands (*Strangulatio manualis*)	1 (5.0)	0
Twine (*Suspensio*)	0	1 (5.25)
Forced starvation	0	1 (5.25)
Total	20 (100.0)	19 (100.0)

were divorced, 10.5% (2) were widows/widowers, while 15.8% (3) had never married or lived in extramarital union (Table 2). The murderers less frequently completed higher levels of education (15.8%) and primary education (21.1%), while most frequently they completed secondary levels of education (63.1%) (Table 2).

As far as somatic diseases are concerned, six murderers (31.6%) had been diagnosed with some of cardiovascular diseases, while diabetes mellitus type two was the next most common diagnosis (15.8%). Of psychiatric disorders, the murderers had depression (n=1), aggressiveness (n=1), chronic brain syndrome (n=1), insanity (n=1), schizophrenia (n=1), and alcoholism (n=1). Undefined psychiatric diagnoses were present in two persons (10.5%), for three persons (15.8%), no clear data were available, and nine murderers (47.4%) were without a diagnosis. Heteroanamnestic data indicate that a total of 9 murderers (47.4%) of 19 murderers had at least one meeting with a psychiatrist during their lifetime, as well as that none of them took the psychiatric therapy at the time when H-S was committed, regardless of the diagnosis he had.

None of the perpetrators used narcotics during their lifetime, while 8 of them (42.1%) used alcohol. At the moment of death, none of the perpetrators had narcotics in blood, and alcohol was present in three persons in the following concentrations: 1.72‰, 0.65‰, 0.17‰. 26.3% persons had been previously convicted (n=5), 52.6% had not been convicted (n=10), while data were unknown for 21.1% (n=4). Eight out of fourteen murderers who committed H-S with a weapon had a license to use and were the owners of that weapon. Five persons (26.3%) did not use the weapon to commit H-S, so they could not be the owners.

The majority of murders took place in urban areas (70%, n=14) in comparison to rural areas (30%, n=6). Firearms were predominantly used, both for the execution of murders (70%, n=14) and for committing suicide (73.7%, n=14). According to its frequency, the next was a cold weapon – blade in five murders (25%) and three (15.8%) suicides. The perpetrator's hands were used to commit one of the homicides (5%) by strangling. Hanging rope (5.25%) and forced starvation (5.25%) were used as a way to commit the suicide (Table 3). Victims bled to death in 45% (n=9) cases, while in 40% of cases (n=8) death occurred due to multiple head injuries.10% of victims (n=2) died due to polytrauma, and 5% (n=1) due to strangling. Multiple head injuries, which were caused by projectiles, were the leading cause of death of perpetrators in 68.4% (n=13) of cases, followed by bleeding to death in 4 (21.1%), strangling in one (5.25%) and severe malnutrition in one person (5.25%). The injuries on the victims' bodies were most often in the area of head, that is, in eight persons (40%), then in several body regions in six persons (30%), on the chest in five persons (25%) and on the neck in one victim (5%). The murderers usually inflicted more than one injury, which was registered on 12 bodies (60%), and in one extreme case, the murderer inflicted over 80 injuries with a blade.

In all cases (100%), the victims and murderers knew each other, and there were no random tragic events. In seven cases (35%), the perpetrator was the current partner, in five (25%) former partner, in three (15%) a parent, in three (15%) a child, and in two (10%) an employee. Jealousy, breakup, and unrequited love were the leading motives for the execution of H-S in nine cases (45%), then bad financial situation, family problems and disagreements in five (25%), and suffering that the closest people go through due to the illness of a family member in three cases (15%). One murder followed by suicide was triggered by positive symptoms within the clinical symptoms of schizophrenia (5%), and in two cases motives remained unknown (10%).

Discussion

Since H-S is a rare phenomenon and there are no registries of these events in the Republic of Serbia either at the state or local levels, it is not possible to compare the previous years and

jagnoze počinilaca. Rezultati naše studije su pokazali da je gotovo polovina ubica u trenutku izvršenja KS imala prethodni susret sa psihijatrom i neku vrstu psihijatrijske dijagnoze, gde nije uočeno da se neka svojom učestalošću posebno izdvaja. Kod onih koji su izvršili KS u sklopu ljubavnih odnosa, usled ljubomore, neprihvatanja raskida i slično, članovi porodice najčešće navode prethodno ispoljenu agresivnost, posete psihijatru u privatnom okruženju, odlazak u dnevne bolnice. U svakom slučaju nije zabeležena redovnost u posetama lekaru, a nijedan počinilac nije bio ni na psiho- ni na medikamentoznoj terapiji. To može biti posledica trenutne društvene situacije u kojoj mentalna higijena ne zavređuje dovoljno pažnje, a posebno u manjim sredinama i nižim slojevima društva.

Počinioci koji su izvršili KS u sklopu porodičnih odnosa, a da ljubomora nije bila vodeći motiv, najčešće se opisuju od strane članova porodice kao depresivni u vremenu koje je prethodilo događaju. Jedno KS je izvršio počinilac sa dijagnostikovanom šizofrenijom, a upravo se bolest i navodi kao glavni motiv. Drugi autori takođe uviđaju značaj psihičkih bolesti u izvršenju KS i u skladu sa dobijenim rezultatima preporučuju da se više pažnje usmeri mentalnom zdravlju u cilju prevencije ovih događaja (18,19).

Najčešće korišćena oružja za KS su bila vatrena oružja (70-73,7%) i to u nešto nižem procentu nego što su pokazale referente studije (80-97%) (14,20). Razlog za ovakve rezultate može biti mali uzorak, a takođe i novi načini za izvršenje KS koji se razvijaju kroz vreme. Za 42,1% ubica je pokazano da su bili vlasnici oružja i/ili da su imali dozvolu za korišćenje, a većina KS je izvršena upravo vatrenim oružjem. To postavlja pred nas mnoga pitanja koja se tiču kontrole korišćenja oružja i da li je laka dostupnost jedan od faktora rizika za KS. Trebalo bi predložiti reviziju zakona koji se tiču posedovanja i korišćenja vatrenog oružja i strogo ih kontrolisati, što predlažu i drugi autori (2).

Posebno interesantni podaci se tiču broja i lokalizacije rana. Najčešće se radilo o nanošenju više od jedne povrede (60%), čak i kada za to nije bilo potrebe, tj. kada je ubistvo kao primarni cilj već bilo počinjeno. U literaturi je ovaj fenomen poznat kao „*overkill*" fenomen (21).

Dakle, u slučajevima „ *overkill*" fenomena ubice su žrtvama nanosile daleko veći broj povreda nego što je dovoljno za nastupanje smrtnog ishoda, a što se prvenstveno povezuje sa emotivnom motivacijom za izvršenje ovog krivičnog dela. Sa druge strane, bilo da se radi o jednoj ili više povreda, počinioci su u najvećem broju slučajeva ciljali da povrede nanesu u predelu glave i grudnog koša, a naročito kada se radilo upravo o emotivnim odnosima. Sva KS koja su obuhvaćena ovim istraživanjem su bila počinjena od strane osobe koja poznaje žrtvu, a u 90% KS radilo se o porodičnim odnosima. Vodeće mesto su zauzeli partnerski odnosi (60%), a odmah za njima odnosi na relaciji roditelj-dete (30%) i to u oba smera. Prethodno opisani načini ubistva se mogu objasniti upravo ličnim odnosom ubice i žrtve i može se uvideti obrazac koji govori u prilog zločina iz strasti. Ovi podaci odgovaraju podacima iz citiranih istraživanja. Ono što su bili vodeći motivi da se počini KS jesu ljubomora, raskid i neuzvraćena ljubav. U pozadini ovoga, kako navode stručna lica, a protivno pogrešnom shvatanju laika, ne stoji ljubav, već aktiviranje niskih pobuda, povređena sujeta i gubitak kontrole. Uzimajući u obzir da ove karakteristike odgovaraju zločinu iz strasti, korisno je u istraživanja koja se bave ovom temom uključivati psihijatre koji svojom ekspertizom mogu bolje i bliže da protumače karakteristike ovako kompleksnih zločina, ali i karakteristike samih počinilaca. Sve navedeno pomaže da se shvati rizik od ove društvene pojave. Sledeće porodične situacije su se ticale bolesti jednog člana porodice koja je znatno ometala normalan život i funkcionisanje, pa su ova KS počinjena iz milosrđa i na manje dramatičan način od prvih spomenutih. To je po pravilu podrazumevalo manji broj povreda, najčešće samo jednu, a ovim događajima su prethodili planovi, ali ne i svađe.

KS usled finansijskih problema su najčešće prethodile svađe i depresivnost. Najređe se radilo o lošim odnosima radnika i nadređenih lica koji su svojom kulminacijom doveli do KS (10%). Definišući odnose između ubica i žrtava i prepoznavanjem verovatnog motiva za KS, neki autori su napravili klasifikaciju KS, koja se razlikuje od klasifikacije napravljene na osnovu psihopatologija ubica (15,18).

Bez obzira na to što učestalost KS nije visoka, svojim sadržajem ona zaslužuju određenu pažnju javnosti i medicinskog osoblja. Engleski autori su došli do podataka da se većina ubica javila psihijatru ili lekaru opšte prakse, u periodu od mesec dana koji je prethodio KS (22).

realize whether their rate of occurrence increased, decreased or remained unchanged. The situation is similar in many other countries (7).

Similar to the results of other studies, our results showed that the majority of murderers were males (89.1%), while the majority of victims were females (80%) (13,14). The age of perpetrators ranged from 31 to 74 years, while the largest number of them were in the 5th or 6th decade of life. Victims were approximately 5 years younger, on average, while the youngest victim was 4 years old and the oldest was 91. Almost every perpetrator, before he killed himself, had killed one person, and in one case two persons. American studies, which were conducted first and which are the most numerous, as well as the European data speak about the similar situation in other centers (15,16). In Italy, Britain, and in our study, it was shown that the perpetrators were rarely highly educated, and that they most frequently belonged to lower or middle social class (1,9,17). The most challenging data for collecting and analyzing were those related to the psychiatric diagnosis of perpetrators. The results of our study showed that almost half of murderers at the moment of execution of H-S had previously met a psychiatrist and had a psychiatric diagnosis, where it was not noticed that some of them stood out. In those who committed H-S within love relationships, due to jealousy, non-acceptance of breakup and similar things, family members most often cited previous aggressiveness, visits to a psychiatrist in a private setting, going to day hospitals. In any case, regular visits to the doctor were not observed, and none of the perpetrators were under psychiatric care or received drug therapy. This may be the consequence of the current social situation in which the mental hygiene does not deserve enough attention, and especially in smaller environments and lower strata of society. The perpetrators who committed H-S within family relations, when jealousy was not the leading motive, they were most often described by family members as depressed during the time that preceded the event. One H-S was committed by a perpetrator diagnosed with schizophrenia, and the disease itself was stated as the main motive. Other authors also perceive the significance of mental diseases in the execution of H-S and in accordance with the obtained results, recommend that more attention should be directed towards mental health aimed at preventing these events (18,19).

The most frequently used weapons for H-S were firearms (73.7%), and in a somewhat lower percentage than the reference studies showed (80-97%) (14,20). The reason for these results can be a small sample, and also new ways of execution of H-S that develop over time. It has been shown that 42.1% of murderers were owners of guns and/or that they had a license to use them, while the majority of H-S was committed with a firearm. This raises many questions related to the control of the use of guns and whether availability is one of the risk factors for H-S. A revision of laws related to the possession and use of firearms should be recommended and they should be strictly controlled, which is proposed by other authors, as well (2).

Particularly interesting data are related to the number and localization of wounds. Most often it was about inflicting more than one injury (60%), even when there was no need for that or when murder like the primary goal had already been accomplished. This phenomenon is known as the “overkill phenomenon” in the literature (21). Thus, in case of “overkill phenomenon”, murderers inflicted a far greater number of injuries on their victims than it was sufficient for the fatal outcome, which is primarily associated with the emotional motivation for the execution of this crime. On the other hand, no matter whether it is one or more injury, the perpetrators in most cases aimed to inflict injuries in the area of head and chest, especially when it was about emotional relationships. All H-S that are included in this research were committed by the person who knew the victim, and in 90% within family relationships. The leading place belongs to partnership relations (60%), followed by relations parent-child (30%) in both directions. The previously described ways of homicide can be explained by the personal relationship between the killer and the victim, and one can see the pattern that speaks in favor of crime of passion. These data correspond to the data from the cited studies. The leading motives for committing H-S were jealousy, breakup and unrequited love. In the background of this, as it is stated by experts, and contrary to the misconception of laymen, it is not love, but activation of low motives, hurt vanity and loss of control. Given that these characteristics correspond to the crime of passion, it is useful to include psychiatrists in research dealing with this topic, because they can, with their expertise, analyze more closely the characteristics of such

Pronađena je veza između potencijalno nasilnih adolescenata i kasnije počinilaca. Podatke ovog tipa je izuzetno teško prikupiti, a pre svega je potrebno izgraditi pravilan odnos javnosti sa lekarima i mentalnim tegobama. Ono što je naša studija pokazala, a tiče se prethodnog kritičnog ponašanja ubica, jeste da je 26,3% njih prethodno bilo krivično osuđivano, gotovo polovina je zloupotrebljavala alkohol, dok se u izjavama bližnjih neretko pronalaze navodi koji govore da su ranije tokom života pokazivali agresivno ponašanje. Uzimajući u obzir prirodu i karakteristike ovih podataka nije ih moguće obraditi uobičajenim statističkim metodama, ali ih je važno spomenuti i o njima prodiskutovati. Identifikacija psihičkih bolesti i ponavljanih obrazaca lošeg ponašanja su mogući vid prevencije ovih, ali i sličnih događaja.

Potencijalna ograničenja našeg istraživanja bi mogla da se, pre svega, tiču broja analiziranih KS (n=19). Iako su rezultati naše studije u korelaciji sa referenttnim studijama, važno je istaći da na malom uzorku kakav je obrađen u ovoj studiji postoji veća verovatnoća da dođe do odstupanja od uobičajenih vrednosti. Potom, kako je ovo istraživanje rađeno na Institutu za sudsku medicinu u Beogradu gde se obdukuje najveći broj slučajeva u Republici Srbije, njime ipak nisu obuhvaćene sve obdukovane osobe u našoj zemlji. Tekstualni zapisnici koji se zbog svog kvalitativnog sadržaja teško analiziraju i ostavljaju prostor za subjektivni istraživački doživljaj. Pored svega navedenog, mi ipak smatramo da smo uspeli da dobijemo adekvatne i objektivne rezultate i formiramo senku profila ličnosti osoba koje počine KS, definišemo i objasnimo okolnosti pod kojima se KS događaju, kao i da predočimo koji je značaj, ali i rizik od ovog društvenog fenomena, što je i bio cilj naše studije. Pored zabeleženih slučajeva KS, analizom obdukcionih zapisnika primećen je nezanemarljiv broj pokušaja izvršenja KS. Ono što ih razlikuje od KS jeste to što su napadač ili žrtva preživeli jer je povreda bila nedovoljna da usmrti nekog od učesnika momentalno, a medicinska pomoć brza i efikasna. Iako pokušaji KS nisu bili predmet ove studije, smatramo da je njihov značaj podjednak, jer po svojim karakteristikama i sadržaju oni odgovaraju KS i predlažemo da se u nekim narednim studijama na ovu temu uključe u analizu.

Zaključak

Našom studijom se potvrđuje postojeći obrazac komplikovanih samoubistava. Najčešće se ovi događaji dešavaju u okviru porodice, od strane muškaraca i vatrenim oružjem. Karakteristike ovog fenomena ostaju iste ili slične kroz vreme, a pitanja koja se tiču prevencije ostaju otvorena. U skladu sa dobijenim rezultatima predlažemo da se fokus stavi na uzročne mehinizme kako bi se bolje razumeo, predvideo i potencijalno prevenirao izvestan broj ovih događaja. Potrebno je posvetiti više pažnje mentalnom zdravlju, uočiti negativne obrasce ponašanja u ranim godinama i ne ignorisati najavu ovih događaja koja gotovo po pravilu prethodi samom događaju. Korišćenje i posedovanje vatrenog oružja bi trebalo da bude strogo kontrolisano. Sa što većim brojem prikazanih slučajeva KS, ali i KS u pokušaju, pomažemo da buduća istraživanja budu sadržajnija i omoguće nam kvalitetnije prediktivne i preventivne strategije.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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complex crimes, as well as the characteristics of perpetrators. All of the above mentioned helps to realize the risk of this social phenomenon. In some family situations, when one member was ill and the disease disturbed normal life and functioning, the H-S was committed from mercy and in a less dramatic manner than the previously mentioned H-S. As a rule, it included fewer injuries, usually only one, and these events were preceded by plans, but not by quarrels. Due to financial problems, H-S was most often preceded by quarrels and depression. Bad relations between workers and their superiors, which culminated in H-S, were the rarest (10%). By defining the relationships between murderers and victims, and recognizing the probable motive for H-S, some authors have made the classification of H-S, which is different from the classification made according to the psychopathology of murderers (15,18).

Regardless of the fact that the frequency of H-S is not high, their content deserves a certain attention of the public and medical staff. English authors have come to the data that most murderers reported to a psychiatrist or general practitioner, in the month that preceded the H-S (22). A link was found between potentially violent adolescents and later perpetrators. It is difficult to collect such data, and first of all, it is necessary to build a proper attitude of public towards doctors and mental difficulties. What our study showed, concerning the previous critical behavior of murderers, was that 26.3% of them had been previously convicted, while almost half of them abused alcohol and their closest relatives stated that they had been aggressive before. Taking into consideration the nature and characteristics of these data, they cannot be analyzed with the help of usual statistical methods, but they should be mentioned and discussed. The identification of mental illnesses and repeated patterns of bad behavior are a possible form of prevention of these and similar events.

The potential limitations of our study could be related, first of all, to the number of analyzed H-S (n=19). Although the results of our study are correlated with the reference studies, it is important to point out that in a small sample like the one analyzed in this study, deviation from usual values is highly probable. Furthermore, although this study was conducted at the Institute of Forensic Medicine in Belgrade, where the largest number of autopsies in the Republic of Serbia is performed, not all autopsied persons were included. Also, written records are difficult to be analyzed due to their qualitative content and they leave room for subjective researcher's perspective. In addition to the above mentioned, we still believe that we managed to get adequate and objective results and create a shadow of the personality profile of persons who commit H-S, define and explain the circumstances under which H-S were committed, as well as to present the importance and risk of this social phenomenon, which was the aim of this study.

In addition to the recorded cases of H-S, the analysis of autopsy reports showed a non-negligible number of attempts of H-S. What makes them different from H-S is that the attacker or victim survived because the injury was not sufficient to kill one of the participants immediately, while medical assistance was fast and efficient. Although attempts of H-S were not the subject of this study, we think that they are equally important because, according to their characteristics and content, they correspond to H-S, and therefore, they should be included in the analysis in some future studies on this topic.

Conclusion

The existing pattern of complicated suicides is confirmed in our study. Most frequently, these events take place within the family, they are committed by men and using the firearms. The characteristics of this phenomenon remain the same or similar over time, while the questions of prevention remain open. In accordance with the obtained results, the focus should be placed on causal mechanisms in order to better understand, predict and potentially prevent a certain number of these events. It is necessary to pay more attention to mental health, notice negative patterns of behavior in the early age and not ignore the announcement of these events, which almost as a rule precedes the event itself. Using and owning of firearms should be strictly controlled. With more presented cases of H-S, and attempts of H-S, we help future research be more comprehensive and allow us better predictive and preventive strategies.

Competing interests

The authors declared no competing interests.

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HRONIČNE DEKUBITALNE RANE KOD TRAUMATSKIH I NETRAUMATSKIH PACIJENATA U JEDINICAMA INTENZIVNOG LEČENJA

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SAŽETAK

Uvod/Cilj: Dugoležeći pacijenti u bolnicama, staračkim domovima, a naročito u jedinicama intenzivnog lečenja, izloženi su riziku od nastanka hroničnih rana. Termin „hronična rana“ se odnosi na rane koje ne zarastaju uprkos svim preduzetim merama lečenja u vremenskom trajanju od šest do osam nedelja. Cilj ove retrospektivne kohortne studije je bio da se za petogodišnji period analiziraju podaci o hroničnim dekubitalnim ranama koji su prikupljeni u jedinicama intenzivnog lečenja (JIL) Urgentnog centra Univerzitetskog Kliničkog Centra Srbija sa ciljem utvrđivanja faktora koji utiču na njihov nastanak i zarastanje.
Metode: Retrospektivna kohortna studija je izvedena u periodu od 01.01.2018. do 01.04.2023. godine u Urgentnom centru Univerzitetskog Kliničkog Centra Srbije i to u JIL politraumatskih, neurohirurških i hirurških pacijenata. Studija je obuhvatila 74 pacijenta sa dijagnozom hroničnih dekubitalnih rana. Za sve ispitanike podaci su dobijeni iz istorije bolesti i otpusne liste.
Rezultati: Tokom intrahospitalnog lečenja u JIL dekubitalne rane su evidentirane kod svih 74 pacijenata (56,8% žena i 43,2% muškaraca), a kombinovane hronične rane kod 57 (77,0%). Najveći broj ovih pacijenata je bio starijeg uzrasta (70 i više godina) (31,1%) i sa netraumatskim povredama (62%). Svi pacijenti su bili traheotomisani sa plasiranom gastrostomom. Lokalizacija dekubitalnih rana je najčešće bila na lumbosakralnoj regiji (44,6%), a zatim u trohanteričnoj regiji (23,0%). Među pacijentima najviše je bilo osoba sa hipertenzijom (90,5%), dijabetesom (79,7%) i hroničnom opstruktivnom bolešću pluća (82,4%), a do smrtnog ishoda je došlo kod 28 (37,8%) pacijenata. Neuhranjenost je bila prisutna kod 38 (51,4%), a prekomerna telesna težina i gojaznost kod 11 (14,9%) pacijenata.
Zaključak: Faktore rizika za nastanak dekubitusnih rana treba proceniti u trenutku prvog kontakta lekara sa nepokretnim pacijentom jer je to jedini preduslov za pravovremenu prevenciju. Poseban akcenat treba staviti na starije osobe, pothranjenje i osobe sa komorbiditetima.

Ključne reči: dekubit, intenzivna nega, hronične rane, faktori rizika

Uvod

Hronične rane predstavljaju veliki zdravstveni problem za pacijente, ali i za plastične hirurge i medicinske sestre i tehničare koji se sa njima susreću u svakodnevnom radu. Termin „hronična rana“ se odnosi na onu vrstu rane koja ne zarasta uprkos svim preduzetim merama lečenja u vremenskom periodu od 3 meseca ili je prošla kroz proces reparacije bez uspostavljanja održivog,

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ORIGINAL ARTICLE

CHRONIC PRESSURE ULCERS IN TRAUMA AND NON-TRAUMA PATIENTS IN THE INTENSIVE CARE UNIT

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SUMMARY

Introduction/Aim: Patients, who stay long in hospitals, nursing homes, and especially in intensive care units, are exposed to the risk of developing chronic wounds. The term "chronic wound" refers to wounds that do not heal despite all treatment measures taken in the period of six to eight weeks. The aim of this retrospective cohort study was to analyze data on chronic pressure ulcers that were collected in intensive care units (ICU) of the Urgent Care Center of the Clinical Center of Serbia during the five-year period, with the aim of determining the factors that influence their occurrence and healing.
Methods: The retrospective cohort study was conducted from January 1st, 2018 to April 1st, 2023 at the Urgent Care Center of the University Clinical Center of Serbia in the intensive care units in polytrauma, neurosurgical and surgical patients. The study included 74 patients diagnosed with chronic pressure ulcers. Data for all participants were obtained from medical history and list of discharge.
Results: During in-hospital treatment in ICU, pressure ulcers were found in all 74 patients (56.8% of women and 43.2% of men), while combined chronic wounds were found in 57 (77.0%) patients. The largest number of these patients were elderly (70 and older) (31.1%) and with non-traumatic injuries (62%). All patients were tracheotomized with a gastrostomy tube placed. The localization of pressure ulcers was most often in the lumbosacral region (44.6%), followed by the trochanteric region (23.0%). The majority of patients had hypertension (90.5%), diabetes (79.7%) and chronic obstructive pulmonary disease (82.4%), while 28 patients (37.8%) died. 38 patients were underweighted (51.4%), while 11 (14.9%) patients were overweight and obese.
Conclusion: Risk factors for the occurrence of pressure ulcers should be evaluated at the moment of the first contact of the doctor with the immobile patient because this is the only prerequisite for timely prevention. Special emphasis should be placed on the elderly, underweight and people with comorbidities.

Key words: pressure ulcers, intensive care, chronic wounds, risk factors

Introduction

Chronic wounds represent a major health problem for patients, but also for plastic surgeons and nurses and technicians who encounter them in their daily work. The term "chronic wound" refers to that type of wound that does not heal despite all the treatment measures taken for the period of three months or has gone through the process of reparation without establishing a sustainable, anatomic and functional result (1,2). Chronic wounds are sometimes defined as hard-

anatomskog i funkcionalnog rezultata“ (1,2). Neki definišu hronične rane kao rane koje teško zarastaju u periodu od 4 nedelje do više od 3 meseca (2-4).

Prema Društvu za zaceljivanje rana (engl. *Wound Healing Society* - WHS) hronične rane se prema etiologiji dele na dekubitalne, dijabetesne, venske i arterijske ulkuse (5). Hronične rane predstavljaju jednu vrstu tihe epidemije, jer se obično ne prepoznaju i posmatraju kao hronično komorbiditetno stanje. Procenjeno je da je 1 do 2% svetske populacije izloženo hroničnim ranama tokom svog života u zemljama u razvoju (6,7).

Uočeno je da postoji negativna korelacija zarastanja rana sa starenjem, prisustvom komorbiditeta, ograničenom pokretljivošću itd. (8,9). Komplikacije koje uključuju hronične rane su celulitis, infektivni venski ekcem, gangrena, hemoragije, kao i amputacije. Posledice hroničnih rana su brojne i mogu dovesti do nepokretnosti i određenog stepena invaliditeta, ali i smrnog ishoda (8,9).

Pacijenti koji su hospitalizovani u jedinicama intenzivnog lečenja (JIL) su skloni ka nastanku hroničnih rana zbog dugotrajne vezanosti za postelju, hemodinamske nestabilnosti, slabe perfuzije tkiva i oksigenacije, kao i skupa unutrašnjih i spoljašnjih faktora rizika (10-15). Takođe, studije su pokazale da su lica hospitalizovana u JIL i zavisna od mehaničke ventilacije obično starija i imaju veći rizik za nastanak hroničnih rana (10-15). Terapijski tretman hroničnih rana podrazumeva primenu antibiotika uz debridment koji je u skladu sa postupcima asepse i antisepse, negativnog pritiska, kao i obloga (17).

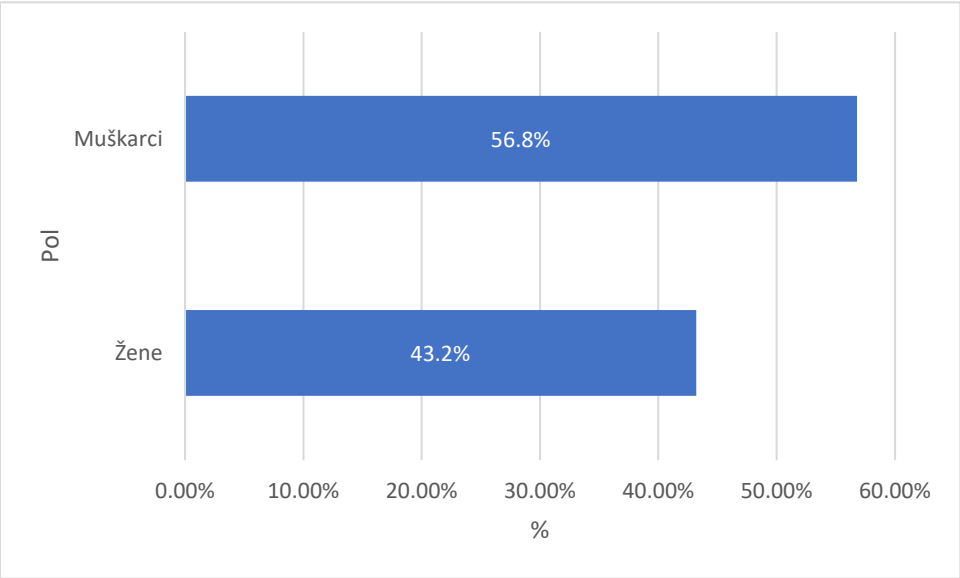
Cilj ove retrospektivne kohortne studije je bio da se za petogodišnji period analiziraju podaci o hroničnim dekubitalnim ranama koji su prikupljeni u jedinicama intenzivnog lečenja (JIL) Urgentnog centra Univerzitetskog Kliničkog Centra Srbija sa ciljem utvrđivanja faktora koji utiču na njihov nastanak i zarastanje.

Metode

Retrospektivna kohortna studija je izvedena u periodu od 01.01.2018. do 01.04.2023. godine u Urgentnom centru Univerzitetskog Kliničkog Centra Srbije i to u JIL politraumatskih, neurohirurških i hirurških pacijenata. Studija je obuhvatila 74 pacijenta sa dijagnozom hroničnih dekubitalnih rana. Za sve ispitanike podaci su dobijeni iz istorije bolesti i otpusne liste pacijenta. Podaci koji su analizirani u ovom radu su: demografske karakteristike (pol, uzrast), razlog hospitalizacije (traumatski/netraumatski), postojanje traheostome i gastrostome, dužina hospitalizacije, komorbiditeti, vrste hroničnih rana, lokalizacija dekubitalnih rana i smrtni ishod. U analizi podataka korišćeni su procena učestalosti i relativni brojevi, kao metode deskritpitvne statistike. Za pravljenje baze i obradu podataka korišćen je *Microsoft Excel 2010*.

Rezultati

Retrospektivna kohortna studija obuhvatila je 74 pacijenta sa dekubitalnim hroničnim ranama tokom vremenskog perioda od 01.01.2018. do 01.04.2023. godine, od kojih su 42 muškarca (56,8%) i 32 žene (43,2%) (Grafikon 1). Najmlađi



Grafikon 1. Distribucija pacijenta sa dekubitalnim hroničnim ranama u odnosu na pol (N=74)

to-heal wounds and that lasts from 4 weeks to more than 3 months (2-4).

According to the Wound Healing Society (WHS), chronic wounds are divided into decubitus, diabetic, venous and arterial ulcers according to their etiology (5). Chronic wounds represent a type of silent epidemic because they are usually not recognized and they are perceived as a chronic comorbid condition. It is estimated that 1 to 2% of the world's population is exposed to chronic wounds during their lifetime in developing countries (6,7).

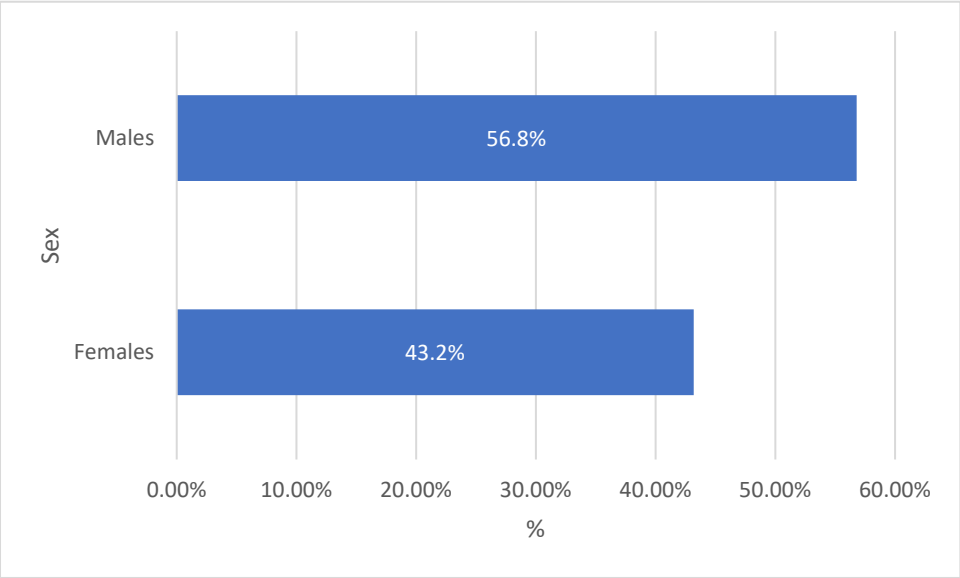
It has been noticed that there is a negative correlation between wound healing and aging, the presence of comorbidities, limited mobility (8,9). Complications that involve chronic wounds are cellulitis, infectious venous eczema, gangrene, hemorrhages, and amputations. The consequences of chronic wounds are numerous and they can lead to immobility and a certain degree of disability, as well as death (8,9).

The patients who are hospitalized in intensive care units (ICUs) are prone to the development of chronic wounds due to the prolonged bed rest, hemodynamic instability, poor tissue perfusion and oxygenation, as well as a set of intrinsic and extrinsic risk factors (10-15). Also, studies have shown that persons who are hospitalized in ICU and who are dependent on mechanical ventilation are usually older and have a greater risk of developing chronic wounds (10-15). The therapeutic treatment of chronic wounds includes the use of antibiotics with a debridement that is in accordance with the procedures of asepsis and antisepsis, negative pressure, as well as dressings (17).

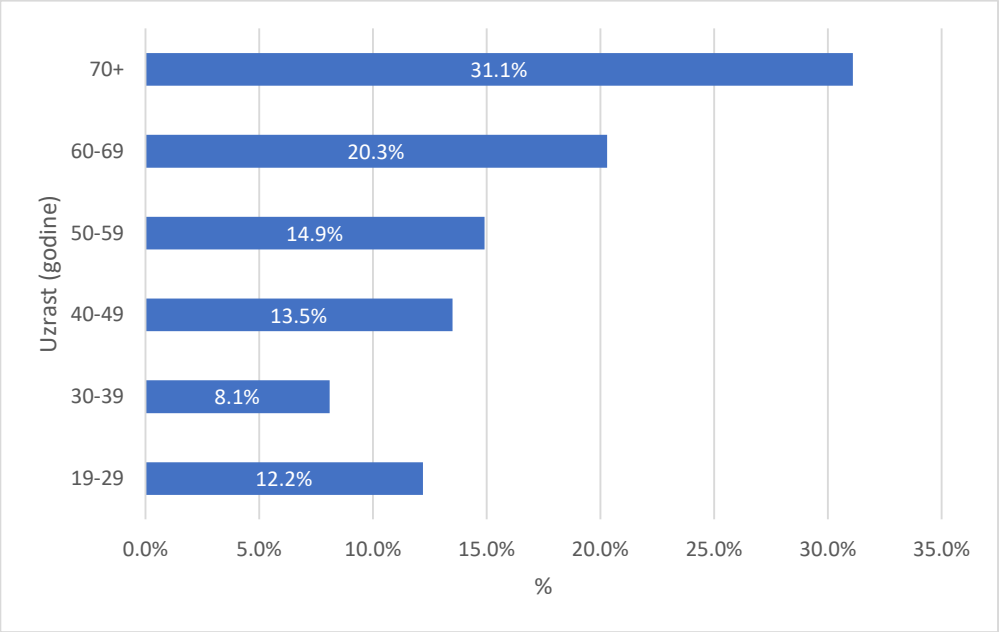
The aim of this retrospective cohort study was to analyze data on chronic pressure ulcers that were collected in intensive care units of the Urgent Care Center of the Clinical Center of Serbia during the five-year period, with the aim of establishing the factors that influence their occurrence and healing.

Methods

The retrospective cohort study was conducted from January 1st, 2018 to April 1st, 2023 at the Urgent Care Center of the University Clinical Center of Serbia, and it included polytrauma, neurosurgical and surgical patients in ICUs. The study included 74 patients diagnosed with chronic pressure ulcers. For all participants, data were obtained from the patients' medical history and list of discharge. Data that were analyzed in this study included the following: demographic characteristics (sex, age), reason of hospitalization (traumatic, non-traumatic), presence of tracheostoma and gastrostomy tube, length of hospitalization, comorbidities, type of chronic wound, localization of pressure ulcers and deathly outcome. The estimates of frequency and relative numbers were used in the analysis of data, as well as the methods of descriptive statistics. Microsoft Excel 2010 was used for the creation of database and analysis of data.



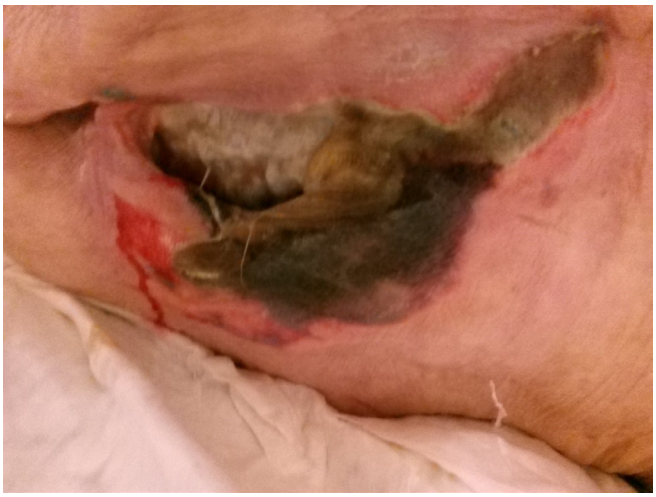
Graph 1. Distribution of patients with chronic pressure ulcers in relation to sex (N=74)



Grafikon 2. Distribucija pacijenta sa dekubitalnim hroničnim ranama u odnosu na uzrast (N=74)

pacijent imao je 19 godina, a najstariji 91 godinu, prosečna starost iznosila je 57,28 (±20,13) godina. Medijana uzrasta 60,5 godina. Najveći broj pacijenata je bio uzrasta 70 i više godina (31,1%) i 60-69 godina (20,3%) (Grafikon 2). Traumatskih pacijenata ukupno je bilo 28 (37,8%), a netraumatskih 46 (62,2%). Kombinovane hronične rane su zabeležene kod 57 (77,0%) pacijenata.

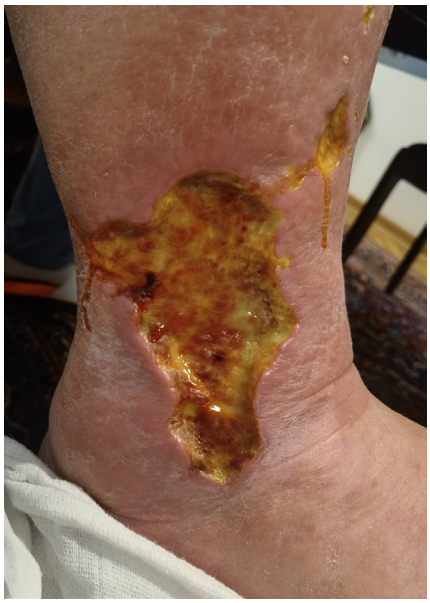
Lokalizacija dekubitalnih rana je najčešće bila na lumbosakralnoj regiji (33 tj. 44,6%) (Slika 1), a zatim u trohanteričnoj regiji 17 (23,0%), skapularnoj regiji 11 (14,9%), maleolusnoj regiji i na tabanima 7 (9,5%) (Slika 2), lakatnoj regiji 5 (6,8%) i parijetookcipitalnoj regiji 1 (1,4%).



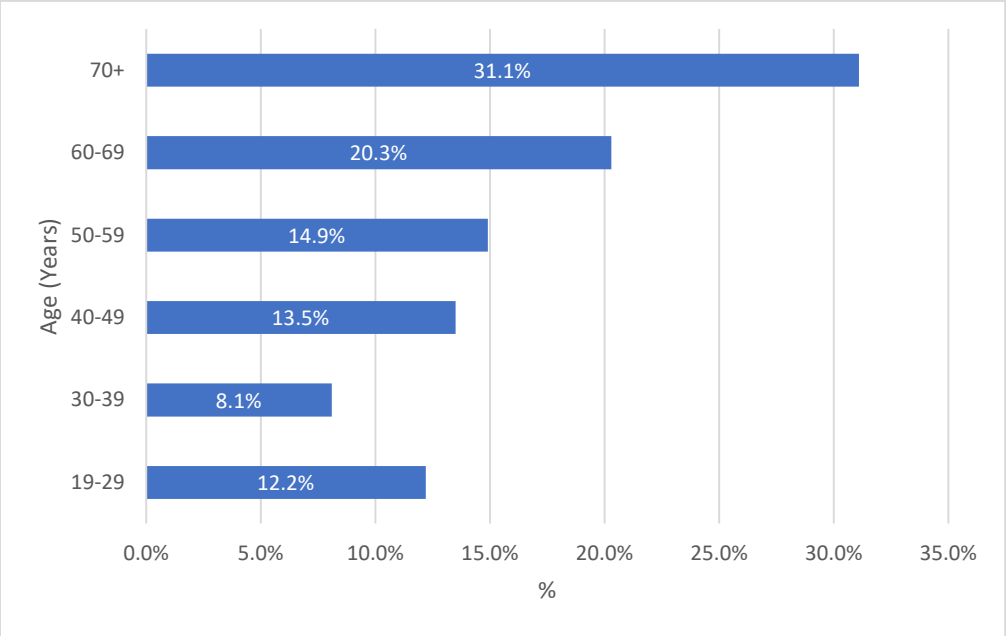
Slika 1. Prikaz sakralnog dekubita kod traumatskog pacijenta povređenog u saobraćajnom udesu sa pratećim subduralnim hematomom

Vremenski period intrahospitalnog lečenja trajao je najkraće 42 dana, a najduže 192 dana. Prosečno su pacijenti boravili u bolnici 71,18 (±27,59) dana. Medijana dužine boravka je 67 dana. Svi pacijenti su bili traheotomisani sa plasiranom gastrostomom.

Analiza komorbiditeta je pokazala da je 67 (90,5%) pacijenata imalo hipertenziju, 59 (79,7%) dijabetes, 38 (51,4%) reumatoidni artritis, 61 (82,4%) hroničnu opstruktivnu bolest pluća (HOBP), 35 (47,3%) demenciju, 5 (6,8%) virusni hepatitis C i 5 (6,8%) HIV.



Slika 2. Prikaz ulcerozne promene kod netraumatskog pacijenta sa dijabetesom, hroničnom opstruktivnom bolešću pluća i indeksom telesne mase 25-30kg/m^2



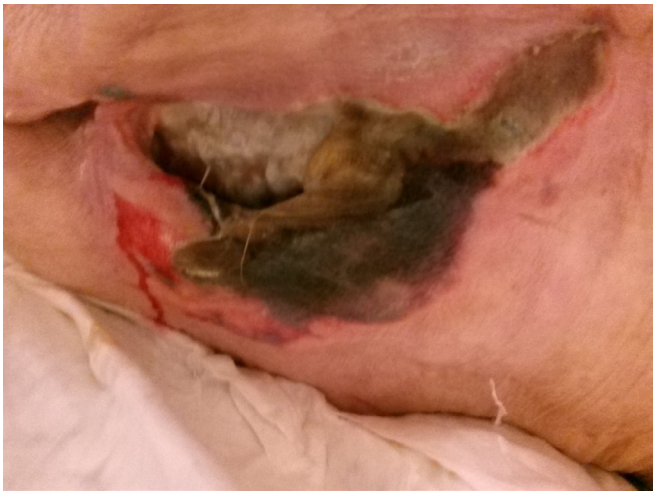
Graph 2. Distribution of patients with chronic pressure ulcers in relation to age (N=74)

Results

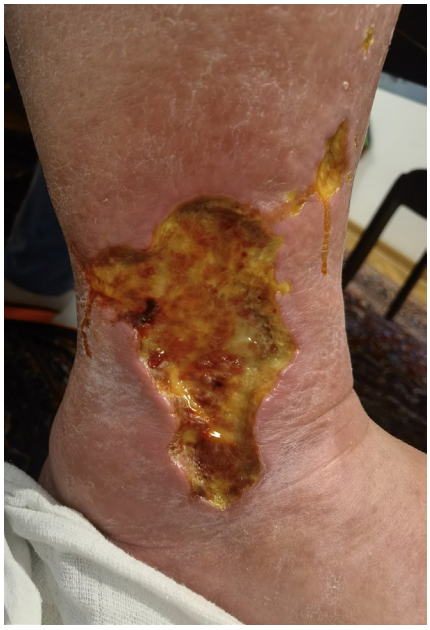
The retrospective cohort study included 74 patients with chronic pressure ulcers during the period January 1st, 2018 – April 1st, 2023, that is, 42 men (56.8%) and 32 women (43.2%) (Graph 1). The youngest patient was 19 years old, while the oldest was 91, and the average age was 57.29 years (+20.13). The age median was 60.5 years. The majority of patients were in the age group 70 and older (31.1%) and 60-69 years (20.3%) (Graph 2). There were 28 trauma patients (37.8%) and 46 non-traumatic patients (62.2%) (Graph 2). Combined chronic wounds were registered in 57 patients (77.0%).

The localization of pressure ulcers was most often in the lumbosacral region (33, that is, 44.6%) (Picture 1), and then in trochanteric region 17 (23.0%), scapular region 11 (14.9%), malleolar region and on the soles 7 (9.5%) (Picture 2), elbow region 5 (6.8%), and parieto-occipital region 1 (1.4%).

The shortest time period of in-hospital treatment was 42 days, while the longest was 192 days. On average, patients stayed in the hospital for 71.18 (+27.59) days. The median length of stay was 67 days. All patients were tracheotomized with a gastrostomy tube placed.



Picture 1. Prikaz sakralnog dekubita kod traumatskog pacijenta povređenog u saobraćajnom udesu sa pratećim subduralnim hematomom



Picture 2. Presentation of ulcerative change in non-trauma patient with diabetes, chronic obstructive lung disease and body mass index 25-30 kg/m^2

U našoj studiji od 74 ispitanika, 38 (51,4%) je bilo pothranjeno (BMI < 18,5 kg/m^2), 25 (33,8%) normalno uhranjeno (BMI - 18,5-24,9 kg/m^2), 10 (13,5%) prekomerno uhranjeno (BMI - 25-29,9 kg/m^2), a 1 (1,4%) gojazan (BMI ≥ 30 kg/m^2).

Došlo je do smrtnog ishoda kod 28 (37,8%) pacijenata.

Diskusija

Pacijenti gerijatrijske populacije sa komorbiditetima su pod visokim rizikom za razvoj dekubitusnih rana, kao i pacijenti sa paraplegijom, odnosno kvadriplegijom. Najefikasniji metod prevencije dekubitalnih rana kao i lečenje kada se pojave jeste izbegavanje povišenog pritiska tako što se vrši mobilnost pacijenta u vidu podsticanja kretanja. Istovremeno, faktore rizika koji promovišu razvoj dekubitalnih rana treba svesti na minimum. Kako bi se to postiglo potrebna je komunikacija među zdravstvenim radnicima; lekarima primarne zdravstvene zaštite, specijalistima, medicinskim sestrama i tehničarima kao i porodicama koje pružaju negu (18).

Šećerna bolest je veliki javnozdravstveni problem. Prema podacima Međunarodne dijabetičke federacije (engl. *International Diabetes Federation* - IDF) prevalencija šećerne bolesti među osobama uzrasta 20-79 godina je, 2010. godine, 6,6 % u svetu, a 8,5% u Europi. Do 2030. godine doći će u svetu do daljeg porasta broja ljudi sa šećernom bolešću tako da će njihov broj iznositi 284,6 miliona. Dvadeset puta veći rizik od amputacije donjih ekstremiteta imaju osobe sa šećernom bolešću. Na osnovu epidemioloških studija procena je da će oko 25% obolelih od dijabetesa melitusa tokom života razviti dijabetičko stopalo sa ulceracijom, a 5-15% će biti podvrgnuto amputaciji donjih ekstremiteta (19-21).

U našoj studiji dijabetes melitus je zabeležen kod 59 (79,7%) pacijenata, a amputacije nisu zabeležene.

U studiji *Jebakumar* i saradnika, prikazano je 813 pacijenata sa ruematoidnim artritisom (RA) tokom vremenskog perioda od 25 godina. Kod 125 pacijenata zabeležene su hronične rane, što je inicijalna dijagnoza RA duže trajala, to je bila veća verovatnoća da će se razviti ulcerozna promena: 5 godina nakon dijagnoze, 5% ispitanika je razvilo ulceroznu promenu, ali zaključno sa 25 godina, 26% ispitanika ga je razvilo (22).

U našoj studiji zabeleženo je 38 (51,4%) pacijenata sa RA u periodu od 5 godina. Verovatnoću za progresiju ulceroznih promena na duži vremenski period nismo ispratili.

Ukoliko pacijent nije u mogućnosti da se pokreće zbog imobilišućih medicinskih faktora, paralize, anestezije ili pak zbog fizičkih ograničenja, spoljašnji pritisak na prominentnim površinskim delovima tela premašuje kapilarni pritisak unutar tkiva, sa posledičnim prekidom cirkulacije, zatim nastupa hipoksija i oštećenje tkiva, a konačno i nekroza. Kritično trajanje ishemije sa posledičnim nastankom hronične rane zavisi od slučaja do slučaja; najčešće se raspon nalazi negde između 30 i 240 min. Studije kontrole slučaja pokazale su da pacijenti sa perifernom arterijskom okluzivnom bolešću imaju veći rizik ne samo od razvoja dekubitalnih ulkusa, već i od nepovoljnog toka s lošim zarastanjem rana (18).

Pretpostavlja se da takvi pacijenti imaju odgođeno vreme reperfuzije nakon uklanjanja spoljašnjeg pritiska. Ti su procesi najjači na delu gde koštane ili hrskavične izbočine poseduju samo tanki mekotkivni omotač (23).

Procesu nastanka hroničnih rana dodatan doprinos daje indeks telesne mase (engl. *Body Mass Index* - BMI). Prospektivna kohortna studija autora *Workum* i saradnika, prikazala je istraživanje korelacije između gojaznosti i nastanka hroničnih rana. Studija je sprovedena od maja 2013. do jula 2017. godine. Obuhvatila je 1911 pacijenata, gde je za analizu uzet uzorak od 1205 pacijenata. Od svih pacijenata, 851 (70,6%) je bio normalno uhranjen, a 354 (29,4%) je imalo BMI ≥ 30kg/m^2. Takođe je zabeleženo da je 40 pacijenata (3,3%) imalo BMI ≥ 40kg/m^2. Došlo se do zaključka da blaga do umerena gojaznost ne predstavlja nezavisan faktor rizika za razvoj dekubita u JIL. Morbidna gojaznost je međutim povezana sa ranijim razvojem hroničnih rana u JIL u komparaciji sa pacijentima koji nisu gojazni (24).

U našoj studiji od 74 ispitanika, 38 (51,4%) je bilo pothranjeno (BMI <18,5 kg/m^2), 25 (33,8%) normalno uhranjeno, a 11 (14,6%) prekomerno uhranjeno (BMI - 25-29,9 kg/m^2) ili gojazno (BMI ≥ 30 kg/m^2). Naši rezultati se slažu sa rezultatima drugih studija gde su pacijenti sa nižim BMI, odnosno pothranjeni, u većem riziku za nastanak hroničnih rana (25).

Pacijenti u našoj studiji lečeni su stadardnim protokolima lečenja hroničnih rana. Akcenat je

The analysis of comorbidities showed that 67 (90.5%) patients had hypertension, 59 (79.7%) diabetes, 38 (51.4%) rheumatoid arthritis, 61 (82.4%) chronic obstructive pulmonary disease (COPD), 35 (47.3%) dementia, 5 (6.8%) viral hepatitis C and 5 (6.8%) HIV.

In our study, of 74 participants, 38 (51.4%) were underweight (BMI <18.5 kg/m^2), 25 (33.8%) had normal weight (BMI – 18.5-24.9 kg/m^2), 10 (13.5%) were overweight (BMI – 25-29.9 kg/m^2), while 1 (1.4%) was obese (BMI > 30 kg/m^2).

Death occurred in 28 (37.8%) patients.

Discussion

Patients of the geriatric population with comorbidities are at a high risk of developing pressure ulcers, as well as patients with paraplegia or quadriplegia. The most effective method of preventing pressure ulcers, as well as treating them when they occur, is to avoid increased pressure by encouraging patient's mobility. At the same time, risk factors that promote the development of pressure ulcers should be minimized. In order to achieve this, communication between healthcare workers, primary care physicians, specialists, nurses and technicians, as well as families that provide care is needed.

Diabetes is a major public health problem. According to data from the International Diabetes Federation (IDF), the prevalence of diabetes among people aged 20-79 in 2010 was 6.6% in the world, and 8.5% in Europe. By 2030, there will be a further increase in the number of people with diabetes in world, so the number of people suffering from diabetes mellitus will be 284.6 million. People with diabetes have a twenty times higher risk of of amputation of lower limbs. Based on epidemiological studies, it is estimated that around 25% of patients suffering from diabetes mellitus will develop a diabetic foot with ulceration during their lifetime, and 5-15% will undergo lower limb amputation (19-21).

In our study, diabetes mellitus was registered in 59 (79.7%) patients, while amputations were not registered.

In the study of Jebakumar and associates, 813 patients with rheumatoid arthritis (RA) were presented during the 25-year time period. Chronic wounds were registered in 125 patients, and the longer the initial diagnosis of RA, the more likely it was to develop an ulcerative change: 5 years after the diagnosis, 5% of participants developed an ulcerative change, but at the end of 25 years, 26% of participants developed this change (22).

In our study, 38 (51.4%) patients with RA were registered during the 5-year period. The possibility for the progression of ulcerative changes for the longer period of time was not monitored.

If a patient is not able to move because of immobilizing medical factors, paralysis, anaesthesia or some physical limitations, the external pressure on prominent surface body parts exceeds the capillary pressure within the tissue, with the consequent interruption of circulation, then hypoxia and tissue damage occur, and finally necrosis. The critical duration of ischemia resulting in the formation of chronic wound varies from case to case; most frequently the range is somewhere between 30 and 240 minutes. Case control studies have shown that patients with peripheral occlusive arterial disease have a higher risk not only of developing pressure ulcers, but also of an unfavorable course with poor wound healing (18).

It is assumed that such patients have a delayed reperfusion time after external pressure is removed. These processes are the strongest in the parts where bony or cartilaginous protrusions have only a thin soft tissue covering (23).

Body mass index (BMI) makes an additional contribution to the process of the formation of chronic wounds. A prospective cohort study of Workum and associates, has presented the research of the correlation between obesity and the development of chronic wounds. The study was conducted from May 2013 to July 2017. It included 1911 patients, where a sample of 1205 patients was used for the analysis. Of all patients, 851 (70.6%) had normal weight, and 354 (29.4%) had BMI > 30 kg/m2. Also, 40 patients (3.3%) had BMI > 40 kg/m2. It was concluded that mild to moderate obesity does not represent an independent risk factor for the development of pressure ulcers in ICUs. However, morbid obesity is associated with earlier development of chronic wounds in the ICU compared to patients who are not obese (24).

In our study, which included 74 participants, 38 (51.4%) were underweight (BMI <18.5 kg/m^2), 25 (33.8%) had normal weight, while 11 (14.6%) were overweight (BMI – 25-29.9 kg/m^2) or obese (BMI >30 kg/m^2). Our results are in accordance with the

stavljen na previjanje pacijenata sa oblozima, debridman, zatim rotiranje pacijenata i primena antidekubitalnih madraca. Primena obloga doprinosi bržem zarastanju rane, većoj komformnosti pacijenta, ima veću apsorptivnu sposobnost (do 20 puta) i ekonomski isplativije je za duži vremenski period u odnosu na klasično previjanje gazom. Nedostatak u primeni gaze je njeno često urastanje u tkivo, a temperatura koja se može postići u rani je najviše do 24°C. Dobar materijal za previjanje treba da poseduje visoku mogućnost apsorpcije, da predstavlja barijeru mikroorganizmima, da dozvoljava evaporaciju kože, da ostavlja nedirnutu okolnu kožu uz mogućnost inspekcije rane, da bolesniku olakšava kretanje i redukuje potrebu čestog previjanja.

Zaključak

Neuhranjenost, hipoperfuzija i komorbiditeti koje ometaju pokretljivost treba prepoznati ako su prisutne i zatim lečiti, a prateće manifestacije, kao što je bol, treba lečiti simptomatski. Tokom daljeg toka lečenja pacijenta, izvodljivost, primenu i efikasnost mera za prevenciju ulkusa treba više puta ponovo procenjivati i dokumentovati, tako da se mogu izvršiti sve neophodne promene. Faktore rizika za nastanak dekubitusnih ulkusa treba proceniti u trenutku prvog kontakta lekara sa nepokretnim pacijentom, ili čim se stanje pacijenta pogorša; ovo je preduslov za pravovremenu prevenciju. Nakon procene rizika, terapijske mere treba preduzeti na osnovu individualnog profila rizika pacijenta, sa naglaskom na aktivnom podsticanju kretanja i pasivnom ublažavanju pritiska čestim promenama položaja.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

Reference

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results of other studies, where patients with lower BMI scores, that is, underweight patients, were at higher risk of developing chronic wounds (25).

The patients in our study were treated with the help of standard protocols for treating chronic wounds. The accent was placed on applying wound dressings, debridement, then rotating patients and using anti-decubitus mattresses. Application of wound dressings contributes to faster healing of the wound, greater patient comfort, has a higher absorptive capacity (up to 20 times) and it is more suitable in terms of their price for the longer period of time compared to classical gauze. The disadvantage of applying gauze is that it often grows into the tissue, and the temperature that can be reached in the wound is up to 24°C. A good dressing material should have high absorbency, be a barrier to microorganisms, allow the skin evaporation, then to leave the surrounding skin untouched with the possibility of inspecting the wound, make it easier for the patient to move and reduce the need for frequent changing of dressings.

Conclusion

Underweight, hypoperfusion and comorbidities that hinder the mobility should be recognized if present and then treated, while accompanying manifestations, such as pain, should be treated symptomatically. During the further course of treatment, the feasibility, application and effectiveness of measures for the prevention of ulcers should be repeatedly evaluated and documented, so that any necessary changes can be made. Risk factors for the occurrence of pressure ulcers should be assessed at the moment of the doctor's first contact with an immobile patient, or as soon as the patient's condition worsens, and this is the prerequisite for timely prevention. After the risk assessment, treatment measures should be taken based on the patient's individual risk profile, with an emphasis placed on active stimulation of movement and passive relief of pressure by frequent changes of position.

Competing interests

The authors declared no competing interests.

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TREND RANOG SIFILISA U BEOGRADU U PERIODU OD 2001. DO 2020. GODINE

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SAŽETAK

Uvod/Cilj: U periodu 2010-2019. godine u zemljama Evropske unije došlo je do porasta obolevanja od sifilisa kod muškaraca za 209,8% i neznatnog porasta kod žena. Naročito je zabeležen porast obolevanja u populaciji muškaraca koji imaju seksualne odnose sa muškarcima (MSM). Cilj ovog rada je bio da utvrdimo trend obolevanja od ranog sifilisa u Beogradu u periodu od 2001. do 2020. godine.
Metode: Za analizu epidemiološke situacije sifilisa na području Beograda, u periodu 2001-2020. godine korišćeni su podaci iz prijava zaraznih bolesti, medicinske dokumentacije, godišnjih izveštaja o radu na sprečavanju, suzbijanju i eliminaciji zaraznih bolesti i rezultati epidemioloških i laboratorijskih ispitivanja. Podaci o broju stanovnika po polu i uzrastu za Beograd su preuzeti iz popisa stanovništva iz 2011. godine, a za godine između popisa korišćene su procene. Na osnovu dobijenih podataka izračunate su sirove, uzrasno specifične i stope incidencije po polu za sifilis. U cilju analize kretanja stopa incidencije za sifilis za period 2001-2020. godine, kao i za period 201-2020. godine, korišćena je *joinpoint* regresiona analiza.
Rezultati: U peridu 2001-2020. godine registrovano je ukupno 938 obolelih od sifilisa, najviša stopa incidencije zabeležena je 2018. godine (8,1/100.000), a najniža 2008. godine (0,5/100.000). U periodu 2001-2008. godine dolazi do opadanja stope incidencije sifilisa za 1,1% godišnje ($p > 0,05$), a u periodu 2009-2020. do značajnog porasta za 24,3% godišnje. U populaciji muškaraca beleži se značajan porast stope incidencije za 20,7% godišnje u periodu 2011-2020. godine, a u populaciji žena za 0,9% godišnje, ali ovaj porast nije bio značajan. Najviše stope incidencije u periodu 2011-2020. godine bile su kod muškaraca uzrasta 30-39 godina, a kod žena za uzrast 20-29 godina. U svim uzrasnim grupama stopa incidencije je bila viša kod muškaraca nego žena, a prosečan odnos obolelih muškaraca i žena je bio 11,9.
Zaključak: Sifilis je i dalje česta polno prenosiva infekcija u Beogradu te su rana dijagnostika i terapija neophodne posebno među pripadnicima vulnerabilnih grupa za polne bolesti da bi se sprečilo širenje ovog oboljenja i nastanak komplikacija. Pošto je čest među ženama u reproduktivnom periodu, antenatalni skrining na ovu infekciju može se preporučiti svim trudnicama, a posebno onim pod povećanim epidemiološkim rizikom.

Key words: sifilis, incidencija, *joinpoint* regresiona analiza

Uvod

Sifilis je sistemsko oboljenje koje izaziva spiroheta *Treponema pallidum*. Prenosi se seksualnim putem, preko krvi i sa inficirane majke na plod. Oboljenje se deli na rani sifilis koji je infektivan i podrazumeva primarni, sekundarni i rani latentni stadijum u trajanju do godinu dana od momenta inficiranja i na kasni sifilis koji nije infektivan, a podrazumeva kasni latentni i tercijarni stadijum. U svetu tokom 2016. godine registrovano je 6,3 miliona novih slučajeva obolelih od sifilisa kod žena i muškaraca starosne dobi od 15 do 49 godina (1).

Prvi zvanični podaci o sifilisu u Beogradu datiraju iz 1899. godine gde je zahvaćenost populacije bila 0,27%, ali bi ovaj podatak prema tvrdnji Mihailovića (2) trebalo uzeti sa rezervom jer je svakako broj obolelih u to vreme bio veći, ali je bilo malo lekara, malo statističara, a i znanja o ovom oboljenju su bila oskudna. Najveći broj inficiranih nalazio se u sekundarnom stadijumu bolesti (74%) i njihovo lečenje se sprovodilo u bolnicama (3). Obolevanje u tom vremenskom periodu se vezivalo za seksualne odnose sa prostitutkama i one su

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TRENDS OF EARLY SYPHILIS IN BELGRADE IN THE PERIOD 2001-2020

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SUMMARY

Introduction/Aim: In the period 2010-2019, in the countries of the European Union, the incidence of syphilis increased by 209.8% in men and in women there was a slight increase. The increase of incidence was particularly noted in the population of men who have sex with men (MSM). The aim of this study was to determine the trend of early syphilis in Belgrade in the period 2001-2020.
Methods: For the analysis of the epidemiological situation of syphilis in the area of Belgrade in the period 2001-2020, data from reports on infectious diseases, medical documentation, annual reports on the work related to the prevention, suppression and elimination of infectious diseases and the results of epidemiological and laboratory tests were used. Data on the number of inhabitants regarding gender and age for Belgrade were taken from the 2011 census, while estimates were used for the years between censuses. Based on the obtained data, raw, age-specific and incidence rates by gender were calculated for syphilis. In order to analyze the trends in incidence rates of syphilis for the period 2001-2020, as well as for the period 2011-2020, joinpoint regression analysis was used.
Results: In the period 2001-2020, a total of 938 cases of syphilis were registered, while the highest incidence rate was registered in 2018 (8.1/100,000), and the lowest in 2008 (0.5/100,000). In the period 2001-2008, the incidence rate of syphilis decreased by 1.1% per year ($p > 0.05$), while in the period 2009-2020, there was a significant increase of 24.3% per year. In the population of men, a significant increase in the incidence rate by 20.7% per year was registered in the period 2011-2020, while in the population of women, this increase was 0.9% per year, and it was not significant. In the period 2011-2020, the highest incidence rates were in men aged 30-39 years, and in women aged 20-29 years. In all age groups, the incidence rate was higher in men than in women, while the average ratio of affected men and women was 11.9.
Conclusion: Syphilis is still a common sexually transmitted infection in Belgrade, and therefore, early diagnosis and therapy are needed, especially among the members of vulnerable groups for sexually transmitted infections, in order to prevent the spread of this disease and the emergence of complications. Since it is common among women in the reproductive period, antenatal screening for this infection can be recommended to all pregnant women, and especially to those at increased epidemiological risk.

Key words: syphilis, incidence, joinpoint regression analysis

Introduction

Syphilis is a systemic disease caused by the spirochete Treponema pallidum. It is transmitted sexually, through blood and from an infected mother to the fetus. The disease is classified into early syphilis, which is infectious and includes primary, secondary and early latent stages lasting up to one year from the moment of infection, and late syphilis, which is not infectious, and includes late latent and tertiary stages. In 2016, 6.3 million new cases of syphilis were registered in the world in women and men aged 15 to 49 (1).

The first official data on syphilis in Belgrade date back to 1899, when 0.27% of the population was affected, but according to Mihailovic (2), this data should be taken with a pinch of salt, because the number of affected people at that time was

bile pod zdravstvenim nadzorom sanitarne policije (4). Porast veneričnih bolesti, naročito sifilisa, u Beogradu, registruje se dvadesetih godina prošlog veka, te se 1928. godine otvara Opštinska ambulanta za kožne i venerične bolesti koja 1938. godine prerasta u Gradsku polikliniku za kožne i venerične bolesti. Oko 80% obolelih je infekciju dobilo usled kontakta sa prostitutkama, a oboleli su najčešće bili iz „radničkih slojeva“ (5).

Prema podacima Marjanovića i saradnika (6) beleži se porast incidencije sifilisa u Beogradu u periodu od 1967. do 1971. godine, a među osobama koje su imale ponavljana obolevanja od veneričnih bolesti najbrojniji su bili radnici zaposleni u uslužnim delatnostima – profesionalni vozači, konobari i nezaposlena lica (7). Tokom devedesetih godina prošlog veka beleži se porast incidencije sifilisa u Beogradu sa najvišom stopom 4,22 na 100,000 za muškarce u 1998. godini i 1,82 na 100,000 za žene u 1997. godini (8). Porast obolevanja je zabeležen kod heteroseksualnih muškaraca koji su zbog ekonomskih sankcija uvedenih Srbiji i Crnoj Gori odlazili na rad u zemlje bivšeg Sovjetskog Saveza, tamo se inficirali, te bolest importovali u Srbiju i prenosili je i na svoje seksualne partnere (8). Početkom novog milenijuma dolazi do pojave epidemija ranog sifilisa u Beogradu, prvenstveno među populacijom muškaraca koji imaju seksualne odnose sa muškarcima (9).

Cilj ovog rada je bio da utvrdimo trend obolevanja od ranog sifilisa kod novoobolelih u Beogradu u periodu od 2001. do 2020. godine.

Metode

Za analizu epidemiološke situacije sifilisa na području Beograda, u periodu 2001-2020. godine korišćeni su podaci iz prijava zaraznih bolesti, medicinske dokumentacije, godišnjih izveštaja o radu na sprečavanju, suzbijanju i eliminaciji zaraznih bolesti i rezultati epidemioloških i laboratorijskih ispitivanja. Usled odsustva podataka o distribuciji obolelih po polu za period prvih deset godina, ovi podaci su prikazani za period 2011-2020. godine. Podaci o beoradskom stanovništvu preuzeti iz popisa stanovništva iz 2011. godine, a za godine između popisa korišćene su procene.

U cilju sagledavanja epidemiološke situacije sifilisa korišćene su sirove, uzrasno specifične i stope incidencije po polu. Stopa incidencije je računata deljenjem broja novoobolelih od sifilisa za jednu godinu sa brojem stanovnika sredinom posmatrane godine.

U cilju analize kretanja stopa incidencije za sifilis za period 2001-2020. godine, kao i za period 2011-2020. godine, korišćena je *joinpoint* regresiona analiza (10). Primenom ove metode doći će se do podatka o prosečnom godišnjem trendu kretanja obolevanja od sifilisa u posmatranim periodima.

Rezultati

U peridu 2001-2020. godine registrovano je ukupno 938 obolelih od sifilisa, najviše stopa incidencije zabeležena je 2018. godine (8,1/100.000), a najniža 2008. godine (0,5/100.000) (tabela 1). U periodu 2011-2020. godina u Beogradu je prijavljeno 803 obolelih od sifilisa, među kojima je bilo 755 muškaraca i 48 žena. U muškoj populaciji, u posmatranom desetogodišnjem periodu, najviša stopa incidencije je bila 2018. godine (17,7/100.000), a najniža 2013. godine (2,3/100.000), a u ženskoj najviša 2012. godine (0,8/100.000), a najniža 2013. godine (0,2/100.000).

Posmatrajući trend kretanja obolevanja od sifilisa uočava se da u periodu 2001-2008. godine dolazi do opadanja stope incidencije za 1,1% godišnje ($p > 0,05$), a u periodu 2009-2020. do značajnog porasta za 24,3% godišnje (grafikon 1). U populaciji muškaraca beleži se značajan porast stope incidencije za 20,7% godišnje u periodu 2011-2020. godine (grafikon 2), a u populaciji žena za 0,9% godišnje, ali ovaj porast nije bio značajan (grafikon 3).

Najviše stope incidencije sifilisa u Beogradu u periodu 2011-2020. godine registrovane su u uzrastu 30-39 godina kod muškaraca i 20-29 godina kod žena (tabela 2). Najniže stope incidencije su kod muškaraca mlađih od 19 godina, a kod žena starijih od 60 godina. U svim uzrasnim grupama stopa incidencije je viša kod muškaraca nego kod žena, odnos obolelih muškaraca i žena kreće se od 3,9-31,7, prosečan odnos iznosi 11,9.

Diskusija

U zemljama Evropske unije u toku 2019. godine registrovano je 35.039 slučajeva ranog sifilisa (19,2 slučaja na 100.000 stanovnika) (11). Ako se posmatra poslednja decenija u periodu od 2010. do 2019. godine u zemljama Evropske unije došlo je do porasta obolevanja od sifilisa kod muškaraca za

certainly higher, but there were few doctors, and knowledge about this disease was scarce. The largest number of infected people was in the secondary stage of disease (74%) and their treatment was carried out in hospitals (3). The disease in that time period was associated with sexual relations with prostitutes and they were under the health supervision of sanitary police (4). The increase in venereal diseases, especially syphilis was registered in Belgrade in the 1920s, and therefore, in 1928, the Municipal Infirmary for Skin and Venereal Diseases was opened and transformed into the City Polyclinic for Skin and Venereal Diseases in 1938. About 80% of the patients got the infection due to the contact with prostitutes and the patients mostly belonged to the "working class" (5).

According to Marjanovic and associates (6), there was an increase in syphilis in Belgrade in the period 1967-1971, while among persons who had repeated venereal diseases, the most numerous were workers employed in service industries – professional drivers, waiters and the unemployed (7). During the 1990s, an increase in the incidence was registered in Belgrade with the highest rate of 4.22 per 100,000 for men in 1998 and 1.82 per 100,000 for women in 1997 (8). The increase in morbidity was registered in heterosexual men, who went to work in the countries of the former Soviet Union due to the economic sanctions introduced in Serbia and Montenegro, got infected there and imported the disease to Serbia and transmitted it to their sexual partners (8). At the beginning of the new millennium, epidemics of early syphilis appeared in Belgrade, primarily in the population of men who have sex with men (9).

The aim of this study was to determine the trend in morbidity of early syphilis in newly diagnosed patients in Belgrade from 2001 to 2020.

Methods

For the analysis of the epidemiological situation of syphilis in the Belgrade area, in the period 2001-2020, data from reports of infectious diseases, medical documentation, annual reports on work on the prevention, suppression and elimination of infectious diseases and the results of epidemiological and laboratory tests were used. Due to the fact that there were no data on the distribution of affected persons by sex for the first ten years, these data were presented for the period 2011-2020. Data on the number of inhabitants for Belgrade were taken from the 2011 census, while estimates were used for the years between censuses.

Based on the obtained data, raw, age-specific and incidence rates by gender were calculated for syphilis. The incidence rate was calculated when the number of new cases of syphilis for one year was divided by the population in the middle of the observed year.

In order to analyze the trends in incidence rates for syphilis for the period 2001-2020. year, as well as for the period 2011-2020. year, joinpoint regression analysis was used (10). By applying this method, data will be obtained on the average annual trend in the incidence of syphilis in the observed periods.

Results

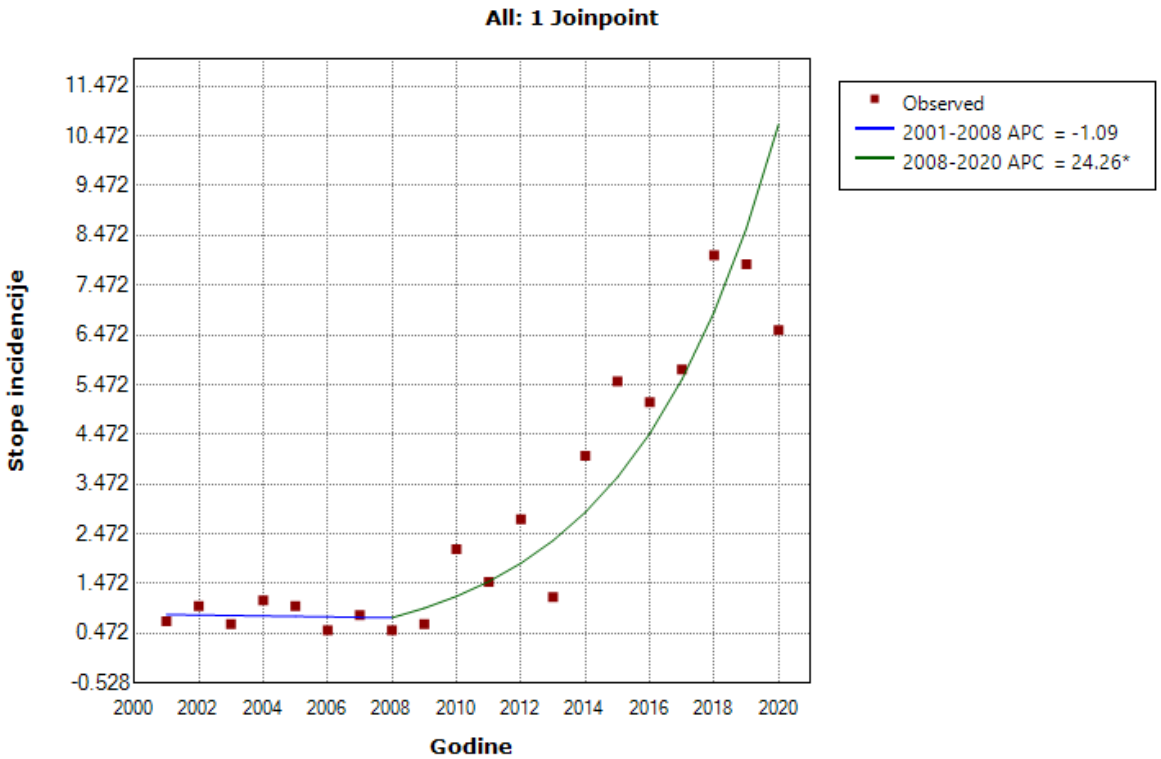
In the period 2001-2020, a total of 938 syphilis cases were registered, while the highest incidence rate was registered in 2018 (8.1/100,000), and the lowest in 2008 (0.5/100,000) (Table 1). In the period 2011-2020, 803 syphilis cases were reported in Belgrade, of whom 755 were men and 48 women. In the male population, in the observed ten-year period, the highest incidence rate was in 2018 (17.7/100,000), and the lowest was in 2013 (2.3/100,000), while in the female population, the highest incidence rate was in 2012 (0.8/100,000), and the lowest in 2013 (0.2/100,000).

Observing the trend in the incidence of syphilis, it can be seen that in the period 2001-2008, the incidence rate decreased by 1.1% per year ($p>0.05$), while in the period 2009-2020, it increased significantly by 24.3% per year (Figure 1). In the male population, a significant increase of 20.7% per year was noted in the period 2011-2020 (Figure 2), and in the female population, 0.9% per year, but this increase was not significant (Figure 3).

The highest incidence rates of syphilis in Belgrade in the period 2011-2020 were registered in the age group 30-39 years in men and 20-29 years in women (Table 2). The lowest incidence rates were in men younger than 19, and in women over the age of 60. In all age groups, the incidence rate was higher in men than in women, the ratio of affected men and women ranged between 3.9-31.7, while the average ratio was 11.9.

Tabela 1. Stope incidencije sifilisa (na 100.000), ukupno i prema polu, Beograd, 2001-2020. godine

Godine	Ukupno	Muškarci	Žene
2001	0,7	/	/
2002	1,0	/	/
2003	0,7	/	/
2004	1,1	/	/
2005	1,0	/	/
2006	0,5	/	/
2007	0,8	/	/
2008	0,5	/	/
2009	0,7	/	/
2010	2,2	/	/
2011	1,5	2,8	0,3
2012	2,8	5,0	0,8
2013	1,2	2,3	0,2
2014	4,0	7,8	0,7
2015	5,5	11,1	0,6
2016	5,1	9,3	0,7
2017	5,8	11,7	0,5
2018	8,1	17,7	0,2
2019	7,9	15,4	1,1
2020	6,6	13,5	0,3



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 1 Joinpoint.

Grafikon 1. Trend incidencije (na 100.000) za sifilis, za oba pola, Beograd, 2001-2020. godine

Table 1. Incidence rates of syphilis (per 100,000), total and by gender, Belgrade, 2001-2020

Years	Total	Males	Females
2001	0.7	/	/
2002	1.0	/	/
2003	0.7	/	/
2004	1.1	/	/
2005	1.0	/	/
2006	0.5	/	/
2007	0.8	/	/
2008	0.5	/	/
2009	0.7	/	/
2010	2.2	/	/
2011	1.5	2.8	0.3
2012	2.8	5.0	0.8
2013	1.2	2.3	0.2
2014	4.0	7.8	0.7
2015	5.5	11.1	0.6
2016	5.1	9.3	0.7
2017	5.8	11.7	0.5
2018	8.1	17.7	0.2
2019	7.9	15.4	1.1
2020	6.6	13.5	0.3

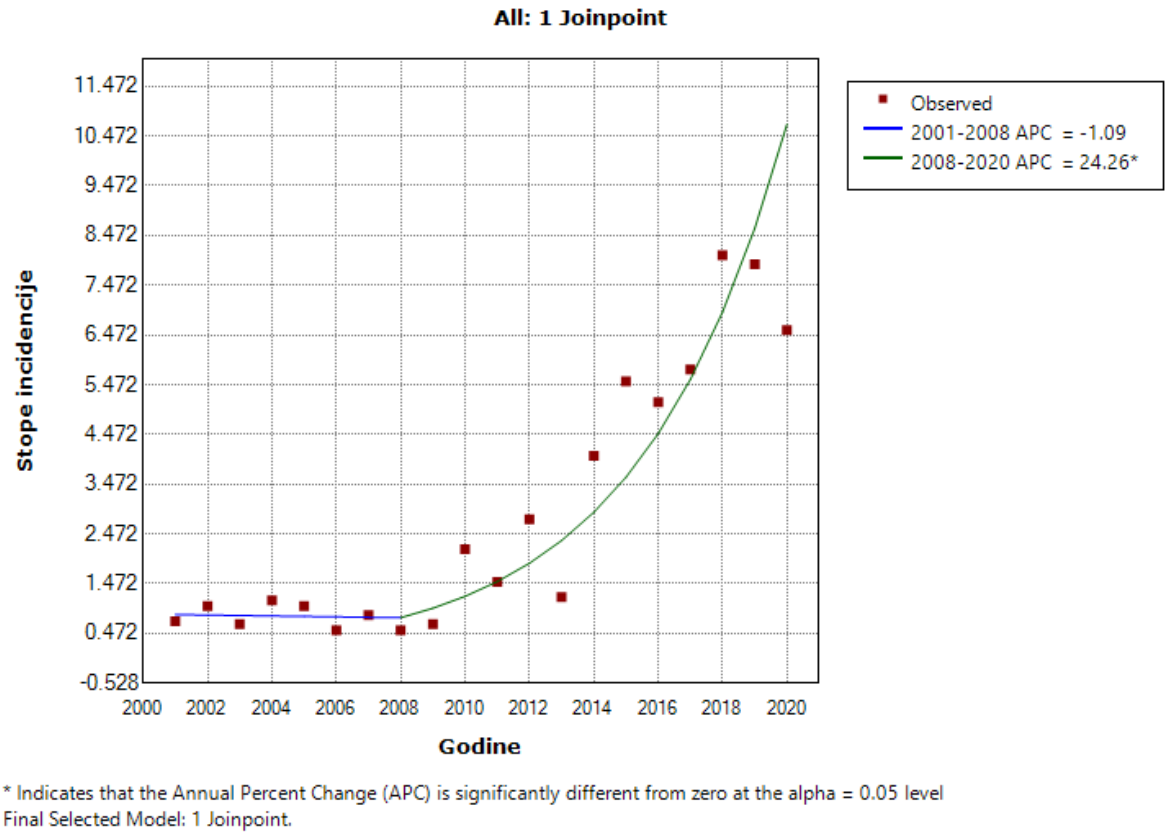
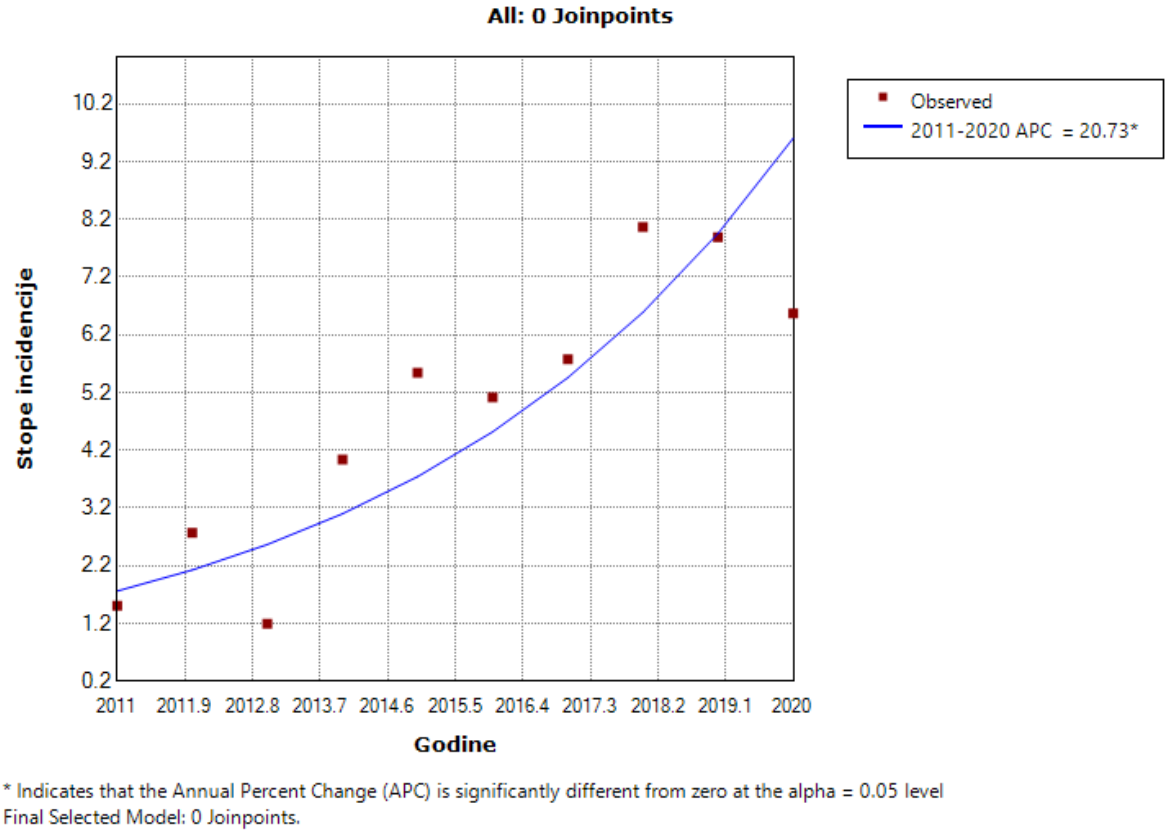
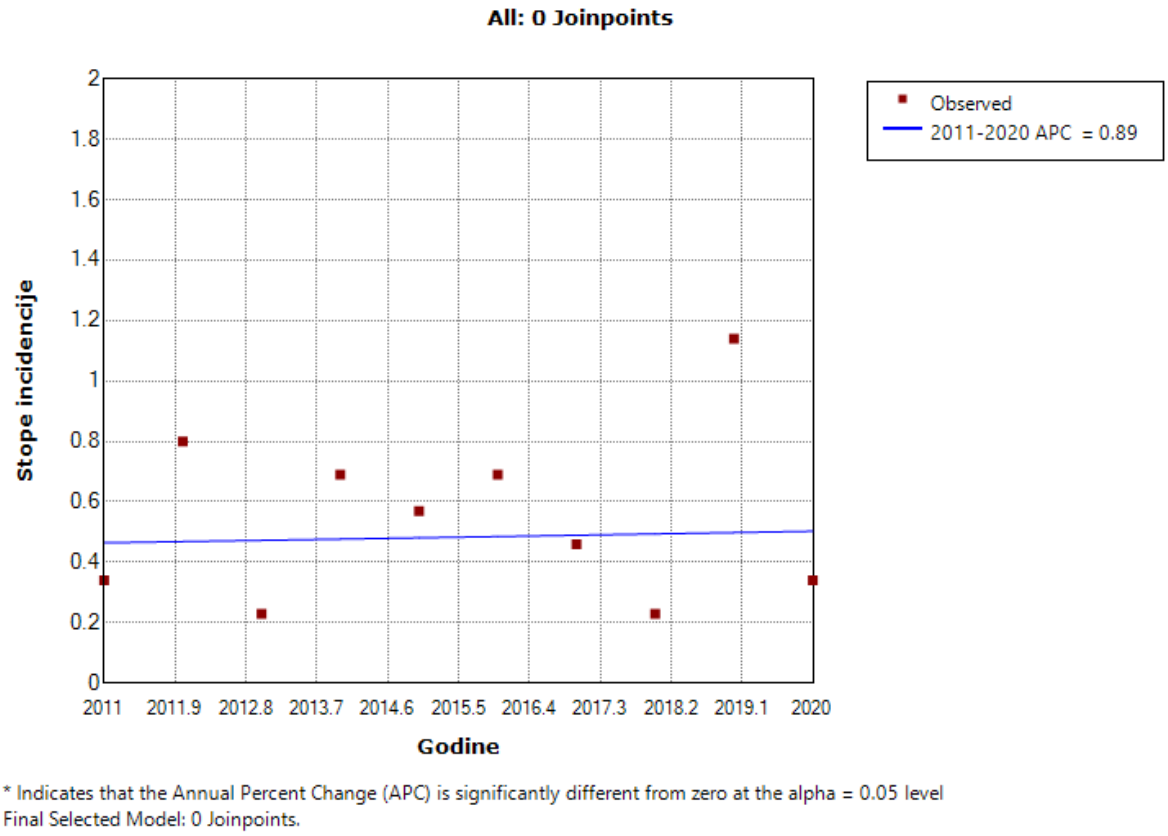


Figure 1. Incidence rates (per 100,000) trend for syphilis, for both genders, Belgrade, 2001-2020



Grafikon 2. Trend incidencije (na 100.000) za sifilis, muškarci, Beograd, 2011-2020. godine



Grafikon 3. Trend incidencije (na 100.000) za sifilis, žene, Beograd, 2011-2020. godine

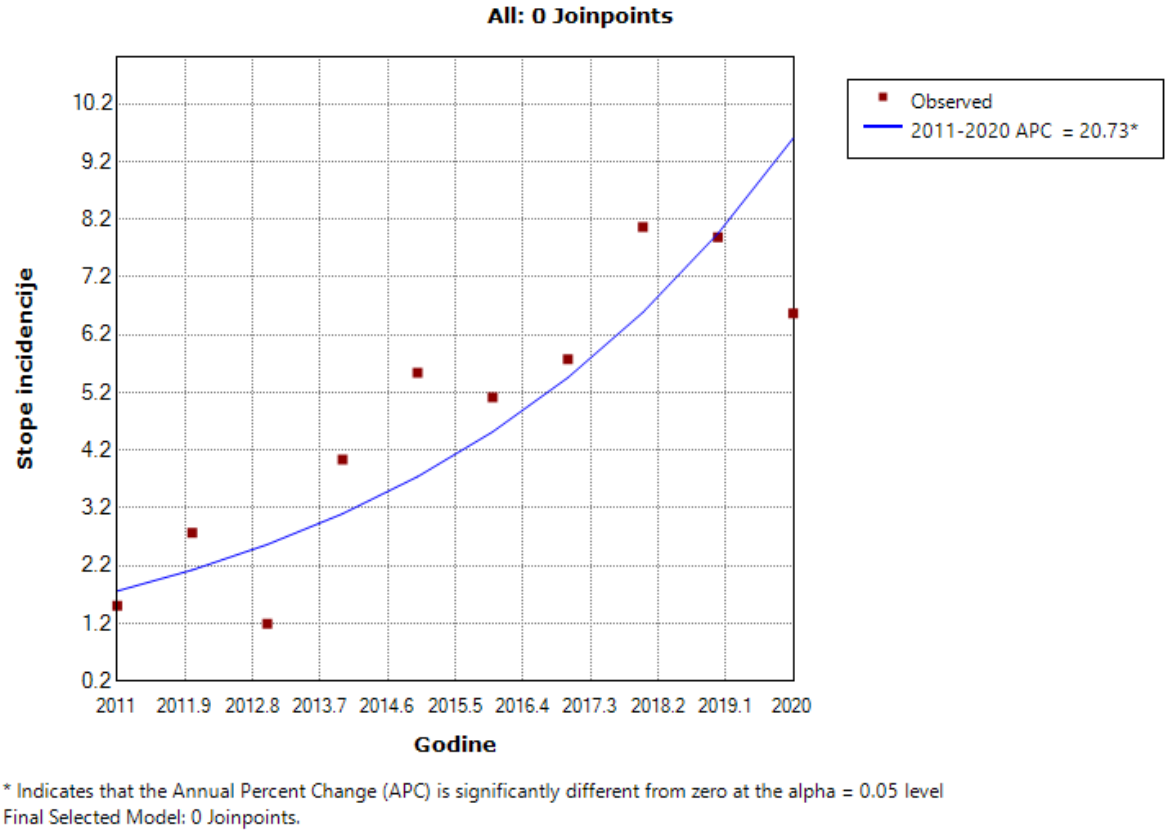


Figure 2. Incidence rates (per 100,000) for syphilis, males, Belgrade, 2001-2020

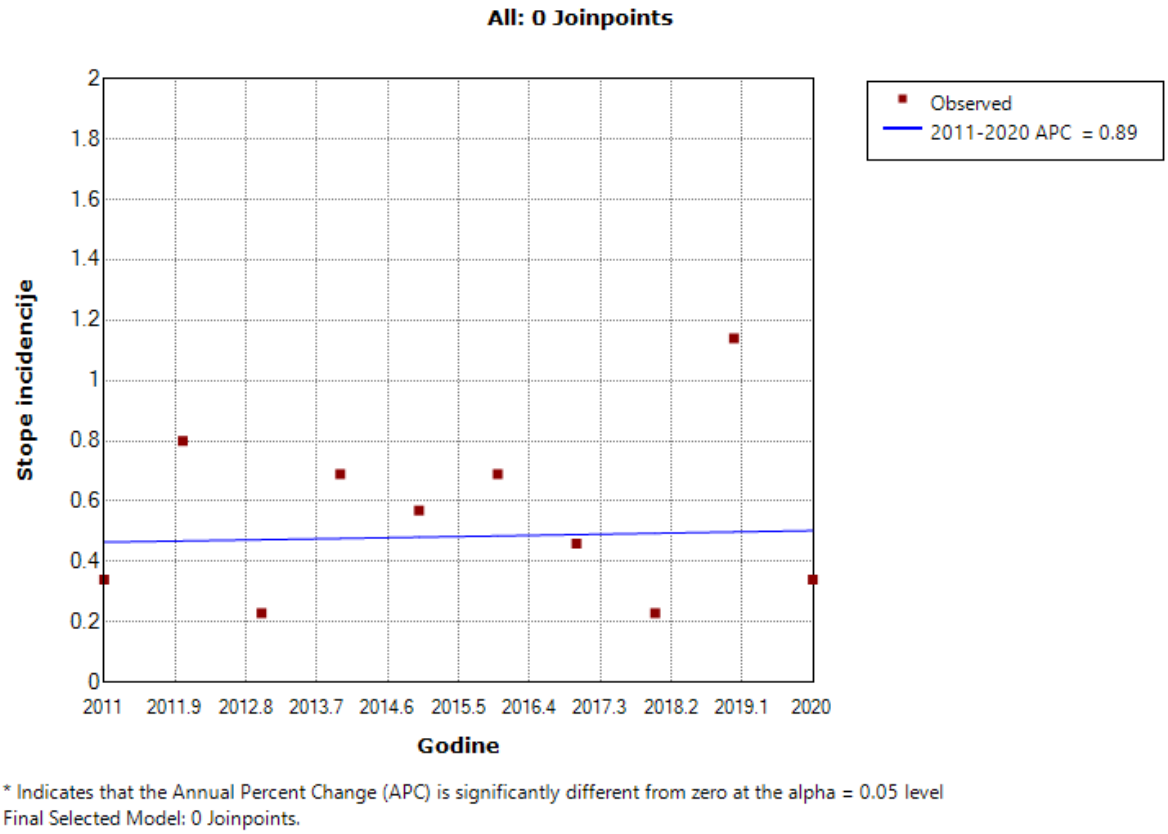


Figure 3. Incidence rates (per 100,000) trend for syphilis, females, Belgrade, 2001-2020

Tabela 2. Ukupan broj novoobolelih od sifilisa i prosečna incidencija (na 100.000), po polu i uzrastu, i odnos polova, Beograd, 2001-2020. godine

	Muškarci		Žene		
Uzrasne grupe	**Broj slučajeva**	**Prosečna stopa incidencije**	**Broj slučajeva**	**Prosečna stopa incidencije**	**Odnos polova Muškarci/Žene**
<19	12	0,7	3	0,19	3,9
20-29	207	18,8	14	1,24	15,2
30-39	302	24,1	10	0,76	31,7
40-49	158	15,1	8	0,70	21,5
50-59	56	4,9	10	0,75	6,5
>60	20	1,2	3	0,1	11,9

209,8% (sa 6,1 na 100.000 u 2010. godini na 12,8 na 100.000 u 2019. godini) i neznatnog porasta kod žena (sa 1,3 na 100.000 u 2010. godini na 1,5 na 100.000 u 2019. godini) (12). Porast obolevanja je naročito zabeležen u populaciji muškaraca koji imaju seksualne odnose sa muškarcima (MSM). Naime, čak 74% registrovanih slučajeva pripadalo je ovoj populaciji, naročito u zemljama Zapadne Evrope gde je taj procenat iznosio preko 75%, dok je udeo obolelih iz MSM populacije u zemljama našeg okruženja (Mađarska i Rumunija) bio oko 20% (11).

Prema rezultatima našeg istraživanja u poslednjoj deceniji najveće stope sifilisa u Beogradu su zabeležene 2018. godine i iznosile su 8,1 novoobolelih na 100.000 stanovnika. Karakteristike trenda obolevanja od sifilisa u poslednjih deset godina (2011-2020) kod nas su u skladu sa rezultatima iz zemalja Evropske unije (11). Došlo je do porasta obolevanja među muškarcima za 482,1% (sa 2,8 na 100.000 u 2011. godini na 13,5 na 100.000 u 2020. godini), dok su stope incidencije kod žena ostale neizmenjeno niske (0,34 na 100.000). Kao i u Evropi, i u našoj sredini se znatan porast obolevanja od sifilisa registovao u MSM populaciji (9). Ovo bi se moglo objasniti visokorizičnim seksualnim ponašanjem (seksualni odnosi bez upotrebe kondoma, veći broj seksualnih partnera, upotreba seksualizovanih droga), lakšim pronalaženjem seksualnih partnera preko mobilnih aplikacija i društvenih mreža, kao i upotrebom pre ekspozicione profilakse (PrEP) za HIV (13-15). Kao faktori udruženi sa obolevanjem od sifilisa u Evropi u heteroseksualnoj populaciji navode se promiskuitet, prostitucija, upotreba alkohola i droga, kao i socijalno ekonomski činioci poput siromaštva i statusa migranata i izbeglica (12).

Koinfekcija sifilisa i HIV-a zabeležena je kod 34% MSM osoba u Evropskoj uniji tokom 2019. godine (11). Podaci o karakteristikama obolelih MSM osoba od ranog sifilisa u Beogradu za period 2010-2014. godina pokazuju da je HIV koinfekcija registrovana kod 22,7% osoba (9). Česta udruženost ovih infekcija upućuje na neophodnost testiranja obolelih od sifilisa na HIV, kao i periodično testiranje na sifilis seksualno aktivnih osoba koje žive sa HIV infekcijom.

Najveće stope obolevanja od sifilisa kod muškaraca zabeležene su u zemljama Zapadne Evrope i u 2019. godini iznosile su 15 na 100.000, dok su kod žena najviše stope zabeležene u Bugarskoj i Mađarskoj (3 na 100.000) (11). Odnos obolelih muškaraca i obolelih žena (*Male/Female ratio*) kretao se od 15:1 u zemljama Zapadne Evrope do 2:1 u zemljama Istočne Evrope. Uzrasno specifične stope obolevanja od sifilisa su konstantno bile najveće u starosnoj grupi od 25 do 44 godina, a skoro su se udvostručile u grupama od 25 do 34 godine i od 35 do 44 godine (11). Rezultati našeg istraživanja su u skladu sa podacima iz Evrope. Naime, kod muškaraca su stope obolevanja od sifilisa najveće u starosnoj grupi od 30 do 39 godina, a kod žena u uzrastu od 20 do 29 godina, dok je prosečan odnos obolelih muškaraca i obolelih žena u periodu od 2011. do 2020. godine bio 16:1.

S obzirom na to da je sifilis u Beogradu najčešće registrovan među ženama u reproduktivnom periodu, antenatalni skrining na ovu infekciju je preporučljiv kod svih trudnica, naročito kod onih pod povećanim epidemiološkim rizikom (16).

Zaključak

U novom milenijumu zabeležen je porast trenda obolevanja od sifilisa u Beogradu. Iako se

Table 2. Total number of syphilis cases and average incidence (per 100.000) distributed by age, sex, and male to female ratio, Belgrade 2001-2020

	Men		Women		
Age group	**Number of cases**	**Average incidence**	**Number of cases**	**Average incidence**	**Sex ratio Male/Female**
<19	12	0.7	3	0.19	3.9
20-29	207	18.8	14	1.24	15.2
30-39	302	24.1	10	0.76	31.7
40-49	158	15.1	8	0.70	21.5
50-59	56	4.9	10	0.75	6.5
>60	20	1.2	3	0.1	11.9

Discussion

In 2019, 35,039 cases of early syphilis were registered in the countries of the European Union (19.2 cases per 100,000) (11). If the last decade in the period 2010-2019 is observed in the countries of the European Union, the incidence of syphilis in men increased by 209.8% (from 6.1 per 100,000 in 2010 to 12.8 per 100,000 in 2019) and there was a slight increase in women (from 1.3 per 100,000 in 2010 to 1.5 per 100,000 in 2019) (12). The increase in morbidity was particularly noted in the population of men who have sex with men (MSM). Namely, even 74% of the registered cases belonged to this population, especially in the countries of the Western Europe, where that percentage was over 75%, while the share of patients from the MSM population was around 20% in the surrounding countries (Hungary and Romania) (11).

According to the results of our research in the last decade, the highest rates of syphilis in Belgrade were registered in 2018 and they amounted to 8.1 new cases per 100,000 inhabitants. The characteristics of trends of syphilis in the last ten years (2011-2020) in our country are in accordance with the results from the countries of the European Union (11). The incidence increased in men by 482.1% (from 2.8 per 100,000 in 2011 to 13.5 per 100,000 in 2020), while the incidence rates in women were unchanged and stayed low (0.34 per 100,000). As in Europe, a significant increase in the incidence of syphilis was registered in the MSM population (9). This could be explained by high-risk sexual behavior (sex without condoms, more sexual partners, use of sexualized drugs), easier finding of sexual partners through mobile applications and social networks, as well as the use of pre-exposure prophylaxis (PrEP) for HIV (13-15). Promiscuity, prostitution, alcohol and drug use, as well as socio-economic factors such as poverty and the status of migrants and refugees are cited as factors associated with syphilis in Europe in the heterosexual population (12).

The co-infection of syphilis and HIV was recorded in 34% of MSM in the European Union in 2019 (11). Data on the characteristics of MSM with early syphilis in Belgrade for the period 2010-2014 show that HIV co-infection was registered in 22.7% of people (9). The frequent association of these infections points to the necessity of testing syphilis patients for HIV, as well as periodical testing for syphilis of sexually active persons living with HIV infection.

The highest incidence rates of syphilis in men were registered in the countries of Western Europe and they amounted to 15 per 100,000 in 2019, while in women the highest rates were registered in Bulgaria and Hungary (3 per 100,000) (11). The male/female ratio ranged from 15:1 in Western European countries to 2:1 in Eastern European countries. The highest age-specific incidence rates of syphilis were constantly in the age group 25-44 years, and they almost doubled in the age groups 25-34 years and 35-44 years (11). The results of our research are consistent with data from Europe. Namely, the highest incidence rates of syphilis in men were in the age group 30-39 years, and in women in the age group 20-29 years, while the average male/female ratio was 16:1 in the period 2011-2020.

Given that syphilis in Belgrade was most often registered in women in the reproductive period, antenatal screening for this infection is recommended to all pregnant women, especially those at increased epidemiological risk (16).

radi o „staroj veneričnoj bolesti“, sifilis je i dalje česta bakterijska polno prenosiva infekcija u našoj sredini te su rana dijagnostika i terapija neophodne posebno među pripadnicima vulnerabilnih grupa za polne bolesti da bi se sprečilo širenje ovog oboljenja i nastanak komplikacija.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Conclusion

In the new millennium, an increase in the trend of morbidity of syphilis was registered in Belgrade. Although it is an "old venereal disease", syphilis is still a common bacterial sexually transmitted infection in our environment, and early diagnosis and therapy are needed, especially among the members of vulnerable groups in order to prevent the spread of this disease and the occurrence of complications.

Competing interests

The authors declared no competing interests.

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KRETANJE OBOLEVANJA I UMIRANJA OD KOLOREKTALNOG KARCINOMA KOD MUŠKARACA I ŽENA CENTRALNE SRBIJE ZA PERIOD 1999-2020. GODINE

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SAŽETAK

Uvod/Cilj: Kolorektalni karcinom je treći vodeći maligni tumor po obolevanju u svetu, odmah posle karcinoma dojke i pluća, i drugi vodeći maligni tumor prema broju umrlih, iza raka pluća. Cilj ove deskriptivne studije je bio da se analizira kretanje obolevanja i umiranja od karcinoma kolorektuma kod muškaraca i žena Centralne Srbije u periodu od 1999. do 2020. godine.
Metode: Podaci o obolelima i umrlima od kolorektalnog karcinoma (šifre C18 - C20, prema Internacionalnoj klasifikaciji bolesti), kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2020. godine, preuzeti su iz registara za rak u Centralnoj Srbiji i od Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut". Izračunate su sirove, uzrasno-specifične i standardizovane stope incidencije i mortaliteta za rak kolorektuma. U cilju analize kretanja stopa incidencije i mortaliteta korišćena je *joinpoint* regresiona analiza.
Rezultati: U periodu od 1999. do 2020. godine u Centralnoj Srbiji je od kolorektalnog karcinoma prosečno obolevalo 1696 muškaraca i 1112 žena, a umiralo 990 muškaraca i 676 žena. Prosečna standardizovana stopa incidencije (na 100.000) je bila 34,4 za muškarce i 19,5 za žene, a prosečna standardizovana stopa mortaliteta (na 100.000) 18,4 za muškarce i 10,1 za žene. Prosečne uzrasno specifične stope incidencije i mortaliteta od kolorektalnog karcinoma rastu sa godinama starosti kod oba pola. U periodu 1999-2020. godine, standardizovane stope incidencije kolorektalnog karcinoma značajno rastu za 0,7% godišnje za žene i 1% godišnje za muškarce. Kod žena uočava se značajan porast stopa mortaliteta od kolorektalnog karcinoma od 2,6% godišnje u periodu 1999-2006. godine, a potom pad od 1,2% godišnje za period 2006-2020. Međutim, kod muškaraca se uočava značajan porast u periodu 1999-2010., a zatim pad od 1,2% godišnje, ali bez statističke značajnosti.
Zaključak: Neophodno je raditi na unapređenju sprovođenja organizovanog skrininga za rak kolorektuma, kao i na edukaciji stanovništva o faktorima rizika za nastanak ovog malignoma i mogućnostima prevencije.

Ključne reči: kolorektalni karcinom, incidencija, mortalitet, trend, joinpoint regresiona analiza

Uvod

Prema podacima GLOBOCAN-a za 2020. godinu, od malignih tumora u svetu je obolelo blizu 20 miliona ljudi (1). Iste godine od kolorektalnog karcinoma obolelo je skoro 2 miliona ljudi (1.931.590 novoobolelih), što čini 10% svih novoobolelih od malignih tumora. U 2020. godini, broj novoobolelih od kolorektalnog karcinoma u populaciji muškaraca u svetu je bio 1.065.960, dok je obolelih žena bilo 865.630. Kolorektalni karcnom je treći vodeći uzrok obolevanja od malignih tumora u svetu, odmah posle karcinoma dojke i pluća, kada se oba pola posmatraju zajedno (1). Treći je vodeći uzrok obolevanja u muškoj populaciji, iza karcinoma pluća i prostate, a drugi u populaciji žena, iza karcinoma dojke (1). U svetu je, 2020. godine, od karcinoma debelog creva umrlo 973.173 osoba, što čini 9,4% svih umrlih od malignih tumora (1). Umrlih muškaraca bilo je 515.637, a žena 419.536 (1). I pored postojanja savremenih metoda skrininga koje bi u velikoj meri mogle smanjiti umira-

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TRENDS IN MORBIDITY AND MORTALITY OF COLORECTAL CANCER IN MEN AND WOMEN OF CENTRAL SERBIA DURING THE PERIOD 1999-2020

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SUMMARY

Introduction/Aim: Colorectal cancer is the third leading cancer in terms of morbidity in the world, right after breast and lung cancer, and the second leading malignant tumor according to the number of deaths, after lung cancer. This descriptive study aimed to analyze the trends in incidence and mortality from colorectal cancer in men and women in Central Serbia from 1999 to 2020.
Methods: Data on patients and deaths from colorectal cancer (codes C18-C20, according to the International Classification of Diseases), as well as on the number of inhabitants, by sex and age, for the period from 1999 to 2020, were taken from cancer registries in Central Serbia and at the request of the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut". Crude, age-specific and standardized incidence and mortality rates for colorectal cancer were calculated. In order to analyze trends in incidence and mortality rates, joinpoint regression analysis was used.
Results: In the period from 1999 to 2020 in Central Serbia, an average of 1696 men and 1112 women were diagnosed with colorectal cancer, and 990 men and 676 women died. In the mentioned period, the average standardized incidence rate (per 100,000) was 34.4 for men and 19.5 for women, and the average standardized mortality rate (per 100,000) was 18.4 for men and 10.1 for women. Average age-specific incidence and mortality rates from colorectal cancer increase with age in both sexes. In the period 1999-2020, the standardized incidence rates of colorectal cancer are increasing significantly by 0.7% per year for women and 1% per year for men. In women, a significant increase in the mortality rate from colorectal cancer of 2.6% per year is observed in the period 1999-2006 year, and then a decline of 1.2% per year for the period 2006-2020. However, in men, a significant increase is observed in the period 1999-2010, followed by a decrease of 1.2% per year, but without statistical significance.
Conclusion: It is necessary to work on improving the implementation of organized screening for colorectal cancer, as well as on educating the population about the risk factors for the occurrence of this malignancy and the possibilities for prevention.

Keywords: colorectal cancer, incidence, mortality, trend, joinpoint regression analysis

Introduction

According to GLOBOCAN data for 2020, nearly 20 million people fell ill with malignant tumors worldwide (1). In the same year, almost 2 million people (1,931,590 new cases) were diagnosed with colorectal cancer, which is 10% of all new cases of malignant tumors. In 2020, the number of new cases of colorectal cancer in the population of men was 1,065,960 in the world, while the number of women was 865,630. Colorectal cancer is the third leading cause of morbidity of malignant tumors in the world, right after breast and lung cancer, when both sexes are considered together (1). It is the third leading cause of morbidity in men, after lung and prostate cancer, and the second in the female population, after breast cancer (1). In 2020, 973,173 people died from colorectal cancer worldwide, which is 9.4% of all deaths from malignant tumors (1). There were 515,637 men who died, and 419,536 women (1). Despite the existence of modern screening methods that

nje od ovog tumora, danas kolorektalni karcinom predstavlja drugi vodeći uzrok umiranja među svim malignim tumorima u svetu, iza karcinoma pluća, kada se posmatraju oba pola (1). Međutim, kod muškaraca je treći vodeći uzrok umiranja, iza raka pluća i jetre, a kod žena iza raka dojke i pluća (1).

Opterećenje kolorektalnim karcinomom je najveće u Aziji, gde se godišnje zabeleži više od polovine svih novootkrivenih i umrlih slučajeva (2). U Kini se godišnje dijagnostikuje više od pola miliona novoobolelih od kolorektalnog karcinoma, a umre oko 280.000 ljudi (2). Međunarodna agencija za istraživanje raka (engl. *International Agency for Research on Cancer* – IARC) procenjuje da će globalno opterećenje kolorektalnim karcinomom porasti za 56% u periodu 2020-2040. godine, na više od 3 miliona novih slučajeva godišnje. Procenjeno povećanje broja smrtnih slučajeva od ove bolesti je još veće, i iznoi 69%, odnosno oko 1,6 miliona smrtnih slučajeva u svetu u 2040. godini. Očekuje se da će do najvećeg povećanja doći u zemljama sa visokim indeksom razvoja.

Dokazano je da različiti faktori mogu povećati ili smanjiti rizik od razvoja kolorektalnog karcinoma. Osim toga, većina ovih faktora utiče i na rizik od razvoja drugih malignih bolesti (2). Konzumiranje alkohola bilo je odgovorno za više od 160.000 novih slučajeva raka kolorektuma u 2020. godini, odnosno 8% svih slučajeva dijagnostikovanih te godine. Konzumiranje alkohola takođe povećava rizik za nastanak najmanje još šest drugih vrsta raka, uključujući rak jetre i rak dojke. Drugi poznati faktori rizika od raka uključuju pušenje i infekciju humanim papiloma virusom. Još jedan faktor koji povećava rizik od razvoja kolorektalnog karcinoma je gojaznost (2). Gojaznost je bila odgovorna za više od 85.000 slučajeva raka kolorektuma dijagnostikovanih 2020. godine, ili oko 4,4% svih slučajeva raka kolorektuma dijagnostikovanih te godine (3). Gojaznost takođe povećava rizik osobe da razvije najmanje još sedam drugih vrsta raka.

Cilj ove deskriptivne studije je bio da se analizira kretanje obolevanja i umiranja od kolorektalnog karcinoma kod muškaraca i žena Centralne Srbije u periodu od 1999. do 2020. godine.

Metode

Podaci o obolelima i umrlima od kolorektalnog karcinoma (šifre C18-C20 prema Internacionalnoj klasifikaciji bolesti), kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2015. godine, preuzeti su iz registara za rak u Centralnoj Srbiji Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut" (4). Za period 2016-2020. podaci o obolelima i umrlima od kolorektalnog karcinoma dobijeni su na zahtev od Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut". Broj obolelih i umrlih od kolorektalnog karcinoma za svaku godinu dobijen je sabiranjem obolelih i umrlih od karcinoma kolona (šifra C18), rektosigmoidnog prelaza (šifra C19) i rektuma (šifra C20).

Na osnovu dobijenih podataka izračunate su sirove, uzrasno specifične i standardizovane stope incidencije i mortaliteta za kolorektalni karcinom. Metodom direktne standardizacije izračunate su standardizovane stope incidencije i mortaliteta, a kao standardna populacija odabrana je *Segi*-ju (1960) (5).

U cilju analize kretanja standardizovanih stopa incidencije i mortaliteta od kolorektalnog karcinoma za period od 1999-2020. godine korišćena je *joinpoint* regresiona analiza (*Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodu *Kim et al*. (6).

Rezultati

Prosečno procentualno učešće obolelih od kolorektalnog karcinoma u strukturi obolevanja od svih malignih tumora u Centralnoj Srbiji, u periodu 1999–2020. godine, kod muškaraca iznosilo je 12,5% dok je kod žena iznosilo 9% (tabela 1). Procentualno učešće umrlih od kolorektalnog karcinoma u strukturi umiranja od svih malignih tumora iznosilo je 12% kod muškaraca, a 10,9% kod žena

U periodu od 1999. do 2020. godine u Centralnoj Srbiji godišnje je od kolorektalnog karcinoma prosečno obolevalo 1696 muškarca i 1112 žena, a umiralo je prosečno 990 muškaraca i 676 žena (Tabela 2). Muškarci su češće i obolevali i umirali od kolorektalnog karcinoma u odnosu na žene. Prosečna standardizovana stopa incidencije za navedeni period iznosila je 34,4/100.000 za muškarace i 19,5/100.000 za žene, a prosečna standardizovana stopa mortaliteta je bila 18,4/100.000 za muškarace i 10,1/100.000 za žene. Prosečna standardizovana stopa incidencije kod muškaraca bila je 1,76 puta veća nego kod žena, dok je stopa mortaliteta bila 1,82 puta veća kod muškaraca nego žena.

could greatly reduce dying from this tumor, today colorectal cancer presents the second leading cause of death among all malignant tumors in the world, after lung cancer, when both sexes are considered (1). However, it is the third leading cause of death in men, after lung and liver cancer, and in women, after breast and lung cancer (1).

The burden of colorectal cancer is greatest in Asia, where more than half of all new cases and deaths are recorded annually (2). In China, more than half a million new cases of colorectal cancer are diagnosed annually, and about 280,000 people die (2). The International Agency for Research on Cancer (IARC) estimates that the global burden of colorectal cancer will increase by 56% between 2020 and 2040, to more than 3 million new cases per year. The estimated increase in the number of deaths caused by this disease is even higher, amounting to 69% or about 1.6 million deaths in the world in 2040. It is expected that the highest increase will occur in countries with a high index of development.

It has been proven that different factors can increase or decrease the risk of developing colorectal cancer. In addition, most of these factors also affect the risk of developing other malignant diseases (2). Alcohol consumption was responsible for more than 160,000 new cases of colorectal cancer in 2020, that is, 8% of all cases diagnosed that year. Alcohol consumption also increases the risk of at least six other types of cancer, including liver cancer and breast cancer. Other known risk factors for cancer include smoking and human papillomavirus infection. Another factor that increases the risk of developing colorectal cancer is obesity (2). Obesity was responsible for more than 85,000 cases of colorectal cancer that were diagnosed in 2020, or about 4.4% of all cases of colorectal cancer that were diagnosed during that year (3). Obesity also increases the risk of developing at least seven other types of cancer.

The aim of this descriptive study was to analyze the trends in morbidity and mortality of colorectal cancer in men and women in Central Serbia from 1999 to 2020.

Methods

Data on new cases and deaths caused by colorectal cancer (codes C18-C20 according to the International Classification of Diseases), as well as on the number of inhabitants, by gender and age for the period 1999-2015, were taken from the registries for cancer of the Public Health Institute “Dr Milan Jovanovic Batut” for Central Serbia (4). For the period 2016-2020, data on new cases and deaths from colorectal cancer were obtained at the request of the Public Health Institute “Dr Milan Jovanovic Batut”. The number of new cases and deaths from colorectal cancer for each year was obtained by adding the new cases and deaths from cancer of the colon (code C18), rectosigmoid transition (code C19) and rectum (code C20).

Raw, age-specific and standardized incidence and mortality rates for colorectal cancer were calculated based on the obtained data. Standardized incidence and mortality rates were calculated using the direct standardization method, while Segi’s population was used as the standard population (1960) (5).

In order to analyze trends in standardized incidence and mortality rates of colorectal cancer for the period 1999-2020, jointpoint regression analysis was used according to the method of Kim et al. (Jointpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) (6).

Results

The average percentage share of people affected by colorectal cancer in the structure of all malignant tumors in Central Serbia, during the period 1999-2020, was 12.5% in men, and 9% in women (Table 1). The percentage share of deaths caused by colorectal cancer in the structure of deaths from all malignant tumors was 12% in men and 10.9% in women.

From 1999 to 2020, in Central Serbia, on average, 1696 men and 1112 women were affected by colorectal cancer annually, while 990 men and 676 women died (Table 2). Men got ill and died more frequently in comparison to women. The average standardized incidence rate for the given time period amounted to 34.4/100,000 for men and 19.5/100,000 for women, while the average standardized mortality rate was 18.4/100,000 for men and 10.1/100,000 for women. The average standardized incidence rate in men was 1.76 times higher than in women, while the mortality rate was 1.82 times higher in men than in women.

Tabela 1. Procentualno učešće novoobolelih i umrlih od kolorektalnog karcinoma (C18-C20) među novoobolelima i umrlima od svih malignih tumora u muškoj i ženskoj populaciji, Centralna Srbija, 1999–2020. godine

Godine	Procentualno učešće novoobolelih od kolorektalnog karcinoma među novoobolelima od svih malignih		Procentualno učešće umrlih od kolorektalnog karcinoma među umrlima od svih malignih tumora	
	Muškarci	Žene	Muškarci	Žene
1999	12,3	9,0	10,8	10,5
2000	11,2	8,1	11,6	10,8
2001	12,0	8,7	10,9	10,2
2002	12,8	9,2	11,7	10,8
2003	12,9	9,4	11,2	11,2
2004	12,4	9,5	11,5	10,8
2005	12,9	9,8	12,2	12,4
2006	11,5	8,6	11,6	11,6
2007	13,3	10,7	11,5	11,0
2008	14,4	8,7	11,9	11,9
2009	12,1	8,4	12,4	11,4
2010	14,3	10,7	12,4	11,0
2011	10,6	8,1	11,6	11,3
2012	12,4	8,5	13,0	11,2
2013	12,8	9,0	13,2	10,6
2014	11,9	8,9	12,0	10,5
2015	13,4	9,4	12,7	10,8
2016	12,3	8,1	12,6	10,1
2017	11,8	8,0	12,7	10,1
2018	12,7	8,9	12,2	10,3
2019	12,0	8,8	12,6	10,4
2020	12,7	9,7	12,7	10,1
1999-2020	12,5	9,0	12,0	10,9

Prosečne uzrasno specifične stope incidencije od kolorektalnog karcinoma rastu sa godinama starosti kod oba pola. Najviše stope incidencije kod oba pola su zabeležene za uzrast 70 i više godina (262,1/100.000 muškaraca i 126/100.000 žena) (Tabela 3).

Kada se posmatraju uzrasno specifične stope incidencije od kolorektalnog karcinoma kod muškaraca značajan porast je zabeležen u uzrastu 60-69 godina od 1,7% godišnje i u uzrastu od 70 i više godina od 0,9 % godišnje. Kada se posmatraju svi uzrasti zajedno, standardizovana stopa incidencije značajno raste za 1% godišnje (Tabela 3, Grafikon 1). Kod žena uzrasta 50-59 godina zabeležen je značajan porast od 1% godišnje, a u uzrastu 60-69 godina porast od 1,4% godišnje. Standardizovane stope incidencije kod žena svih uzrasta su značajno rasle za 0,7% godišnje u periodu 1999-2020. godine.

Umiranje od kolorektalnog karcinoma je retko pre 30 godine kod oba pola, a zatim prosečne uzrasno specifične stope mortaliteta rastu su sa godinama starosti i najviše su kod osoba starih 70 i više godina (200,7/100.000 kod muškaraca i 106,0/100.000 kod žena) (Tabela 4). U svim uzrasnim grupama stope mortaliteta kod muškaraca su veće nego kod žena.

Kod muškaraca uzrasta 60-69 godina zabeležen je značajan godišnji porast stopa mortaliteta od 0,8% godišnje, a u uzrastu 70 i više godina značajan porast od 2,3% godišnje za period 1999-2013., a potom pad od 1,2% godišnje, ali bez značajnosti. Standardizovane stope mortlaliteta kod muškaraca bile su u značajnom porastu od 1,8% godišnje u

Table 1. Percent share of new cases and deaths from colorectal cancer (C18-C20) among new cases and deaths from all malignant tumors in the male and female population, Central Serbia, 1999–2020

Godine	Percent number of new cases of colorectal cancer of all malignant tumors		Percent number of deaths from colorectal cancer of all malignant tumors	
	Men	Women	Men	Women
1999	12.3	9.0	10.8	10.5
2000	11.2	8.1	11.6	10.8
2001	12.0	8.7	10.9	10.2
2002	12.8	9.2	11.7	10.8
2003	12.9	9.4	11.2	11.2
2004	12.4	9.5	11.5	10.8
2005	12.9	9.8	12.2	12.4
2006	11.5	8.6	11.6	11.6
2007	13.3	10.7	11.5	11.0
2008	14.4	8.7	11.9	11.9
2009	12.1	8.4	12.4	11.4
2010	14.3	10.7	12.4	11.0
2011	10.6	8.1	11.6	11.3
2012	12.4	8.5	13.0	11.2
2013	12.8	9.0	13.2	10.6
2014	11.9	8.9	12.0	10.5
2015	13.4	9.4	12.7	10.8
2016	12.3	8.1	12.6	10.1
2017	11.8	8.0	12.7	10.1
2018	12.7	8.9	12.2	10.3
2019	12.0	8.8	12.6	10.4
2020	12.7	9.7	12.7	10.1
1999-2020	12.5	9.0	12.0	10.9

The average age-specific incidence rates of colorectal cancer increased with age in both sexes. Both in men and women, the highest incidence rates were registered in the age group 70 years and older (262.1/100,000 men and 126/100,000 women) (Table 3).

Considering the age-specific incidence rates of colorectal cancer in men, a significant increase of 1.7% per year was registered in the age group 60-69 years and 0.9% in the age group 70 years and older. When all age groups are considered together, the standardized incidence rate increased significantly by 1% annually (Table 3, Figure 1). In women aged 50-59 years, a significant increase of 1% per year was registered, and 1.4% per year in the age group 60-69 years. Standardized incidence rates in women of all ages increased significantly by 0.7% per year in the period 1999-2020.

Dying from colorectal cancer is rare before the age of 30 among both sexes and then the average age-specific mortality rates increase with age and are the highest in people aged 70 years and older (200.7/100,000 in men and 106.0/100,000 in women) (Table 4). In all age groups, mortality rates in men are higher than in women.

Among men aged 60-69 years, a significant annual increase in the mortality rate of 0.8% per year was recorded, and in those aged 70 years and older, a significant increase of 2.4% per year for the period 1999-2013, and then a decrease of 1.2% per year, but without significance. Standardized mortality rates in men increased significantly by 1.8% per year in 1999-2010, then decreased by 1.2% (Table 4, Figure 2). In women aged 70 years and older, a significant increase of 2.4% per year was recorded from 1999 to 2008, and then there

Tabela 2. Broj novoobolelih i umrlih, standardizovane stope incidencije i mortaliteta (na 100.000 stanovnika) kolorektalnog karcinoma (C18-C20) po polu, Centralna Srbija, 1999–2020. godine

Godine	Muškarci				Žene			
	Number of new cases	Inc	Number of deaths	Mt	Number of new cases	Inc	Number of deaths	Mt
1999	1225	26,6	751	15,8	870	16,0	561	9,7
2000	1265	27,9	834	17,7	876	16,2	588	9,7
2001	1456	31,6	780	15,9	975	18,1	566	9,2
2002	1599	33,3	879	17,2	1053	18,9	602	9,2
2003	1591	33,6	855	17,2	1094	19,4	654	10,5
2004	1590	33,2	887	17,7	1135	20,5	647	10,2
2005	1635	34,4	957	18,7	1147	20,2	759	11,6
2006	1479	31,2	925	17,9	1007	17,8	712	11,0
2007	1788	37,8	950	17,9	1305	22,6	667	9,8
2008	1907	39,5	995	19,0	1046	18,2	753	11,4
2009	1693	35,7	1054	19,8	1057	19,2	743	10,9
2010	1943	40,4	1066	20,1	1342	24,7	711	10,5
2011	1502	30,3	994	18,6	1044	18,2	718	11,0
2012	1721	34,6	1134	20,1	1052	18,2	732	10,5
2013	1746	33,6	1131	19,9	1116	18,3	680	9,7
2014	1635	31,4	1028	18,3	1123	18,6	696	10,1
2015	1947	36,9	1120	19,7	1244	20,7	696	9,9
2016	1852	35,4	1100	18,9	1104	18,8	662	9,5
2017	1820	35,3	1111	19,3	1105	18,4	680	9,0
2018	2004	38,6	1066	18,7	1230	21,7	698	9,7
2019	1918	36,9	1094	18,7	1223	21,4	690	9,9
2020	1985	38,4	1057	18,1	1312	22,3	652	9,3
1999-2020	1696	34,4	990	18,4	1112	19,5	676	10,1

Inc–standardizovana stopa incidencije prema populaciji sveta (na 100.000 stanovnika); Mt–standardizovana stopa mortaliteta prema populaciji sveta (na 100.000 stanovnika)

periodu 1999-2010. godine, a potom sledi pad za 1,2% (Tabela 4, Grafikon 2). Kod žena uzrasta 70 i više godina zabeležen je značajan porast od 2,4% godišnje od 1999-2008, a potom u periodu 2008-2020. dolazi do značajnog pada od 1,5% godišnje. Kada se posmatraju standardizovane stope kod žena uočava se značajan trend porasta mortaliteta od 2,6% godišnje u periodu 1999-2006. godine, a potom pad od 1,2% godišnje za period 2006-2020.

Diskusija

U periodu od 1999. do 2020. godine u Centralnoj Srbiji je od kolorektalnog karcinoma prosečno obolevalo 1696 muškarca i 1112 žena godišnje. Muškarci su češće obolevali od kolorektalnog karcinoma u odnosu na žene. Prosečna standardizovana stopa incidencije za navedeni period iznosila je 34,4/100.000 kod muškaraca i 19,5/100.000 kod žena. Stope incidencije kolorektalnog karcinoma rastu sa godinama starosti kod oba pola.

Stope incidencije i mortaliteta od kolorektalnog karcinoma variraju širom sveta. Kolorektalni karcinom je češći kod muškaraca nego kod žena i 3-4 puta češći u razvijenim nego u zemljama u razvoju (6). U zemljama koje prolaze kroz tranziciju, stope incidencije imaju tendenciju da ravnomerno rastu sa povećanjem stepena razvoja, što ukazuje na uzročnu povezanost. Najviše stope incidencije su u razvijenim zemljama. U 2020. godini najviše stope incidencije zabeležene su u zemljama Evrope, Australiji i Novom Zelandu, dok najniže stope incidencije imaju zemlje Afrike i Centralne i Južne Azije.

Standardizovana stopa incidencije za karcinom kolorektuma u svetu u 2020. godini iznosi-

Table 2. The number of new cases and deaths, standardized incidence and mortality rates (per 100,000) caused by colorectal cancer (C18-C20) by sex, Central Serbia, 1999–2020

Years	Men				Women			
	Number of new cases	Inc	Number of deaths	Mt	Number of new cases	Inc	Number of deaths	Mt
1999	1225	26.6	751	15.8	870	16.0	561	9.7
2000	1265	27.9	834	17.7	876	16.2	588	9.7
2001	1456	31.6	780	15.9	975	18.1	566	9.2
2002	1599	33.3	879	17.2	1053	18.9	602	9.2
2003	1591	33.6	855	17.2	1094	19.4	654	10.5
2004	1590	33.2	887	17.7	1135	20.5	647	10.2
2005	1635	34.4	957	18.7	1147	20.2	759	11.6
2006	1479	31.2	925	17.9	1007	17.8	712	11.0
2007	1788	37.8	950	17.9	1305	22.6	667	9.8
2008	1907	39.5	995	19.0	1046	18.2	753	11.4
2009	1693	35.7	1054	19.8	1057	19.2	743	10.9
2010	1943	40.4	1066	20.1	1342	24.7	711	10.5
2011	1502	30.3	994	18.6	1044	18.2	718	11.0
2012	1721	34.6	1134	201	1052	18.2	732	10.5
2013	1746	33.6	1131	19.9	1116	18.3	680	9.7
2014	1635	31.4	1028	18.3	1123	18.6	696	10.1
2015	1947	36.9	1120	19.7	1244	20.7	696	9.9
2016	1852	35.4	1100	18.9	1104	18.8	662	9.5
2017	1820	35.3	1111	19.3	1105	18.4	680	9.0
2018	2004	38.6	1066	18.7	1230	21.7	698	9.7
2019	1918	36.9	1094	18.7	1223	21.4	690	9.9
2020	1985	38.4	1057	18.1	1312	22.3	652	9.3
1999-2020	1696	34.4	990	18.4	1112	19.5	676	10.1

Inc–standardized incidence rate according to the world population (per 100,000); Mt–standardized mortality rate according to the world population (per 100,000)

was a significant decrease of 1.5% per year. When standardized rates in women are observed, a significant trend of increase in mortality of 2.6% per year was noticed in the period 1999-2006, and then a decrease of 1.2% per year in the period 2006-2020.

Discussion

In the period 1999-2020, an average of 1,696 men and 1,112 women fell ill with colorectal cancer per year in Central Serbia. Men suffered from colorectal cancer more often than women. The average standardized incidence rate for the mentioned period was 34.4/100,000 in men and 19.5/100,000 in women. Incidence rates of colorectal cancer increase with age in both men and women.

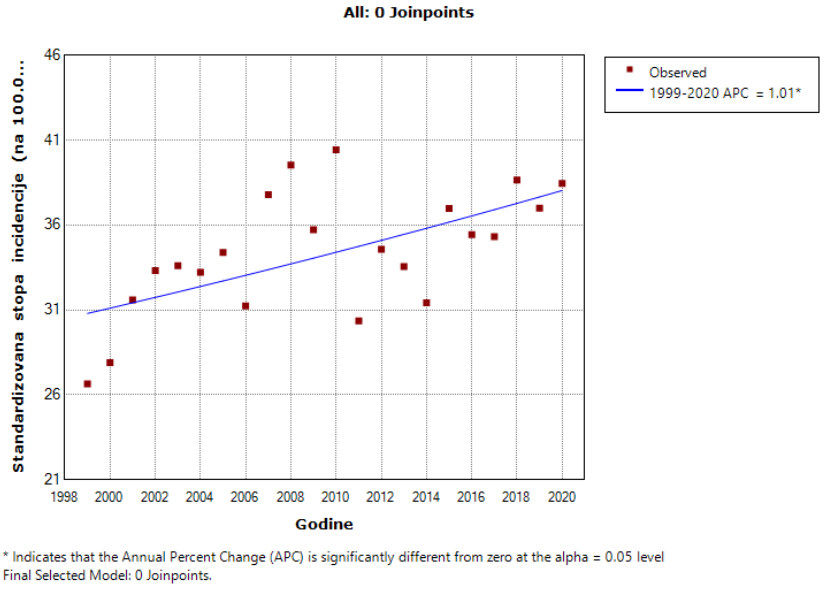
Incidence and mortality rates of colorectal cancer vary worldwide. Colorectal cancer is more common in men than women and 3-4 times more common in developed than developing countries (7). In transition countries, incidence rates tend to rise steadily with increasing levels of development, suggesting a causal relationship. The highest incidence rates are in developed countries. In 2020, the highest incidence rates were registered in European countries, Australia and New Zealand, while the lowest incidence rates were found in the countries of Africa and Central and South Asia.

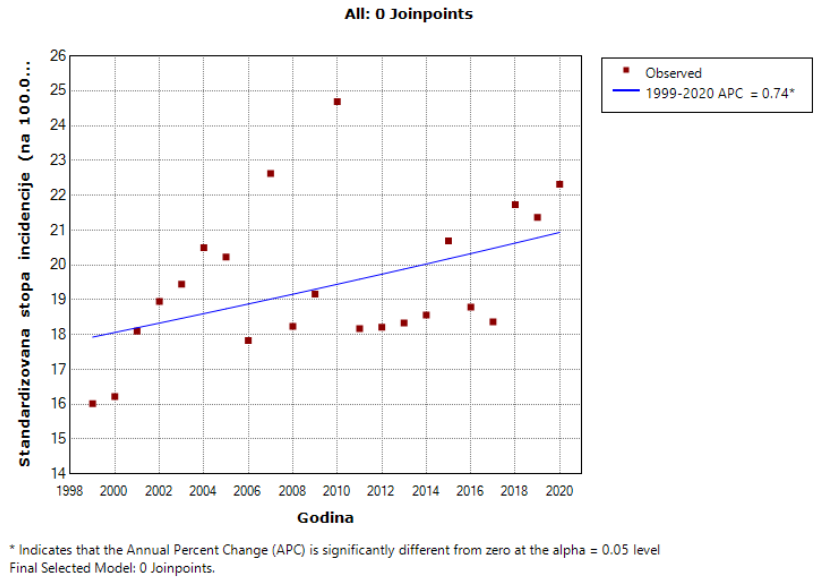
The standardized incidence rate for colorectal cancer in the world in 2020 was 19.5/100,000 (1). In 2020, as far as both sexes are concerned, Hungary had the highest standardized incidence rate of colorectal cancer in Europe, and also in

Tabela 3. Prosečne uzrasno-specifične i standardizovane stope incidencije (na 100.000), *joinpoint* analiza kretanja stopa incidencije kolorektalnog karcinoma (C18-C20) po polu, Centralna Srbija, period 1999-2020. godina

	Muškarci			Žene		
Uzrasne grupe	**Inc**	**Period**	**APC (95%IP)**	**Inc**	**Period**	**APC (95%IP)**
< 30	0,7	1999-2008 2008-2020	12 (-1,1 – 26,9) -9,3* (-16,3- -1,6)	0,6	1999-2020	-1,9 (-5,9 – 2,2)
30-39	6,5	1999-2020	-1,8 (-4,4 – 1,0)	5,5	1999-2020	0,1 (-2,2 – 2,5)
40-49	23,0	1999-2020	-0,9 (-2,1 – 0,3)	19,4	1999-2020	-0,2 (-1,5 – 1,1)
50-59	80,3	1999-2020	1,7 (-0,5 – 3,9)	51,7	1999-2020	1,0* (0,3 – 1,7)
60-69	186,7	1999-2020	1,7* (0,8 – 2,5)	95,6	1999-2020	1,4* (0,5 – 2,3)
70+	262,2	1999-2020	0,9* (0,3 – 1,5)	126,0	1999-2020	0,0 (-0,7 – 0,6)
Stand. stope	34,4	1999-2020	1,0* (0,4 – 1,6)	19,5	1999-2020	0,7* (0,1 – 1,4)

Inc – Stope incidencije; ** Standardizovane stope prema populaciji sveta (na 100.000); APC –Annual Percent Change – prosečna procentualna godišnja promena; 95%IP- 95% interval poverenja; *-APC je značajno različit od 0 za alfa=0,05



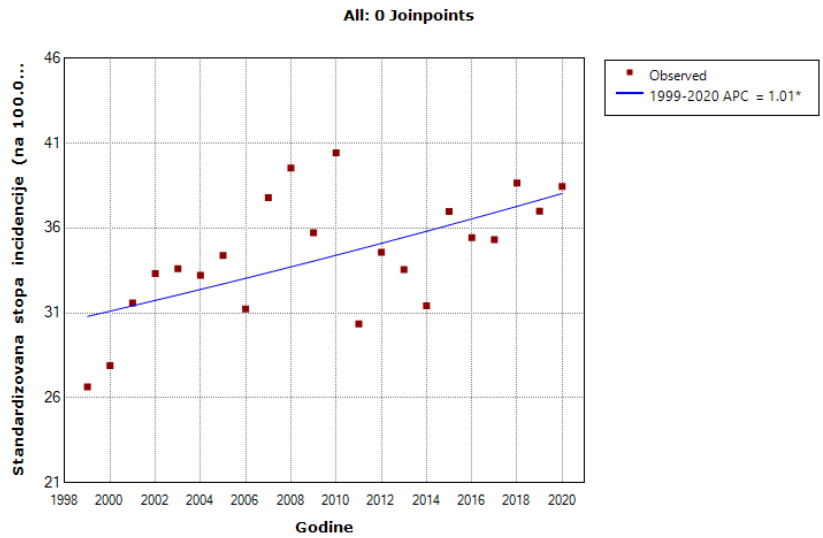


Grafikon 1. *Joinpoint* analiza kretanja stopa incidencije kolorektalnog karcinoma (C18-C20) po polu, Centralna Srbija, period 1999-2020. godine (a) muškarci, b) žene

Table 3. Average age-specific and standardized incidence rates (per 100,000), joinpoint regression analysis of trends in incidence of colorectal cancer (C18-C20) by sex, Central Serbia, 1999-2020

	Men			Women		
Age groups	**Inc**	**Period**	**APC (95%CI)**	**Inc**	**Period**	**APC (95%CI)**
< 30	0.7	1999-2008 2008-2020	12 (-1.1 – 26.9) -9.3* (-16.3- -1.6)	0.6	1999-2020	-1.9 (-5.9 – 2.2)
30-39	6.5	1999-2020	-1.8 (-4.4 – 1.0)	5.5	1999-2020	0.1 (-2.2 – 2.5)
40-49	23.0	1999-2020	-0.9 (-2.1 – 0.3)	19.4	1999-2020	-0.2 (-1.5 – 1.1)
50-59	80.3	1999-2020	1.7 (-0.5 – 3.9)	51.7	1999-2020	1.0* (0.3 – 1.7)
60-69	186.7	1999-2020	1.7* (0.8 – 2.5)	95.6	1999-2020	1.4* (0.5 – 2.3)
70+	262.2	1999-2020	0.9* (0.3 – 1.5)	126.0	1999-2020	0.0 (-0.7 – 0.6)
Stand. rates**	34.4	1999-2020	1.0* (0.4 – 1.6)	19.5	1999-2020	0.7* (0.1 – 1.4)

Inc–Incidence rates;**Standardized rates according to the world population (per 100,000); APC –Annual Percent Change; 95%CI-95% confidence interval;*-APC is significantly different from 0 at the alpha=0.05



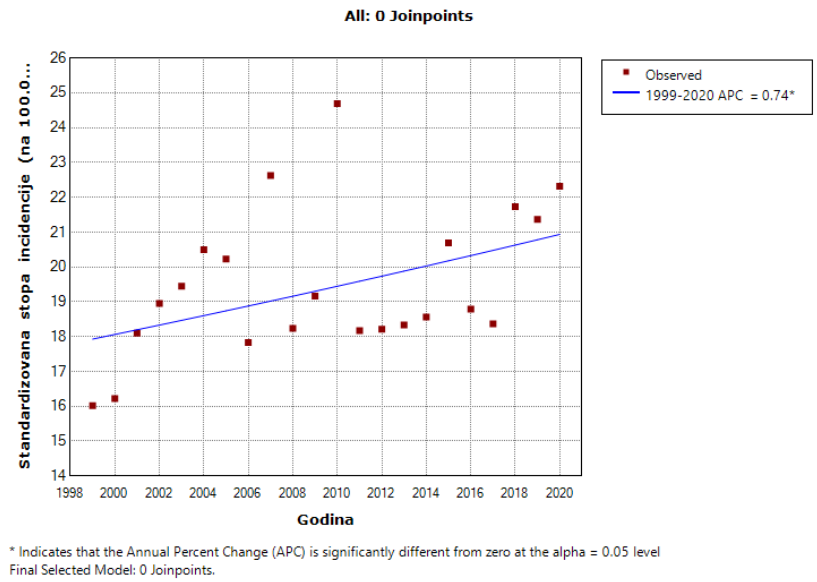
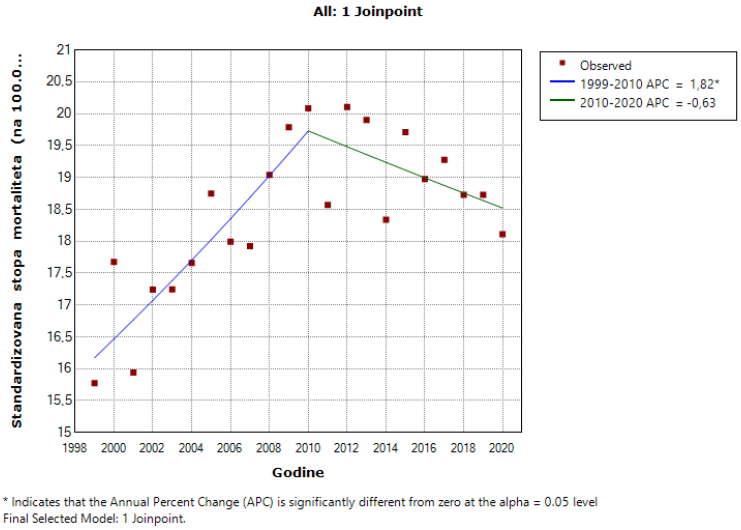


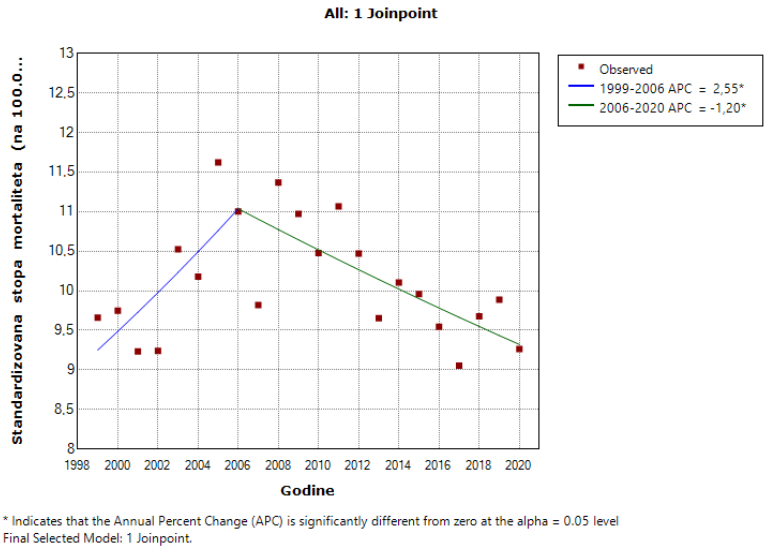
Figure 1. Jointpoint analysis of trends in incidence rates of colorectal cancer (C18-C20) by sex, Central Serbia, period 1999-2020, a) men, b) women

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope incidencije (na 100.000), *joinpoint* analiza kretanja stopa mortaliteta kolorektalnog karcinoma (C18-C20) po polu, Centralna Srbija, period 1999-2020. godina

	Muškarci			Žene		
Uzrasne grupe	**Mt**	**Period**	**APC (95%IP)**	**Mt**	**Period**	**APC (95%IP)**
< 30	0,2	1999-2020	-	0,2	1999-2020	-
30-39	2,1	1999-2020	-1,1 (-3,8 – 1,8)	1,9	1999-2020	1,9 (-0,3 – 4,1)
40-49	9,2	1999-2020	-0.4 (-1.9 – 1.1)	6,9	1999-2020	-1,1 (-2,3 – 0,0)
50-59	31,9	1999-2010 2010-2020	2,4* (0,3 – 4,7) -2,7* (-5,1 – -0,2)	20,2	1999-2020	0,3 (-0,9 – 1,5)
60-69	92,1	1999-2020	0,8* (0,3 – 1,3)	46,1	1999-2020	-0,2 (-0,9 – 0,5)
70+	200,7	1999-2013 2013-2020	2,3* (1,7 – 3,0) -1,3 (-3,0 – 0,5)	106,0	1999-2008 2008-2020	2,4* (0,9 – 4,0) -1.5* (-2,4--0,5)
Stand. stope**	18,4	1999-2010 2010-2020	1,8* (1,1 – 2,6) -1,2 (-0,6 – -1,4)	10,1	1999-2006 2006-2020	2,6* (0,4 – 4,7) -1,2*(-1.9 – -0,5)

Mt – Stope mortaliteta; **Standardizovane stope prema populaciji sveta (na 100.000); APC –Annual Percent Change – prosečna procentualna godišnja promena; 95%IP- 95% interval poverenja; *-APC je značajno različit od 0 za alfa=0,05





Grafikon 2. *Joinpoint* analiza kretanja stopa mortaliteta kolorektalnog karcinoma po polu, Centralna Srbija, period 1999-2020. godina, a) muškarci, b) žene

Table 4. Average age-specific and standardized mortality rates (per 100,000), joinpoint analysis of trends in mortality rates of colorectal cancer by sex, Central Serbia, period 1999-2020

	Men			Women		
Age groups	**Mt**	**Period**	**APC (95%CI)**	**Mt**	**Period**	**APC (95%CI)**
< 30	0.2	1999-2020	-	0.2	1999-2020	-
30-39	2.1	1999-2020	-1.1 (-3.8 – 1.8)	1.9	1999-2020	1.9 (-0.3 – 4.1)
40-49	9.2	1999-2020	-0.4 (-1.9 – 1.1)	6.9	1999-2020	-1.1 (-2.3 – 0.0)
50-59	31.9	1999-2010 2010-2020	2.4* (0.3 – 4.7) -2.7* (-5.1 – -0.2)	20.2	1999-2020	0.3 (-0.9 – 1.5)
60-69	92.1	1999-2020	0.8* (0.3 – 1.3)	46.1	1999-2020	-0.2 (-0.9 – 0.5)
70+	200.7	1999-2013 2013-2020	2.3* (1.7 – 3.0) -1.3 (-3.0 – 0.5)	106.0	1999-2008 2008-2020	2.4* (0.9 – 4.0) -1.5* (-2.4--0.5)
Stand. rates**	18.4	1999-2010 2010-2020	1.8* (1.1 – 2.6) -1.2 (-0.6 – -1.4)	10.1	1999-2006 2006-2020	2.6* (0.4 – 4.7) -1.2*(-1.9 – -0.5)

Mt–mortality rates; ** Standardized mortality rates according to the world population (per 100,000); APC – Annual Percent Change; 95%CI-95% confidence interval;*-APC is significantly different from zero at alpha=0,05

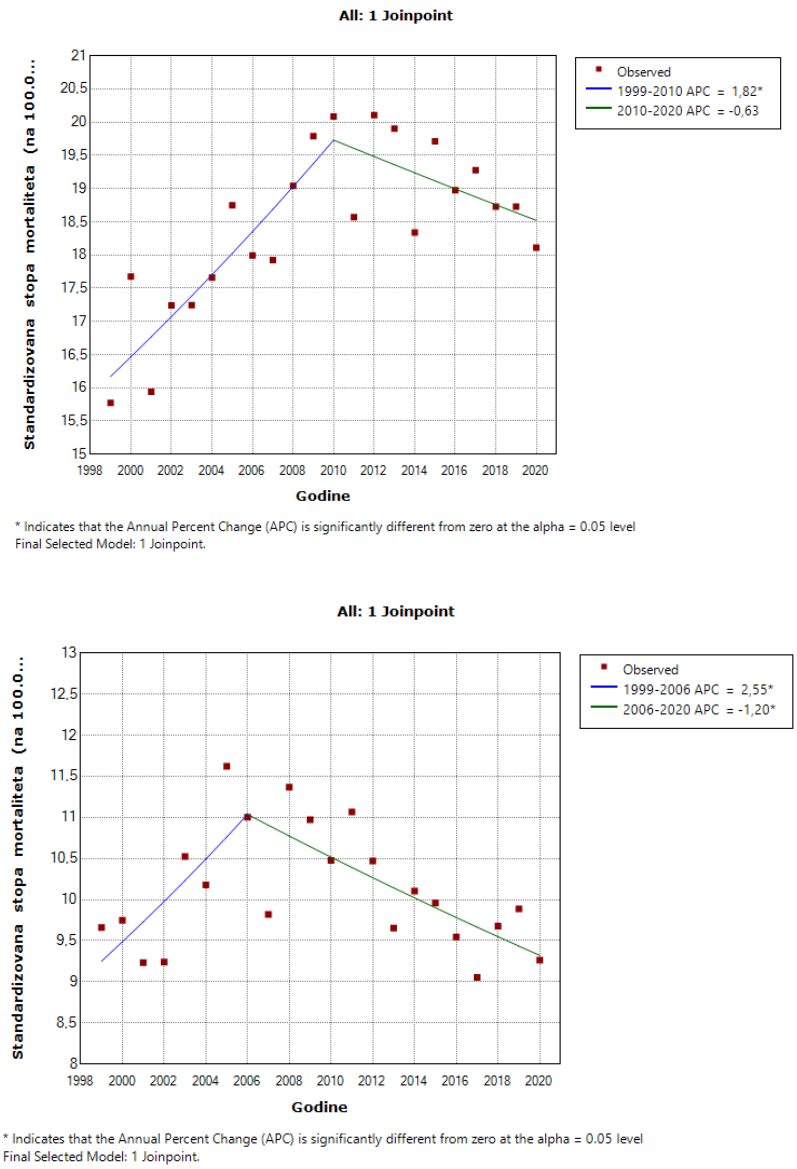


Figure 2. Joinpoint analysis of trends in mortality rates of colorectal cancer by sex, Central Serbia, period 1999-2020, a) men, b) women

la je 19,5/100.000 (1). Posmatrano za oba pola u 2020. godini Mađarska je imala najveću standardizovanu stopu incidencije kolorektalnog karcinoma u Evropi, ali i u svetu, (45,3/100.000), zatim Slovačka (43,9/100.000), Norveška (41,9/100.000), Holandija (41/100.000) i Danska (40,9/100.000) (1). Ako se posmatra samo muški pol za istu godinu situacija je slična, na prvom mestu je Mađarska (62/100.000), zatim Slovačka (60,7/100.000), Slovenija (55,8/100.000) i Portugal (55,2/100.000) (1). Kod ženskog pola najveću standardizovanu stopu incidencije 2020. imala je Norveška (38,7/100.000), potom Danska (35,6/100.000), Holandija (34,3/100.000) i Mađarska (33,1/100.000). Zemlje sa najmanjim stopama incidencije ovog tumora za oba pola u 2020. godini (<6,7/100.000) bile su Indija, Pakistan, Avganistan, i zemlje Afričkog kontinenta. U Evropi, najmanje stope incidencije zabeležene su u Albaniji (7,7/100.000), Austriji (21,0/100.000) i Švajcarskoj (22,3/100.000)

Trendovi incidencije i mortaliteta od kolorektalnog karcinoma u svetu mogu se podeliti u tri različite kategorije. Prva kategorija, koju čine srednje razvijene zemlje, kao što su Brazil, Rusija, Kina, Latinska Amerika, i Baltičke zemlje. Ove zemlje prolaze kroz ekonomsku tranziciju, što je verovatno uzrok povećanja obolevanja. Druga kategorija, koju čine uglavnom visoko razvijene zemlje kao što su Kanada, Velika Britanija, Danska i Singapur beleže porast incidencije, ali pad mortaliteta, zbog poboljšanja mogućnosti lečenja. Na kraju, treću kategoriju čine zemlje sa najvišim stepenom razvoja, kao što su Sjedinjene Američke Države, Island, Japan, i Francuska koje beleže pad incidencije i mortaliteta zbog napretka u prevenciji i lečenju (7,8). Zabeleženi padovi mortaliteta mogu se povezati sa povećanim preživljavanjem usled razvoja i primene savremenijih načina lečenja ovog tumora. Takođe, uklanjanje polipa i rana detekcija prekanceroznih i kanceroznih lezija pomoću metoda skrininga igraju značajnu ulogu. Uvođenje programa skrininga u početku dovodi do porasta stopa incidencije jer se diganostikuju prethodno neprepoznate bolesti, ali posmatrano u dužem periodu smanjuju mortlitet zahvaljujući uklanjanju promena (8)

U periodu 1999-2020. godine, u Centralnoj Srbiji standardizovane stope incidencije kolorektalnog karcinoma značajno rastu, i to za 0,7% godišnje za žene i 1% godišnje za muškarce. Prema podacima American Cancer Society stope incidencije pokazuju porast od 1975. i tokom osamdesetih godina prošlog veka, nakon čega se uočava njihov pad (9). U SAD poslednjih decenija beleži se pad stopa incidencije kolorektalnog karcinoma kod starijih od 50 godina, dok je primećen porast incidencije kod osoba uzrasta 20 do 49 (7). Stopa incidencije kolorektalnog karcinoma za uzrast 20-49 godina bila je 9,3/100.000 1975. godine dok je u 2015. godini iznosila 13,7/100.000 (porast od 47,31%), dok su stope incidencije u uzrasnoj grupi 50 i više godina u stalnom padu. U SAD u periodu 2000-2020. godina, stope incidencije u periodu 2000-2007. opadaju za 2,4% godišnje, 2007-2012. za 3,4% godišnje, da bi potom u periodu 2012-2020. pad bio svega 0,9% godišnje (10). Smjanjenje incidencije u ranim 2000. pripisuje se podjednako smanjenoj učestalosti faktora rizika i povećanom skriningu (9). Sa druge strane, pad trenda u kasnim 2000. godinama se prvenstveno pripisuje velikom obuhvatu skrininga kolonoskopijom u starosnoj grupi 50+, koji je sa 20% u 2000. godini porastao na 61% u 2018. godini (11). Pokazalo se da uvođenje skrining programa u početku dovodi do povećanja incidencije usled detekcije nedijagnostikovanih obolenja, ali dugoročno dovodi do pada u incidenciji zbog sve češćeg otkrivanja prekanceroznih lezija (12).

Procenjuje se da će do 2040. godine broj slučajeva kolorektalnog karcinoma u svetu porasti na više od 3 miliona novih slučajeva godišnje i oko 1,6 miliona smrtnih slučajeva (2). Ovakav porast se očekuje usled eknomskog napredovanja slabije i srednje razvijenih država, kao i preovladavnja faktora rizika u tim populacijama. Neki od faktora rizika su: fizička neaktivnost, alkohol, pušenje, hrana bogata životinjskim mastima i crvenim mesom, gojaznost itd. (7).

U 2020. godini najviše stope mortaliteta od raka kolorektuma zabeležene su u Australiji i Novom Zelandu, Evropskim zemljama, dok najniže stope incidencije imaju zemlje Afrike i Centralne i Južne Azije. Prosečna standardizovana stopa mortaliteta u svetu iznosila je 9/100.000. Najveća standardizovana stopa mortaliteta za oba pola u 2020. bila je u Slovačkoj (21/100.000), zatim Mađarskoj (20,2/100.000), Hrvatskoj (19,6/100.000) itd (1). Ako se posmatra samo muški pol vodeće zemlje su Slovačka (29,6/100.000), Mađarska (29/100.000), Hrvatska (28,2/100.000), Moldavija (26,7/100.000), a za žene to su Slovačka (14,8/100.000), Mađarska (14/100.000), Hrvatska (13,5/100.000), Singapur (12,8/100.000). Države sa

the world (45.3/100,000), followed by Slovakia (60.7/100,000), Slovenia (55.8/100,000), Norway (41.9/100,000), the Netherlands (41/100,000) and Denmark (40.9/100,000) (1). If only the male sex is observed for the same year, the situation is similar, that is, Hungary is in the first place (62/100,000), followed by Slovakia (60.7/100,000), Slovenia (55.8/100,000) and Portugal (55.2/100,000) (1). In women, the highest standardized incidence rate in 2020 was in Norway (38.7/100,000), followed by Denmark (35.6/100,000), the Netherlands (34.3/100,000) and Hungary (33.1/100,000). In 2020, the countries with the lowest incidence rates of this tumor for both sexes (<6.7/100,000) were India, Pakistan, Afghanistan and the countries of the African continent. In Europe, the lowest incidence rates were registered in Albania (7.7/100,000), Austria (21.0/100,000) and Switzerland (22.3/100,000).

In the world, the trends in incidence and mortality of colorectal cancer can be divided into three different categories. The first category, which consists of moderately developed countries, such as Brazil, Russia, China, Latin America and the Baltic countries. These countries are going through economic transition, which is probably the cause of the increase in morbidity. The second category, which consists mainly of highly developed countries such as Canada, Great Britain, Denmark and Singapore, recorded an increase in incidence, but a decrease in mortality, due to improved treatment options. Finally, the third category consists of countries with the highest level of development, such as the United States of America, Iceland, Japan, and France, which record a decrease in incidence and mortality due to improved prevention and treatment (7,8). The decrease in mortality can be associated with the increased survival due to the development and application of contemporary methods of treatment of this tumor. Also, removing polyps and early detection of precancerous and cancerous lesions with the help of screening methods have an important role. The introduction of screening programs initially leads to an increase in incidence rates because previously unrecognized diseases are diagnosed, but when observed in the long term, they reduce mortality because changes are removed (8).

In the period 1999-2020, in Central Serbia, standardized incidence rates of colorectal cancer increased significantly, by 0.7% per year for women and 1% per year for men. According to the data of the American Cancer Society, incidence rates showed an increase since 1975 and during the 1980s, and after that their decrease was observed (9). In the last decades, in the USA, incidence rates of colorectal cancer decreased in people older than 50, while the increase in incidence was observed in people aged 20 to 49 years (7). The incidence rate of colorectal cancer in the age group 20-49 years was 9.3/100,000 in 1975, while in 2015 it amounted to 13.7/100,000 (increase of 47.31%), while the incidence rates in the age group 50 years and older constantly decreased. In the period 2000-2020, in the USA, incidence rates in the period 2000-2007 decreased by 2.4% per year, and in the period 2007-2012 by 3.4% per year, while in the time period 2012-2020, the decline was only 0.9 per year (10). The decrease in incidence in the early 2000s was attributed equally to a reduced frequency of risk factors and increased screening (9). On the other hand, the trend of decline in the late 2000s was primarily attributed to the high coverage of colonoscopy screening in the age group 50+, which increased from 20% in 2000 to 61% in 2018 (11). It was shown that the introduction of screening programs initially led to an increase in incidence because undiagnosed diseases were detected, but in the long term, it led to a decrease in incidence due to the more frequent detection of precancerous lesions (12).

It is estimated that by 2040, the number of colorectal cancer cases worldwide will increase to more than 3 million new cases per year and about 1.6 million deaths (2). This increase is expected due to the economic progress of less and moderately developed countries, as well as due to the prevalence of risk factors in these populations. Some of the risk factors are: physical inactivity, alcohol, smoking, food rich in animal fat and red meat, obesity, etc. (7).

In 2020, the highest mortality rates of colorectal cancer were registered in Australia and New Zealand, European countries, while the lowest incidence rates were in the countries of Africa and Central and East Asia. The average standardized mortality rate in the world was 9/100,000. The highest standardized mortality rate for both sexes in 2020 was in Slovakia (21/100,000), followed by Hungary (20.2/100,000), Croatia (19.6/100,000), etc. (1). When only the male gender is observed,

najmanjim standardizovanim stopama mortaliteta za oba pola (<4,6/100.000) 2020. godine bile su Egipat, Sudan, Avganistan, Indija, Pakistan itd (1,3). Za muški pol to su bile Bolivija (3,9/100.000), Pakistan (3,5/100.000), Indija (3,6/100.000), Mongolija (4/100.000) (1,3). Kod žena je slična situacija: Indija (2,1/100.000), Pakistan (2,5/100.000), Sudan (3,6/100.000), Egipat (3,5/100.000) itd. U Centralnoj Srbiji, prosečna standardizovana stopa mortaliteta je bila 18,4/100.000 kod muškaraca i 10,1/100.000 kod žena.

U periodu 1999-2020. godine u Centralnoj Srbiji kod žena uočava se značajan trend porasta stopa mortaliteta kolorektalnog karcinoma od 2,6% godišnje u periodu 1999-2006. godine, a potom pad od 1,2% godišnje za period 2006-2020. Međutim, kod muškaraca se uočava značajan porast u periodu 1999-2010. za 1,8% godišnje, a zatim pad od -1,2% godišnje, ali pad nije bio značajan. Kod muškaraca uzrasta 60-69 godina zabeležen je značajan godišnji porast stopa mortaliteta od 0,8% godišnje za period 1999-2020., a u uzrastu 70 i više godina porast od 2,3% godišnje samo za period 1999-2013. godine. Trend porasta je prisutan i kod muškaraca uzrasta 50-59 godina u periodu 1999-2010. godine za 2,4% godišnje, a potom pad od 1,3% godišnje. Kod žena uzrasta 70 i više godina zabeležen je značajan porast stopa mortaliteta od 2,4% godišnje u periodu 1999-2008, a potom u periodu 2008-2020. dolazi do značajnog pada od 1,5% godišnje.

U SAD stope mortaliteta su se generalno smanjile od 1975. godine, najviši značajan pad je u starosnoj grupi od 75 i više godina (7). Povećanje mortaliteta beleži se u Latinskoj Americi, Karibima i Aziji (13,14). Ovo je posledica slabije razvijene zdravstvene zaštite u tim zemljama, kao i nedostupnosti adekvatnih metoda skrininga (15).

Kina je jedna od zemalja gde se godišnje beleže visoke stope mortaliteta. Kretanje stopa mortaliteta u ovoj državi pokazuje značajan porast od 4,1% godišnje u periodu 2002-2015. godina (16). Ubrzan privredno-ekonomski razvoj i sve više prihvatanje zapadnog načina života smatraju se glavnim uzrokom za primećeni porast. Ovo se poklapa sa podacima iz drugih država u razvoju kao što su zemlje Južne Amerike, Istočne Evrope i Rusija (8). Sa druge strane stope mortaliteta opadaju u razvijenim zemljama (8). Smatra se da je to posledica obuhvata velikog procenta populacije savremenim skrining metodama.

U Sjedinjenim Američkim Državama stope mortaliteta kolorektalnog karcinoma pokazuju pad kod žena još od 1947, a tek od 1980. kod muškaraca (11). Posmatrajući trendove mortaliteta u poslednje tri decenije nema velikih razlika po polu. Pad mortaliteta do 2000. godine pripisuje se poboljšanju u lečenju (12%), promeni u faktorima rizika (35%) i skriningu (53%).

Više od polovine svih slučajeva kolorektalnog karcinoma može se pripisati faktorima životnog stila, uključujući nezdravu ishranu, nedovoljnu fizičku aktivnost, prekomerno konzumiranje alkohola i pušenje (17). Ovakav životni stil se povezuje sa zemljama sa visokim prihodima, gde su stope incidencije kolorektalnog karcinom najviše (7). Na globalnom nivou, povećanje incidencije kolorektalnog karcinoma se smatra markerom ekonomske tranzicije. S druge strane brojne studije su pokazale da ljudi sa zdravim načinom života imaju 27% do 52% manji rizik od kolorektalnog karcinoma u poređenju sa onima koji ne vode zdrav stil života (18). Nepromenljivi faktori koji povećavaju rizik su genetski faktori i medicinska istorija, uključujući u ličnoj ili porodičnoj anamnezi kolorektalni karcinom ili adenoma i u ličnoj anamnezi dugotrajnu hroničnu inflamatornu bolesti creva. Većina ljudi sa povećanim rizikom zbog medicinske ili porodične istorije treba da počne sa skriningom na kolorektalni karcinom pre 45. godine (11). Smanjenje telesne težine, fizička aktivnost i dijeta bogata ribom, voćem i povrćem mogu smanjiti rizik od razvoja kolorektalnog karcinoma. Podvrgavanje organizovanim skrining programima povećava šansu za otkrivanje kolorektalnog karcinoma dok je u ranoj, i potencijalno lakšoj i izlečivoj fazi.

Zaključak

Trend porasta obolevanja od kolorektalnog karcinoma ukazuje na neophodno unapređenje sprovođenja organizovanog skrininga za kolorektalni karcinom u Centralnoj Srbiji, kao i na važnost sprovođenja edukacije stanovništva o faktorima rizika za nastanak ovog malignoma i mogućnostima prevencije. Poslednjih godina, kod oba pola, beleži se pad umiranja od kolorektalnog karcinoma, što govori o unapređenju dijagnostike i lečenja ovog malignoma.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

the leading countries were Slovakia (29.6/100,000), Hungary (29/100,000), Croatia (28.2/100,000), Moldova (26.7/100,000), and for women, the following countries: Slovakia (14.8/100,000), Hungary (14/100,000), Croatia (13.5/100,000), Singapore (12.8/100,000). In 2020, the countries with the lowest standardized mortality rates for both sexes (<4/6/100,000) were Egypt, Sudan, Afghanistan, India, Pakistan, etc. (1,3). In men, these countries were Bolivia (3.9/100,000), Pakistan (3.5/100,000), India (3.6/100,000), Mongolia (4/100,000) (1,3). In women, the situation was similar: India (2.1/100,000), Pakistan (2.5/100,000), Sudan (3.6/100,000), Egypt (3.5/100,000), etc. In Central Serbia, the average standardized mortality rate was 18.4/100,000 in men and 10.1/100,000 in women.

In the period 1999-2020, in Central Serbia in women, a significant trend of increase in the mortality rate of colorectal cancer of 2.6% per year was observed in the period 1999-2006, and then a decline of 1.2% per year in the period 2006-2020. However, in men, a significant increase can be observed in the period 1999-2010, by 1.8% per year and then a decline of -1.2% per year, but the decline was not significant. In men aged 60-69 years, a significant annual increase in the mortality rate of 0.8% per year was registered in the period 1999-2020, and in the age group 70 years and older, the increase of 2.3% per year was observed only in the period 1999-2013. The trend of increase of 2.4% per year was also present in men aged 50-59 in the period 1999-2010, followed by a decrease of 1.3% per year. In women aged 70 years and older, a significant increase in mortality rates of 2.4% per year was registered in the period 1999-2008, followed by a significant decrease of 1.5% per year in the period 2008-2020.

In the USA, mortality rates have generally declined since 1975, and the highest significant decline was in the age group 75 years and older (7). An increase in mortality was noted in Latin America, the Caribbean and Asia (13,14). This is the consequence of less developed health care in those countries, as well as the unavailability of adequate screening methods (15).

China is one of the countries where annual high mortality rates were recorded. The trends in mortality rates in this country showed a significant increase of 4.1% per year in the period 2002-2015 (16). Rapid socio-economic development and the increasing acceptance of the Western way of life are deemed to be the main reasons for the observed increase. This is in line with data from other developing countries, such as the countries of South America, Eastern Europe, and Russia (8). On the other hand, mortality rates are decreasing in developed countries (8). It is considered to be the consequence of great coverage of population with modern screening methods.

In the United States of America, mortality rates of colorectal cancer in women have decreased since 1947, and only since 1980 in men (11). Considering mortality trends in the last three decades, there has been no significant difference regarding gender. The decline in mortality by 2000 was attributed to the improvement in treatment (12%), changes in risk factors (35%) and screening (53%).

More than half of all cases of colorectal cancer can be attributed to lifestyle factors, including unhealthy diet, insufficient physical activity, excessive alcohol consumption, and smoking (17). This lifestyle is associated with high income countries, where the incidence rates of colorectal cancer are the highest (8). Globally, the increase in the incidence of colorectal cancer is considered to be the marker of economic transition. On the other hand, numerous studies have shown that people with a healthy lifestyle have a 27% to 52% lower risk of colorectal cancer compared to those who do not lead a healthy lifestyle (18). Non-modifiable factors that increase the risk are genetic factors and medical history, including colorectal cancer or adenoma in the personal or family history and a long term chronic inflammatory bowel disease in the personal medical history. The majority of people who are at an increased risk of colorectal cancer due to their medical or family history should start screening for CRC before the age of 45 (11). Weight loss, physical activity and diet rich in fish, fruit and vegetables can reduce the risk of developing colorectal cancer. Organized screening programs increase the chance of detecting colorectal cancer while it is in an early, potentially easier and curable stage.

Conclusion

The trend of increasing incidence of colorectal cancer points to the necessary improvement of organized screening for colorectal cancer in Central Serbia, as well as the importance of educating the population about the risk factors for the

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occurrence of this malignancy and the possibilities of prevention. In recent years, in both sexes, a decrease in deaths caused by colorectal cancer has been noted, which speaks of the improvement of diagnostics and treatment of this malignancy.

Competing interests

The authors declared no competing interests.

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POVEZANOST UPOTREBE LEKOVA ZA EREKTILNU DIFUNKCIJU SA SEKSUALNIM PONAŠANJEM I POLNO PRENOSIVIM INFEKCIJAMA KOD MUŠKARACA KOJI IMAJU SEKSUALNE ODNOSE SA MUŠKARCIMA U BEOGRADU

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SAŽETAK

Uvod/Cilj: Lekovi za erektilnu disfunkciju (ED) se sve više koriste u rekreativne svrhe i poboljšanje seksualnih performansi. Oralni inhibitori fosfodiesteraze 5 su najpopularniji tip lekova za ED među muškarcima koji imaju seksualne odnose sa muškarcima (MSM). Cilj ovog istraživanja bio je da se proceni prevalencija upotrebe lekova za ED među MSM populacijom u Beogradu i njena povezanost sa njihovim ponašanjem i polno prenosivim infekcijama.
Metod: Studija preseka je sprovedena u dve zdravstvene ustanove u Beogradu i obuhvatila je 469 MSM osoba. Anonimnim upitnikom prikupljeni su od svih ispitanika podaci o demografskim karakteristikama, seksualnom ponašanju i polno prenosivim infekcijama, upotrebi lekova za ED i drugih rekreativnih droga u prethodnih šest meseci.
Rezultati: Od svih 469 ispitanika 16,2% je koristilo lekove za ED. Prema rezultatima multivarijantne logističke regresione analize ispitanici koji su koristili lekove za ED u odnosu na one koji ih nisu koristili bili su stariji (Unakrsni odnos -UO=2,60, 95% Interval poverenja – 95%IP 2,77–3,84, p<0,001), imali su veći broj seksualnih partnera u poslednjih šest meseci (UO=1,83; 95%IP 1,53–2,18; p<0,001), češće su upotrebljavali marihuanu (UO= 2,55; 95%IP 1,31–4,93; p=0,006) i praktikovali hemseks (seksualni odnos pod uticajem droga koje olakšavaju i poboljšavaju seks) tokom poslednjih šest meseci (UO=3,33; 95%IP 1,69–6,67; p<0,001).
Zaključak: Upotreba lekova za ED među MSM populacijom udružena je sa većim stepenom upotrebe rekreativnih droga i visokorizičnim seksualnim ponašanjem. Neophodne su edukativne poruke o rizicima i posledicama upotrebe lekova za ED.

Ključne reči: lekovi, erektilna disfunkcija, muškarci koji imaju seksualne odnose sa muškarcima, seksualno ponašanje, polno prenosive infekcije

Uvod

Pored upotrebe u lečenju erektilne disfunkcije (ED), lekovi za ED se sve češće koriste i u rekreativne svrhe sa ciljom da poprave seksualnu performansu korisnika kako u populaciji heteroseksualaca (1) tako i među muškarcima koji imaju seksualne odnose sa muškarcima – MSM (2). ED je česta kod MSM osoba inficiranih HIV infekcijom stoga im zdravstveni radnici često propisuju lekove za ED (3). S druge strane, MSM osobe koje ne pate od ED koriste ovu grupu lekova i bez recepta lekara da bi povećali dužinu trajanja i kvalitet erekcije te da bi mogli da imaju seksualne odnose sa većim brojem seksualnih partnera i izbegli eventualne neželjene probleme sa erekcijom (2).

Inhibitori fosfodiesteraze tipa 5 (engl. *Phosphodiesterase 5 inhibitors* – PDE5) za oralnu upotrebu (sildenafil, tadalafil i vardenafil) su najpopularniji lekovi za ED kod pripadnika MSM populacije (4). Oni se često koriste u kombinaciji sa nekim drugim psihoaktivnim supstancama što može biti praćeno

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THE RELATIONSHIP OF ERECTILE DYSFUNCTION DRUGS USE WITH SEXUAL BEHAVIOUR AND SEXUALLY TRANSMITTED INFECTIONS AMONG MEN WHO HAVE SEX WITH MEN IN BELGRADE

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SUMMARY

Background/Aim: Erectile dysfunction (ED) drugs are increasingly being used for recreational purposes and improving sexual performance. Oral phosphodiesterase 5 inhibitors are the most popular type of ED drugs among men who have sex with men (MSM). The aim of this study was to assess the prevalence of ED drugs use among MSM in Belgrade and its association with their behaviour and sexually transmitted infections.
Methods: A cross-sectional study was conducted at two public health care services in Belgrade and it covered 469 MSM. Data on demographic characteristics, sexual history, sexual behaviour, ED drugs and other recreational drugs use in the previous six months were collected from all participants by the use of a questionnaire.
Results: Of all 469 respondents, 16.2% have been using ED drugs. According to the results of multivariate logistic regression analysis, ED drugs users, compared to non-users were older (Odds Ratio – OR=2.60, Confidence interval – 95%CI 2.77-3.84, (p<0,001), had greater number of sexual partners in the last six months (OR= 1.83, 95%CI 1.53-2.18, p<0.001), and more frequently used cannabis (OR=2.55, 95%CI 1.31-4.93, p=0.006) and chemsex in the past six months (OR=3.33, 95%CI 1.69-6.67, p<0.001).
Conclusion: ED drugs use among MSM is associated with higher levels of recreational drugs use and high-risk sexual behaviour. Educational messages about the risks and consequences of using ED drugs are needed.

Key words: drugs, erectile dysfunction, men who have sex with men, sexual behaviour, sexually transmitted infections

Introduction

In addition to being used in the treatment of erectile dysfunction (ED), ED medications are increasingly being used for recreational purposes with the aim of improving the sexual performance of users in the heterosexual population (1), as well as in men who have sex with men – MSM (2). ED is common in MSM who are infected with HIV, and therefore, healthcare professionals often prescribe drugs for ED (3). On the other hand, MSM people who do not suffer from ED use this group of drugs even without doctor's prescription to increase the duration and quality of erections, so that they could have sexual relations with a larger number of sexual partners and avoid possible unwanted problems with erections (2).

Phosphodiesterase 5 inhibitors (PDE5) for oral use (sildenafil, tadalafil and vardenafil) are the most popular drugs for ED in MSM population (4). They are often used in combination with some other psychoactive substances, which can be accompanied by high-risk sexual behavior (promiscuity, sex without condoms, and group sex) and the consequent transmission of sexually transmitted infections – STIs (5-8). The

visoko rizičnim seksualnim ponašanjem (promiskuitet, seks bez kondoma i grupni seks) i posledičnim prenošenjem polno prenosivih infekcija – PPI (5-8). Naročito je opasna istovremena primena ovih lekova sa popersom (amil nitrit) koja dovodi do pada sistemskog arterijskog pritiska i protoka krvi kroz koronarne arterije sa kritičnom stenozom (9). S obzirom na to da nemamo podatke o upotrebi lekova za ED među MSM populacijom u Srbiji, cilj ovog istraživanja je bio da se utvrdi učestalost njene primene i udruženost sa seksualnim ponašanjem i obolevanjem od PPI među MSM populacijom u Beogradu.

Metode

U okviru ovog istraživanja je sprovedena studija preseka u periodu od 1. avgusta 2022. godine do 31. januara 2023. godine među pripadnicima MSM populacije koji su došli na pregled ili u savetovalište za polne bolesti Gradskog zavoda za kožne i venerične bolesti u Beogradu i na regularnu kontrolu u ambulantu za HIV infekciju na Infektivnoj klinici Kliničkog centra Srbije. Svi ispitanici su popunjavali anonimni upitnik koji je sadržao pitanja o osnovnim demografskim karakteristikama (uzrast, obrazovanje i zaposlenost), razlogu dolaska kod lekara, HIV-statusu, upotrebi pre-ekspozicione profilakse za HIV (engl. *Pre-exposure prophylaxis* - PrEP), lečenoj bakterijskoj polnoj infekciji (rani sifilis, gonoreja i hlamidijaza) u poslednjih godinu dana, kao i o broju seksualnih partnera, upotrebi kondoma tokom analnog seksa, grupnom seksu i upotrebi rekreativnih droga tokom seksa u poslednjih šest meseci (popers i marihuana). Takođe su odgovarali na pitanja o konzumiranju alkohola u poslednjih godinu dana, kao i o upotrebi intravenskih droga u poslednjih 6 meseci. Trebalo je da svi ispitanici zaokruže na ponuđenoj listi koje ilegalne droge [seksualizovane droge – hemseks (engl. *chemsex*) koje se uzimaju pre ili tokom seksualnog odnosa da bi olakšale i poboljšale seks: gama-hidroksibutirat (GHB)/gama-butirolakton (GBL), ekstazi, amfetamin, kristalni metamfetamin, kokain, ketamin i mefedron, ili ostale rekreativne droge: marihuanu, popers i lekove za ED] su koristili u poslednjih 6 meseci. Prema skraćenoj verziji upitnika Svetske Zdravstvene Organizacije – AUDIT (engl. *Alcohol Use Disorders Identification Test*, test za identifikaciju poremećaja upotrebe alkohola) o konzumiranju alkohola u poslednjih godinu dana (10) prema frekvenciji pijenja i količini unetog alkohola ispitanici su podeljeni u tri grupe (manje rizično pijenje, riskantno pijenje i visoko rizično pijenje). Prema vrednostima skora iz odgovora na prva dva pitanja iz AUDIT testa, manje rizično pijenje definisano je skorom ≤1, riskantno pijenje skorom >1 na drugo pitanje iz testa, a visoko rizično pijenje skorom ≥6 (10).

Svim pacijentima koji su imali simptome i/ili znake PPI, ili podatak o izloženosti PPI rađeni su testovi na bakterijske polne bolesti. Za dijagnozu gonoreje rađen je direktni mikroskopski preparat brisa uretre sa identifikacijom karakterističnih intracelularnih diplokoka u leukocitima, a dijagnoza hlamidijaze potvrđena je pozitivnim *Chlamydia trachomatis* PCR (engl. *Polymerase chain reaction*, polimeraza lančana reakcija) testom iz brisa uretre. Dijagnoza ranog sifilisa (primarni, sekundarni i rani latentni stadijum sifilisa) je potvrđena pozitivnim serološkim testovima na sifilis (engl. *Venereal Disease Research Laboratory* – VDRL, laboratorijski test za istraživanje veneričnih bolesti i engl. *Treponema Pallidum Haemagglutination Assay* – TPHA, *Treponema Pallidum* hemaglutinacioni test). Ispitanici koji nisu imali simptome PPI nisu bili testirani na polne bolesti. Etički odbor Gradskog zavoda za kožne i venerične bolesti u Beogradu dao je dozvolu za ovo istraživanje (br. 1861/3).

Varijable su predstavljene brojevima i procentima. U statističkoj analizi razlika između upoređivanih grupa korišćene su univarijantna i multivarijantna logistička regresiona analiza. U multivarijantnu analizu uključene su sve varijable koje su prema rezultatima univarijantne analize, bile povezane sa upotrebom lekova za ED na nivou statističke značajnosti $p \leq 0,1$. Varijable koje su bile ograničene samo na deo ispitivane populacije, kao što su PrEP i broj korišćenih rekreativnih droga, dodavane su jedna po jedna u nove modele multivarijantne analize. Metod selekcije je bio unazadni (engl. *backward*) Wald test. Sve p vrednosti su bile bazirane na dvosmernom (engl. *two-tailed*) testu, a vrednosi $p < 0,05$ su smatrane statistički značajnim. Za analizu baze podataka je korišćen softverski paket programa *IBM SPSS Statistics for Windows*, version 23 (*Armonk, NY, IBM Corp.*).

Rezultati

U studiju je uključeno 469 MSM osoba od kojih je 76 (16,2%) koristilo lekove za ED. U poređenju

simultaneous use of these drugs with poppers (amyl nitrite) is particularly dangerous because it leads to a decrease in systemic arterial pressure and blood flow through coronary arteries with critical stenosis (9). Given that we do not have data on the use of ED drugs among the MSM population in Serbia, the aim of this study was to determine the frequency of its use and the connection with sexual behavior and sexually transmitted infections (STIs) among the MSM population in Belgrade.

Methods

Within this research, a cross-sectional study was conducted from August 1st, 2022 to January 31st, 2023 in the population of MSM who came for an examination or to the counseling center for sexually transmitted diseases of the City Institute for Skin and Venereal Diseases in Belgrade and to the regular check-up at the Clinic for HIV infection of the Clinical Center of Serbia. All respondents filled out the anonymous questionnaire, which contained questions about basic demographic characteristics (age, education and employment), reasons for visiting the doctor, HIV status, use of pre-exposure prophylaxis for HIV (PrEP), treated bacterial sexual infections (early syphilis, gonorrhea and Chlamydia) during the last year, as well as the number of sexual partners, use of condoms during anal sex, group sex and use of recreational drugs during sex in the last six months (poppers and marijuana). Also, they answered questions about alcohol consumption in the past year and about the intravenous drug use in the past 6 months. All respondents had to circle on the offered list which illegal drugs [sexualized drugs – chemsex that are taken before or during sexual intercourse to facilitate and improve sex: gamma-hydroxybutyrate (GHB)/gama-butyrolactone (GBL), ecstasy, amphetamine, crystal methamphetamine, cocaine, ketamine and mephedrone, or other recreational drugs: marijuana, poppers and ED drugs], they have used during the past 6 months. According to the abbreviated version of the questionnaire of the World Health Organization – AUDIT test (Alcohol Use Disorders Identification Test) about alcohol consumption in the last year (10) related to the frequency of drinking and the amount of alcohol consumed, the participants were divided into three groups (low-risk drinking, risky drinking and high-risk drinking). According to the scores from the first two questions from the AUDIT test, low risk drinking was defined by the score <1, risky drinking by the score >1for the second test question and high-risk drinking by the score >6 (10).

All patients who had symptoms and/or signs of STIs, or the information about the exposure to STIs, were tested for bacterial venereal diseases. For the diagnosis of gonorrhea, a direct microscopic preparation of the urethral swab was made with the identification of characteristic intracellular diplococci in leukocytes, while the diagnosis of Chlamydia was confirmed by positive Chlamydia trachomatis PCR test from the urethral swab. The diagnosis of early syphilis (primary, secondary and early latent stage of syphilis) was confirmed by positive serological tests for syphilis (Venereal Disease Research Laboratory – VDRL and Treponema Pallidum Haemagglutination Assay – TPHA). The participants who had no symptoms of STIs were not tested for sexually transmitted diseases. The Ethics Committee of the City Institute for Skin and Venereal Diseases in Belgrade gave permission for this research (No. 1861/3).

Variables are represented by numbers and percentages. Univariate and multivariate logistic regression analysis were used in the statistical analysis of differences between the compared groups. All variables, which were connected with the use of ED drugs at the level of statistical significance $p < 0.1$ according to the results of univariate analysis, were included in multivariate analysis. The variables, which were limited to one part of the examined population, such as PrEP and the number of used recreational drugs, were added one by one to the new models of multivariate analysis. The selection method was the backward Wald test. All p values were based on the two-tailed test, while the values $p<0.05$ were considered to be statistically significant. The software package IBM SPSS for Windows, version 23 (Armonk, NY, IBM Corp.) was used for the analysis of database.

Results

The study included 469 MSM, of whom 76 (16.2%) used ED medications. In comparison to the participants who did not use ED drugs (393 persons, 83.8%), the users of ED drugs were older ($p<0.001$), they used PrEP more often ($p<0.001$), had more sexual partners ($p<0.001$), anal sex without condom use ($p=0.07$) and practiced

sa ispitanicima koji nisu koristili lekove za ED (393 osobe, 83,8%), korisnici lekova za ED su bili stariji (p<0,001), češće su koristili PrEP (p<0,001), imali su veći broj seksualnih partnera (p<0,001), analni seks bez upotrebe kondoma (p=0,07) i praktikovali su grupni seks (p<0,001) u toku poslednjih šest meseci (Tabela 1). Ispitanici koji su koristili lekove za ED su češće imali neku od bakterijskih PPI u poslednjih godinu dana (p=0,004), dijagnostikovana im je nova bakterijska PPI (p=0,009) i češće su imali ponovne bakterijske PPI (p<0,001). U odnosu na novopostavljenu dijagnozu bakterijske polne infekcije među svim ispitanicima sifilis je bio najčešći i registrovan je kod 122 osobe (26%), zatim gonoreja kod 41 ispitanika (8,9%) i hlamidijaza kod 16 ispitanika (3,5%). Između ispitivanih grupa nisu postojale značajne razlike prema obrazovanju, zaposlenosti, razlogu dolaska lekaru i prema HIV pozitivnom statusu.

Prema rezultatima prikazanim u Tabeli 2, MSM osobe koje su koristile lekove za ED u odnosu na ispitanike koji ih nisu koristili, češće su upotrebljavale marihuanu (p<0,001), popers (p<0,001) i hemseks (p<0,001) tokom poslednjih šest meseci, a i koristile su veći broj različitih rekreativnih droga (p<0,001). Između ispitanika nisu postojale značajne razlike prema upotrebi alkohola, učestalosti konzumiranja rekreativnih droga i vremena u kom su imali poslednji seksualni odnos bez upotreba droga (engl. *sober sex*).

Rezultati multivarijantne analize su predstavljeni u Tabeli 3. U odnosu na osobe koje nisu koris-

Tabela 1. Ukupan broj novoobolelih od sifilisa i prosečna incidencija (na 100.000), po polu i uzrastu, i odnos polova, Beograd, 2011-2020. godine

Varijable	Ispitanici koji koriste lekove za ED (n=76) Broj (%)	Ispitanici koji ne koriste lekove za ED (n=393) Broj (%)	p vrednost*
Uzrast (godine)			
≤ 25	2 (2,6)	72 (18,3)	<0,001
26-35	17 (22,4)	152 (38,7)	
36-45	43 (56,6)	118 (30,0)	
45+	14 (18,4)	51 (13,0)	
Dužina trajanja obrazovanja (godine)			
≤ 12	33 (43,4)	201(51,1)	0,219
>12	43 (56,6)	192 (48,9)	
Zaposlenost	61 (80,3)	313 (74,6)	0,902
Razlog posete lekaru			
Simptomi PPI	25 (32,9)	104 (26,5)	0,134
Izloženost PPI	17 (22,4)	63 (16,0)	
Simptomi nevezani sa PPI	34 (44,8)	226 (57,5)	
HIV pozitivan status	35 (46,1)	159 (40,5)	0,365
Upotreba PrEP-a	9 (22,0)	11 (4,7)	<0,001
Broj seksualnih partnera u poslednjih šest meseci:			
1-3	7 (9,2)	210 (53,4)	<0,001
4-9	21 (27,6)	119 (30,3)	
10+	48 (63,2)	64 (16,3)	
Analni seks bez upotrebe kondoma u poslednjih šest meseci	60 (78,9)	262 (66,7)	0,037
Grupni seks u poslednjih šest meseci	46 (60,5)	76 (19,3)	<0,001
Bakterijske PPI u poslednjih godinu dana	36 (47,4)	119 (30,3)	0,004
Novodijagnostikovana bakterijska PPI	39 (51,3)	139 (35,4)	0,009
Ponovno obolevanje od bakterijske PPI	19 (25,0)	40 (10,2)	<0,001

* Prema rezultatima univarijantne logističke regresione analize; PPI – polno prenosive infekcije; HIV – virus humane imunodeficijencije; PrEP – Pre-ekspoziciona profilaksa za HIV.

group sex (p<0.001) in the last six months (Table 1). The participants, who used ED medications, had more often a bacterial STI in the past year (p=0.004), were diagnosed with a new bacterial STI (p=0.009), and had a recurrent bacterial STI more often (p<0.001). In relation to the newly diagnosed bacterial sexual infection among all participants, syphilis was the most common and was registered in 122 persons (26%), followed by gonorrhea in 41 participants (8.9%) and Chlamydia in 16 participants (3.5%). There was no significant difference between the examined groups regarding education, employment, reason for visiting the doctor and HIV positive status.

According to the results shown in Table 2, MSM who used ED drugs in comparison to non-users, used marijuana more frequently in the past six months (p<0.001), as well as poppers (p<0.001), chemsex (p<0.001), and different recreational drugs (p<0.001). There were no significant differences between the participants in relation to alcohol consumption, frequency of recreational drugs use and the time when they had the last sexual intercourse without the use of drugs (sober sex).

The results of multivariate analysis are presented in Table 3. Compared to people who did not use ED drugs, the participants who used them were significantly more often older (Odds Ratio – OR=2.60, Confidence interval – 95%CI 2.77-3.84, p<0.001) had a larger number of sexual partners in the last six months (OR=1.83; 95%CI 1.53-2.18; p<0.001), used marijuana more

Table 1. Distribution of participants who used drugs for erectile dysfunction (ED) and those who did not in relation to demographic characteristics, sexual behavior and sexually transmitted infections (STIs)

Variables	Participants who use ED drugs (n=76) Number (%)	Participants who do not use ED drugs (n=393) Number (%)	p value*
Age (years)			
≤ 25	2 (2.6)	72 (18.3)	<0.001
26-35	17 (22.4)	152 (38.7)	
36-45	43 (56.6)	118 (30.0)	
45+	14 (18.4)	51 (13.0)	
Duration of education (years)			
≤ 12	33 (43.4)	201(51.1)	0.219
>12	43 (56.6)	192 (48.9)	
Employment	61 (80.3)	313 (74.6)	0.902
Reason for visiting the doctor			
Symptoms of STI	25 (32.9)	104 (26.5)	0.134
Exposure to STI	17 (22.4)	63 (16.0)	
Symptoms not related to STI	34 (44.8)	226 (57.5)	
HIV positive status	35 (46.1)	159 (40.5)	0.365
Use of PrEP-a	9 (22.0)	11 (4.7)	<0.001
Number of sexual partners in the last six months			
1-3	7 (9.2)	210 (53.4)	<0.001
4-9	21 (27.6)	119 (30.3)	
10+	48 (63.2)	64 (16.3)	
Anal sex without the use of condoms in the last six months	60 (78.9)	262 (66.7)	0.037
Group sex in the last six months	46 (60.5)	76 (19.3)	<0.001
Bacterial STI in the last year	36 (47.4)	119 (30.3)	0.004
Newly diagnosed bacterial STI	39 (51.3)	139 (35.4)	0.009
Recurrent bacterial STI	19 (25.0)	40 (10.2)	<0.001

* according to the results of univariate logistic regression analysis; STI – sexually transmitted infection; HIV – human immunodeficiency virus; PrEP – Pre-exposure prophylaxis for HIV.

Tabela 2. Distribucija ispitanika koji su koristili lekove za erektilnu disfunkciju (ED) i onih koji nisu u odnosu na upotrebu alkohola i drugih rekreativnih droga

Varijable	Ispitanici koji koriste lekove za ED (n=76) Broj (%)	Ispitanici koji ne koriste lekove za ED (n=393) Broj (%)	p vrednost*
Konzumiranje alkohola u poslednjih godinu dana:**			
Manje rizično pijenje	53 (69,7)	292 (74,3)	0,215
Riskantno pijenje	20 (26,3)	97 (24,7)	
Visoko rizično pijenje	3 (3,9)	4 (1,0)	
Upotreba marihuane u poslednjih šest meseci	35 (46,1)	64 (16,3)	<0,001
Upotreba popersa u poslednjih šest meseci	38 (50,0)	90 (22,9)	<0,001
Upotreba hemseksa u poslednjih šest meseci	45 (59,2)	78 (19,8)	<0,001
Učestalost upotrebe rekreativnih droga:			
Jednom mesečno	40 (52,6)	89 (58,6)	0,822
2-4 puta mesečno	26 (34,2)	37 (24,3)	
2-3 puta nedeljno	7 (9,2)	21 (13,8)	
≥ 4 puta nedeljno	3 (3,9)	5 (3,3)	
Broj rekreativnih droga korišćenih u poslednjih šest meseci:			
1	16 (21,1)	83 (54,6)	<0,001
2	14 (18,4)	35 (23,0)	
3-8	46 (60,5)	34 (22,4)	
Poslednji seksualni odnos bez upotrebe droga (engl. sober sex):			
Prošlog meseca	58 (76,3)	105 (69,1)	0,597
Pre više od 3 meseca	5 (6,6)	31 (20,4)	
Pre više od 6 meseci	4 (5,3)	9 (5,9)	
Pre više od godinu dana	9 (11,8)	7 (4,6)	

* Prema rezultatima univarijantne logističke regresione analize; **Konzumiranje alkohola je bazirano prema odgovorima na prva dva pitanja iz skraćenog upitnika Svetske zdravstvene organizacije AUDIT (engl. *Alcohol Use Disorders Identification Test*, test za identifikaciju poremećaja upotrebe alkohola); Manje rizično pijenje alkohola: skor ≤1, riskantno pijenje: skor >1 prema drugom pitanju iz upitnika i visoko rizično pijenje: skor ≥6 (10).

Tabela 3. Rezultati multivarijantne logističke regresione analize

	Ispitanici koji su koristili lekove za ED vs. ispitanici koji nisu koristili lekove za ED		
Varijable	**Unakrsni odnos**	**95% interval poverenja**	**p vrednost***
Uzrast	2,6	1,7-3,8	<0,001
Broj seksualnih partnera u poslednjih šest meseci	1,8	1,5-2,2	<0,001
Upotreba marihuane u poslednjih šest meseci	2,6	1,3-4,9	0,006
Hemseks u poslednjih šest meseci	3,3	1,7-6,7	<0,001

ED – erektilna disfunkcija; *p vrednost prema rezultatima multivarijantne analize.

Table 2. Distribution of participants who used drugs for erectile dysfunction (ED) and those who did not in relation to alcohol consumption and use of other recreational drugs

Variables	Participants who use drugs for ED (n=76) Number (%)	Participants who do not use drugs for ED (n=393) Number (%)	p value*
Alcohol consumption in the last year:**			
Low-risk drinking	53 (69.7)	292 (74.3)	0.215
Risky drinking	20 (26.3)	97 (24.7)	
High-risk drinking	3 (3.9)	4 (1.0)	
Use of marijuana in the last six months	35 (46.1)	64 (16.3)	<0.001
Use of poppers in the last six months	38 (50.0)	90 (22.9)	<0.001
Use of chemsex in the last six months	45 (59.2)	78 (19.8)	<0.001
Frequency of recreational drugs use:			
Once in a month	40 (52.6)	89 (58.6)	0.822
2-4 times a month	26 (34.2)	37 (24.3)	
2-3 times a week	7 (9.2)	21 (13.8)	
≥ 4 times a week	3 (3.9)	5 (3.3)	
Number of recreational drugs used in the last six months:			
1	16 (21.1)	83 (54.6)	<0.001
2	14 (18.4)	35 (23.0)	
3-8	46 (60.5)	34 (22.4)	
The last sexual intercourse with no drugs used (sober sex):			
Last month	58 (76.3)	105 (69.1)	0.597
More than 3 months ago	5 (6.6)	31 (20.4)	
More than 6 months ago	4 (5.3)	9 (5.9)	
A year ago	9 (11.8)	7 (4.6)	

*according to the results of univariate logistic regression analysis; **Alcohol consumption was based on responses to the first two questions from the shortened version of the Alcohol Use Disorders Identification Test of the World Health Organization; Low-risk drinking: score ≤1, risky drinking: score >1 according to the second question from the AUDIT test and high risk drinking: score ≥6 (10).

Table 3. Results of multivariate logistic regression analysis

	Participants who used ED drugs vs. participants who did not use ED drugs		
Variable	**Odds Ratio**	**95% Confidence Interval**	**p value***
Age	2.6	1.7-3.8	<0.001
Number of sexual partners in the last six months	1.8	1.5-2.2	<0.001
Use of marijuana in the last six months	2.6	1.3-4.9	0.006
Chemsex in the last six months	3.3	1.7-6.7	<0.001

ED –erectile dysfunction; *p-value according to the results of multivariate analysis.

tile lekove za ED, ispitanici koji su ih koristili bili su značajno češće stariji (Unakrsni odnos – UO=2,60, Interval poverenja– 95%IP 2,77-3,84, (p<0,001), imali su veći broj seksualnih partnera u poslednjih šest meseci (UO=1,83; 95%IP 1,53–2,18; (p<0,001), češće su upotrebljavali marihuanu (UO=2,55; 95%IP 1,31–4,93; p=0,006) i praktikovali hemseks tokom poslednjih šest meseci (UO=3,33; 95%IP 1,69-6,67; p<0,001).

Diskusija

Prema našim rezultatima 16,2% MSM osoba je koristilo lekove za ED tokom prethodnih šest meseci. Ovo je u skladu sa većinom studija koje su opisale da se procenat korisnika lekova za ED u MSM populaciji kretao od 12% (11) do 21% (4,12), mada su neka istraživanja sprovedena u Sjedinjenim Američkim Državama registrovala i veći procenat korisnika – oko 30% (13,14). Prema rezultatima multivarijantne regresione analize ispitanici koji su koristili lekove za ED u odnosu na one koji ih nisu koristili, bili su starijeg uzrasta, imali su veći broj seksualnih partnera u poslednjih šest meseci, češće su koristili marihuanu i praktikovali hemseks.

Većina naših ispitanika koji su koristili lekove za ED (75%) su bili stariji od 36 godina, što je u skladu sa rezultatima ostalih istraživanja. U studiji sprovedenoj u San Francisku 63% ispitanika koji su koristili Viagru (sildenafil) bilo je starije od 35 godina (12), dok je prosečna starost MSM osoba koje su koristile Viagru u Australiji bila 36,1 (11), a u studiji sprovedenoj u Sjedinjenim Američkim Državama 44,6 godina (2). Ovo bi se moglo objasniti činjenicom da su starije osobe već ranije u životu imale iskustvo sa ED usled medicinskih stanja povezanih sa starenjem, kao i time da stariji muškarci češće koriste lekove za ED kako bi održali erekciju i produžili trajanje seksualnog odnosa s obzirom na to da tokom analnog seksa uglavnom imaju insertivnu ulogu (11). Osobe koje žive sa HIV-om znatno češće imaju ED te ne čudi to što češće koriste ovu grupu lekova u odnosu na HIV-negativne osobe (12), ali to nismo primetili u našem istraživanju.

Skoro ⅔ naših ispitanika koji su koristili lekove za ED imalo je više od 10 seksualnih partnera u toku prethodnih šest meseci i češće je koristilo rekreativne droge u odnosu na ispitanike koji nisu koristili lekove za ED. Oni su češće imali visokorizično seksualno ponašanje (analni seks bez kondoma i grupni seks), bakterijske PPI u prethodnih godinu dana, dijagnostikovanu novu bakterijsku PPI i češće su obolevali od ponovnih bakterijskih PPI. Sifilis je bila infekcija koja se najčešće registrovala među našim ispitanicima što je u skladu sa aktuelnom epidemiološkom situacijom polnih bolesti u Srbiji (15). *Paul* i saradnici (14) su u svom istraživanju opisali da su korisnici Viagre imali veći broj seksualnih partnera, praktikovali su insertivni analni seks bez kondoma i imali neku bakterijsku PPI u prethodnih godinu dana. Istraživanje *Kim* i saradnika (13) je takođe opisalo da su korisnici Viagre u odnosu na one koji je nisu koristili, znatno češće imali seks sa većim brojem partnera i podatak o bakterijskoj PPI u poslednjih godinu dana. Studija sprovedena u Australiji je pokazala da su MSM osobe koje koriste lekove za ED znatno češće praktikovale grupni seks (16). Lekovi za ED imaju pozitivan efekat na seksualnu aktivnost sa većim brojem partnera i na produžetak trajanja seksualnog odnosa što povećava rizik za prenošenje kako HIV-a tako i ostalih PPI.

Kao što smo već napomenuli, prema rezultatima našeg istraživanja korisnici lekova za ED su znatno češće koristili marihuanu, popers i ostale seksualizovane droge. Hemseks droge se koriste pre ili tokom seksualnog odnosa da bi olakšale stupanje u seksualne odnose i poboljšale seksualno zadovoljstvo i ovaj fenomen je predominantno opisan među MSM populacijom (17). Hemseks je pozitivno povezan sa visoko rizičnim seksualnim ponašanjem i prenošenjem HIV-a i PPI (18). *Chu* i saradnici (20) su objavili da je 36% MSM kombinovalo Viagru sa ostalim ilegalnim rekreativnim drogama, a veliki broj studija je potvrdio pozitivnu vezu između upotrebe lekova za ED i ostalih rekreativnih droga (1,14,19). Prema podacima Kim i saradnika (13) Viagra se najčešće kombinovala sa ekstazijem, metamfetaminom i popersom i 73% korisnika je verovalo da im istovremena upotreba ovih droga poboljšava seksualno iskustvo. *Crosby* i saradnici (20) su opisali često kombinovanje lekova za ED sa ekstazijem i kokainom. Iako je istovremena upotreba lekova za ED i popersa (opisana i kod naših ispitanika) kontraindikovana, to ne sprečava korisnike da ih zajedno konzumiraju. Česta upotreba marihuane među našim ispitanicima koji su koristili lekove za ED ne čudi jer je marihuana i inače najčešće korišćena ilegalna droga u Srbiji (21).

Naša studija ima nekoliko ograničenja. Glavno je to što je sprovedena među MSM osobama koje su dolazile u zdravstvene ustanove i upitno je da li se dobijeni rezultati mogu generalizovati na čitavu

frequently (OR=2.55; 95%CI 1.31-4.93; p=0.006) and practiced chemsex during the last six months (OR=3.33; 95%CI 1.69-6.67; p<0.001).

Discussion

According to our results, 16.2% of MSM used ED drugs in the past six months. This is consistent with the results of most studies, which reported that the percentage of ED drug users in the MSM population ranged between 12% to 21% (4,12), although some studies that were conducted in the United States of America registered a higher percentage of users – about 30% (13,14). According to the results of multivariate regression analysis, the participants, who used ED drugs in comparison to those who did not, were older, had a greater number of sexual partners in the last six months, used marijuana more often and practiced chemsex.

The majority of our participants, who used ED drugs (75%), were older than 36, which is consistent with the results of other studies. In the study, which was conducted in San Francisco, 63% of participants who used Viagra (sildenafil) were older than 35 (12), while the average age of men who had sex with men and who used Viagra was 36.1 in Australia (11), and 44.6 years in one study conducted in the United States of America (2). This could be explained by the fact that older people had experienced ED previously due to medical conditions related to aging, as well as by the fact that older men use medications for ED more often in order to maintain the erection and prolong the sexual intercourse given that they have an insertive role during anal sex (11). People living with HIV have ED significantly more often, and therefore, they use this group of drugs more often than HIV-negative people (12), but we did not notice that in our research.

Almost ⅔ of our participants who used ED drugs had more than 10 sexual partners in the previous six months and they used recreational drugs more often in comparison to other participants who did not use ED drugs. High risk sexual behavior (anal sex without condoms and group sex) was more often present in these participants, as well as bacterial STIs in the previous year, new bacterial STI and recurrent bacterial STIs. Syphilis was the most frequently registered infection among our respondents, which is in line with the current epidemiological situation in Serbia regarding sexually transmitted diseases (13). Paul and associates (14) described in their study that Viagra users had a greater number of sexual partners, practiced insertive anal sex without condoms and had some bacterial STI in the previous year. In the study of Kim and associates (13), it was also described that Viagra users, compared to those who did not use Viagra, significantly more often had sex with a greater number of partners and reported bacterial STI in the past year. A study conducted in Australia showed that MSM who used ED medications practiced group sex more often (16). ED medications have a positive effect on sexual activity with more partners and on the prolongation of sexual intercourse, which increases the risk of transmitting both HIV and other STIs.

As we have already mentioned, according to the results of our research, the users of ED drugs used marijuana, poppers and other sexualized drugs significantly more often. Chemsex drugs are used before or during sexual intercourse in order to facilitate the intercourse and enhance sexual satisfaction, and this phenomenon has been predominantly described among the MSM population (17). Chemsex is positively associated with high-risk sexual behavior and transmission of HIV and other STIs (18). Chu and associates (20) reported that 36% of MSM combined Viagra with other illegal recreational drugs, while a large number of studies confirmed the positive association between ED drugs use and other recreational drugs (1,14,19). According to Kim and associates (13), Viagra was most often combined with ecstasy, methamphetamine, and poppers, and 73% of users believed that the simultaneous use of these drugs improved their sexual experience. Crosby and associates (20) described the frequent combination of ED drugs with ecstasy and cocaine. Although the simultaneous use of ED drugs and poppers (also described in our participants) is contraindicated, this does not prevent users from using them together. The frequent use of marijuana among our participants who used drugs for ED is not surprising because marijuana is the most commonly used illegal drug in Serbia (21).

Our study has several limitations. The main reason is that it was conducted among MSM persons who came to healthcare institutions, and it is questionable whether the obtained results can be generalized to the entire MSM population. Also, we did not collect data from the participants

MSM populaciju u Srbiji. Takođe nismo uzimali podatke od ispitanika koliko su često koristili lekove za ED i kako su dolazili do njih, da li preko lekarskog recepta ili bez njega i da li su lek koristili u terapijske ili rekreativne svrhe. Takođe, nismo se bavili ispitivanjem da li osobe koje koriste lekove za ED, zaista i imaju ED.

Zaključak

Upotreba lekova za ED kod MSM osoba udružena je sa većim stepenom primene rekreativnih droga i visokorizičnim seksualnim ponašanjem. Dermatovenerolozi, posebno oni koji rade sa MSM populacijom, bi trebalo da sa pacijentima diskutuju, ne samo o potencijalnim štetnim dejstvima lekova za ED, već i o riziku kombinovanja ovih lekova sa drugim rekreativnim drogama i rizicima za PPI i HIV koji postoje kod korisnika lekova za ED.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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about how often they used ED drugs and how they obtained them, whether they had a prescription or not and whether they used the drug for therapeutic or recreational purposes. Also, we did not examine whether people, who used ED drugs, really had ED.

Conclusion

ED drug use among MSM is associated with a higher level of recreational drug use and high-risk sexual behavior. Dermatovenerologists, especially those working with the MSM population, should discuss with their patients not only the potential adverse effects of ED medications, but also the risk of combining these medications with other recreational drugs and the risk of HIV and STIs in ED drug users.

Competing interests

The authors declared no competing interests.

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FAKTORI RIZIKA ZA NASTANAK KARCINOMA DOJKE KOD ŽENA U CRNOJ GORI

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SAŽETAK

Uvod/Cilj: Brojni faktori rizika dovode se u vezu sa rakom dojke koji je vodeći uzrok obolevanja i umiranja u svetu. Cilj istraživanja je bio da se analiziraju faktori koji dovode do nastanka karcinoma dojke.
Metode: Ova serija slučajeva, obuhvatila je 154 žene sa karcinomom dojke kod kojih je ova dijagnoza po prvi put postavljena tokom 2018. godine u Kliničkom centru za onkologiju i radioterapiju Crne Gore. Od svih ispitanica podaci su prikupljeni upitnikom.
Rezultati: Prosečna starost žena sa karcinomom dojke je bila 46,42 (±12,77) godine. Reproduktivne karakterike žena pokazuju da je 95,5% žena menarhu imalo pre 15 godine života, a dete/decu je imalo 85,7% žena. Najveći broj (86,4%) žena je dete rodilo između 26 i 32 godine života. Od žena koje su rodile, 31,8% je imalo jedno, 49,3% dvoje i 18,9% troje i više dece. Većina žena (86,4%) je dojila dete. Oko ⅓ ispitanica je redovno koristila oralnu kontracepciju. Svaka druga žena je bila sadašnji pušač, a 28,6% bivši. Alkohol je redovno konzumiralo 3,9% žena, a povremeno 81,2%. Zdrav način ishrane imalo je 63,6% žena, 85,1% je sprovodilo fizičku aktivnost svakodnevno. Pozitivnu porodičnu anamnezu za rak dojke je imalo 16,2% žena. Od preventivnih aktivnosti žene sa rakom dojke su u 92,9% slučajeva imale preglede dojke od strane ginekologa, 36,4% je poznavalo tehniku samopregleda dojke, a na mamografskom pregledu je bilo 33,8% ispitanica (odnosno 58,4% žena uzrasta 50 iviše godina).
Zaključak: Neophodno je izabrati zdrave stilove života i edukovati se o važnosti preventivnih pregleda dojke, savladati tehnike samopregleda dojki i shvatiti važnost mamografije kao skrininga za rano otkrivanje raka dojke koji se predlaže u uzrastu od 50 do 69 godine života, na svake dve godine. Na ovaj način drastično se smanjuju troškovi lečenja i obezbeđuje bolji ishodi, a na prvom mestu bolji kvalitet života.

Ključne reči: karcinom, dojka, faktori rizika, prevencija

Uvod

Rak dojke je veliki javnozdravstveni problem na globalnom nivou i ima epidemijske razmere, a posledice obolevanja i umiranja pogađaju praktično sve segmente društva. Rak dojke je vodeći malignom u ženskoj populaciji Crne Gore, kako na osnovu incidencije tako i na osnovu mortalitetne statistike (1). Oko 60% žena u Crnoj Gori usled raka dojke umre pre 65 godine života (1).

Prema podacima Svetske zdravstvene organizacije (SZO), 2020. godina, broj nvoobolelih od raka dojke je bio oko 2,3 miliona, a umrlih oko 685 hiljada na globalnom nivou (2). Azija (obolelih - oko 1 milion i umrlih - oko 346 hiljada) i Evropa (obolelih – oko 532 hiljade i umrlih - oko 142 hiljade) su vodeće po broju obolelih i umrlih (2). U Evropi su najviše standardizovane stope incidencije u Zapadnoj Evropi (90,7/100.000), a najniže u Centralnoj i Istočnoj Evropi (57,1/100.000) (2). Standardizovana stopa mortaliteta najviše je u Zapadnoj Evropi (15,6/100.000), a najniža u Južnoj Evropi (13,3/100.000) (2).

Rak dojke takođe se dijagnostikuje u muškoj populaciji, ali izuzetno retko (3). U istraživanju sprovedenom u Centralnoj Srbiji, za period 2009-2020. godina, prosečna standardizovana stopa incidencije za rak dojke je bila 50,2 puta veća kod žena nego kod muškaraca, a stopa mortaliteta 49,5 puta (3)

Brojne studije su pokazale da primena organizovanog skrininga za rak dojke doprinosi ranom otkrivanju poremećaja zdravlja i redukciji mor-

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RISK FACTORS OF BREAST CANCER IN WOMEN IN MONTENEGRO

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SUMMARY

Introduction/Aim: Numerous risk factors are associated with breast cancer, which is the leading cause of morbidity and mortality in the world. The aim of this study was to analyze the factors that lead to the occurrence of breast cancer.
Methods: This case study included 154 women who were diagnosed with breast cancer for the first time during 2018 at the Clinical Center for Oncology and Radiotherapy of Montenegro. Data were collected from all respondents using a questionnaire.
Results: The average age of women with breast cancer was 46.42 (±12.77). The reproductive characteristics of women show that 95.5% of women had menarche before the age of 15, while 85.7% of them had child/children. The largest number of women (86.4%) gave birth to a child between the ages of 26 and 32. Of all the women who gave birth to a child, 31.8% had one child, 49.3% two children and 18.9% three and more children. The majority of women (86.4%) were breastfeeding their children. About ⅓ of respondents used the oral contraception regularly. Every second woman was a current smoker, and 28.6% were ex-smokers. Alcohol was regularly consumed by 3.9% of women, and occasionally by 81.2%. 63.6% of women had a healthy diet, while 85.1% were physically active on a daily basis. 16.2% of women had a positive family history of breast cancer. As far as preventive activities are concerned, women with breast cancer in 92.9% cases had breast examinations by gynecologists, 36.4% knew the technique of self-examination, while 33.8% of respondents (that is, 58.4% of women aged 50 years and older) underwent mammography.
Conclusion: It is necessary to choose healthy lifestyles and educate oneself about the importance of preventive breast examinations, learn the techniques of self-examination of breasts and realize the importance of mammography as a screening test for the early detection of breast cancer, which is recommended between the ages of 50 and 69, every two years. Thus, treatment costs are drastically reduced, better outcomes are ensured, and first of all, the quality of life is improved.

Key words: cancer, breast, risk factors, prevention

Introduction

Breast cancer is the major public health problem at the global level and has the proportions of an epidemic, while the consequences of morbidity and mortality affect practically all segments of society. Breast cancer is the leading malignancy in the female population of Montenegro, based on the incidence, as well as mortality statistics (1). About 65% of women in Montenegro die of breast cancer before the age of 65 (1).

According to the data of the World Health Organization (WHO) in 2020, the number of new cases of breast cancer was about 2.3 million, while the number of deaths was 685,000 globally (2). Asia (about 1 million new cases and 346,000 deaths) and Europe (532,000 new cases and 142,000 deaths) are the leading countries in relation to the number of cases and deaths (2). In Europe, the highest standardized incidence rates are in Western Europe (90.7/100,000), while the lowest are in Central and Eastern Europe (57.1/100,000) (2). The highest standardized mortality rate is in Western Europe (15.6/100,000), while the lowest is in Sothern Europe (13.3/100,000) (2).

taliteta i unapređenja kvaliteta života (4,5). Neophodno je zbog navedenog raditi na promociji skrininga za rak dojke, jer se jedino na ovaj način može doprineti poboljšanju epidemiološke situacije u svakoj zemlji po pitanju raka dojke (6).

Cilj istraživanja je bio da se analiziraju faktori koji dovode do nastanka karcinoma dojke.

Metode

Ovom serijom slučajeva, obuhvaćene su 154 žene sa histopatološki potvrđenom dijagnozom karcinoma dojke kod kojih je ova bolest po prvi put bila dijagnostikovana tokom 2018. godine u Kliničkom centru Crne Gore i to u Klinici za onkologiju i radioterapiju. Od svih ispitanica podaci su prikupljeni upitnikom koji je sadržao 25 pitanja koja su se odnosila na demografske karakteristike ispitanica, njihovo reproduktivnog zdravlja, navike i preventivne aktivnosti. Upitnik je bio anoniman i svaka ispitanica je potpisala pisanu saglasnost za uključivanje u studiju. Etički komitet Kliničkog centra Crne Gore je odobrio istraživanje. Dobijeni rezultati su prikazani tabelarno, korišćenjem apsolutnih vrednosti i proporcija.

Rezultati

Studijom je obuhvaćeno 154 žena sa dijagnostikovanim karcinomom dojke tokom 2018. godine. Najmlađa žena imala je 23 godine, a najstarija 75 godine. Prosečna starost žena je bila 46,42 (±12,77) godine. Od 154 ispitanice, 83 (53,9%) je imalo završenu srednju školu, 45 (29,2%) višu/visoku, a 26 (16,9%) je bilo bez škole ili sa osnovnom (tabela 1). Oko ¾ žena je stanovalo u gradskoj sredini, a oko ¼ u ruralnoj sredini. Najveći broj ispitanica (66,9%) je bilo u braku, a ni jedna u vanbračnoj zajednici.

Reproduktivne karakterike žena pokazuju da je 95,5% žena menarhu imalo pre 15 godine života, a živorođeno dete je rodilo 85,7% žena. Najveći broj (86,4%) žena je dete rodio između 26 i 32 godine života. Od žena koje su rodile, 31,8% je imalo jedno, 49,3% dvoje i 18,9% troje i više dece. Većina žena (86,4%) je dojila dete. Među ženama koje su dojile, bilo je najviše onih koje su dojile ≤6 meseci (53%) i 7-12 meseci (43,5%). Oko ⅓ ispitanica je redovno koristila oralnu kontracepciju.

Svaka druga žena je bila sadašnji pušač, a 28,6% bivši. Alokohol je često konzumiralo 3,9% žena, a povremeno 81,2%. Zdravu ishranu imalo je 63,6% žena, 85,1% je sprovodilo fizičku aktivnost svakodnevno. Prekomernu telesnu težinu smatralo je da ima 8,4% žena, a 98,7% je bilo izloženo svakodnevnom stresu. Bilo kada u toku života rendgen zračenju je bilo izloženo 94,2% žena, a pozitivnu porodičnu anamnezu za rak dojke je imalo 16,2% žena.

Tabela 1. Demografske karakteristike žena sa karcinomom dojke hospitalizovanih u Klinici za onko-logiju i radioterapiju u Kliničkom centru Crne Gore, 2018. godine

Karakteristike	Broj % (N=154)
Godine starosti (godine)	
< 40	7 (4,5)
40-49	58 (37,7)
50-59	37 (24,0)
60-69	36 (23,4)
70+	16 (10,4)
Obrazovanje	
Bez ili sa osnovnom školom	26 (16,9)
Srednja škola	83 (53,9)
Viša/Visoka škola	45 (29,2)
Mesto stanovanja	
Gradska sredina	122 (79,2)
Ruralna sredina	32 (20,8)
Bračni status	
Brak	104 (66,9)
Razveden/razvedena	20 (13,6)
Udovac/udovica	16 (10,4)
Neudat/neudata	14 (9,1)

Od preventivnih aktivnosti žene sa rakom dojke su u 92,9% slučajeva išle na redovne ginekološke preglede, 36,4% je poznavalo tehnike samopregleda dojke, a na mamografskom pregledu je bilo 33,8% ispitanica (odnosno 58,4% žena uzrasta 50 i više godina).

Diskusija

Rezultati naše studije ukazuju da su žene sa novodijagnostikovanim karcinom bile izložene brojnim faktorima rizika (stare 40 i više godina – 95,5%, nižeg stepena obrazovanja – 70,8%, pušači – 81,8%, korisnice alkohola – 85,1%, izložene stresu – 98,7%, sa pozitivnom porodičnom anamnezom za rak dojke – 16,2%, menarha pre 15 godine – 95,5%, trudnoća posle 32 godine – 8,3%, neradjanje – 14,3%, nedojenje – 13,6%, dužina dojenja 6 meseci i kraće – 53%). Od preventivnih aktivnosti u 92,9% slučajeva žene su išle na redovne ginekološke preglede, ali samo 36,4% je poznavalo tehnike samopregleda dojke i 33,8% je bilo na ma-

Breast cancer is also diagnosed in the male population, but extremely rarely (3). In a study conducted in Central Serbia for the period 2009-2020, the average standardized incidence rate for breast cancer was 50.2 times higher in women than in men, while the mortality rate was 49.5 times higher (3).

Numerous studies have shown that the implementation of organized screening for breast cancer contributes to the early detection of health disorders and the reduction of mortality and improvement of the quality of life (4,5). Therefore, it is necessary to work on the promotion of screening for breast cancer, because this is the only way to contribute to the improvement of the epidemiological situation in each country regarding breast cancer (6).

The aim of the study was to analyze the factors that lead to the occurrence of breast cancer.

Methods

This case study included 154 women with the histopathologically confirmed diagnosis of breast cancer, in whom this disease was diagnosed for the first time during 2018 at the Clinical Center of Montenegro, namely at the Clinic for Oncology and Radiotherapy during 2018. Data were collected from all respondents using a questionnaire, which contained 25 questions related to the demographic characteristics of respondents, their reproductive health, habits and preventive activities. The questionnaire was anonymous and each respondent signed a written consent for the inclusion in the study. The study was approved by the Ethics Committee of the Clinical Center of Montenegro. The obtained results were presented in tables using the absolute values and proportions.

Results

The study included 154 women diagnosed with breast cancer in 2018. The youngest woman was 23 years old, while the oldest was 75 years old. The average age of women was 46.42 (SD=12.77). Of 154 respondents, 83 (53.9%) had completed secondary school, 45 (29.2%) had graduated from college/faculty, while 26 (16.9%) had no schooling or had finished primary school (Table 1). About ¾ of women lived in urban areas, and about ¼ in rural areas. The largest number of respondents (66.9%) was married, and none of them lived in the common-law marriage. The reproductive characteristics of women showed that 95.5% of women had menarche before the age of 15, while 85.7% of women gave birth to a live child. The largest number of women (86.4%) gave birth to a child between the ages of 26 and 32. Of those women who gave birth to a child, 31.8% had one child, 49.3% two children, and 18.9% three and more children. The majority of women (86.4%) were breastfeeding their child. Among the women who breastfed, the majority of them breastfed <6 months (53%) and 7-12 months (43.5%). About ⅓ of respondents regularly used the oral contraception.

Table 1. Demographic characteristics of women with breast cancer hospitalized at the Clinic for Oncology and Radiotherapy of the Clinical Center of Montenegro, 2018.

Characteristics	Number (%) (N=154)
Age (years)	
< 40	7 (4.5)
40-49	58 (37.7)
50-59	37 (24.0)
60-69	36 (23.4)
70+	16 (10.4)
Education	
Without or with primary school	26 (16.9)
Secondary school	83 (53.9)
College/Faculty	45 (29.2)
Place of residence	
Urban areas	122 (79.2)
Rural areas	32 (20.8)
Marital status	
Married	104 (66.9)
Divorced	20 (13.6)
Widow/widower	16 (10.4)
Not married	14 (9.1)

Every other woman was a current smoker, and 28.6% former smokers. Alcohol was often consumed by 3.9% of women, and occasionally by 81.2%. 63.6% had a healthy diet, while 85.1% were physically active every day. 8.4% thought they were overweight, and 98.7% were exposed to everyday stress. 94.2% of women were exposed to X-ray radiation during lifetime, and 16.2% of women had a positive family anamnesis for breast cancer.

As far as preventive activities are concerned, women with breast cancer went to regular gynecological examinations in 92.9% of cases, 36.4% knew the techniques of breast self-

Tabela 2. Reproduktivne karakteristike žena sa karcinomom dojke hospitalizovanih u Klinici za onkologiju i radioterapiju u Kliničkom centru Crne Gore, 2018. godine

Karakteristike	Broj % (N=154)
Menarha (godina)	
≤15	147 (95,5)
≥16	7 (4,5)
Porađaj	
Da	132 (85,7)
Ne	22 (14,3)
Uzrast pri prvom porađaju (godine)*	
<25	7 (5,3)
26-32	114 (86,4)
≥33	11 (8,3)
Broj živorođene dece*	
1	42 (31,8)
2	65 (49,3)
3+	25 (18,9)
Dojenje	
Da	114 (86,4)
Ne	40 (13,6)
Dužina dojenja (u mesecima)**	
≤6	52 (53,0)
7-12	57 (43,2)
>12	5 (3,8)
Oralna kontracepcija	
Da	54 (35,1)
Ne	100 (64,9)

*Ukupan broj ispitanica je 132; **Ukupan broj ispitanica je 114.

Tabela 3. Navike, lična i porodična anamneza žena sa karcinomom dojke hospitalizovanih u Klinici za onkologiju i radioterapiju u Kliničkom centru Crne Gore, 2018. godine

Karakteristike	Broj % (N=154)
Sadašnji pušač	
Da	82 (53,2)
Ne	28 (18,2)
Bivši	44 (28,6)
Konzumiranje alkohola	
Redovno	6 (3,9)
Ponekad	125 (81,2)
Ne	23 (14,9)
Pravilna ishrana	
Da	98 (63,6)
Ne	56 (36,4)
Svakodnevna fizičku aktivnost	
Da	131 (85,1)
Ne	23 (14,9)
Stepen uhranjenosti (lična procena)	
Normalna	141 (91,6)
Prekomerna telesna težina	13 (8,4)
Izloženost stresu	
Da	152 (98,7)
Ne	2 (1,3)
Izloženost rendgen zračenju bar jednom u životu	
Da	145 (94,2)
Ne	9 (5,8)
Porodična anamneza za rak dojke	
Da	25 (16,2)
Ne	129 (83,8)

mografskom pregledu (odnosno 58,4% žena uzrasta 50 i više godina).

Veliki broj autora navodi da su brojni faktori, genetski, kao i faktori sredine, odgovorni za nastanak raka dojke. Rizik od raka dojke se povećava sa godinama starosti, prisustvom BRCA1 i BRCA2 gena, pozitivnom porodičnom istorijom za rak dojke, menarhom pre 12. godine života, gustinom dojke (više vezivnog nego masnog tkiva), postojanjem nekanceroznih bolesti dojke (atipična hiperplazija, lobularni karcinom in situ, itd.), zračenjem u oblasti grudi, korišćenjem leka dietilstilbestrola, fizičkom neaktivnošću, prekomernom telesnom težinom, korišćenjem oralnih kontraceptiva i hormonske supstitucione terapije, nedojenjem, trudnoćom posle 30 godine života, neraćanjem, konzumiranjem alkohola i pušenjem (7-12).

U meta-analizi koju su sproveli *Wu* i sar., koja je obuhvatila 31 studiju sa 63.786 ispitanika, uočeno je da manji rizik od raka dojke imaju žene koje su fizički aktivne (RR = 0,88; 95% interval poverenja - IP = 0,85-0,91 (7). Druga meta-analiza autora *Anothaisintawee* i sar., pokazala je da rizik od raka dojke značajno raste primenom oralnih kontraceptiva (Unakrsni odnos - UO =1,10; 95%IP = 1,03-1,18) i hormonske supstitucione terapije (UO = 1,23; 95%IP = 1,21-1,25), kao i postojanjem pozitivne lične anamneze za dijabete melitus (UO = 1,14; 95%IP = 1,09- 1,19) (8). Međutim, dojenje bilo je značajni protektivni faktor za nastanak raka dojke (UO = 0,72; 95%IP = 0,58-0,89). U studiji *Migliavacca Zucchetti* i sar. trudnoća i dojenje smanjuju rizik od raka dojke i efekat je proporcionalan ukupnom trajanju laktacije i broju trudnoća (9).

U velikom broju radova uočeno je da postoji negativna veza između raka dojke i fizičke aktivnosti (10). Pretpostavlja se da fizička aktivnost doprinosi redukciji štetnih efekata zapaljenja (inflamatornih

Table 2. Reproductive characteristics of women with breast cancer hospitalized at the Clinic for Oncology and Radiotherapy of the Clinical Center of Montenegro, 2018.

Characteristics	Number (%) (N=154)
Menarche (age)	
≤15	147 (95.5)
≥16	7 (4.5)
Delivery	
Yes	132 (85.7)
No	22 (14.3)
Age at the first delivery (years)*	
<25	7 (5.3)
26-32	114 (86.4)
≥33	11 (8.3)
Number of live births*	
1	42 (31.8)
2	65 (49.3)
3+	25 (18.9)
Breastfeeding	
Yes	114 (86.4)
No	40 (13.6)
Duration of breastfeeding (in months)**	
≤6	52 (53.0)
7-12	57 (43.2)
>12	5 (3.8)
Oral contraception	
Yes	54 (35.1)
No	100 (64.9)

* Total number of respondents is 132; **Total number of respondents is 114. .

Table 3. Habits, personal and family medical history of women with breast cancer hospitalized at the Clinic for Oncology and Radiotherapy of the Clinical Center of Montenegro, 2018.

Characteristics	Number (%) (N=154)
Current smoker	
Yes	82 (53.2)
No	28 (18.2)
Former	44 (28.6)
Alcohol consumption	
Regular	6 (3.9)
Sometimes	125 (81.2)
No	23 (14.9)
Adequate diet	
Yes	98 (63.6)
No	56 (36.4)
Daily physical activity	
Yes	131 (85.1)
No	23 (14.9)
Level of obesity (personal estimate)	
Normal	141 (91.6)
Overweight	13 (8.4)
Exposure to stress	
Yes	152 (98.7)
No	2 (1.3)
Exposure to X-ray radiation at least once in a lifetime	
Yes	145 (94.2)
No	9 (5.8)
Family history of breast cancer	
Yes	25 (16.2)
No	129 (83.8)

examination, and 33.8% of respondents had a mammographic examination (that is, 58.4% of women aged 50 and older).

Discussion

The results of our study indicate that women with newly diagnosed cancer were exposed to numerous risk factors (aged 40 years and older – 95.5%, lower level of education – 70.8%, smokers – 81.8%, alcohol users – 85.1%, exposed to stress – 98.7%, with a positive family history of breast cancer – 16.2%, menarche before the age of 15 – 95.5%, pregnancy after the age of 32 – 8.3%, not giving birth – 14.3%, not breastfeeding – 13.6%, length of breast feeding 6 months and shorter – 53%). As far as preventive activities are concerned, in 92.9% of cases, women went to regular gynecological examinations, while only 36.4% knew the techniques of self-examination, and 33.8% had a mammographic examination (58.4% of women aged 50 years and older).

A large number of authors state that numerous factors, genetic factors and environmental factors are responsible for the occurrence of breast cancer. The risk of breast cancer increases with age, the presence of BRCA1 and BRCA2 genes, a positive family history of breast cancer, menarche before the age of 12, breast density (more connective than fat tissue), the existence of non-cancerous breast diseases (atypical hyperplasia, lobular carcinoma in situ, etc.), radiation in the chest area, use of the drug diethylstilbestrol, physical inactivity, obesity, use of oral contraceptives and hormone replacement therapy, non-breastfeeding, pregnancy after the age of 30, not giving birth to a child, alcohol consumption and smoking (7-12).

In a meta-analysis conducted by Wu and associates, which included 31 studies with

Tabela 4. Preventivne aktivnosti žena sa karcinomom dojke hospitalizovanih u Klinici za onkologiju i radioterapiju u Kliničkom centru Crne Gore, 2018. godine

Karakteristike	Broj % (N=154)
Pregled dojke od strane ginekologa	
Da	143 (92,9)
Ne	11 (7,1)
Poznavanje tehnike samopregleda dojke	
Da	56 (36,4)
Ne	98 (63,6)
Mamografski pregled bilo kada u životu među svim ženama	
Da	52 (33,8)
Ne	102 (66,2)
Mamografski pregled bilo kada u životu među ženama uzrasta 50 i više godina*	
Da	52 (58,4)
Ne	37 (41,6)

*Ukupan broj žena uzrasta 50 i više godina je 89.

citokina) i modulaciji imunološkog odgovora kada je u pitanju rak dojke. Takođe, uočeno je da fizička aktivnost može doprineti smanjivanju rizika od recidiva i smrtnog ishoda kod osoba sa rakom dojke (10). Pozitivan efekat fizičke aktivnosti ogleda se i u redukciji telesne mase, jer je u mnogim radovima ukazano da gojaznost predstavlja faktor rizika (11). Interesantni su podaci istraživanja *King* i sar. da fizička aktivnost može odložiti početak nastanka raka dojke među ženama koje imaju BRCA1 i BRCA2 mutacije (12).

Usled veće svesti o raku dojke od strane žena i/ili promena u zdravstvenom sistemu, drastično se povećava broj žena koje su imale pregled dojki od strane lekara. Međutim, iako postoji porast pregleda dojki u ženskoj populaciji, ukupan broj žena koje redovno rade preglede i dalje je mali (13). U prospektivnoj studiji sprovedenoj u Ženevi bilo je uključeno 932 žene uzrasta 50-69 godina i praćene su 8 meseci. Posle posmatranog perioda mali je procenat žena prihvatio organizovani skrining (11,6%) i oportunistički skrining (39,4%) za rak dojke. Neophodno je razviti svest o neophodnosti podvrgavanju mamografiji.

Broj mamografskih pregleda u Crnoj Gori značajno se povećao kod žena, ali je to još uvek nedovoljno. Samo 33,8% ispitanica (odnosno 58,4% žena uzrasta 50 i više godina), 2018. godine, imalo je bar jedan mamografski pregled. Motivacioni faktor za odlazak na pregled dojki je bila pozitivna porodična anamneza. U zemljama u okruženju, stalno raste broj udruženja pacijenata, kao i grupa za podršku, koje pružaju podršku ženama za rano otkrivanje raka dojke, kao i za realizaciju svih drugih preventivnih mera.

Glavni nedostatak ove studije je što nismo izabrali za ispitanike adekvatnu kontrolnu grupu. Neophodna su dalja istraživanja ove problematike kroz analitičke studije.

Zaključak

Neophodno je raditi na edukaciji žena o važnosti dojenja, prestanku pušenja, adekvatnoj ishrani, fizičkoj aktivnosti, samopregledu dojki i prihvatanju mamografskog skrininga koji se predlaže u uzrastu od 50 do 69 godine života. Neophodno je raditi na stalnom unapređenju organizovanog skrininga u svakoj zemlji i prati njegove rezultate.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Table 4. Preventive activities of women with breast cancer hospitalized at the Clinic for Oncology and Radiotherapy at the Clinical Center of Montenegro, 2018.

Characteristics	Number (%) (N=154)
A clinical breast exam	
Yes	143 (92.9)
No	11 (7.1)
Knowing the technique of breast self-exam	
Yes	56 (36.4)
No	98 (63.6)
Mammographic examination at any time in life among all women	
Yes	52 (33.8)
No	102 (66.2)
Mammographic examination at any time in life among women aged 50 and older*	
Yes	52 (58.4)
No	37 (41.6)

*Total number of women aged 50 and older is 89.

63,786 respondents, it was noticed that women, who were physically active, had a lower risk of breast cancer (RR=0.88; 95% confidence interval – CI = 0.85-0.91 (7). Other meta-analyses of Anothaisintawee and associates showed that the risk of breast cancer increases significantly with the use of oral contraceptives (Odds Ration – OR = 1.10; 95%CI – 1.03-1.18) and hormone replacement therapy (OR = 1.23; 95%CI = 1.21-1.25), as well as when a positive family history of diabetes mellitus exists (OR = 1.14; 95%CI = 1.09-1.19) (8). However, breastfeeding was a significant protective factor for the development of breast cancer (OR = 0.72; 95%CI = 0.58-0.89). In a study of Migliavacca Zucchetti and associates, pregnancy and breastfeeding reduce the risk of breast cancer and the effect is proportional to the total duration of lactation and the number of pregnancies (9).

In a large number of studies, it was observed that there was a negative relationship between breast cancer and physical activity (10). It is assumed that physical activity contributes to the reduction of harmful effects of inflammation (inflammatory cytokines) and the modulation of the immune response when it comes to breast cancer. Also, it was observed that physical activity may contribute to reducing the risk of recurrence and death in persons with breast cancer (10). A positive effect of physical activity is also reflected in the reduction of body weight, as many studies have shown that obesity is a risk factor (11). Interesting data from the study of King and associates show that physical activity may postpone the onset of breast cancer among women who have BRCA1 and BRCA2 mutations (12).

Due to greater awareness of women regarding breast cancer and/or changes in the healthcare system, the number of women who had their breasts examined by a doctor is increasing drastically. However, although there is an increase in breast examinations in the female population, the total number of women who regularly go to check-ups is still low (13). In a prospective study conducted in Geneva, 932 women aged 50-69 were included and followed for 8 months. After the observed period, a small percentage of women accepted the organized screening (11.6%) and opportunistic screening (39.4%) for breast cancer. It is necessary o develop awareness about the necessity of undergoing mammography.

The number of mammography examinations in Montenegro increased significantly among women, but it is still insufficient. In 2018, only 33.8% of respondents (or 58.4% of women aged 50 and over) had at least one mammographic examination. A positive family history was a motivating factor for going to the breast examination. In neighboring countries, the number of patient associations is constantly increasing, as well as of support groups, which provide support to women for the early detection of breast cancer, and for the realization of other preventive measures.

The main limitation of this study is that we did not select an adequate control group for our respondents. Further research of this topic through analytical studies is necessary.

Conclusion

It is necessary to work on the education of women about the importance of breastfeeding, cessation of smoking, adequate diet, physical activity, breast self-examination and acceptance of mammographic screening, which is recommended at the age of 50 to 69 years. It is necessary to work on the constant improvement of organized screening in every country and observe its results.

Competing interests

The authors declared no competing interests.

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UTICAJ PLAVE SVETLOSTI IZ PRIRODNIH I VEŠTAČKIH IZVORA NA KOŽU

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SAŽETAK

Plava svetlost obuhvata zrake manje energije u odnosu na UV zračenje, ali ima veću moć prodiranja u dermis, čak do dubine od 1mm. Cilj ovog preglednog rada je bio da se na osnovu dostupne literature analiziraju biološki efekti prirodne i veštačke plave svetlosti na kožu, kao i da se predlože preventivne mere za zaštitu kože od njenih štetnih efekata. Najnovija istraživanja ukazuju da plava svetlost ima različite direktne i indirektne efekte na kožu. Direktni efekti plave svetlosti na kožu su prekomerno stvaranje reaktogenih vrsta kiseonika, azota i hiperpigmentacija, a indirektno utiče na kožu poremećajem cirkadijalnog ritma i lučenjem melatonina. Plava svetlost ima direktan uticaj na hromofore koje su prisutne u koži i dovodi do njihove aktivacije. Njihovom aktivacijom dolazi do prekomerne proizvodnje reaktivnih vrsta kiseonika i oslobađanja reaktivnih vrsta azota, odnosno azot monoksida (NO), što pokreće melanogenezu i hiperpigmentaciju. Takođe, dolazi do smanjenja vitalnosti ćelija i/ili proliferacije keratinocita i melanocita, zatim povećane sinteze proinflamatornih interleukina i faktora nekroze tumora alfa i izmenjenog metabolizma kolagena. Plava svetlost smanjuje antioksidativnu zaštitu kože izazivajući razgradnju prisutnih karotenoida. Može se koristiti u kliničkoj praksi u prevenciji i tretmanu određenih dermatoza, kao i u tretmanima fotorejuvenacije u estetskoj medicini. Neophodna su dalja istraživanja u ovoj oblasti.

Ključne reči: plava svetlost, koža, prevencija

Uvod

Sunce emituje vidljivu i nevidljivu svetlost. Ultraljubičasto zračenje (UV) (talasna dužina 280-400 nm) je nevidljivo i čini 3-7% sunčevog spektra, ali i pored toga se najviše istražuje njegovo dejstvo na kožu. U okviru ovog dela sunčevog zračenja, razlikuju se ultraljubičasti zraci (engl. *ultraviolet*) A, B i C (1-4). Infracrveni zraci (engl. *infrared*) nisu vidljivi i predstavljaju elektromagnetne talase dužine od 700 nm do 1 mm (1,4). Ovu energiju osećamo kao toplotu. Sa druge strane, vidljiva svetlost (engl. *visible light* - VIS) je elektromagnetno zračenje koje ljudsko oko može da vidi i čija boja (od crvene do ljubičaste) zavisi od talasne dužine zraka (400-700 nm). Ona čini skoro polovinu sunčevog zračenja.

Plava svetlost (engl. *blue light*) je deo vidljive svetlosti čiji su zraci talasnih dužina između 400 i 500 nm. Ova svetlost se naziva i visokoenergetskom vidljivom svetlošću (engl. *high energy visible light* - HEV) jer u celom spektru vidljive svetlosti ima zrake najkraćih talasnih dužina, ali i najveće energije (2). Poslednjih godina istraživanja ukazuju na njen značaj za oksidativni stres i fotostarenje, kao i na druge neželjene efekte za kožu. Istraživanja vezana za plavu svetlost privlače sve veću pažnju zbog dodatnog izlaganja ljudi ovoj svetlosti kroz različite veštačke izvore kao posledica sve češće upotrebe mobilnih telefona, računara, laptopova, televizora, unutrašnjeg osvetljenja, itd. (2-6).

Uočeno je da plava svetlost utiče na cirkadijalni ritam i samim tim indirektno na kožu. Određen napredak u proučavanju bioloških efekata plave svetlosti je postignut, ali kompletan spektar, tačna priroda i mehanizam delovanja su i dalje nepoznati (1-5). Poslednjih decenija menja se učestalost

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REVIEW PAPER

THE INFLUENCE OF BLUE LIGHT FROM NATURAL AND ARTIFICIAL SOURCES ON THE SKIN

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SUMMARY

Blue light includes rays of lower energy in comparison to UV radiation, but it has a greater power of penetrating the dermis, even to a depth of 1mm. The aim of this review article was to analyze the biological effects of natural and artificial blue light on the skin based on the available literature, as well as to propose preventive measures in order to protect the skin from its harmful effects. The latest research has shown that blue light has various direct and indirect effects on the skin. The direct effects of blue light on the skin are the excessive creation of reactive oxygen species, nitrogen and hyperpigmentation, and it indirectly affects the skin by disrupting the circadian rhythm and secreting melatonin. Blue light has a direct effect on chromophores that are present in the skin and leads to their activation. Their activation leads to the excessive production of reactive oxygen species and release of reactive nitrogen species, that is, nitrogen monoxide (NO), which triggers melanogenesis and hyperpigmentation. Also, there comes to the decrease in cell vitality and/or proliferation of keratinocytes and melanocytes, then increased synthesis of pro-inflammatory interleukins and tumor necrosis factor alpha and altered collagen metabolism. Blue light reduces the antioxidative protection of the skin by causing the degradation of present carotenoids. It can be used in clinical practice in the prevention and treatment of certain dermatoses, as well as in photorejuvenation treatments in aesthetic medicine. Further research in this field is necessary.

Key words: blue light, skin, prevention

Introduction

The sun emits visible and invisible light. Ultraviolet radiation (UV) (wavelength 280-400 nm) is invisible and makes up 3-7% of the sun's spectrum, but despite this, its effect on the skin is the most researched. Ultraviolet rays A, B and C are distinguished within this part of the solar radiation (1-4). Infrared rays are not visible and they represent electromagnetic waves with a length of 700 nm to 1 mm (1,4). We feel this energy as heat. On the other hand, visible light (VIS) is electromagnetic radiation that the human eye can see and whose color (from red to violet) depends on the wavelength of the rays (400-700 nm). It makes up almost half of the solar radiation.

Blue light is a part of visible light whose rays have wavelength between 400 and 500 nm. This light is also called high energy visible light (HEVL) because it has rays of the shortest wavelengths, but also of the highest energy in the whole spectrum of visible light (2). In recent years, research has pointed to its importance for oxidative stress and photoaging, as well as other unwanted effects for the skin. The research related to blue light is attracting more and more attention due to the additional exposure of people to this light through various artificial sources as the result of more frequent use of mobile phones, computers, laptops, televisions, indoor lighting, etc. (2-6).

It has been noticed that blue light affects the circadian rhythm and thus indirectly affects the skin. Some progress in the study of the biological effects of blue light has been achieved, but the

i intenzitet izlaganju plavoj svetlosti, zbog čega se nameće pitanje da li trenutne doze kojima je čovek izložen na dnevnom nivou mogu intenzivirati neželjene efekte plave svetlosti na kožu.

Cilj ovog preglednog rada je bio da se na osnovu dostupne literature analiziraju biološki efekti prirodne i veštačke plave svetlosti na kožu, kao i da se predlože preventivne mere za zaštitu kože od njenih štetnih efekata.

Metode

Ovim preglednim radom obuhvaćena su istraživanja dobijena pretraživanjem literature putem *PubMed* baze na osnovu sledećih ključnih reči: „plava svetlost“, i „koža“, ili „veštačka plava svetlost“ i „koža“. Pretraživanjem je obuhvaćen period od deset godina (od 2014. do 2023. godine). Na osnovu pretraživanja literature identifikovano je 766 publikovanih radova. Kriterijumi za izbor literture za uključivanje u pregledni rad su bili: tekstovi koji su ispitivali vezu između kože i plave svetlosti, objavljeni na engleskom jeziku i koji su bili u celosti dostupni. Kriterijumi za isključivanje su bili: tekstovi koji nisi ispitivali vezu između kože i plave svetlosti, tekstovi u kojima su istraživanja sprovođena na životinjama i tekstovi koji nisu bili napisani na engleskom jeziku. Takođe, pretražena je i citirana literatura svakog izabranog rada, a potom su oni koji zadovoljavaju kriterijume uključeni u pregledni rad.

Direktni i indirektni uticaj plave svetlosti na kožu

Do skoro se smatralo da VIS i konkretno plava svetlost, nemaju uticaj na kožu. Međutim, novije studije ukazuju da plava svetlost ima različite direktne i indirektne efekte na kožu (1-4, 6,7). Direktni efekti plave svetlosti na kožu su prekomerno stvaranje reaktogenih vrsta kiseonika, azota i hiperpigmentacija, a indirektni je poremećaj cikardijalnog ritma.

Plava svetlost ima direktan uticaj na melanogenezu (proizvodnja melanina pod kontrolom tirozinaze), dovodi do njenog indukovanja, izaziva hiperpigmentaciju, pojavu melazme i staračkih pega (1,2). U studiji na 22 zdrava humana dobrovoljaca utvrđeno je da plava svetlost dovodi do pojave hiperpigmentacije, koja je tamnija i duže ostaje na koži, nego ona koja nastaje pod uticajem UV zračenja (1,8). Takođe, odmah dolazi do pojave eritema, koji bledi nakon trideset minuta i potpuno nestaje nakon 2 sata. To znači da kao posledica apsorpcije plave svetlosti od strane pigmenta melanina dolazi do oslobađanja toplote koja vodi vazodilataciji krvnih sudova i pojave eritema (8). Međutim pigmentacija izazvana UV zračenjem je u početku sive boje, a nakon 24 sata prelazi u braon boju i nije okružena eritemom ni u jednom trenutku. Izlaganje opsina 3 (OPN3) u melanocitima plavoj svetlosti dovodi do povećanja fluksa kalcijuma i pokretanja signalne kaskadne rekacije koja uključuje kalcijum-zavisno aktiviranje protein-kinaza, fosforilacije transkripcionog faktora povezanog s mikroftalmijom (MITF) i posledično do povećane sinteze ključnih enzima melanogeneze – tirozinaze i dopahrom tautomeraze koji dovode do formiranja proteinskih kompleksa (tirozinaza-dopahrom tautomeraza kompleks) odgovornih za produženu, perzistentnu pigmentaciju (7). Kod osoba sa tamnijom puti (Fitzpatrick tipovi III-VI) nakon izlaganja kože plavoj svetlosti dolazi do formiranja većeg broja pomenutih proteinskih kompleksa koji dovode do produžene aktivnosti tirozinaze (čime se objašnjava perzistentna, dugotrajna hiperpigmentacija), u odnosu na osobe svetlije puti (Fitzpatrick tip I i II) (2,7,9).

Plava svetlost ima direktan uticaj na hromofore (flavini, porfirini, nitrozovani proteini i opsini) koje su prisutne u koži i aktivira ih. Aktivacija pomenutih hromofora dovodi do prekomerne proizvodnje reaktivnih vrsta kiseonika (engl. *reactive oxygen species*, ROS) i oslobađanja reaktivnih vrsta azota, odnosno azot monoksida (NO). Generisane ROS dovode do pokretanja melanogeneze i pojave hiperpigmentacija (10). Pokazano je da ceo spektar plave svetlosti izaziva prekomerno stvaranje ROS u kultivisanim ljudskim keratinocitima i melanocitima, kao i kod humanih dobrovoljaca (1). Glavne hromofore odgovorne za prekomernu sintezu ROS jesu flavini u mitohondrijama (flavin adenin dinukleotid-FAD i flavin mononukleotid-FMN) i porfirin, odnosno hem (10).

Stvoreni ROS izazivaju oksidativna oštećenja u koži, oštećenja DNK, smanjuju ekspresiju gena koji regulišu funkciju mitohondrija, pa čak kod humanih keratinocita kao klastogeni i aneugeni mogu izazvati aberaciju (1,2). Povećana produkcija ROS izazvana plavim svetlom je povezana i sa smanjenom vitalnošću ćelija i/ili proliferacijom keratinocita i melanocita (supresijom ekspresije gena uključenih u proliferaciju), zatim povećanom proinflamator-

complete spectrum, exact nature and mechanism of action are still unknown (1-5). In recent decades, the frequency and intensity of exposure to blue light has changed, which raises the question of whether the current doses to which humans are exposed on a daily basis can intensify the unwanted effects of blue light on the skin.

The aim of this review article was to analyze the biological effects of natural and artificial blue light on the skin based on the available literature, as well as to propose preventive measures to protect the skin from its harmful effects.

Methods

This review article included the research that was obtained by searching the literature through the PubMed database based on the following key words: "blue light" and "skin", or "artificial blue light" and "skin". The search covered the ten-year period (from 2014 to 2023). Based on the literature search, 766 published papers were identified. The inclusion criteria for the selection of literature in this review article were the following: texts that examined the connection between the skin and blue light, published in English with full texts available. The exclusion criteria were the following: texts that did not examine the connection between the skin and blue light, texts in which research was conducted on animals and texts that were not written in English. Also, the literature of each selected paper was searched and cited, and then those texts that met the criteria were included in the review article.

Direct and indirect effects of blue light on the skin

It has been considered until recently that VIS and specifically blue light have no effect on the skin. However, recent studies have pointed that blue light has various direct and indirect effects on the skin (1-4, 6,7). The direct effects of blue light on the skin are the excessive creation of reactive oxygen species, nitrogen and hyperpigmentation, while the indirect effects include the disruption of the circadian rhythm.

Blue light has a direct effect on melanogenesis (melanin production under the control of tyrosinase), leads to its induction, causes hyperpigmentation, the appearance of melasma and age spots (1,2). In the study of 22 healthy human volunteers, it was found that blue light leads to the appearance of hyperpigmentation, which is darker and lasts longer on the skin than that which appears under the influence of UV radiation (1,8). Also, erythema appears immediately, fades after thirty minutes and disappears completely after 2 hours. This means that heat is released as the result of the absorption of blue light by melanin pigment, which leads to the vasodilatation of blood vessels and the appearance of erythema (8). However, the pigmentation caused by UV radiation is grey in the beginning, and after 24 hours it turns brown and is not surrounded by erythema at all. The exposure of opsin 3 (OPN3) in melanocytes to blue light leads to an increase in calcium flux and the initiation of signaling cascade reaction that includes calcium-dependent activation of protein kinase, phosphorylation of microphthalmia-associated transcription factor (MITF), resulting in the increased synthesis of key enzymes of melanogenesis – tyrosinase and dopachrome tautomerase which lead to the formation of protein complexes (tyrosinase-dopachrome tautomerase complex) that are responsible for the prolonged, persistent pigmentation (7). In people with darker skin (Fitzpatrick types III-IV), after exposure of the skin to blue light, a greater number of the above mentioned complexes are formed, which lead to the prolonged activity of tyrosinase (which0 explains the persistent, long-lasting hyperpigmentation), in comparison to people with lighter skin (Fitzpatrick type I and II) (2,7,9).

Blue light has a direct effect on the chromophores (flavins, porphyrins, nitrosated proteins and opsins) present in the skin and activates them. The activation of the mentioned chromophores leads to the excessive production of reactive oxygen species (ROS) and the release of reactive nitrogen species, that is, nitrogen monoxide (NO). Generated ROS lead to the initiation of melanogenesis and the appearance of hyperpigmentation (10). It has been shown that the entire spectrum of blue light causes the excessive production of ROS in cultured human keratinocytes and melanocytes, as well as in human volunteers (1). The main chromophores responsible for the excessive ROS synthesis are flavins in mitochondria (flavin adenine dinucleotide-FAD and flavin mononucleotide-FMN) and porphyrin, that is, heme (10).

The created ROS create oxidative damage in the skin, DNA damage, reduce the expression of genes

nom signalizacijom (povećava se sinteza proinflamatornih interleukina IL-6, IL-8 IL-1α i faktora nekroze tumora alfa, TNFα) i izmenjenim metabolizmom kolagena (smanjena sinteza prokolagena 1, smanjena kontraktilnost kolagenih vlakana) (1). Dodatno, plava svetlost dovodi do povećane ekspresije matriksnih metaloproteinaza (MMP-1 i 9) i njihovog oslobađanja koje dovodi do razgradnje prisutnog kolagena, sprečavanja reparacije prisutnih i sinteze novih kolagenih vlakana (1,2). Generisanju ROS doprinosi i činjenica da plava svetlost smanjuje antioksidativnu zaštitu kože izazivajući razgradnju prisutnih karotenoida (11). Plava svetlost, naročito ona niže talasne dužine (ispod 453 nm), izaziva oksidativni stres u opsegu koji je ekvivalent 25% oksidativnog stresa izazvanog UVA zračenjem (3). Za oksidativni stres su odgovorni fotosenzitivni proteini flavini koji dovode do stvaranja superoksidnog anjona (O_2^-) – glavnog slobodnog radikala u ovom procesu (12). Takođe, dokazano je u *in vitro*, *in vivo* i *ex vivo* studijama da doprinose i fotostarenju kože (2,13).

Međutim, plava svetlost preko uticaja na cirkadijalni ritam i lučenje melatonina, može indirektno uticati i na kožu. Melatonin, hormon koji luči epifiza, je snažan antioksidans, „hvatač" ROS i stimulator ekspresije gena enzima uključenih u antioksidativni potencijal kože. Kroz ovu antioksidativnu aktivnost, melatonin smanjuje negativan uticaj UV zračenja na kožu, sprečava DNK oštećenja i štiti mitohondrije. Melatonin stimuliše zarastanje rana, ima anti-inflamatorni efekat, utiče na proliferaciju keratinocita i rast kose i može inhibirati melanogenezu i apoptozu, zbog čega se smatra jedinjenjem koje umanjuje znake starenja (engl. *anti-aging*). Njegova koncentracija u telu starenjem opada, kao i razlika u lučenju melatonina tokom noći i dana, zbog čega plava svetlost ima mnogo veći uticaj na mlađu populaciju u odnosu na stariju (14).

Pomenuti efekat na cirkadijalni ritam uključuje stimulaciju senzora svetlosti koji se nalaze u retini oka (centralni mehanizam), kao i periferni mehanizam koji podrazumeva direktnu interakciju sa ćelijama kože. Narušavanjem normalnog cirkadijalnog ritma, plava svetlost može negativno uticati na procese obnavljanja kože koji se odvijaju tokom noći (1,15). Brojne studije su pokazale da plava svetlost talasnih dužina između 459 i 484 nm dovodi do stimulacije melanopsina, hromofore iz grupe proteina opsina prisutnih u retini oka koji su odgovorni za prilagođavanje cirkadijalnog ritma tela ciklusu svetlo/mrak, ukazujući na činjenicu da bi plava svetlost iz veštačkih izvora (digitalni/elektronski uređaji) mogla ometati normalni cirkadijalni ritam, pa samim tim imati uticaj i na fiziološke funkcije kože (10,15). Pokazano je da cirkadijalni ritam ima uticaj na pojedine fiziološke procese u koži. Tako su brzina protoka krvi kroz kožu, propustljivost kože za hidrofilna i lipofilna jedinjenja i transepidermalni gubitak vode veći uveče i tokom noći nego tokom dana, dok je temperatura kože i aktivnost sebacealnih žlezda najveća tokom dana, a opada uveče i tokom noći. Takođe, najintenzivnija proliferacija keatinocita vrši se tokom noći, preciznije oko ponoći (15).

Uticaj plave svetlosti iz veštačkih izvora na kožu

Duteil i saradnici su upoređivali intenzitet plave svetlosti koju emituju digitalni monitori sa intenzitetom plave svetlosti koju emituje sunce, a zatim u *in vivo* studiji na 12 humanih dobrovoljaca (Fitzpatrick tipovi III i IV) procenili uticaj veštačke plave svetlosti na pigmentaciju kože. Ispitivana talasna dužina zraka bila je u opsegu one koju inače emituju digitalni uređaji (mobilni telefoni, računari, televizori) – između 420 i 490 nm, sa pikom u intervalu od 440 do 460 nm, u zavisnosti od uređaja. Zaključeno je da sunce emituje 100 do 1000 puta više plave svetlosti od testiranih digitalnih uređaja. Intenzitet svetlosti je najveći za sunce, a zatim za TV, ekran računara, ekran laptopa, a najmanji za mobilni telefon. Dalje, u *in vivo* studiji u kojoj je vršena procena uticaja veštačke svetlosti na pigmentacije na koži, polovina lica ispitnika je bila izložena plavoj svetlosti simulatora ksenonske svetlosti filtriranog da emituje isti spektar kao ekrani uređaja, a druga polovina lica bila je potpuno zaštićena. Izlaganje je trajalo 8 sati dnevno, 5 uzastopnih dana, nakon čega su upoređivane pigmentne promene na obe polovine lica. Autori su zaključili da izlaganje plavoj svetlosti koju emituju digitalni monitori 8 sati dnevno tokom 5 uzastopnih dana ne dovodi do pogoršanja pigmentnih promena ili do pogoršanja melazme (16). *Ceresnie* i sar. su došli do sličnih zaključaka - nema ni *in vitro* ni *in vivo* dokaza koji bi upućivali da izloženost plavoj svetlosti elektronskih uređaja može dovesti do pigmentacije kože, crvenila, žutila ili pogoršanje melazme. Takođe, izloženost plavoj svetlosti elektronskih uređaja nije klasifikovana kao faktor koji

that regulate mitochondrial function, and even in human keratinocytes as clastogenic and aneugenic can cause aberration (1,2). The increased production of ROS caused by blue light is associated with decreased cell vitality and/or proliferation of keratinocytes and melanocytes (suppression of the expression of genes that are involved in the proliferation), then increased pro-inflammatory signaling (increased synthesis of pro-inflammatory interleukins IL-6, IL-8, IL-1α and tumor necrosis factor alpha, TNFα), and altered collagen metabolism (reduced synthesis of procollagen 1, reduced contractility of collagen fibers) (1). In addition, blue light leads to the increased expression of matrix metalloproteinases (MMP-1 and 9) and their release, which leads to the degradation of the present collagen, preventing the repair of the present and the synthesis of new collagen fibers (1,2). The fact that blue light reduces the antioxidative protection of skin causing the degradation of present carotenoids also contributes to the generation of ROS (11). Blue light, especially that of lower wavelengths (below 453 nm), causes oxidative stress in a range equivalent to 25% of the oxidative stress caused by UVA radiation (3). Photosensitive proteins flavins, which lead to the creation of superoxide anion (O2-) as the main free radical in this process, are responsible for oxidative stress (12). It has also been proven in *in vitro*, *in vivo* and *ex vivo* studies that they contribute to skin photoaging (2,13).

However, blue light can indirectly influence the skin by affecting the circadian rhythm and melatonin secretion. Melatonin, a hormone that is secreted by the pineal gland, is a powerful antioxidant, ROS "catcher" and stimulator of gene expression of enzymes involved in the antioxidative potential of the skin. Through this antioxidant activity, melatonin reduces the negative effect of UV radiation on the skin, prevents DNA damage and protects mitochondria. Melatonin stimulates healing of wounds, has an anti-inflammatory effect, affects the proliferation of keratinocytes and hair growth, and can inhibit melanogenesis and apoptosis, and therefore, it is considered to be the compound that reduces the signs of aging. Its concentration in the body decreases with age, as well as the difference in the secretion of melatonin during night and day, which is why blue light has a much greater effect on the younger population in comparison to the elderly (14).

The above mentioned effect on the circadian rhythm includes the stimulation of the light sensors located in the retina of the eye (central mechanism), as well as the peripheral mechanism, which involves direct interaction with skin cells. By disrupting the normal circadian rhythm, blue light can negatively affect skin renewal processes that take place at night (1,15). Numerous studies have shown that blue light with wavelengths between 459 and 484 nm leads to the stimulation of melanopsin, a chromophore from the group of opsin proteins present in the retina of the eye that is responsible for adjusting the circadian rhythm to the cycle light/dark, pointing to the fact that blue light from artificial sources (digital/electronic devices) could disrupt the normal circadian rhythm, and thus have an effect on the physiological functions of the skin (10,15). It has been shown that the circadian rhythm has an influence on certain physiological processes in the skin. Thus, the speed of blood flow through the skin, permeability of the skin for hydrophilic and lipophilic compounds and transepidermal loss of water are higher in the evening and during the night than during the day, while the skin temperature and the activity of the sebaceous glands are highest during the day and decrease in the evening and during the night. Also, the most intensive proliferation of keratinocytes takes place during the night, more precisely around midnight (15).

The effect of blue light from artificial sources on the skin

Duteil and associates compared the intensity of blue light emitted by digital monitors with the intensity of blue light emitted by the sun, and then in in vivo study on 12 human volunteers (Fitzpatrick types III and IV) estimated the impact of artificial blue light on skin pigmentation. The investigated wavelength of rays was in the range of that which is normally emitted by digital devices (mobile phones, computers, televisions) – between 420 and 490 nm, with a peak in the interval from 440 to 460 nm, depending on the device. It was concluded that the sun emits 100 to 1000 times more blue light than the tested digital devices. The light intensity is the highest for the sun, followed by TV, computer screen, laptop screen, while the lowest is for mobile phones. Furthermore, in one in vivo study, in which the impact of artificial light on skin

dovodi do fotostarenja kože (17). Međutim, uticaj ovih uređaja na kožu tokom dužeg vremenskog perioda se još uvek ne zna i ne može se isključiti.

Uticaj plave svetlosti na prirodni ciklus sna

Cirkadijalni ritam ili prirodni ciklus sna se odnosi na endogeni 24-časovni fiziološki, metabolički ritam i ritam ponašanja ljudskog tela i pod značajnim je uticajem plave svetlosti (6,15). Glavni regulator cirkadijalog ritma je hormon melatonin i njegovo lučenje nije isto u toku 24 časa, već je povećano noću, a smanjeno tokom dana. Izlaganje plavoj svetlosti dovodi do akutnog pada nivoa melatonina, kao posledica smanjenja njegove sinteze. Takođe, povećana upotreba digitalnih uređaja poput laptopova i telefona, naročito upotreba do kasno u noć, ometa cirkadijalni ritam tela i utiče na produkciju melatonina, što dovodi do teškoća sa uspavljivanjem i pospanosti tokom dana (6).

Primena plave svetlosti u dermatologiji i estetskoj medicini

Plava svetlost može se koristiti u dermatologiji i estetskoj medicini. U kliničkoj praksi način korišćenja plave svetlosti (njena talasna dužina i intezitet) zavisi od svrhe ili vrste lečenja. Može se koristi kao samostalan tretman (svetlosna terapija, plava LED terapija) ili deo fotodinamske terapije (2,8). U dermatologiji, preciznije fotodermatologiji, pod kontrolisanim uslovima, plava svetlost se koristi u tretmanu psorijaze, blagih do srednje teških akni, aktiničnih keratoza, atopijskog dermatitisa, ali i u okviru fotorejuvenacije u estetskoj medicini (IPL, engl. *intense pulse light therapy*) (1,2,8). Međutim, treba imati u vidu da se za tretmane plavim svetlom koriste uređaji koji emituju svetlost u kratkom vremenskom periodu (najčešće 15-25 minuta) po sesiji i tretmani obično traju nekoliko nedelja (2).

Zaštita kože od dejstva plave svetlosti

Kada su u pitanju kozmetički proizvodi, poslednjih nekoliko godina povećao se broj dostupnih sastojaka za koje se tvrdi da štite kožu od plave svetlosti (18). Kako je plava svetlost deo sunčeve svetlosti, prva linija zaštite jesu organski i neorganski/fizički filteri - sastojci koji pružaju zaštitu kože od sunčevog zračenja. Međutim, svega dva organska filtera imaju širok spektar zaštite i efikasni su protiv plave svetlosti: fenilen bis-difeniltriazin (INCI: *Phenylene Bis-Diphenyltriazine)* i metilen bis-benzotriazolol tetrametilbutilfenol (INCI: *Methylene Bis-Benzotriazolyl Tetramethylbutylphenol*) (14,19). Što se tiče neorganskih/fizičkih filtera, titan dioksid i cink oksid veličine čestica preko 200 nm reflektuju, rasipaju i delom absorbuju vidljivu svetlost i efikasni su u zaštiti kože od plave svetlosti (7,20), ali se dovode u pitanje senzorne karakteristike ovih proizvoda (beli trag na koži) naročito nakon primene kod korisnika tamnije puti. Dalje, oksidi gvožđa – neorganski pigmenti u sastavu proizvoda dekorativne kozmetike (tečni puderi, tonirane kreme), sami ili u kombinaciji sa neorganskim/fizičkim filterima, takođe pružaju zaštitu od plave svetlosti. Dodatnu zaštitu od plave svetlosti pružaju i antioksidansi koji sprečavaju generisanje ROS: biljni ekstrakti (ekstrakt ploda brusnice, zimske trešnje (ašvagande), đumbira, pirinča, nevena, semena kakaa, ploda i semena šargarepe), zatim izolovani biljni karotenoidi (beta karoten, lutein, likopen), niacinamid i pojedine alge (18). Kao novije aktivne supstance koje pružaju zaštitu od plave svetlosti pominju se i one koje imaju aktivnost sličnu melatoninu (engl. *melatonin-like ingredient*), poput ekstrakta ploda gardenije (14).

Ipak, najbolja strategija zaštite bi bila izbegavanje izlaganja sunčevoj svetlosti tokom dana, smanjen uticaj plave svetlosti na cirkadijalni ritam tokom noći, korišćenje kozmetičkih proizvoda za zaštitu kože od sunca sa filterima širokog spektra tokom dana i sa sastojcima koji imaju uticaj na uklanjanje nastalih promena na koži tokom noći (sastojci koji deluju depigmentišuće, podstiču sintezu kolagena i antioksidansi).

Zaključak

Plava svetlost ima različite direktne i indirektne efekete na kožu koji zavise od talasne dužine i intenziteta izlaganja. Plava svetlost se može koristiti u kliničkoj praksi pod kontrolisanim uslovima u prevenciji i tretmanu određenih dermatoza, kao i u tretmanima fotorejuvenacije u estetskoj medicini. Međutim, treba imati u vidu da pored korisnih, plava svetlost iz prirodnih i veštačkih izvora ima i štetne efekte na kožu. Iako je uticaj prirodne plave svetlosti svakako značajniji u odnosu na uticaj svetlosti iz veštačkih izvora, kako će izloženost veštačkoj plavoj svetlosti verovatno nastaviti da raste, potrebna su opsežnija i dugotrajnija ispitivanja u ovoj oblasti.

pigmentation was evaluated, half of the examinee's face was exposed to the blue light of a xenon light simulator, which was filtered to emit the same spectrum as the device's screens, and the other half of the face was completely protected. The exposure lasted 8 hours a day, for 5 consecutive days, after which the pigment changes on both halves of the face were compared. The authors concluded that exposure to blue light emitted by digital monitors 8 hours a day, for 5 consecutive days did not lead to worsening of pigment changes or worsening of melasma (16). Ceresnie and associates came to similar conclusions – there was no *in vitro* and *in vivo* evidence that exposure to blue light from electronic devices can lead to skin pigmentation, redness, yellowing or worsening of melasma. Also, exposure to blue light from electronic devices was not classified as a factor that leads to photoaging of the skin (17). However, the influence of these devices on the skin over a longer period of time has not been known so far and cannot be excluded.

The influence of blue light on the natural sleep cycle

Circadian rhythm or natural sleep cycle refers to the endogenous 24-hour physiological metabolic and behavioral rhythm of the human body and it is significantly influenced by blue light (6,15). The main regulator of the circadian rhythm is the hormone melatonin, and its secretion is not the same during 24 hours, but it increases at night, and decreases during the day. The exposure to blue light leads to an acute decrease in the level of melatonin, as the consequence of its decreased synthesis. Also, the increased use of digital devices, such as laptops and mobile phones, especially late at night, disrupts the circadian rhythm and influences the production of melatonin, which leads to difficulties related to falling asleep and daytime sleepiness (6).

The application of blue light in dermatology and aesthetic medicine

Blue light can be used in dermatology and aesthetic medicine. In clinical practice, the way in which blue light is used (its wavelength and intensity) depends on the purpose or type of treatment. It can be used as an independent treatment (light therapy, blue LED therapy) or as part of photodynamic therapy (2,8). In dermatology, more precisely, in photodermatology, under controlled conditions, blue light is used for the treatment of psoriasis, mild to moderately severe acne, actinic keratoses, atopic dermatitis, as well as in photorejuvenation in aesthetic medicine (intense pulse light therapy, IPL). (1,2,8). However, one should have in mind that devices, which emit light for a short period of time (mostly 15-25 minutes) per session, are used in blue light treatments, and these treatments usually last for several weeks (2).

The protection of the skin from the effects of blue light

When it comes to beauty products, the number of available ingredients, which are claimed to protect the skin from blue light, has increased in the last years (18). Since blue light is part of sunlight, the first line of defense includes organic and inorganic/physical filters – ingredients that protect the skin from solar radiation. However, only two organic filters have a wide range of protection and are effective against blue light: Phenylene Bis-Diphenyltriazine and Methylene Bis-Benzotriazolyl Tetramethylbutylphenol (14,19). As far as inorganic/physical filters are concerned, titanium dioxide and zinc oxide that have particles over 200 nm reflect, scatter and partially absorb visible light and are effective in protecting the skin from blue light (7,20), but the sensory characteristics of these products are questioned (white marks on the skin), especially when they are applied by people with darker skin. Furthermore, iron oxides – inorganic pigments that are ingredients of beauty products (liquid powders, tinted creams), alone or in combination with inorganic/physical filters also have protection against blue light. Additional protection from blue light is also provided by antioxidants that prevent the production of ROS: plant extracts (cranberry extract, winter cherry – ashwagandha, ginger, rice, calendula, cocoa seeds, carrot root extract and its seeds), then isolated plant carotenoids (beta carotene, lutein, lycopene), niacinamide and certain algae (18). Some new active substances that provide the protection from blue light are mentioned, and they are melatonin-like ingredients, such as gardenia fruit extract (14).

However, the best protection strategy would be to avoid exposure to sunlight during the day, and reduce the impact of blue light on the circadian rhythm during the night, to use cosmetic

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Autori su izjavili da nema konflikta interesa.

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products with broad-spectrum filters during the day which protect the skin from the sun and which have ingredients that have the effect of removing the changes on the skin during the night (ingredients that have depigmenting effects, stimulate collagen synthesis and antioxidants).

Conclusion

Blue light has a variety of direct and indirect effects on the skin that depend on the wavelength and intensity of exposure. Blue light can be used in clinical practice under controlled conditions in the prevention and treatment of certain dermatoses, as well as in photorejuvenation and treatments in aesthetic medicine. However, it should be kept in mind that despite its useful effects, blue light from natural and artificial sources also has harmful effects on the skin. Although the influence of natural blue light is certainly more important than the influence of light from artificial sources, more extensive and long-term research in this field is needed since the exposure to artificial blue light will probably continue to increase.

Competing interests

The authors declared no competing interests.

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Acknowledgments should be given to all contributors who have contributed to the realization of the work but who haven't met the criteria for authorship, as well as to all those who have financially and materially assisted in the realization of the research.

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