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EDITORIJAL



„Umetnost i nauka postavljanja pitanja su izvor svakog znanja.”

Isak Njutn

Poštovane kolegice i kolege,

U uslovima veoma dinamičnih globalnih dešavanja punim izazova, Uredništvo „Srpskog medicinskog časopisa Lekarske komore“, uspešno i sa neprekinutim entuzijazmom, nastavlja planirane aktivnosti unapređenja njegovog kvaliteta i naučno-stručnog kredibiliteta. Ove aktivnosti, razume se, ne bi bile moguće bez neumorne i stalne podrške Regionalne lekarske komore Beograda i Lekarske komore Srbije, niti bez poštovanja visokih naučnih i etičkih standarda prilikom odabira i objavljivanja radova.

Kao što je poznato, naš Časopis je, od kraja prošle godine, dobio zvaničnu kategorizaciju kao časopis od nacionalnog značaja (M54) u Republici Srbiji. Ovo je, naravno, samo prvi, ali neophodni korak u njegovom naučnom vrednovanju i pozicioniranju u spektru domaćih i regionalnih medicinskih publikacija. Bibliometrijske analize koje su sprovedli naši strateški partneri i odgovorne državne institucije, uz nezamenljivi doprinos svih naši autora, saradnika, recenzenata i čitalaca u tom zajedničkom naporu, daju nam za pravo da sa optimizmom očekujemo dalji brz i kvalitetan napredak, kako u razvoju samog Časopisa, tako i u njegovoj stručno-naučnoj validnosti.

I u ovom broju Časopisa vam predstavljamo radove koji obrađuju različite aktuelne teme, počev od javnozdravstvenih (bezbednost pacijenata, izazovi evropske integracije u sferi zdravstva, vakcinacija učenika protiv humanog papiloma virusa, kvalitet ishrane radnika), preko medicinski specifičnih (nejasna febrilna stanja, prognostički značaj prevremenog porođaja, preoperativno zbrinjavanje rizičnih hirurških pacijenata), do veoma interesantnih prikaza zahtevnih kliničkih slučajeva (rešavanje teških mekotiivnih defekata posle operacije sarkoma, anafilaksa usled imunoterapije). Na kraju, predstavljamo vam i prikaz nove knjige „Odabrana poglavlja iz pulmologije”.

Rad po pozivu „Suočavanje sa neizvesnim i složenim situacijama: podrška zdravstvenim radnicima u rešavanju izazova bezbednosti pacijenata” autora Hosea Hoakin Mire, bavi se neželjenim događajima, koji često imaju sistemski uzrok, što znači da mogu biti rezultat kombinacije organizacionih, kulturnih i faktora sredine. Uprkos najvećim naporima zdravstvenih radnika da pruže visokokvalitetne usluge, neočekivani neželjeni događaji mogu uticati na pacijenta. I pacijentima i zdravstvenim radnicima može biti teško da se nose sa ovim događajima, pogotovo kada oni dovode do teške povrede pacijenta.

Originalni rad „Prednosti i nedostaci integracije u Evropsku uniju: istraživanje među studentima prve godine medicine u Srbiji” Milene Šantrić-Milićević i saradnika, sumira rezultate istraživanja faktora po-

EDITORIAL

"The art and science of asking questions is the source of all knowledge."
Isaac Newton

Dear colleagues,

In circumstances of challenging and very dynamic global events, the Editorial Board of the *Serbian Journal of the Medical Chamber*, successfully and with undiminished enthusiasm, continues the planned activities of improving its quality and scientific and professional credibility. It goes without saying that these activities would not be possible without the unwavering and constant support of the Regional Medical Chamber of Belgrade and the Medical Chamber of Serbia, nor without respect for high scientific and ethical standards in selecting and publishing articles.

As is already known, late last year, our Journal was officially classified as a journal of national significance (M54) in the Republic of Serbia. This is, of course, only the first but necessary step in its scientific recognition and positioning within the spectrum of domestic and regional medical publications. The bibliometric analyses carried out by our strategic partners and competent government institutions, along with the irreplaceable contribution and joint effort of all our authors, associates, reviewers, and readers, justify our optimism in expecting further swift and positive progress, both in the development of the Journal itself, as well as in its professional and scientific validity.

As always, in this issue of the Journal as well, we present articles dealing with various currently relevant topics – from issues focused on public health (patient safety, challenges of European integration in the field of health, vaccination of students against the human papillomavirus, the quality of workers' nutrition), to specific medical issues (fever of unknown origin, prognostic significance of premature birth, preoperative care of high-risk surgical patients), and very interesting presentations of challenging clinical cases (resolving severe soft tissue defects after sarcoma surgery, anaphylaxis due to immunotherapy). Finally, we present the review of a new book – *Selected Chapters in Pulmonology*.

The invited paper *Navigating Uncertainty and Complexity: Understanding Healthcare Professionals in Addressing Patient Safety Challenges* by Jose Joaquin Mira deals with adverse events that often have a systemic cause, meaning they can result from a combination of organizational, cultural, and environmental factors. Despite the best efforts of healthcare providers to deliver high-quality care, unexpected adverse events can affect a patient. These events can be difficult for both patients and healthcare providers to deal with, particularly when they result in severe harm to the patient.

The original paper *Advantages and disadvantages of integration into the European Union: a survey among medical freshmen in Serbia* by Milena Šantrić-Miličević et al., summarizes the results of research identifying factors associated with pro-integration attitudes to the European Union (EU) among medical freshmen in

vezanih sa pozitivnim stavom prema pristupu Evropskoj uniji (EU) među studentima prve godine medicine u Srbiji. Zaključak autora nedvosmisleno ističe potrebu jače međunarodne inicijative EU i domaćih aktera u promociji integracionog stava i kreiranja uslova za smanjenje emigracije mladih lekara.

Autor originalnog rada „Korišćenje *bejbi frendli* usluga u porodilištima u Srbiji“, Mirjana Živković-Šulović, bavi se istraživanjem faktora koji utiču na unapređenje dojenja u skladu sa preporukama Svetske zdravstvene organizacije za savetovanje o dojenju, korišćenjem podataka dobijenih iz studije *Multiple Indicator Cluster Survey 6 (MICS 6)* za opšti (nacionalni) i za uzorak romske etničke grupe, u Srbiji, 2019. godine.

U svom originalnom radu „Determinante namere vakcinisanja protiv humanog papiloma virusa kod učenika“, Mirjana Milošević-Gačević i Sandra Petrović ističu da se najjači prediktor namere vakcinisanja protiv HPV-a kod mladih odnosi na subjektivnu normu, odnosno društveni pritisak vršnjaka i drugih osoba koje su za njih značajne. Nepoverenje u korisnost vakcinacije, zabrinutost zbog komercijalnog profiterstva i uverenja o zaveri o vakcinama, imaju značajno manji, ali statistički važan doprinos.

Luka Ilić i Aleksandar Jeremić su, u svom originalnom istraživanju „Septično stanje u diferencijalnoj dijagnozi nejasnog febrilnog stanja“, ispitivali incidenciju septičnog stanja, kao etiološkog uzroka, na kliničkom uzorku pacijenata sa nejasnim febrilnim stanjem. Zaključak studije upućuje na to da u diferencijalnoj dijagnozi nejasnog febrilnog stanja treba uvek razmišljati o potencijalnoj sistemske infekciji kao mogućem uzroku, u sklopu koje septično stanje zauzima veoma važno mesto.

U originalnom radu Smiljane Donić i saradnika, pod naslovom „Uzrok prevremenog porođaja kao prognostički faktor neonatalnog ishoda i načina završavanja porođaja“, autori ističu da značajna učestalost prevremenog porođaja, u odnosu na ukupan broj porođaja, ukazuje na ozbiljnost problema i dalju tendenciju rasta broja prevremenih porođaja i pored primenjenih svih preventivnih mera.

U preglednom radu Svetlane Andjelković i Maje Babić „Ishrana radnika koji rade u noćnoj smeni – razlog ili izgovor za nepravilnu ishranu“, naglašava se da smenski radnici obično doživljavaju razmimoilaženje između svojih dnevnih rutina (uključujući i raspored obroka), kao i onih sa porodicom i prijateljima, što, pored drugih razmatranih faktora, dovodi do još težih poremećaja navika u ishrani.

Autori Ana Anđelković i Stefan Tanasić, u prikazu dva slučaja preoperativne pripreme hirurških pacijenata sa kompleksnim kardiološkim stanjima i oboljenjima, pod naslovom „Perioperativno zbrinjavanje pacijenata sa kardiovaskularnim rizikom u abdominalnoj hirurgiji“, ističu potrebu multidisciplinarnog pristupa, kao i prilagođavanja savremenih smernica individualnim potrebama pacijenta.

Grupa autora, na čelu sa Bojanom Petrovićem, u svom prikazu slučaja pod nazivom „Vezani muskulotani režanj trapeziusa u rekonstrukciji defekta u regiji ramena nakon resekcije mekotkivnog sarkoma – prikaz slučaja i pregled literature“, saopštavaju svoje iskustvo u korišćenju lokalnog miokutanog režnja, koji se retko koristi u praksi u toj regiji u sličnim slučajevima, naglašavajući posebno nedostatak i neujednačenost literaturnih podataka i referenci.

Milan Dimitrijević i saradnici, u radu „Anafilaktički šok izazvan subkutanom imunoterapijom alergenom *Ambrosia elatior* – prikaz slučaja“, prikazuju pacijenta koji je razvio kliničku sliku anafilaktičkog šoka u toku indukcione faze subkutane imunoterapije alergenom (SCIT) ekstraktom polena *Ambrosia-e elatior*, njegov klinički tok kao i brzo i efikasno terapijsko zbrinjavanje ovog životno ugrožavajućeg stanja.

U prikazu knjige „Odabrana poglavlja iz pulmologije“, jedan od njenih autora, Mihailo Stjepanović, vrlo sadržajno i slikovito objašnjava motive i vrednosti ovakvog izdavačkog poduhvata koji je, posle više od 20 godina, popunio prazninu u domaćoj stručnoj literaturi iz ove oblasti medicine.

U ime Uredništva, i u svoje lično ime, želim vam svima dobro zdravlje i uspešan rad

S poštovanjem,
Zamenik glavnog urednika
Profesor dr Goran Tulić

Serbia. The author's conclusion unequivocally emphasizes the need for a stronger international initiative by the EU and national stakeholders in promoting pro-integration attitudes and creating conditions for reducing the emigration of young doctors.

The author of the original article *Utilization of baby-friendly services in maternity wards in Serbia*, Mirjana Živković-Šulović, analyzes the factors affecting the promotion of breastfeeding, using data obtained from the Multiple Indicator Cluster Survey 6 (MICS 6), for the national and the Roma ethnic group sample, in Serbia, in 2019.

In their original article *Determinants of the human papillomavirus (HPV) vaccination intention among students*, Mirjana Milošević-Gačević and Sandra Petrović point out that the strongest predictor of HPV vaccination intention among young people is related to the subjective norm, i.e. social pressure from peers and other persons who are important to them. Distrust of the benefits of vaccination, concerns about commercial profiteering, and vaccine conspiracy beliefs have a significantly smaller but statistically significant contribution.

Luka Ilić and Aleksandar Jeremić, in their original article *Septic state in the differential diagnosis of fever of unknown origin* examined the incidence of septic condition, as an etiological cause, in a clinical sample of patients with fever of unknown origin. The conclusion of the study indicates that in the differential diagnosis of fever of unknown origin, one should always consider a potential systemic infection as a possible cause, wherein the septic condition occupies a very important place.

In the original article by Smiljana Donić et al. *Cause of premature birth as a prognostic factor of neonatal outcome and type of delivery*, the authors point out that the significant frequency of premature birth, as compared to the total number of births, indicates the seriousness of this problem as well as a continued rising trend in the number of premature births, despite all preventive measures.

The review article by Svetlana Andjelković and Maje Babić points out that shift workers usually experience a discrepancy between their daily routines (including the meal schedule) and those they have with family and friends, which further leads to even more severe disorders of dietary habits.

In their presentation of two case reports of preoperative preparation of surgical patients with complex cardiac conditions and diseases *Perioperative management of high-risk cardiovascular patients in abdominal surgery*, Ana Anđelković and Stefan Tanasić emphasize the need for a multidisciplinary approach, as well as for adapting modern guidelines to the individual needs of the patient.

In their case report *Pedicled trapezius musculocutaneous flap in the reconstruction of a shoulder defect after the resection of soft tissue sarcoma – case report and literature review*, a group of authors led by Bojan Petrović report their experience in using a local myocutaneous flap, which is, in clinical practice, rarely used in that region in similar cases, emphasizing, in particular, the lack and inconsistency of literature data and references.

Milan Dimitrijević et al., in their article *Anaphylactic shock caused by subcutaneous immunotherapy with the allergen *Ambrosia elatior* – case report*, present a patient who developed a clinical presentation of anaphylactic shock during the induction phase of subcutaneous allergen immunotherapy (SCIT) with *Ambrosia elatior* pollen extract, his clinical course as well as the rapid and effective therapeutic management of this life-threatening condition.

In the review of the *Selected Chapters in Pulmonology*, one of its authors, Mihailo Stjepanović, very meaningfully and vividly explains the motives and values of such a publishing undertaking, which, after more than 20 years, has filled the gap in the national professional literature in this field of medicine.

On behalf of the Editorial Board and myself, I wish you all good health and success in your work.

Sincerely,
Deputy Editor-in-Chief
Prof. Goran Tulić, MD, PhD

SADRŽAJ

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José Joaquín Mira

SUOČAVANJE SA NEIZVESNIM I SLOŽENIM SITUACIJAMA: PODRŠKA ZDRAVSTVENIM RADNICIMA U REŠAVANJU IZAZOVA BEZBEDNOSTI PACIJENATA

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RAD PO POZIVU

INVITED PAPER

NAVIGATING UNCERTAINTY AND COMPLEXITY: UNDERSTANDING HEALTHCARE PROFESSIONALS IN ADDRESSING PATIENT SAFETY CHALLENGES

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SAŽETAK

Pružanje optimalnog kvaliteta zdravstvene zaštite je izazov za zdravstvene stručnjake i zdravstvene sisteme širom sveta. Pacijenti se često oslanjaju na zdravstvene radnike da im pomognu u njihovim zdravstvenim problemima i da pruže najbezbedniju i najbolju moguću zdravstvenu uslugu. Međutim, uprkos najvećim naporima zdravstvenih radnika da pruže visokokvalitetne usluge, neočekivani neželjeni događaji mogu uticati na pacijenta. I pacijentima i zdravstvenim radnicima može biti teško da se nose sa ovim događajima, pogotovo kada oni dovode do teške povrede pacijenta. Pored fizičkih i psiholoških posledica koje ovi neželjeni događaji mogu ostaviti na pacijentima, zdravstveni radnici takođe mogu biti emocionalno pogođeni. Pružaoci zdravstvenih usluga koji su uključeni u neželjene događaje često se nazivaju *sekundarnim žrtvama*. Na njih ne utiču samo neželjeni događaji koje pacijent doživljava, već i reakcija koju ti događaji mogu izazvati kod drugih članova zdravstvenog tima, kao i izvan i unutar zdravstvene ustanove.

Neželjeni događaji često imaju sistemski uzrok, što znači da mogu biti rezultat kombinacije organizacionih, kulturnih i faktora sredine.

Iako se obično zdravstveni radnik nadležan za lečenje pacijenata, koji je direktno povezan sa štetom nanetom pacijentu izdvaja kao odgovoran, u većini slučajeva postoji niz događaja i zdravstvenih radnika uključenih u neželjeni događaj. Sledstveno, drugi članovi zdravstvenog tima takođe mogu biti uključeni u događaj, bilo direktno ili indirektno. Ovo može stvoriti osećaj zajedničke odgovornosti među članovima tima i zajednički osećaj gubitka ili krivice kada dođe do neželjenih događaja.

Pružaoци zdravstvenih usluga i ustanove treba da prepoznaju uticaj neželjenih događaja na pacijente i pružaoce usluga. Pružajući podršku i resurse sekundarnim žrtvama, zdravstvene ustanove mogu da pomognu u ublažavanju emocionalnih posledica ovih događaja i da obezbede zdravstvenim radnicima podršku, kako bi oni mogli da nastave da pružaju visokokvalitetnu zdravstvenu uslugu svojim pacijentima.

U ovom radu su navedeni elementi koji su ključni za bolje razumevanje fenomena *sekundarne žrtve* i principa *kulture pravičnosti*, u skladu sa preporukama ERNST konzorcijuma.

Ključne reči: neželjeni događaji, zdravstveni radnici, lekarske greške, bezbednost pacijenata, kultura pravičnosti

ABSTRACT

Providing optimal quality care is a challenge for professionals and healthcare systems around the world. Patients often rely on healthcare providers to assist them with their health concerns and to provide the safest and best possible care. However, despite the best efforts of healthcare providers to deliver high-quality care, unexpected adverse events can affect a patient. These events can be difficult for both patients and healthcare providers to deal with, particularly when they result in severe harm to the patient.

In addition to the physical and psychological toll that these adverse events can take on patients, healthcare providers can also be emotionally affected. Healthcare providers who are involved in adverse events are often referred to as *second victims*. These professionals are not only directly affected by the adverse events experienced by the patient but also by the response that these events can provoke in other healthcare team members, directives, and within the health institution.

Adverse events often have a systemic cause, meaning they can result from a combination of organizational, cultural, and environmental factors.

Although usually the professional in charge of patient care who is directly related to the harm is singled out as responsible, there is a chain of events and professionals involved in most events. As a result, other healthcare team members may also be involved in the event, either directly or indirectly. This can create a sense of shared responsibility among the team and a shared sense of loss or guilt when adverse events occur.

Healthcare providers and organizations need to recognize the impact of adverse events on patients and providers. By providing support and resources to second victims, healthcare organizations can help mitigate the emotional toll of these events and support providers in continuing to provide high-quality care to their patients. This paper outlines key elements for a better understanding of the *second victim* phenomenon and *just culture* principles, in accordance with the ERNST Consortium insights.

Keywords: adverse events, healthcare providers, medical errors, patient safety, just culture

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UVOD

Neizvesne i složene situacije su svojstvene kliničkoj praksi. Iako ovo nisu novi fenomeni, čini se da sve više prepoznajemo i drugačije procenjujemo njihov uticaj na ishode. Razumemo da je pružanje zdravstvene usluge onima kojima je poverena odgovornost za lečenje i negu pacijenata ključno za postizanje pozitivnih rezultata.

Neizvesnost i složenost doprinose nastanku događaja opasnih po život, ubodnim povredama iglom, neočekivanim smrtnim ishodima, incidentima nasilja usmerenim protiv zdravstvenih radnika, stagnaciji u oporavku pacijenata, žalbama, kao i greškama koje štete pacijentima. Ostali faktori koji doprinose greškama uključuju i umor, ometanje, nedostatke u opremi i komunikaciji, kao i zastarele protokole, što sve može uticati na ishode. Osim toga, ako ne razgovaramo o greškama i otvoreno ne srušimo zid ćutanja, naši pacijenti od toga neće imati koristi.

Studije su otkrile da godišnje približno 8% do 12% hospitalizovanih pacijenata [1] i oko 2% pacijenata u primarnoj zdravstvenoj zaštiti [2] doživljava neželjene događaje, od kojih bi se polovina mogla sprečiti [3,4]. Svaki neželjeni događaj se odnosi na jednog ili više zdravstvenih radnika koji se moraju suočiti sa ovim stresnim situacijama oslanjajući se na svoje lične resurse, podršku svojih kolega ili institucionalne resurse. Ovako nastaje fenomen *sekundarne žrtve*, što je termin koji je uveo profesor Albert Wu 2000. godine [5]. Ovaj fenomen je Evropski konzorcijum osnovan u okviru Evropske mreže istraživača koja se bavi sekundarnim žrtvama (engl. *European Consortium established within the European Researchers' Network Working on Second Victims – ERNST*) definisao na sledeći način [6]: „svaki zdravstveni radnik, direktno ili indirektno uključen u nepredviđeni neželjeni događaj i povredu pacijenta ili nenamernu grešku u zdravstvenoj zaštiti, i koji i sam postaje žrtva u smislu da je i na njega/nju događaj imao negativni uticaj“.

ERNST konzorcijum, osnovan u septembru 2020. godine, kojeg finansira Program evropske saradnje u nauci i tehnologiji kao KOST Akciju Evropske Komisije broj 19113, bavi se ovim pitanjima u okviru četiri radne grupe. Ove grupe su ažurirale definiciju sekundarne žrtve, uspostavile nivoe intervencije koji obuhvataju preventivne i restorativne aspekte, identifikovale ključne elemente intervencija podrške, uporedile prakse sa drugim visoko pouzdanim sektorima i istražile modele za izgradnju otpornosti. Nadalje, osmišljeni su novi pokazatelji za procenu efikasnosti intervencija; razvijeni su mehanizmi za upoznavanje budućih zdravstvenih radnika sa postupkom prijavljivanja incidenata i sa mehanizmima suočavanja sa svojim iskustvima kao sekundarnim žrtvama; dok su sadržaj obuke o bezbednosti pacijenata i propisi na tu temu analizirani na nivou Evrope, kako bi se promovisao zajednički način delovanja.

INTRODUCTION

Uncertainty and complexity are inherent in clinical practice. While these are not new phenomena, it appears that we are increasingly recognizing and assessing their impact on outcomes differently. We acknowledge that providing care for those entrusted with the responsibility of treating and caring for patients is crucial for achieving positive results.

Uncertainty and complexity contribute to life-threatening events, needle stick injuries, unexpected deaths, violent incidents against healthcare professionals, stagnation in patient progress, complaints, and errors that harm patients. Other contributing factors to errors include fatigue, distractions, equipment and communication gaps, and outdated protocols, all of which can affect outcomes. Additionally, if we fail to discuss errors and break the chain of silence openly, our patients do not benefit.

Studies have revealed that annually approximately 8% to 12% of hospitalized patients [1] and around 2% of those in primary care [2] experience adverse events, with half of these being preventable [3,4]. Each adverse event relates to one or several healthcare professionals who must confront these stressful situations relying on their personal resources, the support of their colleagues, or institutional resources. This gives rise to the *second victim* phenomenon, a term coined by Prof. Albert Wu in 2000 [5], which the European Consortium established within the European Researchers' Network Working on Second Victims (ERNST) has defined as [6] 'any healthcare worker, directly or indirectly involved in an unanticipated adverse patient event, unintentional healthcare error, or patient injury, and who becomes victimized in the sense that they are also negatively impacted'.

The ERNST Consortium, established in September 2020 and funded by the European Cooperation in Science & Technology as Action 19113, addresses these issues through four working groups. These groups have updated the definition of a second victim, established intervention levels encompassing preventive and restorative aspects, identified key elements of support interventions, compared practices with other highly reliable sectors, and explored resilience models. Furthermore, a new metric has been devised to assess intervention effectiveness; mechanisms have been developed to introduce future healthcare professionals to incident reporting and to addressing their experiences as second victims; and patient safety training content and regulations have been analyzed in Europe, to promote a common response.

The ERNST Consortium holds four International Forums annually and offers between 20 and 30 scholarships each year for Training School. The Training School addresses the second victim phenomenon, discusses

ERNST konzorcijum organizuje četiri međunarodna foruma godišnje i obezbeđuje između 20 i 30 stipendija svake godine za Školu obuke. U okviru Škole obuke bavi se fenomenom sekundarne žrtve, vodi diskusija o inovacijama u programima podrške i razmenjuju iskustva o implementaciji i održavanju programa. Završni međunarodni forum, koji se poklapa sa završetkom četvorogodišnje KOST akcije, održaće se u Beogradu 2. i 3. septembra ove godine.

MATERIJALI I METODE

Ovaj rad opisuje glavna rešenja koje predlaže ERNST konzorcijum u pristupu fenomenu sekundarne žrtve. Takođe objašnjava principe koncepta *kulture pravičnosti*.

REZULTATI I DISKUSIJA

Zdravstveni radnici koji preživljavaju iskustvo sekundarne žrtve mogu iziskivati podršku iz svog neposrednog radnog okruženja, kao što je emocionalna prva pomoć [7] koju pružaju obučene kolege, dok u teškim slučajevima može biti potrebna specijalizovana pomoć. U studijama su identifikovane emocionalne posledice kao što su izolacija, stid, strah, flešbekovi, anksioznost i nesanica, sa simptomima koji mogu trajati od nekoliko dana do više nedelja. U nekim slučajevima može doći do posttraumatskog stresnog poremećaja. Nakon ozbiljnog neželjenog događaja koji uključuje pacijenta, zdravstvenim radnicima je potrebna podrška kako bi sprečili dalje negativne posledice po druge pacijente [8], pošto se njihovo rezonovanje i klinički pristup mogu promeniti i zdravstveni radnici mogu pribegavati odbrambenim praksama, potencijalno dovodeći druge pacijente u opasnost. Stoga je u interesu bezbednosti pacijenata da zdravstveni centri osmišljavaju bezbednosne politike koje uključuju programe podrške sekundarnim žrtvama i promovišu principe kulture pravičnosti [9].

Programi podrške sekundarnim žrtvama, koji su prvi put sprovedeni u Sjedinjenim Američkim Državama, služe kao modeli za razvoj novih programa. Inicijative kao što su program „Za tebe“ (engl. *forYOU*) u bolnici u Misuriju [10] i program „Otpornost pri stresnim događajima“ (engl. *Resilience in Stressful Events - RISE*) u bolnici Džons Hopkins u Baltimoru [11], pokazale su da je podrška kolega najdelotvorniji i najprihvatljiviji način pružanja ovog vida podrške. Zahvaljujući naporima ovih pionira u sprovođenju intervencija, sada razumemo potrebe sekundarnih žrtava. Dok osmišljavamo protokole, puteve ili preporuke za rešavanje posledica neželjenih događaja, od suštinskog je značaja da zapamtimo da sekundarne žrtve iziskuju sledeće: da razumeju uzrok događaja, da znaju sa kim da komuniciraju i šta da kažu, da izbegnu osećaj odbačenosti, da dobiju emocionalnu podršku na dan događaja i u toku

innovations in support programs, and shares experiences on program implementation and maintenance. The final international forum, coinciding with the four-year deadline of the COST Action, will take place in Belgrade (Serbia) on September 2nd and 3rd of this year.

MATERIALS AND METHODS

This paper outlines the main approaches proposed by the ERNST Consortium for addressing the second victim phenomenon. It also covers the principles included in the concept of *just culture*.

RESULTS WITH DISCUSSION

Professionals experiencing a second victim situation may require support from their immediate work environment, such as emotional first aid [7] provided by trained colleagues or peers, and in severe cases, they may need specialized assistance. Studies have identified emotional consequences such as isolation, shame, fear, flashbacks, anxiety, and insomnia, with symptoms lasting from days to weeks. In some cases, post-traumatic stress disorder may occur. Following a severe adverse event involving a patient, healthcare providers need support to prevent further negative consequences for other patients [8], as their reasoning and clinical approach may alter and they may resort to defensive practices, potentially putting other patients at risk. Therefore, patient safety benefits from healthcare centers designing safety policies that include support programs for second victims and promote the principles of just culture [9].

Second victim support programs, pioneered in the USA, serve as models for the development of new programs. Initiatives like *forYOU* at the Missouri Hospital [10] and the *Resilience in Stressful Events (RISE)* program at Johns Hopkins Hospital in Baltimore [11] have demonstrated that peer support is the most effective and acceptable means of organizing this support. Thanks to the efforts of these pioneers in implementing interventions, we now understand the needs of second victims. As we design protocols, pathways, or recommendations to address the consequences of adverse events, it is essential to remember that second victims require the following: to understand the cause of the event, to know who to communicate with and what to say, to avoid feelings of rejection, to obtain emotional support for the day of the event and subsequent days, to feel valued, and to have access to legal advice [12].

In the ERNST Consortium, we have analyzed the various intervention approaches and needs of professionals and organizations, and have concluded that the organization of support programs should consider five stages [7]: (1) prevention at both the individual health-

narednih dana, da se osećaju cenjeno, kao i da imaju pristup pravnom savetu [12].

U ERNST konzorcijumu smo analizirali različite pristupe intervencijama i različite potrebe zdravstvenih radnika i zdravstvenih ustanova i zaključili da bi pri organizaciji programa podrške trebalo da se planira sledećih pet faza [7]: (1) prevencija i na individualnom nivou zdravstvenog radnika i na organizacionom nivou, (2) samopomoć pojedinaca i zdravstvenih timova nakon incidenta koji je u vezi sa bezbednošću pacijenata, (3) podrška kolega i trijaža, (4) strukturirana stručna pomoć i (5) klinička podrška. U Evropi, neki od ovih programa su: „Ublažavanje posledica kod sekundarnih žrtava“ (engl. *Mitigating Impact in Second Victims* – MISE [13]), „Drug“ (engl. *Buddy Study*) [14], „Program sistemske kolegijalne pomoći“ (engl. *Systematic Collegial Help Program* – Kohi) [15], kao i program pod nazivom „Procedure kod ozbiljnih neželjenih događaja“ (engl. *Procedure for Serious Adverse Events* – PSAE) Univerzitetske bolnice Clinico San Cecilio [16]. Zaista, postoje dokazi koji upućuju na to da se briga za dobrobit zdravstvenih radnika direktno odražava na bolje ishode, što, na kraju, donosi korist pacijentima.

Ovi programi ne bi trebalo da budu usredsređeni samo na suočavanje sa veoma stresnim situacijama, odnosno vraćanje u normalno emocionalno stanje nakon incidenata [17]. Intervencije podrške sekundarnim žrtvama su usko povezane sa bezbednošću pacijenata i moraju biti praćene mehanizmima za upravljanje inherentnim rizicima u okviru zdravstvenih aktivnosti koje se sprovedu unutar službi, odeljenja i institucija. U suprotnom, zdravstveni radnici postaju ranjivi kada stvari krenu kako ne treba, samo zato što nisu primenjena savremena znanja i odgovarajući alati u organizovanju i sprovođenju kliničkih aktivnosti, odnosno nije uzeta u obzir realnost zdravstvene prakse, koja nije bez svojih rizika.

Shvatili smo da je najveća greška uverenje da samo loši zdravstveni radnici prave greške [18]. Na ovaj način se pažnja usredsređuje isključivo na odgovornost pojedinca, te se ništa ne menja. Time se samo produžava prećutivanje i okrivljavanje a ne postiže se bila kakva pozitivna promena. Sledstveno, pacijenti pretrpe najviše štete.

Poslednjih godina prikupljamo informacije o tome kako organizacioni faktori, stilovi rukovođenja, inherentna složenost zadatka, individualne razlike u odgovoru na stres i drugi povezani faktori utiču na intenzitet emocionalnog iskustva sekundarne žrtve. Slika 1 ilustruje faktore koji predstavljaju okidače ovog negativnog iskustva.

Koncept kulture pravičnosti odnosi se na organizaciono okruženje u kojem rukovodioci podstiču otvorene diskusije o sistemskim propustima, nenačelnim greškama i oblastima gde je potrebno unapre-

care professional and organizational levels, (2) self-care of healthcare individuals and teams after a patient safety incident, (3) peer support and triage, (4) structured professional support, and (5) clinical support. In Europe, some of these programs include the *Mitigating Impact in Second Victims* (MISE) [13], the *Buddy Study* [14], the *Systematic Collegial Help Program* (Kohi) [15], and the *Procedure for Serious Adverse Events* (PSAE) of the Clinico San Cecilio University Hospital [16]. Indeed, there is evidence suggesting that the well-being of providers translates into better outcomes, which ultimately benefit patients.

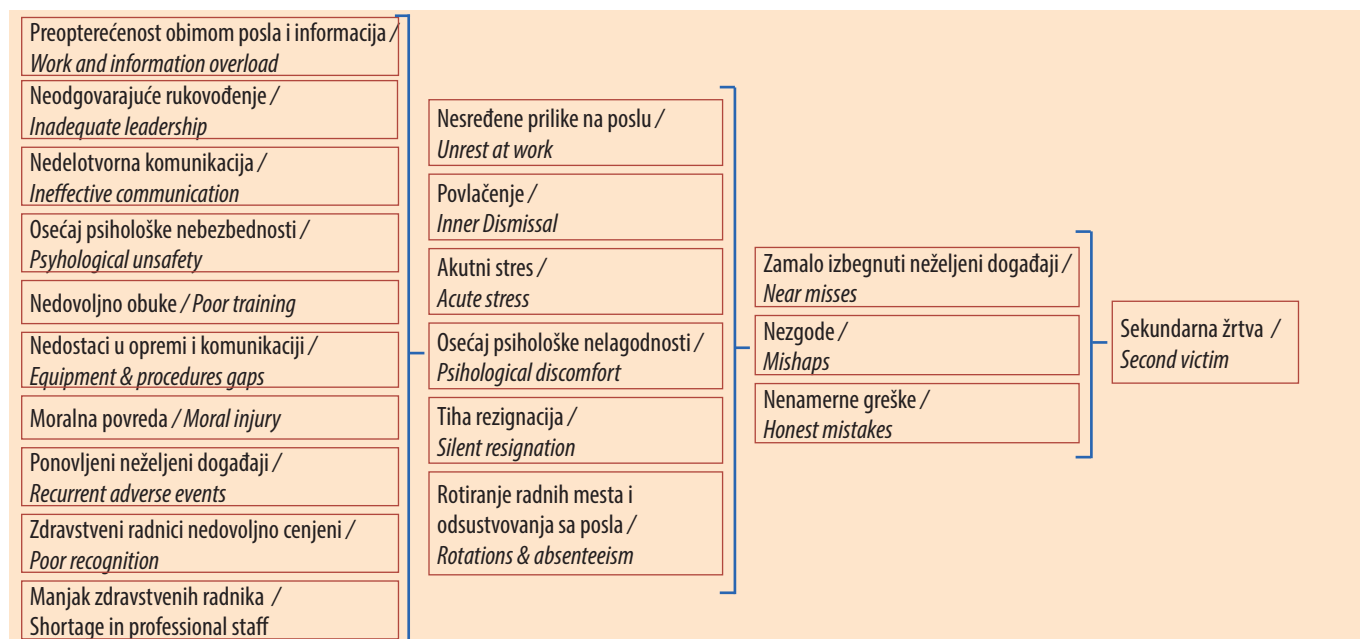
These programs should not only focus on coping with highly stressful situations or regaining emotional normality after incidents [17]. Second victim support interventions are closely linked to patient safety and must be accompanied by mechanisms for managing the inherent risks in healthcare activities within services, departments, and institutions. Otherwise, professionals are left vulnerable when things go wrong simply because current knowledge and appropriate tools were not applied to organize and execute clinical activities, i.e., the reality of healthcare practice, which is not without risks, was not taken into account.

We have learned that the worst mistake when dealing with errors is to believe that only bad healthcare professionals make mistakes [18]. This idea solely focuses on individual responsibility, and consequently, nothing changes. It merely perpetuates silence and blame failing to bring about any positive change. Ultimately, the patients suffer the most.

In recent years, we have been accumulating information about how organizational factors, leadership styles, the inherent complexity of the task, individual differences in stress response, and other associated factors justify the intensity of the emotional experience of the second victim. Figure 1 illustrates the factors triggering this negative experience.

The concept of just culture refers to an organizational environment where managers encourage open discussions about system failures, unintentional errors, and areas for improvement in patient care. It involves avoiding complacency, taking things for granted, fear of speaking up, ignoring fatigue or overload, and acknowledging the uncertainty and complexity of clinical decisions to minimize patient safety incidents. In this context, the priority is to encourage incident reporting, analyze the root causes of incidents, and implement support programs for professionals who have been involved in an honest mistake (Figure 2).

This approach relies on the responsibility of healthcare institution managers to foster an open and honest environment where professionals feel evaluated and treated consistently, constructively, and fairly. Simulta-



Slika 1. Faktori koji predstavljaju okidače za fenomen sekundarne žrtve

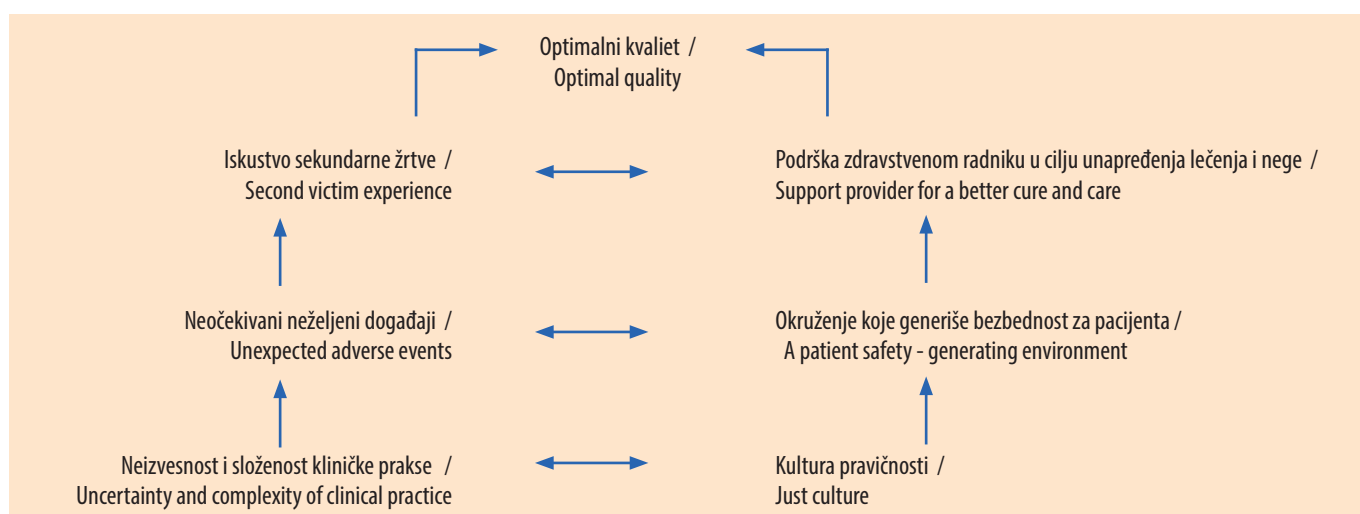
Figure 1. Factors triggering the second victim phenomenon

čiti bezbednost pacijenata. U tom smislu je potrebno izbeći samoljublje i uzimanje stvari zdravo za gotovo, prevazići strah od otvorenog iznošenja činjenica, ne ignorisati umor ili preopterećenje poslom i prepoznati neizvesnosti i složenosti kliničkih odluka, kako bi se minimizirali incidenti koji ugrožavaju bezbednost pacijenata. U tom kontekstu, prioritet je podstaći prijavljivanje incidenata, analizirati osnovne uzroke incidenata i sprovesti programe podrške za zdravstvene radnike koji su počinili nenamernu grešku (Slika 2).

Ovaj pristup se oslanja na odgovornost rukovodilaca u zdravstvenim ustanovama da neguju otvoreno i pošteno okruženje u kome zdravstveni radnici osećaju da njihov rad i oni sami bivaju procenjavani i tretirani na dosledan, konstruktivan i pravičan način. Istovremeno, zdravstveni radnici su dužni da na odgovarajući način

neously, professionals have a duty of care to follow procedures, guidelines, and standards appropriately and to seek ways to create increasingly safer environments.

When discussing just culture, we must differentiate between honest mistakes and those that are not [19]. In 2016, the National Patient Safety Foundation and, in 2018, the National Health Service, in the United Kingdom, proposed a logical, simple, and effective scheme to establish this differentiation [20]. Essentially, after each event, we can assess whether other staff members or teams with similar qualifications and training levels would have acted the same (substitution test) and whether the professional(s) involved were aware of violating predetermined standards (intention test). However, just culture also entails providing guarantees to patients (and by extension to society) that honesty,



Slika 2. Kultura pravičnosti i iskustvo sekundarne žrtve

Figure 2. Just culture and the second victim experience

prate procedure, smernice i standarde, te da iznalaze načine za stvaranje sve bezbednijeg okruženja.

Kada je u pitanju kultura pravičnosti, moramo razlikovati nenamerne greške i one koje to nisu [19]. Godine 2016, Nacionalna fondacija za bezbednost pacijenata (engl. *National Patient Safety Foundation*), te 2018. godine, Nacionalna zdravstvena služba (engl. *National Health Service*), u Ujedinjenom Kraljevstvu, predložile su logičnu, jednostavnu i efikasnu šemu za uspostavljanje ove diferencijacije [20]. U suštini, nakon svakog događaja, možemo proceniti da li bi drugi članovi osoblja ili timovi sa sličnim kvalifikacijama i nivoima obučenosti postupili isto (test supstitucije) i da li su uključeni zdravstveni radnici bili svesni kršenja unapred određenih standarda (test namere). Međutim, kultura pravičnosti takođe podrazumeva pružanje garancija pacijentima (samim tim i društvu) da poštenje, odgovornost i transparentnost nastavljaju da postoje i kada se dogode nenamerne greške ali i kada dođe do nepromišljenog i bespotrebnog preduzimanja neadekvatnih postupaka ili preuzimanja određenih rizika.

Pogrešne predstave o ljudskoj nesavršenosti, prevladavajuća kultura okrivljavanja i sledstveno pripisivanje povezane odgovornosti često ometaju identifikaciju neposrednih uzroka nenamernih grešaka. Ovim se stvara iskrivljena predstava o tome zašto dolazi do grešaka i koje radnje treba preduzeti u vezi sa onima koji su u njih uključeni, u cilju sprečavanja ponovljenih grešaka. Sekundarne žrtve su ilustracija ove neravnoteže između razumevanja ljudskog faktora i društvene konceptualizacije kliničke greške [21].

Pravna sigurnost u pogledu profesionalnog angažovanja u bezbednosti pacijenata je još jedno ključno pitanje koje zahteva pažnju. Obično se koriste dva glavna pristupa. Prvi je pristup usredsređen na pojedinca, gde odgovornost za grešku leži na zdravstvenom radniku koji ju je napravio. Ovaj pristup pojednostavljuje razumevanje kauzalnosti greške, pripisujući grešku isključivo pojedincu, a posledica je često kaznena. Kao alternativa ovakvom pristupu jeste pristup u kojem je fokus stavljen na sistem a koji prepoznaje da nastajanju greške doprinosi niz faktora. U okviru ovog pristupa se traži pravična kompenzaciju za oštećenu stranu i on je usmeren ka razumevanju bazičnih uzroka grešaka, kako bi se sprečilo njihovo ponavljanje. Shodno tome, naglasak nije na kazni već na sistemskim promenama. No, važno je napomenuti da su mnogi pravni sistemi širom sveta usvojili prvi pristup, što zahteva dalja proučavanja kako bi se odvagale prednosti i nedostaci svakog od njih.

Trenutno se primenjuju dva moguća zakonska rešenja [22]. Prvi je sistem vanugovorne odgovornosti za štetu koji je rasprostranjen širom sveta. U ovom slučaju se mora sprovesti parnica, pri čemu dve strane su-

responsibility, and transparency are upheld both when honest errors occur, and when inappropriate behaviors or certain risks are recklessly assumed.

Misconceptions about human fallibility, the prevalence of blame culture, and the associated attributions of responsibility often hinder the identification of the immediate causes of honest errors. This distorts understanding regarding why errors occur and what actions should be taken concerning those involved, in order to prevent the recurrence of errors. Second victims exemplify this imbalance between understanding the human factor and the social conceptualization of clinical error [21].

Legal certainty regarding professional engagement in patient safety is another crucial issue that requires attention. Typically, two main approaches are employed. Firstly, the person-centered view, where responsibility for a mistake lies with the professional who made it. This approach simplifies the understanding of error causation, attributing the error solely to the individual. However, the consequence is often punitive. Alternatively, the system-focused view acknowledges that a series of contributing factors are at the core of a mistake. This approach seeks fair compensation for the injured party and aims to understand the root causes, in order to prevent reoccurrence. Consequently, the emphasis is not on punishment but on systemic change. Notably, many legal systems around the world have adopted the former approach, necessitating further study to weigh out the pros and cons of each.

Two legal schemes are already being applied [22]. The first is the tort liability system which is widespread around the world. In this case, litigation is required, and two parts contrast their arguments and evidence in front of a judge or jury. The alternative to this is the so-called *no-fault system*. In this case, medical misadventure can be compensated without the need to prove fault. This is applied in some countries such as New Zealand, Denmark, and Finland.

The blame culture fosters defensive practices and discourages physicians from actively engaging in incident reporting, thus impeding progress in patient safety. Solutions to these challenges are not straightforward, and evidence regarding the best approach to reform is inconclusive, necessitating further research. However, it is evident that addressing the well-being of professionals and promoting speaking up is paramount to enhancing our capacity to avoid adverse events and improve patient outcomes [23]. Additionally, understanding the causes of errors, involving healthcare professionals in safety practices, and fostering a culture where mistakes are acknowledged but are not recurrent are crucial steps on this journey.

protstavljaju svoje argumente i dokaze pred sudijom ili porotom. Alternativa ovome je takozvani sistem odgovornosti za štetu bez krivice (engl. *no-fault system*). U ovom slučaju, medicinski nesrećni slučaj se može kompenzovati bez potrebe za dokazivanjem krivice. Ovo se primenjuje u nekim zemljama kao što su Novi Zeland, Danska i Finska.

Kultura okrivljavanja podstiče defanzivne prakse i obeshrabruje lekare da se aktivno angažuju u izveštavanju o incidentima, čime se ometa napredak u bezbednosti pacijenata. Rešenja za ove izazove nisu jednostavna, i još uvek nema nedvosmislenih dokaza o najboljem pristupu reformi, zbog čega su potrebna dalja istraživanja. Međutim, očigledno je da je izuzetno značajno da se vodi računa o dobrobiti zdravstvenih radnika i promoviše otvoreno iznošenje činjenica u cilju poboljšanja našeg kapaciteta da izbegnemo neželjene događaje i poboljšamo ishode pacijenata [23]. Takođe, razumevanje uzroka grešaka, uključivanje zdravstvenih radnika u bezbednosne prakse i negovanje kulture u kojoj se greške priznaju, ali se ne ponavljaju, ključni su koraci na ovom putu.

ZAKLJUČAK

Prelazak sa reaktivne kulture na kulturu koja generiše bezbednost zahteva implementaciju i proširenje bezbednih praksi i upravljanja rizikom unutar zdravstvenih ustanova. Ovaj proces počinje sa visokoškolskim ustanovama, koje treba da sagledaju postojeće nedostatke u obuci budućih zdravstvenih radnika po pitanju kvaliteta usluga i bezbednosti zdravstvene zaštite pacijenata. Trebalo bi da taj proces sprovedu najbolji lideri u zdravstvenim ustanovama, koji treba da promovišu odgovornost i osnaže zdravstvene radnike da vide da njihov rad i oni sami bivaju procenjavani i tretirani na dosledan, konstruktivan i pravičan način, te da ih podstaknu da uče iz svojih grešaka.

Uspostavljanje kulture pravičnosti može da pomogne u ostvarivanju ovih ciljeva. Kultura pravičnosti stavlja naglasak na to da se stručni kadar ne smatra odgovornim za sistemske nedostatke, probleme u komunikaciji ili radne uslove, koji su van njihove kontrole. Istovremeno, nepromišljeno postupanje i nemar se smatraju neprihvatljivim oblicima ponašanja koji se ne smeju tolerisati.

Iskustvo sekundarne žrtve, koje uključuje osećanje odgovornosti za nenamernu grešku, zabrinutost za pacijenta sa komplikovanim tokom bolesti ili osećaj da nije dovoljno učinjeno za pacijenta, treba prepoznati kao problem koji je u vezi sa radnim mestom, a ne samo kao mentalni problem. Ovo iskustvo je mnogo češće među zdravstvenim radnicima nego što se obično misli i ono direktno i negativno utiče na njihovu sposobnost da pruže optimalnu kvalitetnu negu.

CONCLUSION

Transitioning from a reactive culture to a safety-generating culture requires implementing and expanding safe practices and risk management within healthcare institutions. This process starts with higher education institutions, which should review the existing gaps in the training of future healthcare professionals on patient care quality and safety. It should be enforced by the top leaders in healthcare facilities, who must promote accountability and empower professionals to feel evaluated and treated consistently, constructively, and fairly, and learn from their mistakes.

Establishing just culture can help in achieving these objectives. Just culture emphasizes not holding professionals responsible for system failures, communication issues, or working conditions beyond their control. At the same time, reckless behavior and negligence are considered unacceptable forms of conduct that must not be tolerated.

The second victim experience, which includes feelings of responsibility for an unintentional error, worrying about a patient with a complicated course of disease, or the feeling of not having done enough for a patient, should be recognized as a workplace problem and not solely a mental health issue. This experience is much more common among healthcare professionals than is commonly believed and it directly and negatively impacts their ability to provide optimal quality care.

It is of the utmost importance that future research delves into the question of whether healthcare organizations with robust safety cultures take concrete steps to provide much-needed support to professionals grappling with the debilitating effects of the second victim experience. Such an analysis would not only aid in identifying and addressing the underlying causes of this pervasive problem but also help in creating a more empathetic and supportive healthcare system for all.

Conflict of interest: None declared.

Od suštinskog značaja je da se buduća istraživanja bave pitanjem da li zdravstvene ustanove sa snažnom kulturom bezbednosti preduzimaju konkretne korake kako bi pružile preko potrebnu podršku zdravstvenim radnicima koji se bore sa iscrpljujućim posledicama iskustva sekundarne žrtve. Takva analiza ne samo da bi pomogla u identifikovanju i rešavanju osnovnih uzroka ovog sveprisutnog problema, već bi pomogla i u stvaranju sistema zdravstvene zaštite u kojem prevladava veći stepen empatije i podrške za sve.

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LITERATURA / REFERENCES

1. Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Murillo J, Ruiz-López P, Limón-Ramírez R, Terol-García E; ENEAS work group. Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. *J Epidemiol Community Health*. 2008 Dec;62(12):1022-9. doi: 10.1136/jech.2007.065227.
2. Aranaz-Andrés JM, Aibar C, Limón R, Mira JJ, Vitaller J, Agra Y, et al. A study of the prevalence of adverse events in primary healthcare in Spain. *Eur J Public Health*. 2012 Dec;22(6):921-5. doi: 10.1093/eurpub/ckr168.
3. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. *Qual Saf Health Care*. 2008 Jun;17(3):216-23. doi: 10.1136/qshc.2007.023622.
4. Panagioti M, Khan K, Keers RN, Abuzour A, Phipps D, Kontopantelis E, et al. Prevalence, severity, and nature of preventable patient harm across medical care settings: systematic review and meta-analysis. *BMJ*. 2019 Jul 17;366:l4185. doi: 10.1136/bmj.l4185.
5. Wu AW. Medical error: the second victim. The doctor who makes the mistake needs help too. *BMJ*. 2000;320(7237):726-7. doi: 10.1136/bmj.320.7237.726.
6. Vanhaecht K, Seys D, Russotto S, Strametz R, Mira J, Sigurgeirsdóttir S, et al.; European Researchers' Network Working on Second Victims (ERNST). An Evidence and Consensus-Based Definition of Second Victim: A Strategic Topic in Healthcare Quality, Patient Safety, Person-Centeredness and Human Resource Management. *Int J Environ Res Public Health*. 2022;19(24):16869. doi: 10.3390/ijerph192416869.
7. Seys D, Panella M, Russotto S, Strametz R, Joaquín Mira J, Van Wilder A, et al. In search of an international multidimensional action plan for second victim support: a narrative review. *BMC Health Serv Res*. 2023 Jul 31;23(1):816. doi: 10.1186/s12913-023-09637-8.
8. Pellino G, Pellino IM, Pata F. Uncovering the Veils of Maya on defensive medicine, litigation risk and second victims in surgery: care for the carers to protect the patients. *Colorectal Dis*. 2021;23(2):548-549. doi: 10.1111/codi.15451.
9. Tasker A, Jones J, Brake S. How effectively has a Just Culture been adopted? A qualitative study to analyse the attitudes and behaviours of clinicians and managers to clinical incident management within an NHS Hospital Trust and identify enablers and barriers to achieving a Just Culture. *BMJ Open Qual*. 2023 Jan;12(1):e002049. doi: 10.1136/bmjopen-2022-002049.
10. Scott SD, Hirschinger LE, Cox KR, McCoig M, Hahn-Cover K, Epperly KM, et al. Caring for our own: deploying a systemwide second victim rapid response team. *Jt Comm J Qual Patient Saf*. 2010;36(5):233-40. doi: 10.1016/s1553-7250(10)36038-7.
11. Edrees H, Connors C, Paine L, Norvell M, Taylor H, Wu AW. Implementing the RISE second victim support programme at the Johns Hopkins Hospital: a case study. *BMJ Open*. 2016;6(9):e011708. doi: 10.1136/bmjopen-2016-011708.
12. Mira JJ, Lorenzo S, Carrillo I, Ferrús L, Silvestre C, Astier P, et al.; RESEARCH GROUP ON SECOND AND THIRD VICTIMS. Lessons learned for reducing the negative impact of adverse events on patients, health professionals and healthcare organizations. *Int J Qual Health Care*. 2017;29(4):450-460. doi: 10.1093/intqhc/mzx056.
13. Mira JJ, Carrillo I, Guilbert M, Lorenzo S, Pérez-Pérez P, Silvestre C, et al.; Spanish Second Victim Research Team. The Second Victim Phenomenon After a Clinical Error: The Design and Evaluation of a Website to Reduce Caregivers' Emotional Responses After a Clinical Error. *J Med Internet Res*. 2017;19(6):e203. doi: 10.2196/jmir.7840.
14. Schröder K, Bovil T, Jørgensen JS, Abrahamsen C. Evaluation of 'the Buddy Study', a peer support program for second victims in healthcare: a survey in two Danish hospital departments. *BMC Health Serv Res*. 2022;22(1):566. doi: 10.1186/s12913-022-07973-9.
15. Krommer E, Ablöschner M, Klemm V, Gatterer C, Rösner H, Strametz R, et al. Second Victim Phenomenon in an Austrian Hospital before the Implementation of the Systematic Collegial Help Program KoHi: A Descriptive Study. *Int J Environ Res Public Health*. 2023;20(3):1913. doi: 10.3390/ijerph20031913.
16. Cobos-Vargas A, Pérez-Pérez P, Núñez-Núñez M, Casado-Fernández E, Bueno-Cavanillas A. Second Victim Support at the Core of Severe Adverse Event Investigation. *Int J Environ Res Public Health*. 2022;19(24):16850. doi: 10.3390/ijerph192416850.
17. Guerra-Paiva S, Lobão MJ, Simões DG, Fernandes J, Donato H, Carrillo I, et al. Key factors for effective implementation of healthcare workers support interventions after patient safety incidents in health organisations: a scoping review. *BMJ Open*. 2023;13(12):e078118. doi: 10.1136/bmjopen-2023-078118.
18. Kennedy D. Analysis of sharp-end, frontline human error: beyond throwing out "bad apples". *J Nurs Care Qual*. 2004;19(2):116-22. doi: 10.1097/00001786-200404000-00008.
19. Meadows S, Baker K, Butler J. The Incident Decision Tree: Guidelines for Action Following Patient Safety Incidents. In: Henriksen K, Battles JB, Marks ES, et al., editors. *Advances in Patient Safety: From Research to Implementation (Volume 4: Programs, Tools, and Products)*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. Dostupno na: <https://www.ncbi.nlm.nih.gov/books/NBK20586/>
20. Henriksen K, Battles JB, Marks ES, Lewin DI, editors. *Advances in Patient Safety: From Research to Implementation (Volume 4: Programs, Tools, and Products)*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005.
21. Mira JJ. Understanding Honest Mistakes, Second Victims and Just Culture for Patient Safety. *J Healthc Qual Res*. 2023;38(5):259-261. doi: 10.1016/j.jhqr.2023.08.001.
22. Gil-Hernández E, Carrillo I, Tumelty ME, Sruловичi E, Vanhaecht K, Wallis KA, et al. How different countries respond to adverse events whilst patients' rights are protected. *Med Sci Law*. 2023;258024231182369. doi: 10.1177/00258024231182369.
23. Jones A, Blake J, Adams M, Kelly D, Mannion R, Maben J. Interventions promoting employee "speaking-up" within healthcare workplaces: A systematic narrative review of the international literature. *Health Policy*. 2021;125(3):375-384. doi: 10.1016/j.healthpol.2020.12.016.

CURRICULUM VITAE



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PREDNOSTI I NEDOSTACI INTEGRACIJE U EVROPSKU UNIJU: ISTRAŽIVANJE MEĐU STUDENTIMA PRVE GODINE MEDICINE U SRBIJI

ORIGINALNI RAD

ORIGINAL ARTICLE

ADVANTAGES AND DISADVANTAGES OF THE INTEGRATION TO THE EUROPEAN UNION: THE SURVEY AMONG MEDICAL FRESHMEN IN SERBIA

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SAŽETAK

Cilj: Cilj studije je bio da se ispituju faktori povezani sa pozitivnim stavom prema pristupu Evropskoj uniji (EU) među studentima prve godine medicine u Srbiji.

Metode: U periodu od 2010. do 2021. godine, u okviru modula za učenje na daljinu „Medicina i društvo“, ukupno 1333 bruoša Medicinskog fakulteta Univerziteta u Beogradu (1333/1940, odnosno stopa odgovora 68,7%) je odgovorilo na pitanja u polustrukturiranom upitniku koji je ispitivao njihovu percepciju prednosti i nedostataka integracije u EU. Povezanost pro-EU stava (u odnosu na one protiv –EU ili neopredeljene) sa uočenim prednostima i nedostacima predstavljena je korišćenjem odnosa šanse (OR) i 95% intervala poverenja (CI).

Rezultati: Ukupno 48,5% ispitanika je bilo za EU integracije, 42,7% je bilo neodlučno, a 8,9% je bilo protiv integracije Srbije u EU (tj. 585, 525 i 107, respektivno). Ispitanici muškog pola su imali 55% veću verovatnoću da budu u grupi sa Pro – EU stavom (OR: 1,55, 95% CI:1,14–2,10), kao i ispitanici koji su bili u stanju da identifikuju prednosti EU integracije kao što je lakša mobilnost (OR: 2,87, 95% CI : 1,80–4,57), veća raznovrsnost mogućnosti za posao (OR: 2,06, 95% CI: 1,45–2,93), i oni koji nisu smatrali da je konkurencija na tržištu zdravstvene zaštite EU nedostatak integracije u EU (OR: 8,56, 95 % CI: 1,79–40,92). Pro – EU stav je bio manje verovatan među ispitanicima koji su identifikovali visoku učestalost emigracije doktora medicine kao nedostatak EU integracija, za 45% (OR: 0,55, 95% CI: 0,36–0,84).

Zaključak: Tokom poslednje decenije, udeo srpskih bruoša medicine sa proevropskim i neodlučnim stavom ukazuje na potrebu jače međunarodne inicijative EU i domaćih aktera. Prednosti kao što su lakša mobilnost, konkurencija na tržištu zdravstvene zaštite EU i razne mogućnosti zapošljavanja promovisu integracioni stav, za razliku od emigracije lekara.

Ključne reči: EU, student, stavovi, Srbija

ABSTRACT

Aim: The study aimed to identify factors associated with pro-integration attitudes to the European Union (EU) among Serbian medical freshmen to promote integration.

Methods: In the period from 2010 to 2021, within the scope of the distance learning module “Medicine & Society”, a total of 1333 freshmen of the Faculty of Medicine of the University of Belgrade (1333/1940, i.e., response rate 68.7%) has responded to the semi-structured questionnaire inquiring their perception of the EU integration advantages and disadvantages.

The association of the pro-EU attitude (vs cons-EU / undecided) with perceived advantages and disadvantages was presented using the odds ratio (OR) and 95% confidence interval (CI).

Results: A total of 48.5% of respondents were pro-EU integration, 42.7% were undecided and 8.9% were cons-EU (i.e., 585, 525, and 107, respectively) integration of Serbia. The pro-EU attitude was 55% more likely among male respondents (OR: 1.55, 95% CI:1.14–2.10), among respondents who were able to identify advantages of EU integration such as easier mobility (OR: 2.87, 95% CI: 1.80–4.57), variety of job opportunities (OR: 2.06, 95% CI: 1.45–2.93), and among those for whom competition at the EU healthcare market is not a disadvantage of the EU-integration (OR: 8.56, 95% CI: 1.79–40.92). The pro-EU attitude was less likely among respondents who identified high emigration of medical doctors as a disadvantage of the EU integration, by 45% (OR: 0.55, 95% CI: 0.36–0.84).

Conclusion: During the last decade, the share of Serbian medical freshmen with pro-EU and undecided attitudes suggests the need for a stronger international initiative of EU and national actors. Advantages such as easier mobility, competition in the EU healthcare market, and a variety of employment opportunities promote an integrationist attitude, in contrast to the large emigration of medical doctors.

Keywords: EU, student, attitudes, Serbia

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UVOD

Prošlo je manje od tri godine od podnošenja aplikacije do potvrđivanja statusa Srbije kao kandidatske zemlje od strane Evropskog saveta u martu 2012. godine, i obrazlažućih i bilateralnih pregleda tokom jeseni 2013. godine [1]. Nakon početka pregovora o pristupanju u januaru 2014. godine [2], do sada je otvoreno 12 od 35 poglavlja, dok su dva privremeno zatvorena (poglavlja 25 - nauka i istraživanje i 26 - obrazovanje i kultura). Međutim, pregovaračka poglavlja 2 (Sloboda kretanja radnika), 19 (Socijalna politika i zapošljavanje) i 28 (Zaštita potrošača i zdravlje) još uvek nisu otvorena [1].

Opšti stav u Srbiji prema integraciji u Evropsku uniju (EU) oscilira prema dinamici procesa evropske integracije, od pozitivnog do negativnog [2]. Najviši nivo opšte podrške integraciji u EU zabeležen je 2009. godine nakon što je stanovništvo doživelo liberalizaciju viznog režima, ali je ova podrška značajno opala u narednim godinama, s obzirom na to da je samo 41% ispitanika u 2012. i 55% u 2018. godini imalo pozitivan stav [1]. Trenutna međunarodna politika Srbije je u korist evropske integracije [3], a retorika vlade raspravlja o mogućim koristima harmonizacije domaćeg regulatornog i zakonodavnog okvira sa stečevinom EU, odnosno celokupnom zakonodavstvu EU.

Značajan deo ne-EU medicinskih studenata razmišlja o radu u nekoj od zemalja EU nakon diplomiranja [4]. Njihovi glavni razlozi za rad u EU su problemi s kojima se suočavaju u zemlji, poput nezadovoljstva standardom života, visoke stope nezaposlenosti mladih zdravstvenih radnika u Srbiji, relativno niske plate i prekovremeni rad. U potrazi za boljim životom, većom slobodom kretanja, profesionalnim napretkom i uživanjem u prednostima šireg tržišta zdravstvene zaštite nego u Srbiji, mladi medicinski diplomci mogli bi videti EU kao privlačnu priliku za život, studije i rad [5]. Sličan uticaj na pro-EU stavove primećen je i u drugim zemljama kandidatima za EU, poput Turske [6]. Stoga, poznavanje dinamike pregovaračkog procesa sa EU može uticati na formiranje stavova zdravstvenih radnika prema integraciji u EU. Cilj studije bio je identifikovati faktore koji utiču na stav prointegracije prema Evropskoj uniji (EU) među srpskim studentima medicine kako bi se promovisala integracija.

METODE

Stavovi prema integraciji u EU ispitivani su među brutošima integrisanih medicinskih studija na Medicinskom fakultetu Univerziteta u Beogradu (MFUB). Anketa je sprovedena tokom najdinamičnijeg perioda integracije u EU u periodu od 2010/11 (aplikacija za članstvo u EU) do 2021/2022 (1).

INTRODUCTION

Less than three years passed from the submission of the application to the confirmation of Serbia's status as a candidate country by the European Council in March 2012, and the explanatory and bilateral screenings in autumn 2013 [1]. After the start of [2] accession negotiations in January 2014, 12 out of 35 chapters have been opened so far, and two have been temporarily closed (chapters 25 - science and research and 26 - education and culture). However, negotiating chapters 2 (Freedom of movement of workers), 19 (Social policy and employment), and 28 (Consumer protection and health) have not yet been opened [1].

The general attitude in Serbia towards integration into the European Union (EU) oscillates according to the dynamics of the European integration process, from positive to negative [2]. The highest level of general support for EU integration was recorded in 2009 after the population experienced the liberalization of the visa regime, but this support dropped significantly in the following years, as only 41% of respondents in 2012 and 55% in 2018 had a positive attitude [1]. The current international policy of Serbia is in favor of European integration [3], and the government's rhetoric discusses the possible benefits of harmonizing the domestic regulatory and legislative framework with the acquis of the EU, that is, the entire legislation of the EU.

A significant portion of non-EU-medical students is contemplating working in some of the EU countries upon graduation [4]. Their main reasons for working in the EU are the problems they face in the country, such as dissatisfaction with the standard of living, the high unemployment rate of young health workers in Serbia, relatively low wages, and overtime work. In search of a better life, greater freedom of movement, professional advancement, and enjoying the benefits of a wider healthcare market than in Serbia, young medical graduates could see the EU as an attractive opportunity to live, study, and work [5]. A similar influence on pro-EU attitudes was observed in other EU-candidate countries, such as Turkey [6]. Therefore, the knowledge of the dynamics of the negotiation process with the EU can influence the formation of the attitude of the health workforce towards EU integration. The study aimed to identify factors influencing the attitude of pro-integration to the European Union (EU) among Serbian medical freshmen to promote integration.

METHODS

The attitudes toward EU integration were surveyed among freshmen at the integrated medical studies at the Faculty of Medicine of Belgrade University (FMUB). The survey was conducted during the most dynamic

Ukupna stopa odgovora bila je 68,7% (odnosno 1333 ispitanika od ukupno 1940 bruceša). Ispitanici su bili svi bruceši koji su pohađali modul učenja na daljinu "Medicina i društvo" na medicinskim studijama na MFUB-u (oko 50 do 150 bruceša godišnje).

Instrument istraživanja bio je polustrukturirani upitnik, sa dva glavna pitanja: 1. "Definišite svoj stav u vezi sa integracijom Srbije u EU: da li ste za, protiv ili neodlučni i zašto" i 2. "Razmislite o vašim očekivanjima od pridruživanja EU iz različitih perspektiva i opišite prednosti i mane integracije u EU". Analiza sadržaja primenjena je kako bi se bruceši grupisali u tri grupe koje predstavljaju broj studenata sa stavom za EU, protiv EU i neodlučnih. Zatim su istraženi pol (muški i ženski), i šest širokih kategorija prednosti integracije u EU (lakša mobilnost, obrazovne mogućnosti, pristup inovativnim tehnologijama zdravstvene zaštite, učešće u EU projektima, raznovrsne mogućnosti zapošljavanja i bolja dostupnost zdravstvene zaštite), i nedostaci integracije u EU (teškoće u zaštiti lokalnih kulturnih vrednosti, pretnje zdravstvenoj sigurnosti zbog opuštenih prekograničnih kontrola, teškoće u zaštiti nacionalnih finansija, omogućena emigracija medicinskih doktora, jaka konkurencija na tržištu zdravstvene zaštite EU, i zahtevna administracija na tržištu zdravstvene zaštite EU).

Pored deskriptivne statistike, sprovedene su bivarijantne i multivarijantne logističke regresione analize, koristeći stav za EU kao zavisnu varijablu nasuprot stavu protiv EU / neodlučnom stavu. Značajne varijable iz bivarijantne analize testirane su u multivarijantnom modelu regresije kako bi se identifikovali faktori povezani sa stavom za EU. Rezultati regresionih analiza predstavljeni su kao odnosi verovatnoće (OR) sa intervalom poverenja od 95% (CI) i smatrani su značajnim ako je p-vrednost manja od 0,05. Analize su rađene pomoću softverskog paketa IBM SPSS Statistics verzije 22.

REZULTATI

U najdinamičnijem periodu integracije u EU, 36,6% ispitanika bili su za integraciju u EU, dok je 49,4% bilo neodlučno, a 14,0% bilo je protiv integracije Srbije u EU (tj. 488, 658 i 187, redom).

Tabela 1 pokazuje da su muški bruceši bili za 52% više skloni (OR: 1,52, 95% CI: 1,15-2,03) da imaju stav za EU integraciju. Stav "za" bio je verovatniji među brucešima koji su prepoznali prednosti integracije u EU, kao što su lakša mobilnost (OR: 2,14, 95% CI: 1,36-3,37), bolji pristup zdravstvenoj zaštiti u EU (OR: 2,89, 95% CI: 2,05-4,06), raznovrsne mogućnosti zapošljavanja u EU (OR: 2,38, 95% CI: 1,17-3,19), i bolji pristup tehnologijama zdravstvene zaštite u EU (OR: 1,99, 95% CI: 1,25-3,19). Stav "za" EU integraciju bio je manje vero-

period of EU integration in the period from 2010/11 (application for EU membership) to 2021/2022 [1].

The overall response rate was 68.7% (that is 1333 respondents out of a total of 1940 freshmen). Respondents were all freshmen who attended the distance learning module 'Medicine & Society' at medical studies at FMUB (approximately between 50 and 150 freshmen per year).

The survey instrument was a semi-structured questionnaire, with two main questions: 1. 'Define your attitude regarding the EU integration of Serbia: are you pro, cons or undecided and why' and 2. 'Think about your expectations from joining the EU from different perspectives and describe the advantages and disadvantages of EU integration'. The content analysis was applied to group freshmen into three groups representing the number of students with *pro-EU*, *cons-EU*, and undecided attitudes. Then, explored were sex (males and females), and the six broad categories of the advantages of EU integration (easier mobility, educational opportunities, access to innovative health care technologies, participation in the EU projects, variety of job opportunities, and better health care accessibility), and disadvantages of EU integration (difficulties to protect local cultural values, threats to health safety due to relaxed cross-border control, difficulties to protect national finances, enabled emigration of medical doctors, strong competition at the EU healthcare market, and demanding administration at the EU healthcare market).

In addition to descriptive statistics, bivariate and multivariate logistic regression analyses were performed, using the *pro-EU* attitude as an outcome variable versus the *cons-EU* / undecided attitude. Significant variables from the bivariate analysis were tested in the multivariate regression model to identify factors associated with the *pro-EU* attitude. The results of regression analyses were presented as odds ratios (OR) with a 95% confidence interval (CI) and they were considered significant if the p-value was less than 0.05. The analyses were done by IBM SPSS Statistics software package version 22.

RESULTS

In the most dynamic period of EU integration, 36.6% of respondents were *pro-EU*, while 49.4% were undecided and 14.0 % were *con-EU* (i.e., 488, 658, and 187, respectively) integration of Serbia.

Table 1 shows that male freshmen were by 52% more likely (OR: 1.52, 95% CI: 1.15-2.03) to have a *pro-EU* attitude. The *pro* attitude was more likely among freshmen who identified advantages of EU integration such as easier mobility (OR: 2.14, 95% CI: 1.36-3.37), better healthcare access in EU (OR: 2.89, 95% CI: 2.05-

Tabela 1. Obrazloženje varijabli stavova medicinskih bruća za integraciju Srbije naspram kontra/neodlučnih u Evropskoj uniji (n=1333)**Table 1.** Explanatory variables of medical freshmen's attitude pro integration of Serbia vs cons/undecided in the European Union (n=1333)

Varijable / Variables	Analiza bivarijantne logističke regresije / Bivariate logistic regression analysis OR (95% CI)	Analiza multivarijantne logističke regresije / Multivariate logistic regression analysis OR (95% CI)
Pol, broj bruća / Sex, n of freshmen		
Ženski / Female	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Muški / Male	1.34 (1.04-1.74)	1.52 (1.15-2.03)
Prednosti evropskih integracija, broj bruća / Advantages of EU integration, n of freshmen		
<i>Lakša mobilnost / Easier mobility</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	1.91 (1.44-2.55)	2.14 (1.36-3.37)
<i>Obrazovne mogućnosti / Educational opportunities</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	1.35 (1.05-1.73)	0.66 (0.43-1.01)
<i>Bolja dostupnost zdravstvene zaštite / Better healthcare accessibility</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	1.60 (1.27-2.03)	2.89 (2.05-4.06)
<i>Raznovidnost radnih mogućnosti * / Variety of job opportunities*</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	1.53 (1.22-1.93)	2.38 (1.71-3.32)
<i>Pristup inovativnim tehnologijama zdravstvene zaštite * / Access to innovative healthcare technologies*</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	2.72 (1.98-3.73)	1.99 (1.25-3.19)
<i>Učešće u projektima EU / Participation in EU projects</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	0.75 (0.60-0.94)	0.93 (0.67-1.29)
Nedostaci integracije u EU, broj bruća / Disadvantages of EU integration, n of freshmen		
<i>Teškoće u zaštiti nacionalnih finansija / Difficulties in protecting national finances</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	0.51 (0.37-0.68)	0.54 (0.36-0.82)
<i>Omogućena emigracija medicinskih doktora / Enabled emigration of medical doctors</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	0.51 (0.37-0.70)	0.52 (0.33-0.81)
<i>Teškoće u zaštiti lokalne kulture / Difficulties in protecting local culture</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	0.66 (0.45-0.95)	1.16 (0.70-1.92)
<i>Jaka konkurencija na tržištu zdravstvene zaštite EU / Strong competition in the EU healthcare market</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	/
Da / Yes	0.51 (0.27-1.16)	/
<i>Pretnje zdravstvenoj sigurnosti zbog opuštenih kontrola prelaska / Threats to health safety due to relaxed cross-border control</i>		
Da/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	1.00 referentna kategorija / 1.00 reference category
Da / Yes	0.34 (0.21-0.57)	0.84 (0.42-1.67)
<i>Zahtevna administracija EU / Demanding EU administration</i>		
Ne/ Ne znam / No/ I do not know	1.00 referentna kategorija / 1.00 reference category	/
Da / Yes	0.64 (0.19-2.11)	/

vatan među ispitanicima koji su opazili nedostatke integracije u EU, kao što su teškoće u zaštiti nacionalnih finansija i omogućena emigracija medicinskih doktora, za 46% (OR: 0,54, 95% CI: 0,36-0,82), i za 48% (OR: 0,52, 95% CI: 0,33-0,81) manje verovatni da će imati stav "za" EU integraciju.

DISKUSIJA

U ovoj studiji, više od trećine ispitanika bili su izričito za EU, za razliku od osmine protiv. Nalaz da je gotovo polovina ispitanika neodlučna u vezi sa integracijom Srbije u EU ukazuje na to da ili izbegavaju "politizovane diskusije" ili "nisu dovoljno informisani da bi imali eksplicitan stav". Druga nedavna studija takođe pokazuje da manjina lekara zapravo smatra zastupanje fundamentalnim za medicinski profesionalizam [6]. Međutim, lekcije iz istorije su da je "medicina društvena nauka, a politika ništa drugo nego medicina u velikom obimu [7]" i da "iako mnogi lekari, u suštini naučnici, nalaze političko zastupanje neprijatnim, ono je zapravo neophodan deo posla" [8]. Nalazi ove studije sugerišu da je potrebno mnogo uraditi kako bi se bolje informisalo o koristima koje EU integracija može doneti medicini kao naučnoj disciplini i zdravstvenoj nezi kao praksi, kao i razvoju radne snage u oblasti zdravstva. Predlažemo da iskoristimo trenutak da dalje promoviramo EU integraciju, s obzirom na to da je do sada Srbija otvorila 22 poglavlja od ukupno 35. Ovom studijom mi zastupamo izlazak iz medicinskih eho komora i stažiranje u medicini i javno zdravlje kao oblasti društvene akcije za održivi razvoj u ovom nesigurnom okruženju.

Prednosti poput lakše mobilnosti i većih mogućnosti zapošljavanja u EU posebno su važne za budući razvoj mladih profesionalaca, koji izgledaju željni sticanja savremenog znanja i veština i sticanja novih iskustava koja ih čine proevropski orijentisanim, kao što je visok broj lekara iz Rumunije i Bugarske koji su emigrirali u EU [4] nakon što su ove zemlje postale članice EU. Brucoši s pro-EU stavom ne očekuju neuspeh srpskog poslovanja na tržištu zdravstva EU, pokazujući poverenje bilo u utvrđenim propisima ili u dobrom poslovanju domaćih kompanija. Međutim, prema najnovijem izveštaju Evropske komisije, srpska ekonomija je samo umereno spremna za konkurenciju na evropskom tržištu [9].

Nalazi studije ne bi trebalo generalizovati, jer je uzorak uključivao samo brucoše upisane na online kurseve, tako da su brucoši bez ličnih računara i oni koji preferiraju učenje u učionici isključeni. Međutim, ispitana veza između pro-EU stava i percipiranih prednosti i nedostataka EU integracije pokazala je da medicinskim studentima treba da razviju kompetencije kako bi bili aktivni u promovisanju prava na kvalitetnu zdravstvenu zaštitu kao u EU.

4.06), variety of job opportunities in EU (OR: 2.38, 95% CI: 1.17-3.19), and better access to healthcare technologies in EU (OR: 1.99, 95% CI: 1.25-3.19). The *pro*-EU attitude was less likely among respondents who perceived disadvantages of the EU integration such as difficulties in protecting national finances and enabled emigration of medical doctors by 46% (OR: 0.54 95% CI: 0.36-0.82), and by 48% (OR: 0.52, 95% CI: 0.33-0.81) less likely to have *pro*-EU integration attitude.

DISCUSSION

In this study, more than one-third of the respondents were explicitly *pro*-EU, in contrast to one-eighth of the *cons*-EU. The finding that almost half of the respondents are undecided about the integration of Serbia into the EU indicates that they either avoid "politically charged discussions" or are "not sufficiently informed to have an explicit position". Another recent study also shows that a minority of physicians consider advocacy fundamental to medical professionalism [6]. However, lessons from history are that '*medicine is a social science, and politics is nothing else but medicine on a large scale*' [7] and that '*while many doctors, scientists at heart, find political advocacy uncomfortable, it is a required part of the job*' [8]. This study's findings suggest that much has to be done to better inform about the benefits that EU integration could bring to medicine as a science, health care as a practice, and health workforce development. We suggest seizing the momentum to further promote EU integration, as by now, Serbia has opened 22 chapters out of a total of 35. With this study, we advocate stepping out of medical echo chambers and experiencing medicine and public health as fields of social action for sustainable development in this uncertain environment.

Advantages such as easier mobility and greater job opportunities in the EU are particularly important for the future development of young professionals, who seem eager to acquire modern knowledge and skills and gain new experiences that keep them *pro*-European, as, a high number of physicians from Romania and Bulgaria emigrated to EU after these countries joined EU [4]. Freshmen with a *pro*-EU attitude do not expect the failure of Serbian business in the EU health market, showing confidence either in established regulations or in the good performance of domestic companies. However, according to the latest report from the European Commission, the Serbian economy is only moderately ready to be competitive in the European market [9].

The findings of the study should not be generalized, because the sample included only freshmen enrolled in online courses, so freshmen without personal

U zaključku, tokom poslednje decenije, udeo srpskih medicinskih bruća s pro-EU i neodlučni stav ukazuje na potrebu za jačom međunarodnom inicijativom EU i nacionalnih aktera. Prednosti poput lakše mobilnosti, konkurencije na tržištu zdravstvene zaštite EU i raznolikih mogućnosti zapošljavanja promovišu integracioni stav, suprotno velikoj emigraciji medicinskih doktora. Imajući u vidu potrebu da se razmotre karakteristike domaćeg konteksta za napredak evropske integracije [10], i velike teorije evropske integracije za razumevanje politike identiteta zemalja kandidata za pristupanje EU [10]. Kako bi mogli bolje informisati o toku radnji za usklađivanje srpskog pravnog okvira sa kvalitetom zdravstvene zaštite i tržištem rada EU, daljnje studije trebalo bi da istraže očekivanja studenata zdravstvene nege, pacijenata i zdravstvenih radnika od usklađivanja nacionalne regulative sa telom zakona EU.

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LITERATURA / REFERENCES

1. Pjevočić D, Subotić S. Stavovi građana Srbije prema EU. Politika. Beograd; 2019.
2. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* 2021;20(10):1–26.
3. Stojković D, Glišić M. Odbrana i ekonomija mira u Srbiji: Da li je vojna neutralnost ekonomski korisna? *Ekonomija odbrane i mira.* 2018;00(00):1–17.
4. OSF. Working Together to Address Health Workforce Mobility in Europe Recommendations for Action. 2020.
5. Buchan J, Wismar M, Glinos IA BJ, editor. Health professional mobility in a changing Europe: new dynamics, mobile individuals and diverse responses. Copenhagen: World Health Organization; 2014.
6. Bonica A, Rosenthal H, Rothman DJ. Physician activism in American politics: The opposition to the Price nomination. *PlosOne.* 2019;e0215802.
7. Virchow R. Der Armenarzt. *Med Reform.* 1848;18:125–7.
8. Winslow CE. THE UNTILLED FIELDS OF PUBLIC HEALTH. *Science.* 1920 Jan;51(1306):23–33.
9. European Commission. Serbia 2020 Report. Brussels; 2020.
10. Herfs PGP. Aspects of medical migration with particular reference to the United Kingdom and the Netherlands. *Hum Resour Health.* 2014;12(59):1–7.

computers and who prefer learning in the classroom are excluded. However, the examined link between the pro-EU attitude and the perceived advantages and disadvantages of EU integration showed that medical students need to build competencies to be active in promoting the right to quality health care such as in the EU.

In conclusion, during the last decade, the share of Serbian medical freshmen with pro-EU and undecided attitudes suggests the need for a stronger international initiative of EU and national actors. Advantages such as easier mobility, competition in the EU healthcare market, and a variety of employment opportunities promote an integrationist attitude, in contrast to the large emigration of medical doctors. Given the need to consider the characteristics of the domestic context for the progress of European integration [10] and grand theories of European integration for understanding the identity politics of the accession EU countries [10]. To be able to better inform the course of action for aligning the Serbian legal framework with the healthcare quality and the EU labor market, further study should explore the healthcare students', patients', and health workers' expectations from harmonization of the national regulation with the EU body of law.

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Ethical approval:

The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade (No. 1322/III-6).

Conflict of interest: None declared.

UTILIZATION OF BABY-FRIENDLY SERVICES
IN MATERNITY WARDS IN SERBIAMirjana Živković Šulović¹¹ Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“,
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SAŽETAK

Uvod/cilj: Dojenje, kao tema za zdravstveno vaspitni rad i istraživanja, ne gubi na aktuelnosti, zbog brojnih dobiti i za dete (smanjenje smrtnosti, jačanje imuniteta, smanjenje učestalosti alergija, respiratornih i digestivnih poremećaja, gojaznosti i dijabetesa, povećanje koeficijenta inteligencije) i za majku (smanjenje rizika od hipertenzije, dijabetesa, hiperlipidemije, kardiovaskularnih bolesti, karcinoma dojke i jajnika). Cilj istraživanja je odabir preporuka za efikasne i efektivne zdravstveno vaspitne aktivnosti za povećanje procenta isključivo dojene novorođenčadi i odojčadi mlađe od šest meseci, u Srbiji.

Materijali i metode: Istraživanje je sprovedeno kao sekundarna analiza podataka dobijenih putem istraživanja *Multiple Indicator Cluster Survey 6 (MICS 6)* za opšti (nacionalni) i za uzorak romske etničke grupe, u Srbiji, 2019. godine. Povezanosti korišćenja usluga: kontakt „koža na kožu“, rani podoj i majka uz novorođenče 24 sata i sociodemografskih varijabli majki su ispitane primenom univarijantne i multivarijantne logističke regresione analize. Statistička značajnost je određivana u odnosu na nivo $p < 0,05$ (t-test, hi-kvadrat test i Men-Vitnijev U-test).

Rezultati: U oba uzorka, ispitivane socioekonomske karakteristike majki nisu povezane sa korišćenjem *bejbi friendly* usluga. Značajna statistička razlika postoji u odnosu na tip porođaja u oba uzorka. Žene koje su se porodile carskim rezom ostaju uskraćene za korišćenje postupaka koji imaju dokazane pozitivne efekte po zdravlje deteta i majke. U oba uzorka nađeno je značajno veće korišćenje zajedničkog smeštaja majke i novorođenčeta tokom 24 sata u Beogradskom regionu u kojem se nalazi porodilište koje je nosilac Nacionalnog programa podrške dojenju.

Zaključak: Najefikasnija mera za unapređenje dojenja odnosi se na usvajanje politika podrške dojenju u ustanovi i obavezu edukacije kompletnog osoblja koje je u kontaktu sa majkama tokom boravka u porodilištu (dvadesetočasovna obuka Svetske zdravstvene organizacije za savetovanje o dojenju).

Ključne reči: isključivo dojenje, *bejbi friendly* usluge, edukacija

ABSTRACT

Introduction/aim: Breastfeeding, as a topic for health promotion and research, continues to be relevant due to numerous benefits for both the child (decreased mortality, strengthening of immunity, reduction of allergies, respiratory and digestive disorders, obesity and diabetes, increased IQ) and the mother (reduced risk of hypertension, diabetes, hyperlipidemia, cardiovascular diseases, breast and ovarian cancer). The study aims to propose effective and efficient health promotion activities directed towards increasing the percentage of exclusively breastfed newborns and infants up to six months of age, in Serbia.

Method: The study was conducted as a secondary analysis of data obtained in Multiple Indicator Cluster Survey 6 (MICS 6) for the national and the Roma ethnic group sample, in Serbia, in 2019. The association between the utilization of the following services: skin-to-skin contact, early breastfeeding, and full-time rooming-in for mother and baby, and the socio-demographic variables of mothers, were examined using univariate and multivariate logistic regression analysis. Statistical significance was determined at $p < 0.05$ (Student t-test, Pearson's chi-square test, and Mann-Whitney U-test).

Results: The examined socio-economic characteristics of the mothers in both samples were not associated with the use of baby-friendly services. A significant statistical difference exists in relation to the type of delivery in both samples. Women who gave birth by caesarean section remain deprived of utilizing the procedures that have proven positive short-term and long-term effects on the health of both the child and mother. In both samples, there was a significant increase in rooming-in in the Belgrade region, where the maternity hospital leading the National Breastfeeding Support Program is located.

Conclusion: The most effective measures to improve breastfeeding are related to the adoption of breastfeeding support policies in health facilities and the obligation to train the entire staff who are in contact with mothers during their stay at the maternity hospital (20-hour WHO breastfeeding counseling training).

Keywords: exclusive breastfeeding, baby-friendly services, training

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UVOD

Rukovodeći se značajem dojenja za dugovečnost i zdravlje novorođenčadi i odojčadi, Svetska zdravstvena organizacija (SZO) je usvojila međunarodno dogovoren etički Kodeks (engl. *International Code of Marketing of Breast-Milk Substitutes*) kojim se objašnjava javnosti, zdravstvenim i marketinškim stručnjacima, zdravstvenim sistemima i regulatornim telima u svim zemljama sveta da je dojenje prirodna ishrana koja je najadekvatnija i superiornija od bilo koje veštačke ishrane [1]. Ovim Kodeksom, SZO i Dečiji fond Ujedinjenih Nacija (UNICEF) upućuju zemlje da u sklopu napora za sprečavanje nehranjenosti i bolesti, prioritet treba da daju podršci i promociji dojenja, zakonodavnim i socijalnim akcijama koje ubrzavaju prihvatanje navike dojenja kod zaposlenih majki, oživljavanje praksi dojenja u populaciji u kojoj je ono u opadanju i usvajanje regulativa koje se odnose na sankcionisanje neprihvatljive promocije i prodaje veštačke hrane za novorođenčad i odojčad kao zamene za majčino mleko [1,2].

Dojenje, kao tema za zdravstveno-vaspitni rad i istraživanja, i dalje ne gubi na aktuelnosti zbog brojnih kratkoročnih i dugoročnih dobiti za dete (smanjenje smrtnosti, jačanje imuniteta, smanjenje učestalosti alergija, respiratornih i digestivnih poremećaja, gojaznosti i dijabetesa, te povećanje koeficijenta inteligencije– IQ) [3] i za majku (smanjenje rizika od hipertenzije, dijabetesa, hiperlipidemije, kardiovaskularne bolesti, karcinoma dojke i jajnika) [4].

Cilj promocije dojenja je da se utiče i na donosiocel odluka da, kroz zdravstvenu legislativu, omoguće, u okviru *bejbi friendly* porodilišta, rano uspostavljanje dojenačke prakse, koja bi trebalo da omogući kontakt po tipu „koža na kožu“ (KNK) majke i deteta, a potom i podoj u prvih 60 minuta nakon porođaja [2].

UNICEF i SZO su se pridružili inicijativi *bejbi friendly* bolnica sa ciljem da se odgovorni motivišu za pružanje zdravstvenih usluga usmerenih na implementiranje vodiča „Deset koraka ka uspešnom dojenju“, koji se sastoji iz seta pravnih akata i preporuka za sprovođenje procedura podrške dojenju [5].

Rani početak dojenja smatra se jednom od ključnih intervencija kojima je moguće smanjiti stopu smrtnosti novorođenčadi i odojčadi i poboljšati preživljavanje dece. Kontakt „koža na kožu“ se definiše kao stavljanje novorođenčeta preko golih grudi majke u vreme porođaja u trajanju od najmanje jedan sat, pri čemu se dojenje može započeti odmah [6-8].

Svake godine se usled nedostatka zaštite, promocije i podrške dojenju, beleže i značajni ekonomski gubici. Ključni nalazi „Globalnih troškova nedojenja“ pokazuju da dojenje, prema preporukama SZO, ima potencijal da spreči: (1) globalne gubitke od 574 milijarde dolara (u

INTRODUCTION

Guided by the importance of breastfeeding for the longevity and health of newborns and infants, the World Health Organization (WHO) adopted an internationally agreed upon Code of Ethics (International Code of Marketing of Breast-Milk Substitutes) which explains to the public, health and marketing professionals, health systems and regulatory bodies in all countries of the world that breastfeeding is a natural diet that is the most appropriate and superior to any artificial feeding [1]. With this Code, the WHO and the United Nations International Children's Emergency Fund (UNICEF) instruct countries that, as part of the efforts to prevent malnutrition and disease, priority should be given to the support and promotion of breastfeeding, legislative and social actions that accelerate the acceptance of the habit of breastfeeding among working mothers, the revival of breastfeeding practices in populations where it is declining, and the adoption of regulations related to the sanctioning of unacceptable promotion and sale of artificial food for newborns and infants as a substitute for breast-milk [1,2].

Breastfeeding, as a topic for work and research in the areas of health and education, has not as yet ceased to be relevant, due to numerous short-term and long-term benefits for the child (decreased mortality, strengthening of immunity, reduction of allergies, respiratory and digestive disorders, obesity and diabetes, increased IQ) [3] and the mother (reduced risk of hypertension, diabetes, hyperlipidemia, cardiovascular diseases, breast and ovarian cancer) [4].

The aim of promoting breastfeeding is to influence decision-makers to adopt health legislation that would enable, within the framework of baby-friendly maternity hospitals, the early establishment of breastfeeding practice, which should enable skin-to-skin contact (STS) between mother and child and subsequent breastfeeding, in the first 60 minutes after delivery [2].

UNICEF and WHO joined the Baby-Friendly Hospital initiative aiming to motivate health authorities to provide health services oriented towards implementing the “Ten Steps to Successful Breastfeeding” guide, which consists of a set of legal documents and recommendations for implementing breastfeeding support procedures [5].

Early initiation of breastfeeding is considered one of the key interventions to reduce infant and child mortality and improve child survival. Skin-to-skin contact is defined as placing the newborn over the mother's bare chest at the time of delivery for at least one hour, during which time breastfeeding can be started immediately [6-8].

Every year, due to the lack of protection, promotion, and support for breastfeeding, significant eco-

proseku 0,7% nacionalnog dohotka – BDP); (2) više od 510.000 smrtnih slučajeva; (3) 4,58 miliona slučajeva gojaznosti dece godišnje; (4) gubitak 200 miliona IQ poena godišnje, te da uštedi porodicama više od 10% primanja koja bi izdvojili za kupovinu adaptiranog mleka [9].

Pravni okvir za podršku dojenju u Srbiji predstavlja Uredba o Nacionalnom programu podrške dojenju, porodičnoj i razvojnoj nezi novorođenčeta (2018.) [10], koja je usvojena nakon alarmantnog podatka iz istraživanja MICS 5 da je 2014. godine u Srbiji samo 12,4% dece isključivo dojeno do šestog meseca [11].

Cilj istraživanja usmeren je na istraživanje povezanosti ličnih karakteristika porodilja i korišćenja *bejbi friendly* usluga (kontakt KNK, rani podoj i zajednički smeštaj majke i novorođenčeta 24 sata), u opštoj populaciji i populaciji Romkinja iz romskih naselja, kao i na predlog odgovarajućih mera za unapređenje korišćenja *bejbi friendly* usluga u porodilištima u Srbiji, u skladu sa dobijenim rezultatima.

MATERIJALI I METODE

Istraživanje je sprovedeno kao sekundarna analiza podataka dobijenih putem istraživanja MICS 6 iz 2019. godine, koje je sproveo Republički zavod za statistiku, uz tehničku i finansijsku podršku UNICEF-a, Evropske Unije, Populacionog fonda Ujedinjenih nacija (engl. *United Nations Fund for Population Activities – UNFPA*) i Vlade Republike Srbije [12].

MICS (engl. *Multiple Indicator Cluster Survey*) je višenamenski međunarodni program anketnog istraživanja domaćinstava u cilju prikupljanja međunarodno uporedivih podataka o širokom spektru pokazatelja položaja žena i dece. Istraživanje MICS meri ključne pokazatelje koji omogućavaju zemljama da generišu podatke neophodne za razvoj politika, programa i nacionalnih razvojnih planova, kao i za praćenje napretka u ostvarivanju Ciljeva održivog razvoja (engl. *Sustainable Development Goals – SDG*) [13]. MICS 6 je obuhvatio dva nacionalna reprezentativna uzorka opšte (neromske) populacije i romske populacije koja živi u romskim naseljima u Srbiji.

Za potrebe sekundarne analize u istraživanju su korišćene varijable iz dva od četiri upitnika korišćena u istraživanju MICS 6 za obe populacije: Upitnik domaćinstva za prikupljanje podataka o demografskim i socioekonomskim karakteristikama domaćinstva i Individualni upitnik za žene starosti 15 – 49 godina (odeljak: Zdravlje majke i novorođenčeta). U oba uzorka obuhvaćene su žene starosti 15 – 49 godina koje su u poslednje dve godine rodile živorođeno dete.

Na osnovu pregleda literature, koncipirani su analiza, varijable istraživanja i pregrupisanje unutar varijabli. Izvršena je statistička obrada osam sociodemograf-

mic losses are recorded. Key findings of “Global Costs of Not Breastfeeding” show that breastfeeding, as recommended by the WHO, has the potential to prevent the following: (1) global losses of \$574 billion (on average 0.7% of GDP); (2) more than 510,000 deaths; (3) 4.58 million cases of childhood obesity per year; (4) loss of 200 million IQ points per year. It can also save more than 10% of the family income that would be spent on purchasing formula milk [9].

The legal framework for breastfeeding support in Serbia is represented by the Regulation on the National Program for Breastfeeding Support and Developmental Care of a Newborn (2018) [10], which was adopted after the alarming data from the MICS 5 survey showing that, in 2014, in Serbia, only 12.4% of children exclusively breastfed for the first six months of life [11].

The study aims to investigate the association between the personal characteristics of the mothers giving birth and the use of baby-friendly services (STS, early breastfeeding, and rooming-in), in the general population and the population of Roma women from Roma settlements, as well as to propose appropriate measures to improve the use of baby-friendly services in maternity hospitals in Serbia, in keeping with the results obtained.

MATERIALS AND METHODS

The study was conducted as a secondary analysis of data obtained from the MICS 6 survey from 2019, which was conducted by the Statistical Office of the Republic of Serbia, with the technical and financial support of UNICEF, the European Union, the United Nations Fund for Population Activities (UNFPA), and the Government of the Republic of Serbia [12].

MICS (Multiple Indicator Cluster Survey) is a multipurpose international household survey program aimed at collecting internationally comparable data on a wide range of indicators of the position of women and children. The MICS survey measures key indicators that enable countries to generate data necessary for the development of policies, programs, and national development plans, as well as for monitoring progress in achieving the Sustainable Development Goals (SDG) [13]. MICS 6 included two nationally representative samples of the general (non-Roma) population and the Roma population living in Roma settlements in Serbia.

For the purpose of secondary analysis, the study used variables from two of the four questionnaires used in the MICS 6 survey for both populations: the Household Questionnaire for collecting data on the demographic and socioeconomic characteristics of the household and the Questionnaire for Individual Women Aged 15 – 49 (module: Maternal and Newborn

skih karakteristika za ispitanice obe populacije (starost trudnica, stepen obrazovanja, radni status, indeks blagostanja domaćinstva, mesto boravka/sredina, region i način porođaja) u pogledu njihove povezanosti sa korišćenjem *bejbi friendly* usluga i nege novorođenčeta na rođenju (kontakt KNK, rani podoj i majka uz novorođenče tokom 24 sata), primenom univarijantne i multivarijantne logističke regresione analize. Od testova statističke značajnosti, korišćeni su t-test, hi-kvadratni test i U-test. Statistička značajnost je određivana u odnosu na nivo $p < 0,05$. Za statističku analizu je korišćen statistički softver SPSS, verzija 20.3.

Grafički i tabelarno prikazani najvažniji rezultati istraživanja interpretirani su i diskutovani u svetlu relevantne literature. Na osnovu sprovedenog istraživanja, koncipiran je predlog zdravstveno-vaspitnih mera i aktivnosti usmerenih ka povećanju obima pozitivnih praksi u porodilištima.

REZULTATI

Demografske i socioekonomske karakteristike uzoraka

Nacionalni uzorak je ukupno obuhvatio 331 ženu (ponderisan), a uzorak Romkinja iz romskih naselja je obuhvatio 383 žene. U **Tabeli 1** su prikazane su karakteristike oba uzorka ispitanica. Žene u romskoj populaciji su bile značajno mlađe ($24 \pm 5,3 : 31 \pm 5,5$), ($p < 0,001$). Udeo majki starijih od 30 godina u opštoj populaciji je bio značajno viši ($53,3\% : 11,7\%$), ($p < 0,001$). U nacionalnom uzorku nije bilo ispitanica bez završene škole, dok je u uzorku iz romskih naselja svaka osma ispitanica bila bez obrazovanja, dok je svaka šesta završila srednju ili višu školu. U opštoj populaciji je bilo značajno više radno aktivnih majki ($63\% : 10,7\%$), ($p < 0,001$). Dobar indeks blagostanja domaćinstva imala je svaka druga ispitanica u nacionalnom uzorku, odnosno manje od jedne trećine ispitanica iz romskih naselja, što je značajna statistička razlika ($p < 0,001$). Nije potvrđena statistički značajna razlika ova dva uzorka u pogledu materijalne deprivacije. U gradskim naseljima je živelo statistički značajno više ispitanica iz uzorka romskih naselja. Najveći broj ispitanica u opštoj populaciji je bilo iz regiona Vojvodine, odnosno iz regiona Južne i Istočne Srbije u romskoj populaciji, što je statistički značajno ($p < 0,001$), ali u skladu sa reprezentativnim uzorkom udela romske populacije u regionima. Svaka treća ispitanica u opštoj populaciji je imala porođaj carskim rezom, odnosno svaka peta iz romskih naselja, što je statistički značajno ($p < 0,001$).

Procedura kontakt „koža na kožu“

U nacionalnom uzorku neposredan kontakt „koža na kožu“ posle porođaja vaginalnim ili carskim rezom

Health). Both samples included women aged 15 – 49 who had given birth to a live-born child in the previous two years.

Based on the literature review, we structured the analysis, research variables, and regrouping within the variables. Statistical processing of eight socio-demographic characteristics for the respondents of both populations (age of pregnant women, level of education, employment status, household well-being index, place of residence/environment, region, and type of delivery) was performed in terms of their association with the use of baby-friendly and newborn care at birth services (STS, early breastfeeding and rooming-in), using univariate and multivariate logistic regression analysis. The following tests for statistical significance were used: t-test, chi-square test, and the U-test. Statistical significance was determined in relation to $p < 0.05$. The SPSS statistical software, Version 20.3, was used for statistical analysis.

The most important study results, presented graphically and tabularly, were interpreted and discussed in light of relevant literature. Based on the conducted research, a proposal of health education measures and activities aimed at increasing the volume of positive practices in maternity hospitals was conceived.

RESULTS

Demographic and socio-economic characteristics of the samples

The national sample included a total of 331 women (weighted), and the sample of Roma women from Roma settlements included 383 women. **Table 1** shows the characteristics of both samples of respondents. Women in the Roma population were significantly younger ($24 \pm 5.3 : 31 \pm 5.5$), ($p < 0.001$). The proportion of mothers older than 30 years in the general population was significantly higher ($53.3\% : 11.7\%$), ($p < 0.001$). In the national sample, there were no respondents who did not complete school, while in the sample from Roma settlements, every eighth respondent had no education, and every sixth respondent had completed high school or above. There were significantly more working mothers in the general population ($63\% : 10.7\%$), ($p < 0.001$). Every other respondent in the national sample had a good index of household well-being, while this was true of less than one-third of the respondents from Roma settlements, which is a significant statistical difference ($p < 0.001$). No statistically significant difference between these two samples in terms of material deprivation was confirmed. Statistically significantly more respondents from the sample of Roma settlements

Tabela 1. Osnovne karakteristike majki

Table 1. Characteristics of the mothers

Karakteristike majki / Characteristics of the mothers	Nacionalni uzorak / National sample		Uzorak - romska naselja / Sample of Roma settlements		p-vrednost / p-value
Ukupno / Total	331		383		
	n	%	n	%	
Starost / Age					
Prosečna / Average		31.34		24.34	
Standarda devijacija / Standard deviation		5.595		5.316	< 0.001
Minimum / Min		17		15	
Maksimum / Max		48		47	
≤30 godina / ≤ 30 years	155	(46.7%)	338	(88.3%)	< 0.001
>30 godina / > 30 years	177	(53.3%)	45	(11.7%)	
Obrazovanje majke / Mother's education level					
osnovna i srednja škola / elementary and high school education	174	(52.6%)			
više obrazovanje / higher education	157	(47.4%)			
bez obrazovanja / no education			49	(12.8%)	
osnovna škola / elementary school level			266	(69.5%)	
srednja škola i više / high school level and above			68	(17.8%)	
Radna aktivnost / Employment status					
aktivna / employed	209	(63.0%)	41	(10.7%)	< 0.001
neaktivna / unemployed	123	(37.0%)	342	(89.3%)	
Indeks blagostanja / Well-being index					
loše / poor	99	(30.0%)	197	(51.4%)	< 0.001
srednje / average	57	(17.2%)	68	(17.8%)	
dobro / good	175	(52.8%)	118	(30.8%)	
Materijalna deprivacija / Material deprivation					
≤ 3	267	(80.7%)	328	(85.6%)	0.107
> 3	64	(19.3%)	55	(14.4%)	
Sredina / Living environment					
gradska / urban	197	(59.3%)	259	(67.6%)	0.024
ostalo / other	134	(40.7%)	124	(32.7%)	
Region / Region					
Beograd / Belgrade	90	(27.2%)	89	(23.2%)	< 0.001
Vojvodina / Vojvodina	97	(29.4%)	75	(19.6%)	
Šumadija i Zapadna Srbija / Šumadija and West Serbia	78	(23.4%)	31	(8.1%)	
Južna i Istočna Srbija / South and East Serbia	66	(20.0%)	188	(49.4%)	
Tip porođaja / Type of delivery					
carski rez / caesarean section	105	(32.5%)	70	(18.5%)	< 0.001
vaginalni / vaginal	218	(67.5%)	309	(81.5%)	

sproveden je kod 31,7% majki, odnosno 37,4% ispitanica u uzorku žena iz romskih naselja (Grafikon 1). Nema statističke značajnosti u korišćenju ove usluge u dva posmatrana uzorka.

U Tabeli 2 prikazana je povezanost demografskih i socioekonomskih karakteristika oba uzorka sa korišće-

lived in urban settlements. The largest number of respondents in the general population were from the region of Vojvodina, while the largest number of respondents from the Roma settlements were from the region of South and East Serbia, which is statistically significant ($p < 0.001$), but in keeping with the repre-

Tabela 2. Demografske i socioekonomske karakteristike majki i učestalost procedure: kontakt „koža na kožu“, u oba uzorka**Table 2.** Demographic and socio-economic characteristics of mothers and the frequency of skin-to-skin contact procedures, in both samples

Karakteristike majki / Characteristics of the mothers	Ukupno / Total	Kontakt “koža na kožu” / Skin-to-skin		p-vrednos / p-value
		Yes n (%)	No n (%)	
Nacionalni uzorak / National sample				
Starost / Age				
≤ 30 godina / ≤ 30 years	97 (48.3%)	45 (46.9%)	52 (49.5%)	0.707
> 30 godina / > 30 years	104 (51.7%)	51 (53.1%)	53 (50.5%)	
Obrazovanje majke / Mother's education level				
osnovna i srednja škola / elementary and high school education	107 (53.2%)	51 (53.1%)	56 (53.3%)	0.976
fakultet / university level education	94 (46.8%)	45 (46.9%)	49 (46.7%)	
Radna aktivnost / Employment status				
aktivna / employed	123 (61.8%)	54 (56.8%)	69 (66.3%)	0.168
neaktivna / unemployed	76 (38.2%)	41 (43.2%)	35 (33.7%)	
Indeks blagostanja / Well-being Index				
loše / poor	61 (30.3%)	27 (28.1%)	34 (32.4%)	0.445
srednje / average	33 (16.4%)	19 (19.8%)	14 (13.3%)	
dobro / good	107 (53.2%)	50 (52.1%)	57 (54.3%)	
Materijalna deprivacija / Material deprivation				
≤ 3	160 (80.0%)	77 (81.1%)	83 (79.0%)	0.723
> 3	40 (20.0%)	18 (18.9%)	22 (21.0%)	
Sredina / Living environment				
gradska / urban	117 (58.2%)	54 (56.3%)	63 (60.0%)	0.590
ostalo / other	84 (41.8%)	42 (43.7%)	42 (40.0%)	
Region / Region				
Beograd / Belgrade	61 (26.9%)	29 (30.2%)	32 (30.5%)	0.784
Vojvodina / Vojvodina	58 (27.6%)	25 (26.0%)	33 (31.4%)	
Šumadija i Zapadna Srbija / Šumadija and West Serbia	47 (25.3%)	25 (26.0%)	22 (21.0%)	
Južna i Istočna Srbija / South and East Serbia	35 (20.2%)	17 (17.8%)	18 (17.1%)	
Tip porođaja / Type of delivery				
carski rez / caesarean section	105 (32.5%)	18 (17.1%)	87 (39.9%)	< 0.001
vaginalni / vaginal	218 (67.5%)	87 (82.9%)	131 (60.1%)	
Uzorak romskih naselja / Roma settlements sample				
Starost / Age				
≤ 30 godina / ≤ 30 years	235 (88.0%)	112 (88.2%)	123 (87.9%)	0.934
>30 godina / > 30 years	32 (12.0%)	15 (11.8%)	17 (12.1%)	
Obrazovanje majke / Mother's education level				
bez obrazovanja / no education	36 (13.5%)	12 (9.4%)	24 (17.1%)	0.183
osnovna školav / elementary school level	186 (69.7%)	93 (73.2%)	93 (66.4%)	
srednja škola i više / high school level and above	45 (16.9%)	22 (17.3%)	23 (16.4%)	
Radna aktivnost / Employment status				
aktivna / employed	25 (61.8%)	12 (9.4%)	13 (9.3%)	0.964
neaktivna / unemployed	242 (38.2%)	115 (90.6%)	127 (90.7%)	

Indeks blagostanja / <i>Well-being Index</i>				0.339
loše / <i>poor</i>	144 (53.9%)	68 (53.5%)	76 (54.3%)	
srednje / <i>average</i>	44 (16.5%)	25 (19.7%)	19 (13.6%)	
dobro / <i>good</i>	79 (29.6%)	34 (26.8%)	45 (32.1%)	
Materijalna deprivacija / <i>Material deprivation</i>				0.425
≤ 3	34 (12.7%)	14 (11.0%)	20 (14.3%)	
> 3	233 (87.3%)	113 (89.0%)	120 (85.7%)	
Sredina / <i>Living environment</i>				0.017
gradska / <i>urban</i>	187 (70.0%)	80 (63.0%)	107 (76.4%)	
ostalo / <i>other</i>	80 (30.0%)	47 (37.0%)	33 (23.6%)	
Region / <i>Region</i>				0.549
Beograd / <i>Belgrade</i>	72 (27.0%)	32 (25.2%)	40 (28.6%)	
Vojvodina / <i>Vojvodina</i>	59 (22.1%)	29 (22.8%)	30 (21.4%)	
Šumadija i Zapadna Srbija / <i>Šumadija and West Serbia</i>	20 (7.5%)	7 (5.5%)	13 (9.3%)	
Južna i Istočna Srbija / <i>South and East Serbia</i>	116 (43.4%)	59 (46.5%)	57 (40.7%)	
Tip porođaja / <i>Type of delivery</i>				< 0.001
carski rez / <i>caesarean section</i>	60 (16.4%)	3 (2.2%)	57 (25.2%)	
vaginalni / <i>vaginal</i>	305 (83.6%)	139 (97.8%)	226 (74.8%)	

njem procedure „koža na kožu“ neposredno nakon porođaja. Iako postoji statistički značajna razlika između ispitanica dva uzorka u pogledu svih ispitivanih karakteristika, izuzev materijalne deprivacije, unutar samih uzoraka, nema statističke razlike u korišćenju procedure KNK.

U oba uzorka, samo je način porođaja, odnosno zdravstveno stanje ispitanice koje je bilo indikovano za porođaj carskim rezom, statistički značajno povezano sa korišćenjem procedure KNK ($p < 0,001$). U nacionalnom uzorku kod ispitanica koje su imale porođaj carskim rezom, neposredan kontakt „koža na kožu“ ostvaren je kod 17,1%, a u uzorku majki iz romskih naselja kod 2,2% majki.

Rani podoj

U nacionalnom uzorku, procenat dece koja su prvi put podojena u roku od jednog sata po rođenju je bio 7,7%. (Grafikon 1). Rani podoj dobilo je 13,7% dece u uzorku iz romskih naselja, što je statistički značajna razlika.

U oba uzorka, starost, obrazovanje, radni status, sredina i region stanovanja, indeks blagostanja i materijalna deprivacija, nisu pokazali statističku značajnost u pogledu učestalosti ranog podoja. U oba uzorka postoji značajna statistička razlika ($p < 0,001$) u pogledu dostupnosti ranog podoja za žene koje su imale carski rez. U nacionalnom uzorku nijedna žena porođena carskim rezom nije imala rani podaj, odnosno imale su ga svega tri ispitanice iz uzorka majki iz romskih naselja. U Tabeli 3 su prikazane demografske i socioekonomske

sentative sample of the share of the Roma population in the regions. Every third respondent in the general population had a cesarean delivery, i.e., every fifth respondent from Roma settlements, which is statistically significant ($p < 0.001$).

The skin-to-skin procedure

In the national sample, immediate skin-to-skin contact after delivery by vaginal or cesarean section was performed in 31.7% of mothers, i.e., 37.4% of respondents in the sample of women from Roma settlements (Chart 1). There is no statistical significance in the use of this service in the two observed samples.

Table 2 presents the association of demographic and socioeconomic characteristics of both samples with the use of the skin-to-skin procedure immediately after delivery. Although there is a statistically significant difference between the respondents of the two samples in terms of all the examined characteristics, with the exception of material deprivation, within the samples themselves, there is no statistical difference in the use of the STS procedure.

In both samples, only the type of delivery, i.e., the state of health of the respondent indicated for cesarean delivery, was statistically significantly associated with the use of the STS procedure ($p < 0.001$). In the national sample of respondents who gave birth by cesarean section, direct skin-to-skin contact was achieved in 17.1%, and in the sample of mothers from Roma settlements, it was achieved in 2.2% of mothers.

Tabela 3. Demografske i socioekonomske karakteristike majki i učestalost procedure: rani podoj, u oba uzorka**Table 3.** Demographic and socio-economic characteristics of the mothers and the frequency of early breastfeeding, in both samples

Karakteristike majki / <i>Characteristics of the mothers</i>	Total	Rani podoj / <i>Early breastfeeding</i>		p-value
		Yes n (%)	No n (%)	
Nacionalni uzorak / <i>National sample</i>				
Starost / <i>Age</i>				
≤ 30 godina / ≤ 30 years	146 (47.4%)	11 (45.8%)	135 (47.5%)	0.873
> 30 godina / > 30 years	162 (52.6%)	13 (54.2%)	149 (52.5%)	
Obrazovanje majke / <i>Mother's education level</i>				
osnovna i srednja škola / <i>elementary and high school education</i>	165 (53.6%)	14 (58.3%)	151 (53.2%)	0.626
fakultet / <i>university level education</i>	143 (46.4%)	10 (41.7%)	133 (46.8%)	
Radna aktivnost / <i>Employment status</i>				
aktivna / <i>employed</i>	191 (62%)	16 (66.7%)	175 (61.6%)	0.625
neaktivna / <i>unemployed</i>	117 (38%)	8 (33.3%)	109 (38.4%)	
Indeks blagostanja / <i>Well-being Index</i>				
loše / <i>poor</i>	94 (30.6%)	8 (34.8%)	86 (30.3%)	0.138
srednje / <i>average</i>	54 (17.6%)	6 (26.1%)	48 (16.9%)	
dobro / <i>good</i>	159 (51.8%)	9 (39.1%)	150 (52.8%)	
Materijalna deprivacija / <i>Material deprivation</i>				
≤ 3	61 (19.8%)	4 (16.7%)	57 (20.1%)	0.698
> 3	247 (80.2%)	20 (83.3%)	227 (79.9%)	
Sredina / <i>Living environment</i>				
gradska / <i>urban</i>	181 (58.6%)	11 (45.8%)	170 (59.6%)	0.187
ostalo / <i>other</i>	128 (41.4%)	13 (54.2%)	115 (40.4%)	
Region / <i>Region</i>				
Beograd / <i>Belgrade</i>	84 (27.3%)	9 (37.5%)	75 (26.4%)	0.449
Vojvodina / <i>Vojvodina</i>	91 (29.5%)	5 (20.8%)	86 (30.3%)	
Šumadija i Zapadna Srbija / <i>Šumadija and West Serbia</i>	73 (23.7%)	7 (29.2%)	66 (23.2%)	
Južna i Istočna Srbija / <i>South and East Serbia</i>	60 (19.5%)	3 (12.5%)	57 (20.1%)	
Tip porođaja / <i>Type of delivery</i>				
carski rez / <i>caesarean section</i>	95 (30.8%)	0 (0.0%)	95 (33.4%)	< 0.001
vaginalni / <i>vaginal</i>	213 (69.2%)	24 (100.0%)	189 (66.6%)	
Uzorak romskih naselja / <i>Roma settlements sample</i>				
Starost / <i>Age</i>				
≤ 30 godina / ≤ 30 years	306 (89%)	40 (85.1%)	266 (89.6%)	0.365
> 30 godina / > 30 years	38 (11%)	7 (14.9%)	31 (10.4%)	
Obrazovanje majke / <i>Mother's education level</i>				
bez obrazovanja / <i>no education</i>	44 (12.8%)	6 (12.8%)	38 (12.8%)	0.497
osnovna škola / <i>elementary school level</i>	239 (69.5%)	35 (74.5%)	204 (68.7%)	
srednja škola i više / <i>high school level and above</i>	61 (17.7%)	6 (12.8%)	55 (18.5%)	
Radna aktivnost / <i>Employment status</i>				
aktivna / <i>employed</i>	39 (11.3%)	6 (12.8%)	33 (11.1%)	0.740
neaktivna / <i>unemployed</i>	305 (88.7%)	41 (87.2%)	264 (88.9%)	

Indeks blagostanja / <i>Well-being Index</i>				
loše / <i>poor</i>	175 (50.9%)	23 (48.9%)	152 (51.2%)	0.924
srednje / <i>average</i>	62 (18%)	10 (21.3%)	52 (17.5%)	
dobro / <i>good</i>	107 (31.1%)	14 (29.8%)	93 (31.3%)	
Materijalna deprivacija / <i>Material deprivation</i>				
≤ 3	231 (67.2%)	30 (63.8%)	201 (67.7%)	0.558
> 3	113 (32.8%)	17 (36.2%)	96 (32.3%)	
Sredina / <i>Living environment</i>				
gradska / <i>urban</i>	78 (22.7%)	8 (17%)	70 (23.6%)	0.602
ostalo / <i>other</i>	70 (20.3%)	12 (25.5%)	58 (19.5%)	
Region / <i>Region</i>				
Beograd / <i>Belgrade</i>	29 (8.4%)	0 (0%)	29 (9.8%)	0.073
Vojvodina / <i>Vojvodina</i>	167 (48.5%)	27 (57.4%)	140 (47.1%)	
Šumadija i Zapadna Srbija / <i>Šumadija and West Serbia</i>	55 (16.2%)	3 (6.5%)	52 (17.7%)	
Južna i Istočna Srbija / <i>South and East Serbia</i>	285 (83.8%)	43 (93.7%)	242(82.3%)	
Tip porođaja / <i>Type of delivery</i>				
carski rez / <i>caesarean section</i>	231 (67.2%)	30 (63.8%)	201 (67.7%)	0.056
vaginalni / <i>vaqinal</i>	113 (32.8%)	17 (36.2%)	96 (32.3%)	

karakteristike majki oba uzorka, učestalost ranog po-
doja i njihova povezanost.

Zajednički smeštaj majke i novorođenčeta 24 sata

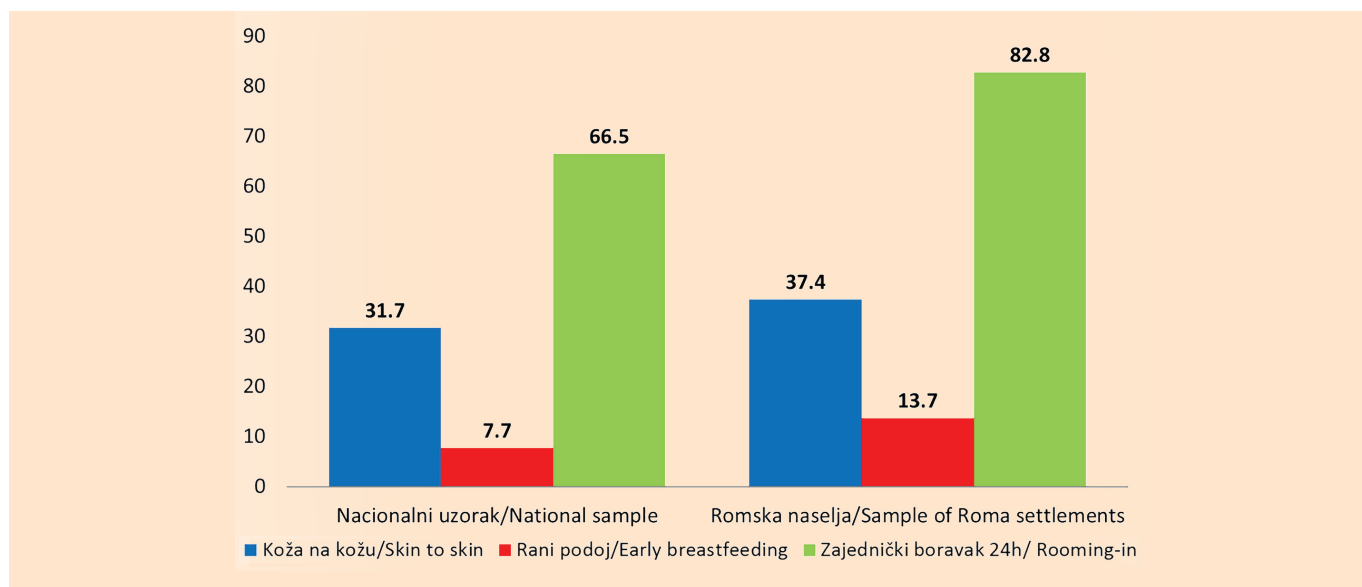
Boravak majke uz novorođenče bio je zastupljen kod 66,3% ispitanica u nacionalnom uzorku i 82,8% ispita-
nica romske nacionalnosti (Grafikon 1), što je statistički
značajna razlika ($p < 0,001$).

Starost, obrazovanje, radni status, sredina, indeks
blagostanja i materijalna deprivacija ispitanica nisu

Early breastfeeding

In the national sample, the percentage of children who
were breastfed for the first time within one hour of
birth was 7.7%. (Graph 1). A total of 13.7% of children
in the sample from Roma settlements received early
breastfeeding, which is a statistically significant differ-
ence.

In both samples, age, education, employment sta-
tus, environment and region of residence, the well-be-
ing index, and material deprivation did not show sta-
tistical significance regarding the frequency of early



Grafikon 1. Korišćenje bejbi frendli usluga u Srbiji, MICS 6 (2019)

Figure 1. Utilization of baby friendly services in Serbia, MICS 6 (2019)

Tabela 4. Demografske i socioekonomske karakteristike majki i učestalost korišćenja usluge: zajednički boravak majke uz novorođenče 24 sata, u oba uzorka**Table 4.** Demographic and socio-economic characteristics of the mothers and the frequency of rooming-in, in both samples

Karakteristike majki / <i>Characteristics of the mothers</i>	Ukupno / <i>Total</i>	Zajednički boravak majke uz novorođenče 24 sata / <i>Rooming-in</i>		p-vrednost / <i>p-value</i>
		Yes <i>n (%)</i>	No <i>n (%)</i>	
Nacionalni uzorak / <i>National sample</i>				
Starost / <i>Age</i>	136 (45.9%)	96 (48.7%)	40 (40.4%)	0.175
≤ 30 godina / <i>≤ 30 years</i>	160 (54.1%)	101 (51.3%)	59 (59.6%)	
> 30 godina / <i>> 30 years</i>				
Obrazovanje majke / <i>Mother's education level</i>	160 (54.1%)	103 (52.3%)	57 (57.6%)	0.389
osnovna i srednja škola / <i>elementary and high school education</i>	136 (45.9%)	94 (47.7%)	42 (42.4%)	
fakultet / <i>university level education</i>				
Radna aktivnost / <i>Employment status</i>	183 (61.8%)	117 (59.4%)	66 (66.7%)	0.224
aktivna / <i>employed</i>	113 (38.2%)	80 (40.6%)	33 (33.3%)	
neaktivna / <i>unemployed</i>				
Indeks blagostanja / <i>Well-being Index</i>	95 (32.2%)	70 (35.5%)	25 (25.5%)	0.598
loše / <i>poor</i>	51 (17.3%)	33 (16.8%)	18 (18.4%)	
srednje / <i>average</i>	149 (50.5%)	94 (47.7%)	55 (56.1%)	
dobro / <i>good</i>	136 (45.9%)	96 (48.7%)	40 (40.4%)	
Materijalna deprivacija / <i>Material deprivation</i>				0.213
≤ 3	60 (20.3%)	44 (22.3%)	16 (16.2%)	
> 3	236 (79.7%)	153 (77.7%)	83 (83.8%)	
Sredina / <i>Living environment</i>				0.767
gradska / <i>urban</i>	168 (56.8%)	113 (57.4%)	55 (55.6%)	
ostalo / <i>other</i>	128 (43.2%)	84 (42.6%)	44 (44.4%)	
Region / <i>Region</i>				< 0.001
Beograd / <i>Belgrade</i>	80 (26.9%)	54 (27.4%)	26 (26%)	
Vojvodina / <i>Vojvodina</i>	82 (27.6%)	42 (21.3%)	40 (40%)	
Šumadija i Zapadna Srbija / <i>Šumadija and West Serbia</i>	75 (25.3%)	49 (24.9%)	26 (26%)	
Južna i Istočna Srbija / <i>South and East Serbia</i>	60 (20.2%)	52 (26.4%)	8 (8%)	
Tip porođaja / <i>Type of delivery</i>				< 0.001
carski rez / <i>caesarean section</i>	80 (27%)	35 (17.8%)	45 (45.5%)	
vaginalni / <i>vaginal</i>	216 (73%)	162 (82.8%)	54 (54.5%)	
Uzorak romskih naselja / <i>Roma settlements sample</i>				
Starost / <i>Age</i>	300 (88.8%)	251 (89.6%)	49 (84.5%)	0.258
≤ 30 godina / <i>≤ 30 years</i>	38 (11.2%)	29 (10.4%)	9 (15.5%)	
> 30 godina / <i>> 30 years</i>				
Obrazovanje majke / <i>Mother's education level</i>				0.063
bez obrazovanja / <i>no education</i>	42 (12.4%)	31 (11.1%)	11 (19%)	
osnovna škola / <i>elementary school level</i>	236 (69.8%)	196 (70%)	40 (69%)	
srednja škola i više / <i>high school level and above</i>	60 (17.8%)	53 (18.9%)	7 (12.1%)	
Radna aktivnost / <i>Employment status</i>				0.405
aktivna / <i>employed</i>	40 (11.8%)	35 (12.5%)	5 (8.6%)	
neaktivna / <i>unemployed</i>	298 (88.2%)	245 (87.5%)	53 (91.4%)	

Indeks blagostanja / <i>Well-being Index</i>				
loše / <i>poor</i>	173 (51.2%)	139 (49.6%)	34 (58.6%)	0.342
srednje / <i>average</i>	60 (17.8%)	53 (18.9%)	7 (12.1%)	
dobro / <i>good</i>	105 (31.1%)	88 (31.4%)	17 (29.3%)	
Materijalna deprivacija / <i>Material deprivation</i>				
≤ 3	285 (84.3%)	239 (85.4%)	46 (79.3%)	0.249
> 3	53 (15.7%)	41 (14.6%)	12 (20.7%)	
Sredina / <i>Living environment</i>				
gradska / <i>urban</i>	231 (68.3%)	192 (68.6%)	39 (67.2%)	0.843
ostalo / <i>other</i>	107 (31.7%)	88 (31.4%)	19 (32.8%)	
Region / <i>Region</i>				
Beograd / <i>Belgrade</i>	82 (24.3%)	75 (26.8%)	7 (12.1%)	0.004
Vojvodina / <i>Vojvodina</i>	65 (19.2%)	50 (17.9%)	15 (25.9%)	
Šumadija i Zapadna Srbija / <i>Šumadija and West Serbia</i>	27 (8%)	17 (6.1%)	10 (17.2%)	
Južna i Istočna Srbija / <i>South and East Serbia</i>	164 (48.5%)	138 (49.3%)	26 (44.8%)	
Tip porođaja / <i>Type of delivery</i>				
carski rez / <i>caesarean section</i>	49 (27%)	39 (14.0%)	10 (17.2%)	0.528
vaginalni / <i>vaginal</i>	287 (73%)	162 (86.0%)	48 (82.8%)	

pokazali statističku značajnost u pogledu učestalosti boravka majke uz dete 24 sata, u oba uzorka. U oba uzorka postoji značajna statistička razlika u odnosu na region. Kod ispitanica nacionalnog uzorka, program boravka majke uz dete je bio najviše zastupljen u Beogradu a najmanje u Vojvodini ($p < 0,001$). Kod romskih ispitanica, program boravka majke uz dete je takođe bio najviše zastupljen u Beogradu a najmanje u regionu Šumadije i Zapadne Srbije ($p = 0,004$). Carski rez je imalo 17,8% ispitanica u nacionalnom uzorku iz programa boravka majke uz dete, te 45,5% onih koje nisu bile u zajedničkom smeštaju, što je statistički značajna razlika ($p < 0,001$). Način porođaja i boravak majke uz dete u uzorku iz romskih naselja nije statistički značajan. U Tabeli 4 je prikazana povezanost demografskih i socioekonomskih karakteristika oba uzorka sa korišćenjem zajedničkog smeštaja majke i deteta 24 sata.

DISKUSIJA

Istraživanje, sprovedeno 2019. godine, pokazalo je da organizovane aktivnosti utiču na unapređenje isključivog dojenja (ID), (engl. *exclusive breastfeeding – EBF*); (povećanje u opštoj populaciji sa 12,8% na 23,7%, od 2014. do 2019.), ali je i alarmiralo da je među romskom populacijom, za pet godina, došlo do pada isključivog dojenja sa 13% (2014) na 8,0% (2019) [12]. Obe vrednosti iz istraživanja 2019. godine su daleko niže od preporučenog cilja Svetske zdravstvene organizacije od najmanje 50% isključivo dojene dece mlađe od šest meseci [13]. Predmetom našeg istraživanja obuhvaćeno je sprovođenje dva od „Deset koraka ka uspešnom

breastfeeding. In both samples, there is a significant statistical difference ($p < 0.001$) regarding the availability of early breastfeeding for women who had had a cesarean section. In the national sample, not a single baby born by cesarean section had early breastfeeding, while only three respondents from the sample of mothers from Roma settlements were able to provide early breastfeeding for their baby. Table 3 presents the demographic and socioeconomic characteristics of the mothers of both samples, the frequency of early breastfeeding, and their association.

Rooming-in

Rooming-in occurred in 66.3% of respondents in the national sample and in 82.8% of the respondents of Roma nationality (Chart 1), which is a statistically significant difference ($p < 0.001$).

Age, education, employment status, environment, well-being index, and material deprivation of the respondents did not show statistical significance regarding the frequency of rooming-in, in both samples. In both samples, there is a statistically significant difference in relation to region. Among the respondents of the national sample, the rooming-in program was most prevalent in Belgrade and least prevalent in Vojvodina ($p < 0.001$). Among Roma respondents, the rooming-in program was also most prevalent in Belgrade and least prevalent in the region of Šumadija and West Serbia ($p = 0.004$). A cesarean section was performed on 17.8% of respondents in the national sample from the rooming-in program, and on 45.5%

dojenju", odnosno, Koraka 4. „Nega neposredno posle rođenja" (kontakt KNK neposredno nakon porođaja u trajanju od najmanje 60 minuta i rani podoj u toku prvog sata po rođenju) i Koraka 7. „Zajednički smeštaj majke i novorođenčeta 24 sata", kao aktivnosti koje dokazano utiču, kako na uspostavljanje isključivog dojenja u porodilištu [14], tako i na nastavak ID-a [15].

Rezultati ovog istraživanja pokazuju da je procedura KNK u nacionalnom uzorku u Srbiji primenjena kod 31,7% porodilja. Prema MICS istraživanjima sprovedenim u regionu (2018 – 2020), ova procedura je primenjivana sa sličnim rezultatima u Crnoj Gori (33,9%), Severnoj Makedoniji (32,8%) i na Kosovu* (UNSCR 1244), (33,2%). U porodilja iz romske populacije u Srbiji kontakt KNK je primenjen kod 37,4% majki, što je više nego u istoj populaciji u Crnoj Gori (29,1%), Severnoj Makedoniji (26,9%) i u uzorku u naseljima Roma, Aškalija i Egipćana na Kosovu* (UNSCR 1244), (32%) [16–18]. Sistematski pregled prevalencije kontakta KNK nakon vaginalnog porođaja u svetu [19] je obuhvatio 35 studija (2007 – 2017) iz 28 zemalja sa predstavnicima svih šest regiona Svetske zdravstvene organizacije, i sa ukupno 429.222 žena. Prevalencija KNK postupka se kretala od 1% do 98%, a viša je u zemljama sa višim nacionalnim dohotkom i u studijama koje su obuhvatile samo vaginalne porođaje (Kanada 81%, Finska 89%, Australija 93%, Danska 95,6%, Hrvatska 97,8%). U zemljama sa niskim BDP-om [20,21] postoji pozitivna povezanost višeg obrazovanja i viših primanja u domaćinstvu sa višom prevalencijom kontakta KNK. U istim istraživanjima postoji i statistički značajna povezanost mesta porođaja (porodilište u odnosu na porođaj u domu porodilje), regiona (gradsko u odnosu na ruralno), kao i korišćenja prenatalne zdravstvene zaštite, što je takođe češće kod žena sa višim obrazovanjem i višim materijalnim statusom domaćinstva.

U brojnim istraživanjima postoji negativna povezanost carskog reza i kontakta KNK [22–24]. Procenat carskih rezova u Srbiji je visok (svaki treći porođaj) [25] i ukazuje na medicinski sistem. U opštoj populaciji, carskim rezom se mnogo češće porađaju žene iz domaćinstava natprosečnog materijalnog stanja, iz gradskih naselja i žene sa višim nivoom obrazovanja [12]. Kod novorođenčadi koja su rođena carskim rezom, stopa dojenja je obično niža u poređenju sa bebama rođenih vaginalnim porođajem, što potvrđuju istraživanja pri otpustu iz porodilišta [22–24]. Neposredni kontakt KNK nakon carskog reza uz upotrebu spinalne ili epiduralne anestezije je moguć jer majka ostaje budna. Međutim, nakon opšte anestezije, novorođenče treba da se stavi „koža na kožu" čim majka bude budna i reaguje [24].

Rani početak dojenja u Srbiji u nacionalnom uzorku (7,7%) je niži nego u zemljama u okruženju: 24,1% u Cr-

of those who did not stay in the same room with their newborn, which is a statistically significant difference ($p < 0.001$). The type of delivery and rooming-in, in the sample of respondents from Roma settlements, is not statistically significant. Table 4 shows the association of demographic and socioeconomic characteristics of both samples with the use of 24-hour shared accommodation for mother and child (rooming-in).

DISCUSSION

A study conducted in 2019 showed that organized activities influence the promotion of exclusive breastfeeding (EBF); (an increase in the general population from 12.8% to 23.7%, between 2014 and 2019), but it was also alarming that among the Roma population, in those five years, there was a drop in exclusive breastfeeding from 13% (2014) to 8.0% (2019) [12]. Both values from the 2019 survey are far lower than the World Health Organization recommended goal of at least 50% of exclusively breastfed children under six months of age [13]. The subject of our study included the implementation of two of the "Ten Steps to Successful Breastfeeding", i.e., Step 4. "Immediate Postnatal Care" (STS contact immediately after birth for at least 60 minutes and early breastfeeding within the first hour after birth) and Step 7. "Rooming-in", as activities that have been proven to influence both the establishing of exclusive breastfeeding in the maternity ward [14] and the continuation of EBF [15].

The results of this study show that the STS procedure in the national sample of Serbia was applied in 31.7% of women giving birth. According to MICS research conducted in the region (2018 - 2020), this procedure was applied with similar results in Montenegro (33.9%), North Macedonia (32.8%), and Kosovo* (UNSCR 1244), (33.2 %). In parturient women from the Roma population in Serbia, 37.4% of mothers had STS, which is more than in the same population in Montenegro (29.1%), North Macedonia (26.9%), and in the sample of Ashkali and Egyptians in Roma settlements in Kosovo* (32%), (UNSCR 1244) [16–18]. A systematic review of the prevalence of STS after vaginal delivery in the world [19] included 35 studies (2007 – 2017) from 28 countries with representatives of all six regions of the World Health Organization, and with a total of 429,222 women. The prevalence of the STS procedure ranged from 1% to 98%, and was higher in countries with higher GDP and in studies that included only vaginal deliveries (Canada 81%, Finland 89%, Australia 93%, Denmark 95.6%, Croatia 97.8%). In countries with low GDP [20,21], there is a positive association of higher education and higher household income with a higher prevalence of STS. In the same study, there is also a statistically significant as-

noj Gori, 9,5% u Severnoj Makedoniji i 32,1% na Kosovu* (UNSCR 1244) [16-18]. U uzorcima iz romske populacije, rani podoj u Srbiji od 13,7% takođe je niži nego u okruženju: u Crnoj Gori 40,9%, u Severnoj Makedoniji 15,7%, a na Kosovu* (UNSCR 1244) 54,9% [16-18].

U studijama prevalencije ranog podoja u zemljama sa niskim BDP-om, pokazani su raznoliki uticaji socio-demografskih varijabli na rano započinjanje dojenja: u regiji severne Tanzanije, socioekonomske karakteristike majke (godine, obrazovanje, bračni status, zanimanje, primanja) nisu bile povezane sa početkom ranog podoja [26]. U istraživanju povezanosti faktora za rani početak dojenja u ruralnoj oblasti Etiopije, majke višeg obrazovanja su imale 3,2 puta veću šansu za rani podoj od majki bez formalnog obrazovanja [27]. Istraživanje povezanosti determinanti sa ranim podojem u Papua Novoj Gvineji pokazalo je povezanost sa godinama porodilje (najniže u grupi 15 – 19, u odnosu na žene starosti 20 – 29 i 30 i više godina), kao i sa regionom [28]. U svim istraživanjima je način porođaja uticao na početak ranog dojenja – žene koje su se porodile carskim rezom imale su značajno manju šansu (i do 93%) za rani podoj [26-28].

Praksa zajedničkog smeštaja u sobu, prema definiciji Svetske zdravstvene organizacije i UNICEF-a, jeste „bolnička praksa u kojoj majke nakon porođaja i zdravo terminsko novorođenče ostaju zajedno u istoj prostoriji 24 sata dnevno od trenutka kada stignu u svoju sobu (*rooming-in*) [29]. Zajednički smeštaj majke i novorođenčeta u istoj sobi olakšava početak dojenja s obzirom da majka može da nauči da prepozna i odgovori na znake da je novorođenče gladno, a takođe omogućava majci da vežba da brine o svom detetu kao i da doji u bezbednom okruženju kada to novorođenče traži. Pokazalo se da su majke koje su smeštene u sobi zajedno sa detetom osetljivije prema svom detetu i da sa ljubavlju i nežnošću odgovaraju na njegove potrebe (majke i bebe bolje spavaju i doživljavaju manje anksioznosti). Pokazalo se, osim toga, da kontakt KNK, koji je lak za korišćenje u sobama, smanjuje postporođajnu depresiju i fiziološki stres majke [30,31].

U našem istraživanju, statistički značajno niži procenat zajedničkog boravka majke uz dete u nacionalnom uzorku u Srbiji (66,5%), u odnosu na uzorak iz romskih naselja (82,8%), jeste rezultat značajno češćih porođaja carskim rezom u nacionalnom uzorku (32,3% : 18,5%). U oba uzorka je zajednički boravak majke uz dete 24 sata značajno češći u Beogradu, u kome je najveće porodilište na Balkanu, a koje je i nosilac Nacionalnog programa podrške dojenju u Srbiji.

Veoma važne poruke o značaju neprekidnog boravka majke uz novorođenče proističu iz studije sprovedene u Finskoj. Naime, nakon drastičnog smanjenja is-

sociation between the place of birth (maternity center versus home birth), region (urban versus rural), as well as the use of prenatal health care, which is also more common among women with a higher education level and with a higher household financial status.

In numerous studies, there is a negative association between cesarean section and STS contact [22-24]. The percentage of cesarean sections in Serbia is high (every third birth) [25] which is indicative of the medical system. In the general population, cesarean births are much more common among women from households with above-average financial means, women from urban settlements, and women with a higher level of education [12]. In newborns born by cesarean section, the rate of breastfeeding is usually lower compared to babies born by vaginal delivery, which has been confirmed by studies examining data obtained at discharge from the maternity ward [22-24]. Direct STS contact after cesarean section with the use of spinal or epidural anesthesia is possible because the mother remains awake. However, after general anesthesia, the newborn should be placed skin-to-skin to the mother as soon as she is awake and responsive [24].

Early initiation of breastfeeding in Serbia, in the national sample (7.7%) is lower than in neighboring countries: 24.1% in Montenegro, 9.5% in North Macedonia, and 32.1% in Kosovo* (UNSCR 1244) [16-18]. The early initiation of breastfeeding in Serbia in samples from the Roma population amounting to 13.7% is also lower than in the surrounding area: in Montenegro 40.9%, in North Macedonia 15.7%, and in Kosovo* 54.9% (UNSCR 1244) [16-18].

In studies on the prevalence of early breastfeeding in low-GDP countries, diverse influences of sociodemographic variables on early initiation of breastfeeding have been shown: in the northern region of Tanzania, socioeconomic characteristics of the mother (age, education, marital status, occupation, income) were not associated with the initiation of early breastfeeding [26]. In a study analyzing the association of factors for early initiation of breastfeeding in a rural area of Ethiopia, mothers with higher education were 3.2 times more likely to initiate early breastfeeding than mothers with no formal education [27]. Research on the association between determinants and early breastfeeding in Papua New Guinea showed an association with the age of the mother (lowest in the 15 – 19 age group, as compared to women aged 20 – 29 and 30 and above), as well as with the region [28]. In all studies, the type of delivery influenced the initiation of early breastfeeding – women who gave birth by cesarean section had a significantly lower chance (up to 93%) of early breastfeeding [26-28].

ključivog dojenja dece starosti šest meseci na samo 1% (2012. godine), u Finskoj je intenziviran program *BFHI* (*Baby Friendly Hospital Initiative*) „Deset koraka ka uspešnom dojenju”. Posle pet godina, procenat zajedničkog boravka majki uz novorođenčad iznosio je 91%. Finska studija je pokazala da porodilišta u njihovim bolnicama primenjuju zajednički smeštaj majke i novorođenčeta u istoj sobi u zadovoljavajućoj meri, jer je značajan broj parova majka-dete zajedno tokom postporođajnog perioda. Ova studija podržava povećanu primenu Koraka 7 programa *BFHI* i kod porodilja koje su porođene carskim rezom. Glavna preporuka je da kompletno osoblje porodilišta jasno razume značaj i svoju ulogu u sprovođenju zajedničkog smeštaja u sobi, sa krajnjim ciljem da isključivo dojenje bude dugoročno. Ključni deo ovoga jeste da su svi članovi osoblja završili dvadesetočasovnu obuku Svetske zdravstvene organizacije za savetovanje o dojenju, jer osoblje koje je završilo ovu edukaciju češće sprovodi zajednički smeštaj majke i novorođenčeta u sobu nego osoblje koje nema ovu obuku [32].

U poslednjem izveštaju programa *BFHI* za Evropski region, u kojoj je učestvovala 31 zemlja, uključujući i Srbiju, 21,4% (6) zemalja je ispunilo preporučeni *BFHI* standard primene procedure KNK (pet minuta nakon porođaja u trajanju najmanje 60 minuta) kod preko 80% žena; 42,8% (12) zemalja je ispunilo preporučeni *BFHI* standard primene ranog podoja (unutar jednog sata nakon porođaja) kod preko 80% žena; 14,3% (4) država je ispunilo novi preporučeni *BFHI* standard Koraka 7 – kod 80% žena razdvajanje majke i novorođenčeta ne treba da traje duže od jednog sata [33].

Tokom zdravstveno vaspitnog rada, a u skladu sa nalazima ovog istraživanja, izdvojile su se važne smerice za obuku svih zainteresovanih strana. Ključne zdravstveno-vaspitne poruke treba da se odnose na rani podoj i kontakt. Rani podoj podstiče proizvodnju majčinog mleka, ubrzava laktogenezu i smanjuje rizik od smrti bebe [3,4,6]. Neposredan i neprekinut kontakt „koža na kožu” olakšava novorođenčetu da ispolji prirodni refleks sisanja, pomaže uspostavljanju mikrobioma kod novorođenčeta i sprečava hipotermiju. Ova dva postupka obično se dešavaju u istom činu i imaju uticaj na emocionalno povezivanje majke i deteta. Sve tri navedene prakse *bejbi friendly* porodilišta svoje utemeljenje pronalaze u medicini zasnovanoj na dokazima, odnosno literaturnim podacima koji govore u prilog zdravstvenih koristi za majku i za dete [19–24, 30–32].

ZAKLJUČAK

Rezultati ovog istraživanja pokazali su da se u porodilištima u našoj zemlji *bejbi friendly* usluge za promociju dojenja ne implementiraju u skladu sa ciljevima iz Nacionalnog programa podrške dojenju, porodičnoj i

The practice of rooming-in, according to the definition by the World Health Organization and UNICEF, is “a hospital practice in which postpartum mothers and a healthy term newborn stay together in the same room 24 hours a day from the moment they arrive in their room (rooming-in) [29]. Putting mother and infant together in the same room makes breastfeeding easier as the mother can learn to recognize and respond to signs that the infant is hungry, and it also allows the mother to practice caring for her infant as well as to breastfeed it in a safe environment when the infant requests it. It has been shown that mothers who are placed in a room together with their child are more sensitive towards their child and respond to their needs with love and tenderness (mothers and babies sleep better and experience less anxiety). In addition, STS contact, which is easy to apply when the mother and baby are staying in the same room, has been shown to reduce postpartum depression and physiological stress of the mother [30,31].

In our study, the statistically significantly lower percentage of rooming-in, in the national sample in Serbia (66.5%), as compared to the sample from Roma settlements (82.8%), is the result of significantly more frequent cesarean births in the national sample (32.3% : 18.5%). In both samples, rooming-in is significantly more common in Belgrade, which is home to the largest maternity hospital in the Balkans and host of the National Breastfeeding Support Program in Serbia.

Very important messages regarding the importance of the mother’s continuous stay with the newborn arise from a study conducted in Finland. Namely, after the drastic reduction of exclusive breastfeeding of babies until the age of six months to only 1% (in 2012), the *BFHI* (*Baby Friendly Hospital Initiative*) “Ten Steps to Successful Breastfeeding” program was intensified in Finland. After five years, the percentage of mothers sharing a room with their newborns was 91%. A Finnish study showed that maternity wards in their hospitals implement rooming-in to a satisfactory extent, as a significant number of mother-child pairs are together during the postpartum period. This study supports the increased use of Step 7 of the *BFHI* program in women who have had a cesarean delivery. The main recommendation is that the entire staff of the maternity ward clearly understand the importance of rooming-in and their own role in implementing this practice, with the ultimate goal of making exclusive breastfeeding long-term. A key part of this is that all staff members have completed 20 hours of World Health Organization breastfeeding counseling training, as staff who have completed this training are more likely to room-in mother and infant than staff who do not have this training [32].

In the latest *BFHI* report for the European Region,

razvojnoj nezi novorođenčeta. Najveća prepreka postizanju ciljeva Nacionalnog programa je veliki procenat porođaja carskim rezom u Srbiji (33%), kao i nizak procenat porođaja uz epiduralnu anesteziju posle kojih se bezbedno mogu primeniti Koraci 3 i 7 Vodiča „Deset koraka ka uspešnom dojenju“.

Iskustva zemalja ili zdravstvenih ustanova koje su ispunile preporučene standarde programa *BFHI* – obuhvat preko 80% majki u porodilištima primenom Koraka 4 i Koraka 7 Vodiča, pokazuju da je preduslov za to ispunjenje Koraka 1 i Koraka 2 Vodiča, a koji se odnose na usvajanje politika podrške dojenju u ustanovi i obavezu kontinuirane edukacije kompletnog osoblja koje je u kontaktu sa majkama tokom boravka u porodilištu (dvadesetočasovna obuka Svetske zdravstvene organizacije za savetovanje o dojenju).

U domenu odabira uspešnih zdravstveno-vaspitnih intervencija koje promovišu dojenje u svrhu dostizanja globalnog cilja jesu širenje znanja i svesti o značaju dojenja, pre svega među kreatorima politika, koordinatorima programa, zdravstvenim radnicima i u zajednici. Neophodno je podsticanje pozitivnih stavova prema dojenju, pre svega ciljne grupe trudnica, ali i zdravstvenih radnika koji imaju neposredni kontakt sa ženama tokom trudnoće na primarnom i sekundarnom nivou zdravstvene zaštite.

Spisak skraćenica

SZO – Svetska zdravstvena organizacija

UNICEF – Dečiji fond Ujedinjenih nacija (engl. *United Nations International Children's Emergency Fund*)

BDP – Bruto domaći proizvod

IQ – Koeficijent inteligencije (engl. *intelligence quotient*)

KNK – Kontakt „koža na kožu“

MICS – Istraživanje višestrukih pokazatelja položaja žena i dece (engl. *Multiple Indicator Cluster Survey*)

ID – Isključivo dojenje (*exclusive breastfeeding – EBF*)

BFHI – Bolnica prijatelj majki i novorođenčadi (engl. *Baby-Friendly Hospital Initiative*)

Sukob interesa: Nije prijavljen.

LITERATURA / REFERENCES

1. World Health Organization. International Code of Marketing of Breast-Milk Substitutes. Geneva: World Health Organization 1981). [Internet]. [Citirano 13. mart 2024.]. Dostupno na: <https://iris.who.int/bitstream/handle/10665/40382/9241541601.pdf?sequence=1>
2. Jama A, Gebreyesus H, Wubayehu T, Gebregyorgis T, Teweldemedhin M, Berhe T, et al. Exclusive breastfeeding for the first six months of life and its associated factors among children aged 6-24 months in Burao district, Somaliland. *Int Breastfeed J*. 2020 Jan 30;15(1):5. doi: 10.1186/s13006-020-0252-7.
3. Binns C, Lee M, Low WY. The Long-Term Public Health Benefits of Breastfeeding. *Asia Pac J Public Health*. 2016 Jan;28(1):7-14. doi: 10.1177/1010539515624964.

wherein 31 countries participated, including Serbia, 21.4% (6) of the countries met the recommended BFHI standard for the application of the STS procedure (five minutes after delivery for at least 60 minutes) in over 80 % woman; 42.8% (12) of countries met the recommended BFHI standard of implementing early breastfeeding (within one hour after delivery) in over 80% of women; 14.3% (4) of countries met the new recommended BFHI standard defined in Step 7 –in 80% of women, mother-infant separation should not last longer than one hour [33].

During health education work, and in keeping with the findings of this study, important guidelines for the training of all stakeholders have emerged. Key health-educational messages should relate to early breastfeeding and contact. Early breastfeeding stimulates the production of breast milk, accelerates lactogenesis, and reduces the risk of infant death [3,4,6]. Immediate and continuous skin-to-skin contact facilitates the newborn's natural sucking reflex, helps establish the newborn's microbiome, and prevents hypothermia. These two processes usually happen as one event and have an impact on the emotional connection between mother and child. All three of the aforementioned practices of baby-friendly maternity hospitals are founded on evidence-based medicine, i.e., literature data that speak in favor of health benefits for the mother and the child [19-24,30-32].

CONCLUSION

The results of this study have shown that, in maternity hospitals in our country, baby-friendly services for the promotion of breastfeeding are not implemented in accordance with the goals of the National Program for Breastfeeding Support and Developmental Care of a Newborn. The biggest obstacle to achieving the goals of the National Program is the high percentage of cesarean deliveries in Serbia (33%), as well as the low percentage of deliveries with epidural anesthesia, after which Steps 3 and 7 of the “Ten Steps to Successful Breastfeeding” Guide can be safely applied.

The experiences of countries or health institutions that have met the recommended standards of the BFHI program – coverage of more than 80% of mothers in maternity hospitals by applying Step 4 and Step 7 of the Guide, show that the prerequisite for this is the fulfillment of Step 1 and Step 2 of the Guide, which refer to the adoption of support policies for breastfeeding in the health institution and the obligation of continuous education of the entire staff who are in contact with mothers during their stay at the maternity hospital (twenty-hour training of the World Health Organization for counseling on breastfeeding).

4. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al.; Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016 Jan 30;387(10017):475–90. doi: 10.1016/S0140-6736(15)01024-7.
5. Bagci Bosi AT, Eriksen KG, Sobko T, Wijnhoven TM, Breda J. Breastfeeding practices and policies in WHO European Region Member States. *Public Health Nutr*. 2016 Mar;19(4):753–64. doi: 10.1017/S1368980015001767. [Internet]. [Citirano 13. mart 2024.]. Dostupno na: <https://pubmed.ncbi.nlm.nih.gov/26096540/>
6. NEOVITA Study Group. Timing of initiation, patterns of breastfeeding, and infant survival: prospective analysis of pooled data from three randomised trials. *Lancet Glob Health*. 2016;4(4): e266–75. doi:10.1016/S2214-109X(16)00040-1.
7. WHO and UNICEF. Capture the Moment – Early initiation of breastfeeding: The best start for every newborn. New York. 2018. [Internet]. [Citirano 13. mart 2024.]. Dostupno na: <https://www.unicef.org/eca/media/4256/file/Capture-the-moment-EIBF-report.pdf>
8. Smith ER, Hurt L, Chowdhury R, Sinha B, Fawzi W, Edmond KM; Neovita Study Group. Delayed breastfeeding initiation and infant survival: A systematic review and meta-analysis. *PLoS One*. 2017 Jul 26;12(7):e0180722. doi: 10.1371/journal.pone.0180722.
9. Sameen A, Sakshi J, Walters D. The Global Cost of Not Breastfeeding. Nutrition International, August 2022. [Internet]. Dostupno na: <https://www.aliveandthrive.org/sites/default/files/2022-07/CONBF%20Global%20Brief-v6%20%281%29.pdf>
10. Uredba o Nacionalnom programu podrške dojenju, porodičnoj i razvojnoj nezi novorođenčeta: 53/2018-3 [Internet]. [Citirano 25. jul 2022.]. Dostupno na: <https://www.pravno-informacioni-sistem.rs/SlGlasnikPortal/eli/rep/sgrs/vlada/uredba/2018/53/1/reg>
11. Republički zavod za statistiku i UNICEF, 2014. Istraživanje višestrukih pokazatelja položaja žena i dece u Srbiji 2014, i Istraživanje višestrukih pokazatelja položaja žena i dece u romskim naseljima u Srbiji 2014, Konačni rezultati. Beograd, Srbija: Republički zavod za statistiku i UNICEF. [Internet]. [Citirano 12. mart 2024.]. Dostupno na: <https://www.unicef.org/serbia/media/6496/file/Istra%C5%BEivanje%20vi%C5%A1estrukih%20pokazatelja%202014.%20-%20Rezime.pdf>
12. MICS Srbija-Istraživanje višestrukih pokazatelja 2019 i Srbija-romska naselja. Istraživanje višestrukih pokazatelja 2019. [Internet]. [Citirano 12. mart 2024.]. Dostupno na: <https://www.unicef.org/serbia/media/16726/file/MICS%206%20Multiple%20Indicator%20Cluster%20Survey%20for%202019.pdf>
13. WHO. Global targets 2025. To improve maternal, infant and young child nutrition. [Internet]. Dostupno na: <https://www.who.int/publications/i/item/WHO-NMH-NHD-14.2>
14. Jaafar S, Ho JJ, Lee K. Rooming-in for new mother and infant versus separate care for increasing the duration of breastfeeding. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD006641. DOI: 10.1002/14651858.CD006641.pub3
15. Potgieter KL, Adams F. The influence of mother-infant skin-to-skin contact on bonding and touch. *S. Afr. j. occup. ther.* 2019 Aug. <http://dx.doi.org/10.17159/2310-3833/2019/vol49n2a3>.
16. Montenegro and Montenegro Roma Settlements Multiple Indicator Cluster Survey 2018 Survey Findings Report December 2019. [Internet]. Dostupno na: https://mics-surveys-prod.s3.amazonaws.com/MICS6/Europe%20and%20Central%20Asia/Montenegro%20%28Roma%20Settlements%29/2018/Survey%20findings/Montenegro%20%28National%20and%20Roma%20Settlements%29%202018%20MICS%20SFR_v4_English.pdf
17. North Macedonia and North Macedonia Roma Settlements Multiple Indicator Cluster Surveys 2018-2019 Survey Findings Reports. May, 2020. [Internet]. Dostupno na: <https://mics-surveys-prod.s3.amazonaws.com/>

Within the domain of the selection of successful health educational interventions that promote breastfeeding with the aim of achieving the global goal is spreading knowledge and awareness about the importance of breastfeeding, primarily among policymakers, program coordinators, health workers, and within the community. It is necessary to encourage positive attitudes towards breastfeeding, primarily among the target group of pregnant women, but also among health workers who have direct contact with women during pregnancy at the primary and secondary levels of health care.

List of abbreviations and acronyms

WHO – World Health Organization
 UNICEF – United Nations International Children's Emergency Fund
 GDP – Gross domestic product
 IQ – intelligence quotient
 STS – skin-to-skin contact
 MICS – Multiple Indicator Cluster Survey
 EBF – exclusive breastfeeding
 BFHI – Baby-Friendly Hospital Initiative

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- MICS6/Europe%20and%20Central%20Asia/North%20Macedonia%2C%20Republic%20of%20%28Roma%20Settlements%29/2018-2019/Survey%20findings/North%20Macedonia%20and%20North%20Macedonia%20Roma%20Settlements%20MICS%202018-19%20SFR_English.pdf
18. Kosovo* (UNSCR 1244) Multiple Indicator Cluster Survey 2019–2020 and Roma, Ashkali and Egyptian Communities in Kosovo Multiple Indicator Cluster Survey 2019–2020 Survey Findings Report November, 2020. [Internet]. Dostupno na: https://mics-surveys-prod.s3.amazonaws.com/MICS6/Europe%20and%20Central%20Asia/Kosovo%20under%20UNSC%20res.%201244%20%28Roma%2C%20Ashkali%2C%20and%20Egyptian%20Communities%29/2019-2020/Survey%20findings/Kosovo%20%28UNSCR%201244%29%20%28National%20and%20Roma%2C%20Ashkali%20and%20Egyptian%20Communities%29%202019-20%20MICS-SFR_English.pdf
19. Abdulghani N, Edvardsson K, Amir LH. Worldwide prevalence of mother-infant skin-to-skin contact after vaginal birth: A systematic review. *PLoS One*. 2018 Oct 31;13(10):e0205696. doi: 10.1371/journal.pone.0205696.
20. Ekholuenetale M, Barrow A, Benebo FO, Idebolo AF. Coverage and factors associated with mother and newborn skin-to-skin contact in Nigeria: a multilevel analysis. *BMC Pregnancy Childbirth*. 2021 Sep 4;21(1):603. doi: 10.1186/s12884-021-04079-8. [Internet]. /
21. Ekholuenetale M, Onikan A, Ekholuenetale C.E. Prevalence and determinants of mother and newborn skin-to-skin contact in The Gambia: a secondary data analysis. *J. Egypt. Public. Health. Assoc.* 95, 18 (2020). doi.org/10.1186/s42506-020-00050-1.
22. Zanardo V, Pigozzo A, Wainer G, Marchesoni D, Gasparoni A, Di Fabio S, et al. Early lactation failure and formula adoption after elective caesarean delivery: cohort study. *Archives of Disease in Childhood*. 2013;98(1):F37–F41. doi: 10.1136/archdischild-2011-301218.

23. Guala A, Boscardini L, Visentin R, Angellotti P, Grugni L, Barbaglia M, et al. Skin-to-Skin Contact in Cesarean Birth and Duration of Breastfeeding: A Cohort Study. *ScientificWorldJournal*. 2017;2017:1940756. doi: 10.1155/2017/1940756.
24. Gouchon S, Gregori D, Picotto A, Patrucco G, Nangeroni M, Di Giulio P. Skin-to-skin contact after cesarean delivery: an experimental study. *Nurs Res*. 2010 Mar-Apr;59(2):78-84. doi: 10.1097/NNR.0b013e3181d1a8bc.
25. Horozović V, Živković-Šulović M, Dukić D, Ljubičić M, Atanasijević D, Brcanski J, et al. Izveštaj o unapređenju kvaliteta rada u zdravstvenim ustanovama u Republici Srbiji 2018. godine. Pokazatelji kvaliteta rada odeljenja ginekologije i akušerstva u bolnicama, Srbija, 2018. (tabela 4, str. 142). [Internet]. Dostupno na: <https://www.batut.org.rs/download/izvestaji/lzvestaj%20kvalitet%202018.pdf>
26. Lyellu HY, Hussein TH, Wandel M, Stray-Pedersen B, Mgongo M, Msuya SE. Prevalence and factors associated with early initiation of breastfeeding among women in Moshi municipal, northern Tanzania. *BMC Pregnancy Childbirth* 20, 285 (2020). <https://doi.org/10.1186/s12884-020-02966-0>.
27. Gebremeskel SG, Gebru TT, Gebrehiwot BG, Meles HN, Tafere BB, Gebreslassie GW, et al. Early initiation of breastfeeding and associated factors among mothers of aged less than 12 months children in rural eastern zone, Tigray, Ethiopia: cross-sectional study. *BMC Res Notes* 12, 671 (2019). <https://doi.org/10.1186/s13104-019-4718-x>
28. Seidu AA, Ahinkorah BO, Agbaglo E, Dadzie LK, Tetteh JK, Ameyaw EK, et al. Determinants of early initiation of breastfeeding in Papua New Guinea: a population-based study using the 2016-2018 demographic and health survey data. *Arch Public Health* 78, 124 (2020). <https://doi.org/10.1186/s13690-020-00506-y>
29. World Health Organization. Implementation guidance: protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services – the revised Baby-friendly Hospital Initiative. Geneva: World Health Organization; 2018.
30. Crenshaw JT. Healthy Birth Practice #6: Keep Mother and Baby Together- It's Best for Mother, Baby, and Breastfeeding. *J Perinat Educ*. 2014 Fall;23(4):211-7. doi: 10.1891/1058-1243.23.4.211./
31. Bigelow A, Power M, MacLellan-Peters J, Alex M, McDonald C. Effect of mother/infant skin-to-skin contact on postpartum depressive symptoms and maternal physiological stress. *JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing*. 2012;41(3):369–382. doi: 10.1111/j.1552-6909.2012.01396_1.x.
32. Hakala M, Kaakinen P, Kääriäinen M, Bloigu R, Hannula L, Elo S. Implementation of Step 7 of the Baby-Friendly Hospital Initiative (BFHI) in Finland: Rolling-in according to mothers and maternity-ward staff. *Eur J Midwifery*. 2018 Aug 23;2:9. doi: 10.18332/ejm/93771.
33. 2022 BFHI Status country Report Summary, Maite Hernandez Aguilar BFHI Network. 2022. [Internet]. [Citirano 13. mart 2024.]. Dostupno na: <https://www.ihan.es/wp-content/uploads/2022-BFHI-Status-Country-Report-summary.pdf>

DETERMINANTE NAMERE VAKCINISANJA PROTIV HUMANOG PAPILOMA VIRUSA KOD UČENIKA

ORIGINALNI RAD

ORIGINAL ARTICLE

DETERMINANTS OF THE HUMAN PAPILLOMAVIRUS (HPV) VACCINATION INTENTION AMONG STUDENTS

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SAŽETAK

Uvod: Humani papiloma virus (HPV) je virus koji je najčešće povezan sa karcinomima. Karcinom grlića materice predstavlja jedan od vodećih problema javnog zdravlja, naročito u zemljama u razvoju. U Republici Srbiji, rak grlića materice je u ženskoj populaciji po učestalosti na petom mestu u odnosu na sve maligne bolesti, a infekcija HPV-om je najvažniji faktor rizika za nastanak ove bolesti. Cilj ove studije je bilo utvrđivanje determinanti namere vakcinisanja protiv HPV virusa kod adolescenata.

Materijali i metode: Istraživanje je sprovedeno kao studija preseka u kojoj je učestvovalo ukupno 748 učenika uzrasta 12 – 19 godina, iz jedne srednje i dve osnovne škole u Šapcu. Instrument istraživanja je bio upitnik, posebno sastavljen za potrebe ovog istraživanja. Da bi se ispitao prediktivni model u objašnjavanju namere vakcinisanja protiv HPV-a kod mladih, primenjena je multipla linearna regresija.

Rezultati: Predloženi model objašnjava 66% namere vakcinisanja protiv HPV-a kod mladih. Najjači prediktor namere vakcinisanja protiv HPV-a kod mladih se odnosi na subjektivnu normu, odnosno društveni pritisak vršnjaka i drugih osoba koje su za njih značajne. Nepoverenje u korisnost vakcinacije, zabrinutost zbog komercijalnog profiterstva i uverenja o zaveri o vakcinama, imaju značajno manji, ali statistički važan doprinos u objašnjavanju namere naših mladih u vezi sa vakcinacijom protiv HPV-a.

Zaključak: Sve veći društveni pritisak da se vakcinišu, kao i promena određenih stavova i uverenja o vakcinama uopšte, može dovesti do povećanja namere mladih da se vakcinišu protiv HPV-a. Sagledavanje ključnih aspekata u odnosu mladih u Srbiji prema HPV vakcinaciji daje mogućnost da se kreiraju javnozdravstvene politike zasnovane na dokazima i planiraju ciljne zdravstveno-vaspitne intervencije usmerene na identifikovane nalaze.

Ključne reči: humani papiloma virus, vakcinacija, adolescenti

ABSTRACT

Introduction: Human papillomavirus (HPV) is the virus that is most often associated with cancers. Cervical cancer is one of the leading public health problems, especially in developing countries. In the Republic of Serbia, cervical cancer is the fifth most common cancer in the female population amongst all malignant diseases, and HPV infection is the most important risk factor for the occurrence of this disease. This study aims to identify the determinants of adolescent HPV vaccination intention.

Materials and methods: The study was conducted as a cross-sectional study including a total of 748 students, aged 12 –19 years, from one high school and two elementary schools in Šabac. The research instrument was a questionnaire, particularly constructed for this study. Multiple regression analysis was applied to examine the predictive model for explaining the HPV vaccination intention in young people.

Results: The proposed model explains 66% of HPV vaccination intention in young people. The strongest predictor of HPV vaccination intention in young people relates to the subjective norm, i.e., social pressure from peers and other people who are important to them. Distrust of the benefit of vaccination, concern about commercial profiteering, and belief in a “vaccine conspiracy” have a significantly smaller but statistically significant contribution in explaining HPV vaccination intention amongst our youth.

Conclusion: Increasing social pressure to get vaccinated, as well as changing certain attitudes and beliefs about vaccines in general, may lead to an increase in the intention of young people to get vaccinated against HPV. Understanding the key aspects of the attitudes of young people in Serbia towards HPV vaccination opens the possibility of creating evidence-based public health policies and planning targeted health-educational interventions directed at the identified findings.

Keywords: human papillomavirus, vaccination, adolescents

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UVOD

Humani papiloma virus (HPV) predstavlja jedan od najčešćih virusa koji je povezan sa karcinomima (čak 690.000 novih slučajeva tokom 2018. godine) [1]. Postoji više od 200 tipova HPV-a i podeljeni su na tipove niskog i visokog onkogenog rizika [2,3]. Najznačajniji predstavnici HPV virusa niskog onkogenog rizika su 6, 11, 42, 43 i 44 a najznačajniji tipovi visokog onkogenog rizika su 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 i 70 [4]. Najveći broj infekcija uzrokovanih HPV virusom može proći spontano, bez ikakvih posledica, dok će određeni broj infekcija izazvati pojavu karcinoma grlića materice, vulve, vagine, anusa, penisa, orofarinksa, i dr.

Karcinom grlića materice predstavlja jedan od vodećih problema javnog zdravlja, naročito u zemljama u razvoju [5,6]. Globalno gledano, karcinom grlića materice se nalazi na četvrtom mestu među karcinomima kod žena, dok se kod žena uzrasta 15 – 44 godine nalazi na drugom mestu [7]. U Republici Srbiji, rak grlića materice je po učestalosti na petom mestu, a njegov potencijalni uzročnik je u najvećem broju slučajeva upravo HPV virus (najonkogeniji su tipovi 16 i 18 koji uzrokuju preko 70% slučajeva). Posmatrajući populaciju starosti od 15 do 44 godine, karcinom grlića materice je na visokom drugom mestu [8]. Važno je naglasiti da, prema dostupnim podacima, rak grlića materice čini 6% smrtnih slučajeva kod žena u Srbiji, te se u tome i ogleda važnost prevencije zaražavanja ovim tipom virusa [9].

Kao najsavremeniji vid primarne prevencije zaražavanja ovim tipom virusa izdvaja se HPV vakcina. Ovaj tip vakcine sprečava razvoj infekcije koja je uzrokovana onim sojevima virusa od kojih je sama vakcina napravljena [10]. Kvadrivalentnu vakcinu (protiv sojeva 6, 11, 16, 18) je odobrila Američka uprava za hranu i lekove (engl. *U.S. Food and Drug Administration – FDA*), 2006. godine, dok je bivalentna (protiv sojeva 16, 18) odobrena 2009. godine i obe se primenjuju za uzrast od 9 do 26 godina, zavisno od države. Sjedinjene Američke Države (SAD) su, 2006. godine, uvele ove vakcine u nacionalni program imunizacije [11] i dokazana je efikasnost i smanjenje prevalencije za tipove 6, 11, 16, 18, u 89 % vakcinisanih slučajeva kod seksualno aktivnih žena uzrasta 14 – 24 godine [12]. Do 2020. godine, vakcina protiv HPV virusa je uvedena u programe imunizacije u 55% (107) država sveta [13].

Vakcinacija HPV vakcinom se preporučuje za adolescente uzrasta 11 ili 12 godina ali se može započeti već sa 9 godina. Ukoliko nije ranije izvršena, vakcinacija se može sprovesti do 26. godine života. Nakon 26. godine, ovaj tip vakcine se ne preporučuje, jer je u najvećem broju slučajeva osoba već bila izložena HPV virusu, te vakcina neće biti dovoljno efikasna. Sama vakcinacija se obavlja u dve ili tri doze, što zavisi od uzrasta i vak-

INTRODUCTION

Human papillomavirus (HPV) is one of the most common viruses associated with cancers (as many as 690,000 new cases in 2018) [1]. There are more than 200 types of HPV, and they are divided into low and high oncogenic risk types [2,3]. The most important types of HPV with low oncogenic risk are 6, 11, 42, 43, and 44, while the most important types of HPV with high oncogenic risk are 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70 [4]. The majority of infections caused by HPV can clear spontaneously, without any consequences, while a certain number of infections will cause cancer of the cervix, vulva, vagina, anus, penis, oropharynx, etc.

Cervical cancer is one of the leading public health problems, especially in developing countries [5,6]. Globally, cervical cancer ranks fourth among cancers in women, while among women aged 15 – 44 years, it ranks second [7]. In the Republic of Serbia, cervical cancer ranks fifth in frequency, and its potential cause, in most cases, is the HPV virus (the most oncogenic are types 16 and 18, which cause over 70% of cases). As to the population aged 15 – 44 years, cervical cancer ranks second [8]. It is important to emphasize that, according to the available data, cervical cancer accounts for 6% of deaths among women in Serbia. This statistic reflects the importance of preventing infection with this type of virus [9].

The HPV vaccine stands out as the most modern form of primary prevention of this type of viral infection. This type of vaccine prevents the development of an infection caused by those strains of the virus from which the vaccine itself is made [10]. The quadrivalent vaccine (against strains 6, 11, 16, and 18) was approved by the U.S. Food and Drug Administration (FDA) in 2006, while the bivalent vaccine (against strains 16 and 18) was approved in 2009. Both are administered between ages 9 and 26, depending on the country. In 2006, the United States of America (USA) introduced these vaccines into the national immunization program [11] and the effectiveness and reduction of prevalence for types 6, 11, 16, and 18 was proven in 89% of vaccinated cases in sexually active women aged 14 – 24 years [12]. By the year 2020, the HPV vaccine had been introduced into immunization programs in 55% (107) of countries worldwide [13].

Vaccination with the HPV vaccine is recommended for adolescents aged 11 or 12, but it can be started as early as 9 years old. If it has not been done before, vaccination can be carried out until the age of 26. After the age of 26, this type of vaccine is not recommended, because in most cases the person has already been exposed to the HPV virus, and the vaccine will not be effective enough. The vaccination itself is administered in two or three doses, which depends on the age and

cinalnog statusa osobe koja se vakciniše [14]. Brojnim istraživanjima je dokazano da oba tipa HPV vakcina stimulišu odgovarajući imuni odgovor i kod žena i kod muškaraca [15,16].

Strateška savetodavna grupa eksperata za imunizaciju Svetske Zdravstvene Organizacije (engl. *Strategic Advisory Group of Experts on Immunization, World Health Organization*) je u aprilu 2022. godine izrazila veliku zabrinutost zbog niskog broja potpuno imunizovanih osoba (2020. godine procenjena globalna pokrivenost drugom dozom kod devojčica iznosila je 13%). Uočena je niska pokrivenost imunizacijom, veoma mali broj novovakcinisanih osoba, visoka stopa prekidanja imunizacije nakon primljene jedne doze vakcine, kao i štetan uticaj pandemije KOVID-19 oboljenja [17].

U Republici Srbiji su registrovane sledeće tri vakcine protiv HPV virusa: *Cervarix*[®], *Gardasil*[®], *Gardasil*[®]9 [18], ali nisu uvedene u kalendar obavezne imunizacije [19], te je i stopa vakcinisanih veoma niska. Jedno od istraživanja koje se bavi problemom imunizacije HPV vakcinom u Republici Srbiji je sprovedeno u Jugoistočnoj Srbiji. U istraživanju je učestvovalo 615 ispitanika, od čega je 499 ispitanika primilo prvu dozu, a 116 drugu dozu. U uzrasnim grupama 9 – 14 godina i 15 – 19 godina je vakcinisano 3,1 puta više devojčica nego dečaka. S obzirom da su roditelji izuzetno važna karika u odobravanju imunizacije, ovim tipom vakcine je vršeno i ispitivanje sociodemografskih karakteristika roditelja gde je utvrđeno da su u 90,2% slučajeva roditelji bili iz urbanih (gradskih) sredina, dok je ostatak bio sa seoskog područja. Takođe je utvrđeno i da su u 59,9% slučajeva roditelji posedovali medicinsko obrazovanje [20].

Na osnovu izveštaja o sprovedenoj imunizaciji na teritoriji Republike Srbije, koji je podneo Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“, zaključno sa 31. 12. 2022. godine, dato je ukupno 20.130 doza vakcine *Gardasil*[®]9. U periodu jun – decembar 2022. godine, na celokupnoj teritoriji Republike Srbije je od predviđenih 41.152 doza vakcine *Gardasil* 9 aplikovano 20.130 doza [21]. Uzimajući u obzir da je imunizaciji podvrgnut mali deo ciljne populacije, 2023. godine je započeta nacionalna kampanja „Zajedno protiv raka grlića materice – HPV NE“ [22].

U Evropskoj uniji su sprovedena brojna istraživanja sa željom da se utvrdi nivo znanja koje poseduju roditelji i adolescenti o HPV virusu i HPV vakcini, a sve sa ciljem poboljšanja procenta vakcinisanih adolescenata [23-26], dok je u Republici Srbiji sprovedeno istraživanje o znanjima, stavovima roditelja i praksi u vezi sa vakcinacijom HPV vakcinom [27].

Cilj ovog istraživanja je bilo utvrđivanje determinanti namere vakcinisanja protiv HPV-a kod adolescenata.

vaccination status of the person being vaccinated [14]. Numerous studies have proven that both types of HPV vaccines stimulate an appropriate immune response in both women and men [15,16].

In April 2022, the Strategic Advisory Group of Experts on Immunization of the World Health Organization expressed great concern about the low number of fully immunized persons (the 2020 estimated global coverage of the second dose in girls was 13%). Low immunization coverage, a very small number of newly vaccinated persons, a high rate of discontinuation of immunization after receiving one dose of the vaccine, as well as the harmful impact of the COVID-19 pandemic were registered [17].

In the Republic of Serbia, the following three vaccines against HPV have been registered: *Cervarix*[®], *Gardasil*[®], and *Gardasil*[®]9 [18], but they have not been introduced into the mandatory immunization schedule [19], and the rate of vaccination is very low. One of the studies dealing with the problem of HPV vaccine immunization in the Republic of Serbia was conducted in Southeast Serbia. A total of 615 subjects participated in the research, of which 499 subjects received the first dose, and 116 the second dose. In the age groups 9 – 14 years and 15 – 19 years, 3.1 times more girls than boys were vaccinated. Given that parents are an extremely important link in the approval of immunization, this type of vaccine was used to examine the socio-demographic characteristics of parents, where it was determined that in 90.2% of cases, the parents were from urban (city) areas, while the rest were from rural areas. It was also determined that in 59.9% of cases, the parents had medical training [20].

Based on the report on immunization carried out in the territory of the Republic of Serbia, submitted by the Institute of Public Health of Serbia Dr Milan Jovanović Batut, as of December 31, 2022, a total of 20,130 doses of *Gardasil*[®]9 vaccine was administered. In the period June – December 2022, 20,130 doses of the planned 41,152 doses of the *Gardasil* 9 vaccine were administered throughout the territory of the Republic of Serbia [21]. As it was established that a small part of the target population was immunized, the national campaign “Together against cervical cancer - HPV NO” was launched in 2023 [22].

In the European Union, numerous studies were conducted with the aim of determining the level of knowledge that the parents and adolescents have about HPV and the HPV vaccine, all with the aim of improving the percentage of vaccinated adolescents [23-26], while in the Republic of Serbia, a study was conducted on knowledge, parental attitudes, and practices regarding HPV vaccination [27].

MATERIJALI I METODE

Tip studije i izbor ispitanika

Studija preseka sprovedena je u okviru jedne srednje i dve osnovne škole u Šapcu, u decembru 2022. godine. Uzorak je obuhvatio 748 mladih iz Srbije, uzrasta od 12 do 19 godina. U istraživanju su učestvovali učenici viših razreda osnovnih škola i učenici od prvog do četvrtog razreda srednje medicinske škole. Upitnici su podeljeni u grupnom okruženju tokom nastave, koristeći format papira i olovke. Svi učesnici su potpisali formular za informisani pristanak i nisu dobili nikakvu nadoknadu za svoje učešće u studiji.

Instrumenti istraživanja

Kao instrument istraživanja korišćen je upitnik koji se sastojao iz nekoliko delova. Prvi deo upitnika obuhvatio je pitanja o sociodemografskim podacima ispitanika (pol, starost, mesto stanovanja, i sl.). U nastavku upitnika korišćene su validirane skale: *Skala za ispitivanje stava o vakcinaciji* (VAKS) [28], *Skala uverenja o zaveri o vakcinama* (VCBS) [29], *Skala znanja o vakcinaciji* (VKS) [30], kao i posebno konstruisani delovi upitnika koji sadrže pitanja o nameri vakcinisanja protiv HPV-a kod ispitanika, subjektivnim normama, i percipiranom kontrolom ponašanja.

Skala za ispitivanje stava o vakcinaciji (VAKS); (engl. *Vaccination Attitudes Examination Scale – VAX*) jeste upitnik od 12 stavki koji procenjuje ukupne stavove o vakcinama. VAKS ima četiri podskale, svaka sa tri stavke: nepoverenje u korisnost vakcinacije (npr. „Osećam se sigurnije nakon vakcinacije“), zabrinutost zbog neočekivanih budućih efekata (npr. „Vakcine mogu izazvati neočekivane probleme kod dece“), zabrinutost zbog komercijalnog profiterstva (npr. „Vakcine zarađuju mnogo novca za farmaceutske kompanije, ali malo za obične ljude“), i davanje prednosti prirodnom imunitetu (npr. „Prirodni imunitet traje duže od vakcinacije“). Svaka stavka se ocenjuje na skali od 6 tačaka, pri čemu 1 znači: „U potpunosti se ne slažem“, a 6 znači: „U potpunosti se slažem“ [28].

Skala uverenja o zaveri o vakcinama (engl. *Vaccine Conspiracy Beliefs Scale – VCBS*) se sastoji od sedam stavki koje mere verovanje u zaveru specifičnu za vakcinu (npr. farmaceutske kompanije prikrivaju opasnosti od vakcine). Svaka stavka je ocenjena na skali od 7 tačaka, pri čemu 1 znači: „U potpunosti se ne slažem“, a 7 znači: „U potpunosti se slažem“ [29].

Skala znanja o vakcinaciji (engl. *Vaccination Knowledge Scale – VKS*) se sastoji od devet stavki o (ne) efikasnosti vakcinacije, opasnostima, i potrebi. Učesnici biraju da li je svaka od tvrdnji tačna ili netačna, a dostupna je i opcija: „Ne znam“. Ukupan broj tačnih

This study aims to define the determinants of adolescent HPV vaccination intention.

MATERIALS AND METHODS

Study type and selection of respondents

This cross-sectional study was conducted in one secondary and two elementary schools in Šabac, Serbia, in December 2022. The sample included 748 young people from Serbia, aged 12 to 19 years. Students of senior grades of the two elementary schools and students of years one to four in the secondary medical school participated in the study. Questionnaires were distributed in a group setting during class, using a paper and pencil format. All participants signed an informed consent form and received no compensation for their participation in the study.

Research instruments

A questionnaire consisting of several segments was used as a research instrument. The first segment included questions about the respondents' sociodemographic data (gender, age, place of residence, etc.). In the remaining segments of the questionnaire, validated scales were used: the *Vaccination Attitudes Examination Scale* (VAX) [28], the *Vaccine Conspiracy Beliefs Scale* (VCBS) [29], the *Vaccination Knowledge Scale* (VKS) [30], as well as specially constructed segments of the questionnaire containing questions about respondents' intentions regarding HPV vaccination, subjective norms, and perceived behavioral control.

The *Vaccination Attitudes Examination Scale* (VAX) is a 12-item questionnaire that assesses overall attitudes about vaccines. The VAX has four subscales, each with three items: mistrust of vaccination benefits (e.g., „I feel safer after vaccination“), concerns regarding unforeseen future effects (e.g., „Vaccines can cause unexpected problems in children“), concerns regarding commercial profiteering (e.g., „Vaccines make a lot of money for pharmaceutical companies but little for ordinary people“), and favoring natural immunity (e.g., „Natural immunity lasts longer than vaccination“). Each item is rated on a 6-point scale, where 1 indicates: „Strongly disagree“ and 6 indicates: „Strongly agree“ [28].

The *Vaccine Conspiracy Beliefs Scale* (VCBS) consists of seven items that measure the belief in a vaccine-specific conspiracy (e.g., pharmaceutical companies cover up vaccine hazards). Each item is rated on a 7-point scale, where 1 indicates: „Strongly disagree“ and 7 indicates: „Strongly agree“ [29].

The *Vaccination Knowledge Scale* (VKS) consists of nine items on the (in)effectiveness of vaccination, dangers, and necessity. Participants choose whether

odgovora (tačan = 1, netačan = 0, ne zna = 0) koristi se za određivanje ocene znanja. Skala ima dobru pouzdanost test-retest ($r = 0,70$) kao i visoku Mokensovu procenu pouzdanosti (0,80) [30].

Namera vakcinisanja protiv HPV-a merena je korišćenjem sledeće tri stavke: „Nameravam da se vakcinišem protiv HPV-a“; „Očekujem da ću se vakcinisati protiv HPV-a“; i „Velika je verovatnoća da ću se vakcinisati protiv HPV-a“. Stavke se boduju na skali od 7 poena, pri čemu je 1 znači: „Apsolutno netačno“, a 7 znači: „Potpuno istinito“.

Subjektivne norme su procenjivane korišćenjem četiri stavke: dve za merenje injunktivnih normativnih uverenja („Većina ljudi koja mi nešto znači smatralo bi da je veoma dobro da dobijem HPV vakcinu“; „Većina ljudi čije mišljenje mi je važno očekuje da se vakcinišem protiv HPV-a“), i dve za merenje deskriptivnih normativnih uverenja („Većina ljudi poput mene će dobiti HPV vakcinu“; „Većina ljudi do čijeg mišljenja mi je stalo dobiće HPV vakcinu“). Učesnici su ocenili svoje slaganje sa svakom tvrdnjom na skali od 7 tačaka, pri čemu je 1 označavalo: „Apsolutno netačno“, a 7 je značilo: „Potpuno istinito“.

Percipirana kontrola ponašanja je merena korišćenjem sledeće dve stavke: „Da li ću biti vakcinisan protiv HPV-a biće u potpunosti moja odluka“; i „Da li ću se vakcinisati protiv HPV-a zavisice u potpunosti od mene“, ocenjeno na skali od 7 poena, pri čemu je 1 označavalo: „Potpuno netačno“, a 7 je označavalo: „Potpuno tačno“.

Analiza podataka

Za određivanje determinanti namere vakcinisanja protiv HPV-a u ovoj studiji, osim deskriptivne statistike i korelacione analize, korišćena je i multipla linearna regresija, u softverskom programu SPSS, verzija 26. Zavisna varijabla u okviru ovog istraživanja bila je namera vakcinisanja protiv HPV-a kod ispitanika, dok su nezavisne varijable bile stavovi o vakcinama, uverenja o zaveri o vakcinama, znanje o vakcinama, subjektivne norme, te percipirana kontrola ponašanja. Za utvrđivanje povezanosti između navedenih nezavisnih varijabli (stavovi o vakcinama, uverenja o zaveri o vakcinama, znanje o vakcinama, subjektivne norme, percipirana kontrola ponašanja), i zavisne varijable (namera vakcinisanja protiv

HPV-a kod ispitanika), korišćena je multipla linearna regresija sa nivoom značajnosti od $p < 0,05$.

REZULTATI

U istraživanju je učestvovalo 748 učenika iz jedne srednje i dve osnovne škole u Šapcu, uzrasta od 12 do 19

each statement is true or false, and the option: “I don’t know” is also available. The total number of correct answers (correct = 1, incorrect = 0, don’t know = 0) is used to determine the knowledge score. The scale has good test-retest reliability ($r = 0.70$) as well as a high Moken’s reliability estimate (0.80) [30].

HPV vaccination intention was measured using the following three items: “I intend to get the HPV vaccination”; “I expect to be vaccinated against HPV”; and “I am very likely to get the HPV vaccine”. Items are scored on a 7-point scale, where 1 means: “Absolutely false” and 7 means: “Completely true”.

Subjective norms were assessed using four items: two items measuring injunctive normative beliefs (“Most people who mean something to me would think it very good that I get the HPV vaccine”; “Most people whose opinions are important to me expect me to get the HPV vaccine”), and two items measuring descriptive normative beliefs (“Most people like me will get the HPV vaccine”; “Most people whose opinions I care about will get the HPV vaccine”). Participants rated their agreement with each statement on a 7-point scale, with 1 indicating: “Absolutely false” and 7 indicating: “Completely true.”

Perceived behavioral control was measured using the following two items: “Whether I get vaccinated against HPV will be entirely my decision”; and “Whether I get vaccinated against HPV will depend entirely on me,” rated on a 7-point scale, where 1 indicated: “Completely false” and 7 indicated: “Completely true.”

Data analysis

To identify the determinants of vaccination intention in this study, apart from descriptive statistics and correlation analysis, multiple linear regression was also applied using the SPSS, Version 26 software. The dependent variable in this study was the HPV vaccination intention of the respondents, while the independent variables were the following: vaccination attitudes, vaccine conspiracy beliefs, vaccination knowledge, subjective norms, and perceived behavioral control. To determine the relationship between the abovementioned independent variables (vaccination attitudes, vaccine conspiracy beliefs, vaccination knowledge, subjective norms, perceived behavioral control) and the dependent variable (HPV vaccination intention of the respondents), multiple linear regression was used with a significance level of $p < 0.05$.

RESULTS

In total, 748 students from one high school and two elementary schools in Šabac, aged 12 to 19, participated in the study (71.3% girls; mean age = 15.78, SD = 1.50).

godina (71,3% devojaka; srednja starost = 15,78, SD = 1,50). Za pojam HPV vakcine znalo je 84,9% naših ispitanika, a kada je u pitanju saznanje o postojanju vakcina 35,5% je saznalo u školi, 23,1% od roditelja, 17,1% u medijima, 16,4% na neki drugi način i samo 2,7% od lekara.

Rezultati pokazuju da se od ukupnog broja ispitanika, jednom dozom vakcinisalo 4,3%, sa dve doze 5%, a sa više od dve doze samo 2%, dok se 83,3% učenika nije vakcinisalo. Namera vakcinisanja protiv HPV-a kod ispitanika je merena uz pomoć sledeće tri stavke: „Nameravam da se vakcinišem protiv HPV-a“; „Očekujem da ću se vakcinisati protiv HPV-a“; i „Velika je verovatnoća da ću se vakcinisati protiv HPV-a“. Unutrašnja konzistentnost ove skale bila je visoka ($\alpha = 0,949$).

Skala koja je ispitivala stavove ispitanika o vakcinaciji (VAKS) pokazala je da kod ispitanika postoji nepoverenje u korisnost vakcinacije, kao i zabrinutost zbog komercijalnog profiterstva. Takođe, ispitanici su pokazali statistički značajno uverenje o postojanju zavere o vakcinama, a u okviru našeg istraživanja, unutrašnja konzistencija Skale uverenja o zaveri o vakcinama (VCBS) je bila jaka u ovom uzorku ($\alpha = 0,923$).

Subjektivne norme su procenjivane korišćenjem četiri stavke: dve za merenje injunktivnih normativnih uverenja („Većina ljudi koja mi nešto znači smatralo bi da je veoma dobro da dobijem HPV vakcinu“; „Većina ljudi čije mišljenje mi je važno očekuje da se vakcinišem protiv HPV-a“), i dve za merenje deskriptivnih normativnih uverenja („Većina ljudi poput mene će dobiti HPV vakcinu“; „Većina ljudi do čijeg mišljenja mi je stalo dobiće HPV vakcinu“). Pouzdanost unutrašnje konzistentnosti bila je zadovoljavajuća u trenutnom uzorku ($\alpha = 0,870$).

Percipirana kontrola ponašanja je merena korišćenjem sledeće dve stavke: „Da li ću biti vakcinisan protiv HPV-a biće u potpunosti moja odluka“; i „Da li ću se vakcinisati protiv HPV-a zavisice u potpunosti od mene“. Korelacija između ove dve stavke je bila prilično jaka i pozitivna ($r = 0,796$), a Spirman-Braunov koeficijent pouzdanosti je bio 0,886. Procenat podataka koji su nedostajali je bio minimalan (3,45%), a nedostajući podaci su adresirani pristupom višestruke imputacije. Korišćen je G*Power softver za procenu statističke moći *post hoc*, a njena vrednost je bila 1,00.

Deskriptivna statistika i korelacije među varijablama studije prikazane su u **Tabeli 1**. Subjektivne norme i nepoverenje u korisnost vakcinacije imali su najveću pozitivnu korelaciju sa namerom vakcinisanja protiv HPV-a, dok uverenja o zaveri o vakcinaciji imaju najveću negativnu korelaciju. Varijable: namera vakcinisanja protiv HPV-a, subjektivne norme, kontrola ponašanja, nepoverenje u korisnost vakcine i zabrinutost za nepredviđene buduće posledice imale su prosečne vred-

In all, 84.9% of our respondents knew about the term HPV vaccine, and as to the way they learned about the existence of the vaccine, 35.5% learned about it at school, 23.1% from their parents, 17.1% from the media, 16.4% in some other way, while only 2.7% of the respondents found out about the vaccine from doctors.

The results show that of the total number of respondents, 4.3% were vaccinated with one dose, 5% with two doses, and only 2% with more than two doses, while 83.3% of students were not vaccinated. Respondent HPV vaccination intention was measured with the help of the following three items: “I intend to get the HPV vaccination”; “I expect to be vaccinated against HPV”; and “I am very likely to get the HPV vaccine”. The internal consistency of this scale was high ($\alpha = 0.949$).

The scale that examined respondent vaccination attitudes (VAX) showed that there was a mistrust of the benefits of vaccination among the respondents, as well as concern regarding commercial profiteering. Also, respondents showed a statistically significant belief in the existence of a vaccine conspiracy, and in our study, the internal consistency of the Vaccine Conspiracy Beliefs Scale (VCBS) was strong in this sample ($\alpha = 0.923$).

Subjective norms were assessed using four items: two measuring injunctive normative beliefs (“Most people who mean something to me would think it very good that I get the HPV vaccine”; “Most people whose opinions are important to me expect me to get the HPV vaccine”), and two to measuring descriptive normative beliefs (“Most people like me will get the HPV vaccine”; “Most people whose opinions I care about will get the HPV vaccine”). Internal consistency reliability was satisfactory in the current sample ($\alpha = 0.870$).

Perceived behavioral control was measured using the following two items: “Whether I get vaccinated against HPV will be entirely my decision”; and “Whether I get the HPV vaccine will be entirely up to me”. The correlation between these two items was quite strong and positive ($r = 0.796$), and the Spearman-Brown reliability coefficient was 0.886. The percentage of missing data was minimal (3.45%), and the missing data were addressed using a multiple imputation approach. G*Power software was used to assess statistical power *post hoc*, and its value was 1.00.

Descriptive statistics and correlations among study variables are shown in **Table 1**. Subjective norms and mistrust of vaccination benefits had the highest positive correlation with HPV vaccination intention, while vaccination conspiracy beliefs had the highest negative correlation. The following variables: HPV vaccination intention, subjective norms, behavioral control, mistrust of vaccine benefits, and concern about unforeseen future effects had mean values higher than

Tabela 1. Deskriptivna statistika i korelacije između proučavanih varijabli

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Namera vakcinisanja protiv HPV-a / HPV vaccination intention	1								
2. Subjektivne norme / Subjective norms	0.76*	1							
3. Percipirana kontrola ponašanja / Perceived behavioral control	0.29*	0.30*	1						
4. Nepoverenje u korisnost vakcinacije / Mistrust of vaccination benefits	0.60*	0.51*	0.28*	1					
5. Zabrinutost zbog nepredviđenih budućih posledica / Concerns regarding unforeseen future effects	-0.06	0.01	0.12*	-0.03	1				
6. Zabrinutost zbog komercijalnog profiterstva / Concerns regarding commercial profiteering	-0.29*	-0.15*	-0.11*	-0.30*	0.47*	1			
7. Davanje prednosti prirodnom imunitetu / Preference for natural immunity	-0.12*	-0.01	-0.05	-0.15*	0.37*	0.60*	1		
8. Uverenja o zaveri o vakcinama / Vaccine conspiracy beliefs	-0.35*	-0.23*	-0.15*	-0.38*	0.38*	0.56*	0.39*	1	
9. Znanje o vakcinaciji / Knowledge about vaccination	0.16*	0.12*	0.16*	0.15*	-0.05	-0.15*	-0.04	-0.13*	1
M	4.80	4.38	5.59	4.21	4.28	3.01	3.08	3.52	3.37
SD	1.91	1.57	1.77	1.35	1.25	1.36	1.37	1.50	2.09

* $p < .005$

nosti veće od teoretskog proseka, dok su preostale varijable imale prosečne vrednosti koje su blizu teoretskog proseka.

Višestruka regresiona analiza

Da bi se ispitao prediktivni model u objašnjavanju namere vakcinisanja protiv HPV-a kod mladih, primenjena je multipla linearna regresija (Tabela 2). Model objašnjava 66% namere mladih u vezi sa vakcinacijom. Najjači prediktor namere vakcinisanja protiv HPV-a kod mladih su subjektivne norme ($\beta = 0.605, p < 0.001$), odnosno društveni pritisak vršnjaka i drugih osoba značajnih za ispitanke. Nepoverenje u korisnost vakcinacije ($\beta = -0.235, p < 0.001$), zabrinutost zbog komercijalnog profiterstva ($\beta = -0.080, p < 0.05$) i uverenja o zaveri o vakcinama ($\beta = -0.077, p < 0.01$) imali su značajno manji, ali statistički značajan doprinos u objašnjavanju namere vakcinisanja.

Table 1. Descriptive statistics and correlation among study variables

the theoretical mean, while the remaining variables had mean values close to the theoretical mean.

Multiple regression analysis

To examine the predictive model in explaining young people's HPV vaccination intention, multiple linear regression was applied (Table 2). The model explains 66% of youth HPV vaccination intentions. The strongest predictor of young people's intention to get vaccinated against HPV are subjective norms ($\beta = 0.605, p < 0.001$), i.e., social pressure from peers and other persons significant to the respondents. Mistrust of the benefits of vaccination ($\beta = -0.235, p < 0.001$), concern about commercial profiteering ($\beta = -0.080, p < 0.05$), and vaccine conspiracy beliefs ($\beta = -0.077, p < 0.01$) had a significantly smaller but statistically significant contribution in explaining vaccination intention.

Tabela 2. Višestruka regresiona analiza

	B	SE	β	t	P
Subjektivne norme / Subjective norms	0.739	0.031	0.605	23.668	0.001
Percipirana kontrola ponašanja / Perceived behavioral control	0.015	0.025	0.014	0.611	0.541
Nepoverenje u korisnost vakcinacije / Mistrust of vaccination benefits	-0.332	0.038	-0.235	-8.736	0.001
Zabrinutost zbog budućih nepredviđenih posledica / Concerns regarding unforeseen future effects	0.019	0.039	0.012	0.476	0.634
Zabrinutost zbog komercijalnog profiterstva / Concerns regarding commercial profiteering	-0.114	0.045	-0.080	-2.541	0.011
Davanje prednosti prirodnom imunitetu / Preference for natural immunity	-0.006	0.038	-0.004	-0.149	0.881
Uverenja o zaveri o vakcinama / Vaccine conspiracy beliefs	-0.098	0.035	-0.077	-2.784	0.005
Znanje o vakcinaciji / Knowledge about vaccination	0.025	0.020	0.027	1.244	0.214

Table 2. Multiple regression analysis

DISKUSIJA

U ovoj studiji smo ispitali determinante namere vakcinisanja protiv HPV-a u populaciji učenika. Ispitivanje stavova je važan korak u predviđanju ponašanja mladih u odnosu na planove za vakcinisanje protiv HPV virusa, koji prema istraživanjima može biti uzročnik karcinoma različite lokalizacije [1], te predstavlja jedan od vodećih problema javnog zdravlja, naročito u zemljama u razvoju [5,6].

Od 2006. godine, vakcine protiv humanog papiloma virusa (HPV), dostupne su i u Evropi, ali obuhvat njihove primene razlikuje se među zemljama [31]. Studija koja je ispitala spremnost da se postignu ciljevi globalne strategije Svetske zdravstvene organizacije (SZO) za vakcinaciju protiv HPV-a i skrining grlića materice (engl. *Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*), u osamnaest istočnoevropskih i centralnoazijskih zemalja, navodi podatak da su samo Turkmenistan i Uzbekistan uspjeli da dostignu cilj koji je postavila SZO, a to je 90% kompletno vakcinisanih djevojčica do 15. godine života [31].

Istraživanja potvrđuju kliničku efikasnost protiv određenih tipova ovog virusa odgovornih za invazivni kancer grlića materice (peti po učestalosti oblik karcinoma u Republici Srbiji) [8], te za cervikalni, vulvovaginalni i analni prekancer [32]. I pored dokaza o efikasnosti vakcina protiv HPV-a, procenat obuhvata HPV vakcinom u pojedinim zemljama nije optimalan, što je slučaj i u našoj zemlji. Prema preporukama Nacionalnog programa obavezne i preporučene imunizacije Srbije, vakcina protiv infekcije humanim papiloma virusom (HPV) predviđena za decu i adolescente uzrasta 9 – 19 godina, nije uvedena u kalendar obavezne imunizacije [19], i prema nalazima nedavnog istraživanja, nije u dovoljnoj meri promovisana [30], što može biti jedan od razloga koji utiču na nisku stopu vakcinisanih.

U okviru našeg istraživanja, subjektivne norme i nepoverenje u korisnost vakcinacije izdvojili su se kao najznačajniji prediktori namere vakcinisanja HPV vakcinom. Ispitanici u okviru naše studije potvrđuju da osobe čije mišljenje vrednuju utiču na njihove stavove i namere da se vakcinišu protiv HPV-a. Slične rezultate pokazuje i studija sprovedena u SAD, koja ističe da društveni uticaji, posebno uticaj vršnjaka, u velikoj meri može generisati stavove prema HPV vakcini. Pomenuta studija ukazuje na to da su ispitanici čiji su se prijatelji vakcinisali HPV vakcinom izrazili dva puta veću nameru vakcinisanja. Takođe, mišljenje roditelja se u okviru američkog istraživanja pokazalo kao veoma značajno, jer su ispitanici koji su dobili preporuku roditelja izrazili dvostruko veću nameru vakcinisanja HPV vakcinom [33].

Osim mišljenja vršnjaka i roditelja, značajan uticaj na formiranje stava o vakcinisanju ima vakcinalni sta-

DISCUSSION

In this study, we examined the determinants of HPV vaccination intention in a student population. Examining attitudes is an important step in predicting young people's behavior regarding their plans for vaccination against HPV, which according to research can be the cause of cancers of various localizations [1] and represents one of the leading public health problems, especially in developing countries [5,6].

Since 2006, vaccines against human papillomavirus (HPV) have been available in Europe, but the coverage of their application varies amongst countries [31]. A study examining the preparedness to achieve the goals of the World Health Organization (WHO) global strategy for HPV vaccination and cervical screening (*Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem*) in eighteen Eastern European and Central Asian countries found that only Turkmenistan and Uzbekistan managed to reach the goal set by WHO, which is 90% of fully vaccinated girls by the age of 15 years [31].

Research has confirmed the clinical effectiveness of the vaccine against certain types of this virus responsible for invasive cervical cancer (the fifth most frequent form of cancer in the Republic of Serbia) [8], as well as for cervical, vulvovaginal, and anal precancer [32]. Despite the evidence of the effectiveness of HPV vaccines, the percentage of HPV vaccine coverage in certain countries is not optimal, which is also the case in our country. According to the recommendations of the National Program of Mandatory and Recommended Immunization of Serbia, the vaccine against human papillomavirus (HPV) infection, intended for children and adolescents aged 9 – 19 years, was not included in the mandatory immunization schedule [19], and according to the findings of a recent study, it is not being sufficiently promoted [30], which may be one of the reasons affecting the low rate of vaccinated subjects.

In our study, subjective norms and mistrust of the benefits of vaccination were singled out as the most significant predictors of the HPV vaccination intention. Respondents in our study confirm that people whose opinions they value influence their attitudes and intentions to get vaccinated against HPV. Similar results were reported by a study conducted in the USA, which points out that social influence, especially the influence of peers, can largely generate attitudes towards the HPV vaccine. The abovementioned study indicates that respondents whose friends were vaccinated with the HPV vaccine expressed a two times higher intention to get vaccinated. Also, the opinion of parents in the American research proved to be very important, because the respondents who were advised by their

tus partnera, što potvrđuje studija sprovedena među mladima u Kentakiju [34]. Pomenuta studija je ukazala na to da je preferencija da partner ispitanika bude vakcinisan protiv HPV-a predviđala pozitivne stavove i prihvatanje vakcine, dok je nedostatak preferencije partnera za vakcinaciju rezultirao negativnim stavom i namerom vakcinisanja [34]. S obzirom da živimo u vreme koje se u velikoj meri oslanja na digitalne medije, nisu iznenađujući rezultati nedavno sprovedenog istraživanja u Sloveniji, koje je ispitivalo stavove studenata medicine u vezi sa HPV vakcinom, gde većina ispitanika smatra da u najvećoj meri informacije dobijene na internetu utiču na nameru vakcinisanja [35]. Identifikovanje pomenutih činilaca se u velikoj meri može iskoristiti u kreiranju budućih intervencija koje će pomoći u formiranju stavova prema HPV imunizaciji.

Rezultati našeg istraživanja, kao drugi značajan prediktivni faktor, ističu nepoverenje adolescenata u korisnost vakcinacije, što se slaže sa nalazima istraživanja koje je sprovedeno u Italiji, a koje ukazuje na to da 38,1 % ispitanika sumnja u korisnost vakcine [36]. Suprotno tome, rezultati studije sprovedene u Turskoj ukazuje na to da skoro polovina ispitanika smatra da je vakcina korisna i pruža zaštitu od karcinoma, ali i pored toga samo 4,3% ispitanika u okviru pomenutog istraživanja je primilo vakcinu protiv humanog papiloma virusa [37]. Razlike u stavovima mogu biti posledica toga što je istraživanje u Turskoj obuhvatilo starije starosne kategorije, dok je naša studija ispitivala stavove adolescenata. Sličnost se ogleda u tome što se u okviru našeg istraživanja samo 2% ispitanika vakcinisalo sa više od dve doze vakcine.

Osim nepoverenja u korisnost vakcine, statistički značajan doprinos u objašnjavanju namere vakcinisanja protiv HPV-a u okviru naše studije leži u tome da ispitanici navode i zabrinutost zbog komercijalnog profiterstva, kao i uverenja o zaveri o vakcinama. Ranija istraživanja potvrđuju naše rezultate ukazujući na postojanje složenih činilaca, najčešće psihičke ili psihosocijalne prirode, koji mogu doprineti nameri osobe da se vakciniše [38], na primer, generalno nepoverenje u vakcine, konspirativna uverenja o vakcinaciji, i slično [39]. Na ovakve stavove u velikoj meri je uticala i nedavna epidemija KOVID-19 oboljenja, gde smo u kontinuitetu bili izloženi različitim neproverenim informacijama u vezi sa vakcinama, koje su se plasirale javnosti putem interneta i različitih društvenih mreža, dajući mogućnost protivnicima vakcinacije (tzv. antivakserima) da budu aktivniji [35,38,39,40].

Nedostatak blagovremenih i jasnih informacija, kao i korišćenje nepouzdanih izvora, u velikoj meri mogu uticati na namere adolescenata u vezi sa vakcinisanjem HPV vakcinom. U okviru naše studije, i pored

parents to get vaccinated expressed a two times higher intention to get vaccinated with the HPV vaccine [33].

Apart from the opinion of peers and parents, the vaccination status of the partner has a significant influence on attitudes about vaccination, as confirmed by a study conducted among young people in Kentucky [34]. The abovementioned study indicated that the preference for the respondent's partner to be vaccinated against HPV predicted positive attitudes and acceptance of the vaccine, while the partner's lack of preference for vaccination resulted in a negative attitude and intention to get vaccinated [34]. Considering that we live in a time that relies heavily on digital media, it is not surprising that the results of a recent survey conducted in Slovenia, which examined the attitudes of medical students regarding the HPV vaccine, indicate that the majority of respondents believe that information obtained on the Internet has the greatest influence on vaccination intention [35]. Identifying the mentioned factors can be used largely in the creation of future interventions that will help in the formation of attitudes toward HPV immunization.

The results of our study highlight, as another significant predictive factor, the mistrust of adolescents in the benefits of vaccination, which agrees with the findings of a study conducted in Italy that indicates that 38.1% of respondents doubt the usefulness of the vaccine [36]. In contrast, the results of a study conducted in Turkey indicate that almost half of the respondents believe that the vaccine is beneficial and provides protection against cancer, but even so, only 4.3% of the respondents in the aforementioned study received the vaccine against human papillomavirus [37]. The differences in attitudes may stem from the fact that the study in Turkey included older age groups, while our study examined the attitudes of adolescents. The similarity is reflected in the fact that in our study only 2% of respondents were vaccinated with more than two doses of the vaccine.

In addition to mistrust of the benefits of the vaccine, a statistically significant contribution to explaining the HPV vaccination intention in our study lies in the fact that respondents also reported concerns about commercial profiteering, as well as beliefs about a vaccine conspiracy. Previous studies confirm our results indicating the existence of complex factors, most often psychological or psychosocial in nature, that can contribute to a person's intention to get vaccinated [38], for example, general mistrust of vaccines, conspiratorial beliefs about vaccination, and the like [39]. Such attitudes were greatly influenced by the recent epidemic of COVID-19, when we were continuously exposed to various unverified information regarding

toga što za pojam HPV vakcine zna 84,9% ispitanika, informacije o postojanju vakcina je 35,5% njih dobilo u školi, 17,1% u medijima, 16,4% na neki drugi način i samo 2,7% od lekara. Slične podatke prijavljuju i rezultati drugih studija [33,35,37]. S obzirom na dokaze da preporuke lekara i drugih zdravstvenih radnika, kao pružaoca usluga, mogu pozitivno uticati na stavove o HPV imunizaciji [20,41,42], buduće intervencije treba da budu usmerene na povećano angažovanje zdravstvenih radnika u edukaciji javnosti o značaju prevencije malignih bolesti izazvanih HPV virusom, kao i u podizanju svesti o efikasnosti HPV vakcine.

ZAKLJUČAK

I pored činjenice da ova studija ima određena ograničenja, u smislu korišćenja prigodnog uzorka, kao i da postoji mogućnost da su ispitanici davali poželjne odgovore, istraživanje je identifikovalo ključne aspekte nepoverenja prema HPV imunizaciji. Najdominantniji su sumnja u korisnost vakcine, zatim konspirativna uverenja o vakcinama, ali i postojanje zabrinutosti u vezi sa komercijalnim profiterstvom. Sagledavanje ključnih aspekata nepoverenja prema vakcinaciji daje mogućnost planiranja edukativnih zdravstvenih intervencija i njihovo usmeravanje na identifikovane oblasti. Studija takođe daje uvid u važne činjenice, da su mladi podložni uticajima okruženja i da subjektivne norme imaju važnu ulogu u formiranju stavova o vakcinaciji protiv HPV virusa, koje se mogu iskoristiti u kreiranju kampanja u budućnosti.

Izjava autora o originalnosti rada

Ovaj rad nije delimično niti u celini objavljen, poslat ili prihvaćen za štampu u drugom časopisu.

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LITERATURA / REFERENCES

1. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health*. 2020 Feb;8(2):e180-e190. doi: 10.1016/S2214-109X(19)30488-7.
2. Ferenczy A, Franco E. Persistent human papillomavirus infection and cervical neoplasia. *Lancet Oncol*. 2002 Jan;3(1):11-6. doi: 10.1016/S1470-2045(01)00617-9.
3. Doorbar J. Host control of human papillomavirus infection and disease. *Best Pract Res Clin Obstet Gynaecol*. 2018 Feb;47:27-41. doi: 10.1016/j.bpobgyn.2017.08.001.
4. Burd EM. Human papillomavirus and cervical cancer. *Clin Microbiol Rev*. 2003 Jan;16(1):1-17. doi: 10.1128/CMR.16.1.1-17.2003.
5. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. *Lancet*. 2013 Sep 7;382(9895):889-99. doi: 10.1016/S0140-6736(13)60022-7.

vaccines, which were marketed to the public via the Internet and various social networks, allowing opponents of vaccination (the so-called anti-vaxxers) to be more active [35,38,39,40].

The lack of timely and clear information, as well as the use of unreliable sources, can greatly influence HPV vaccination intention in adolescents. In our study, although 84.9% of respondents know about the term HPV vaccine, 35.5% of them received information about the existence of the vaccine at school, 17.1% got the information from the media, 16.4% found it in some other way, and only 2.7% obtained this information from doctors. Similar data are reported by the results of other studies [33,35,37]. Considering the evidence that the recommendations of doctors and other health workers, as service providers, can positively influence attitudes about HPV immunization [20,41,42], future interventions should be aimed at increased involvement of health workers in educating the public about the importance of preventing malignant diseases caused by the HPV virus, as well as in raising awareness about the effectiveness of the HPV vaccine.

CONCLUSION

Although this study has certain limitations, in terms of the use of a convenience sample, as well as the possibility that respondents gave answers they felt to be desirable, the research identified key aspects of mistrust towards HPV immunization. The most dominant are doubts regarding the benefits of the vaccine, followed by conspiratorial beliefs about vaccines, but also the existence of concerns about commercial profiteering. Identifying the key aspects of mistrust towards vaccination gives the possibility of planning educational health interventions and directing them towards the identified areas. The study also provides insight into the important fact that young people are susceptible to the influence exerted by their environment and that subjective norms play an important role in forming attitudes about vaccination against the HPV virus, which can be used in creating campaigns in the future.

Authors' statement of originality

This study has not been previously published, submitted, or accepted for publishing, in whole or in part, in any other scientific journal.

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6. LaMontagne DS, Bloem PJN, Brotherton JML, Gallagher KE, Badiane O, Ndiaye C. Progress in HPV vaccination in low- and lower-middle-income countries. *Int J Gynaecol Obstet*. 2017 Jul;138 Suppl 1:7-14. doi: 10.1002/ijgo.12186.
7. Serrano B, Brotons M, Bosch FX, Bruni L. Epidemiology and burden of HPV-related disease. *Best Pract Res Clin Obstet Gynaecol*. 2018 Feb;47:14-26. doi: 10.1016/j.bpobgyn.2017.08.006.
8. HPV Information Centre. Human Papillomavirus and Related Diseases Report Serbia. 2023 March. [Internet]. [Pristupljeno: 25. 8. 2023.] Dostupno na: <https://hvpcentre.net/statistics/reports/SRB.pdf>
9. Marković T. Prevencija karcinoma grlića materice. *Inspirijum*, 2014 Aug; 10:4-13. [Internet]. Dostupno na: <https://scindeks-clanci.ceon.rs/data/pdf/2217-656X/2014/2217-656X1410004M.pdf>
10. Harper DM, Paavonen J. Age for HPV vaccination. *Vaccine*. 2008 Mar 14;26 Suppl 1:A7-11. doi: 10.1016/j.vaccine.2008.01.013.
11. Markowitz LE, Tsu V, Deeks SL, Cubie H, Wang SA, Vicari AS, et al. Human papillomavirus vaccine introduction--the first five years. *Vaccine*. 2012 Nov 20;30 Suppl 5:F139-48. doi: 10.1016/j.vaccine.2012.05.039.
12. Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV After Introduction of the Vaccination Program in the United States. *Pediatrics*. 2016 Mar;137(3):e20151968. doi: 10.1542/peds.2015-1968.
13. Bruni L, Saura-Lázaro A, Montoliu A, Brotons M, Alemany L, Diallo MS, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. *Prev Med*. 2021 Mar;144:106399. doi: 10.1016/j.ypmed.2020.106399.
14. Centers for Disease Control and Prevention. HPV Vaccination Recommendations, 2021 Nov. [Internet]. [Pristupljeno: 17. 7. 2023.] Dostupno na: <https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html>
15. Block SL, Nolan T, Sattler C, Barr E, Giaconetti KE, Marchant CD, et al. Protocol 016 Study Group. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics*. 2006 Nov;118(5):2135-45. doi: 10.1542/peds.2006-0461.
16. Petäjä T, Keränen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years. *J Adolesc Health*. 2009 Jan;44(1):33-40. doi: 10.1016/j.jadohealth.2008.10.002.
17. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations, Weekly Epidemiological Record = Relevé épidémiologique hebdomadaire, 97 (24): 261 – 276. [Internet]. [Pristupljeno: 17. 7. 2023.] Dostupno na: <https://www.alims.gov.rs/humani-lekovi/pretrazivanje-humanih-lekova/?id=399657>
18. ALIMs. Agencija za lekove i medicinska sredstva Srbije. Pretraživanje humanih lekova, 2019. [Internet]. [Pristupljeno: 25. 8. 2023.] Dostupno na: <https://www.alims.gov.rs/humani-lekovi/pretrazivanje-humanih-lekova/?id=399657>
19. Zakon o zaštiti stanovništva od zaraznih bolesti: 15/2016-31, 68/2020-4, 136/2020-3. [Internet]. [Pristupljeno: 25. 8. 2023.] Dostupno na: <https://www.pravnoinformacionisistem.rs/SIGlasnikPortal/eli/rep/sgrs/skupstina/zakon/2016/15/8/reg>
20. Rancic NK, Miljkovic PM, Deljanin ZM, Marinkov-Zivkovic EM, Stamenkovic BN, Bojanovic MR, et al. Knowledge about HPV Infection and the HPV Vaccine among Parents in Southeastern Serbia. *Medicina (Kaunas)*. 2022 Nov 22;58(12):1697. doi: 10.3390/medicina58121697.
21. Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“. Izveštaj o sprovedenoj imunizaciji na teritoriji republike Srbije u 2021. Godini. [Internet]. [Pristupljeno: 26. 10. 2023.] Dostupno na: <https://www.batut.org.rs/download/izvestaji/2022izvestajOSprovedenojImunizaciji.pdf>
22. Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“. Kancelarija za skrining raka, [Internet]. [Pristupljeno: 26. 10. 2023.] Dostupno na: <https://www.skriningsrbija.rs/>
23. Ailloud J, Branchereau M, Fall E, Juneau C, Partouche H, Bonnay S, et al. How can we improve the acceptability of vaccination against Human Papillomavirus (HPV) in France? An original qualitative study with focus groups comprising parents and school staff, interviewed separately. *Vaccine*. 2023 Jul 12;41(31):4594-4608. <https://doi.org/10.1016/j.vaccine.2023.05.072>
24. Mascaro V, Pileggi C, Currà A, Bianco A, Pavia M. HPV vaccination coverage and willingness to be vaccinated among 18-30-year-old students in Italy. *Vaccine*. 2019 May 31;37(25):3310-3316. doi: 10.1016/j.vaccine.2019.04.081.
25. Pența MA, Crăciun IC, Băban A. The power of anticipated regret: Predictors of HPV vaccination and seasonal influenza vaccination acceptability among young Romanians. *Vaccine*. 2020 Feb 5;38(6):1572-1578. doi: 10.1016/j.vaccine.2019.11.042.
26. Marek E, Dergez T, Rebek-Nagy G, Kricskovics A, Kovacs K, Bozsa S, et al. Adolescents' awareness of HPV infections and attitudes towards HPV vaccination 3 years following the introduction of the HPV vaccine in Hungary. *Vaccine*. 2011 Nov 3;29(47):8591-8. doi: 10.1016/j.vaccine.2011.09.018.
27. Marić G, Birčanin Đ, Kisić V, Dotlić J, Zarić M, Kisić-Tepavčević D, et al. Parental perspective on human papillomavirus (HPV) vaccination in Serbia: Knowledge, attitudes and practice. *Sex Reprod Healthc*. 2018 Jun;16:192-198. doi: 10.1016/j.srhc.2018.04.010.
28. Martin LR, Petrie KJ. Understanding the Dimensions of Anti-Vaccination Attitudes: the Vaccination Attitudes Examination (VAX) Scale. *Ann Behav Med*. 2017 Oct;51(5):652-660. doi: 10.1007/s12160-017-9888-y.
29. Shapiro GK, Holding A, Perez S, Amsel R, Rosberger Z. Validation of the vaccine conspiracy beliefs scale. *Papillomavirus Res*. 2016 Dec;2:167-172. doi: 10.1016/j.pvr.2016.09.001.
30. Zingg A, Siegrist M. Measuring people's knowledge about vaccination: Developing a one-dimensional scale. *Vaccine*. 2012;30:3771-7. doi: 10.1016/j.vaccine.2012.03.014.
31. Davies P, Aluloski I, Aluloski D, Brcanski J, Davidzenka A, Durdjeva A, et al. HPV Vaccination and Cervical Cancer Screening Policies and Practices in 18 Countries, Territories and Entities across Eastern Europe and Central Asia. *Asian Pac J Cancer Prev*. 2023 May 1;24(5):1781-1788. doi: 10.31557/AP-JCP.2023.24.5.1781.
32. Joura EA, Kyrgiou M, Bosch FX, Kesic V, Niemenen P, Redman CW, et al. Human papillomavirus vaccination: The ESGO-EFC position paper of the European society of Gynaecologic Oncology and the European Federation for colposcopy. *Eur J Cancer*. 2019 Jul;116:21-26. doi: 10.1016/j.ejca.2019.04.032.
33. McLendon L, Puckett J, Green C, James J, Head KJ, Yun Lee H, et al. Factors associated with HPV vaccination initiation among United States college students. *Hum Vaccin Immunother*. 2021 Apr 3;17(4):1033-1043. doi:10.1080/21645515.2020.1847583.
34. LaJoie AS, Kerr JC, Clover RD, Harper DM. Influencers and preference predictors of HPV vaccine uptake among US male and female young adult college students. *Papillomavirus Res*. 2018 Jun;5:114-121. doi: 10.1016/j.pvr.2018.03.007.
35. Troha M, Šterbenc A, Mlakar M, Poljak M. Human papillomavirus (HPV) infection and vaccination: knowledge and attitudes among healthcare professionals and the general public in Slovenia. *Acta Dermatovenol Alp Pannonica Adriat*. 2018 Jun;27(2):59-64. doi: 10.15570/actaapa.2018.14.
36. Pelullo CP, Esposito MR, Di Giuseppe G. Human Papillomavirus Infection and Vaccination: Knowledge and Attitudes among Nursing Students in Italy. *Int J Environ Res Public Health*. 2019 May 19;16(10):1770. doi: 10.3390/ijerph16101770.

37. Aynaci G, Guksu Z. Awareness of HPV and HPV vaccination in undergraduate students in the North West region of Turkey: Near future outlook. *J Infect Dev Ctries*. 2019 Jun 30;13(6):516-525. doi: 10.3855/jidc.11405.
38. Sociopsihološki aspekti vakcinacije protiv COVID-19 kod mladih u Vojvodini. Filozofski fakultet, Univerzitet u Novom Sadu. Jun 2023. [Internet]. Dostupno na: https://www.researchgate.net/publication/371322326_Sociopsiholoski_aspekti_vakcinacije_protiv_COVID-19_kod_mladih_u_Vojvodini#full-TextFileContent
39. Murphy J, Vallières F, Bentall RP, Shevlin M, McBride O, Hartman TK, et al. Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. *Nat Commun*. 2021 Jan 4;12(1):29. doi: 10.1038/s41467-020-20226-9.
40. Patel PR, Berenson AB. Sources of HPV vaccine hesitancy in parents. *Hum Vaccin Immunother*. 2013 Dec;9(12):2649-53. doi: 10.4161/hv.26224.
41. Kim HW, Lee EJ, Lee YJ, Kim SY, Jin YJ, Kim Y, et al. Knowledge, attitudes, and perceptions associated with HPV vaccination among female Korean and Chinese university students. *BMC Womens Health*. 2022 Feb 23;22(1):51. doi: 10.1186/s12905-022-01624-1.
42. Sanftenberg L, Roggendorf H, Babucke M, Breckwoldt J, Gaertner B, Hetzer B, et al. Medical students' knowledge and attitudes regarding vaccination against measles, influenza and HPV. An international multicenter study. *J Prev Med Hyg*. 2020 Jul 4;61(2):E181-E185. doi: 10.15167/2421-4248/jpmh2020.61.2.1308.

SEPTIČNO STANJE U DIFERENCIJALNOJ DIJAGNOZI NEJASNOG FEBRILNOG STANJA

ORIGINALNI RAD

ORIGINAL ARTICLE

SEPTIC STATE IN THE DIFFERENTIAL DIAGNOSIS OF FEVER OF UNKNOWN ORIGIN

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43. SAŽETAK

Uvod: U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznovrsnom etiologijom. Septično stanje značajno participira kao etiološki faktor nejasnog febrilnog stanja a često se previdi, tj. lečenje se započinje kasno.

Cilj rada: Utvrditi učestalost sepse, ustanoviti demografske karakteristike, kliničku prezentaciju oboljenja, utvrditi proporciju dokazanih izazivača i njihovu raspodelu po vrstama, predstaviti laboratorijske analize bolesnika sa dijagnozom sepse po prijemu i po otpustu iz bolnice.

Materijal i metode: Ispitivanjem su obuhvaćeni pacijenti lečeni na Klinici za infektivne i tropske bolesti Kliničkog centra Srbije, na Odeljenju kliničke farmakoterapije u periodu od 1.12.2014. do 31.12.2017. godine, a kod kojih je u toku ispitivanja etiologije nejasnog febrilnog stanja dokazana sepsa.

Rezultati: Među 420 ispitivanih pacijenata, kod 50 (11,9%) je dokazana sepsa. U istraživanje je bilo uključeno 29 (58%) žena i 21 (42%) muškarac, prosečne starosti $63,76 \pm 13,6$ (24-90) godina. Kod 40 (80%) pacijenata je iz hemokulture dokazan uzročnik oboljenja, dok kod 10 (20%) pacijenata nije. Povišena telesna temperatura se javila kod 49 (98%) ispitanika, kod 24 (47%) postojala je jeza i drhtavica, 13 (25,5%) pacijenata imalo je mučninu, 16 (31,4%) povraćanje. Glavobolja se javila kod 8 (16%) pacijenata, dok su dijareja, dizurične tegobe, kao i poremećaj svesti registrovani kod 11 (21,6%) obolelih. Upoređivanjem srednjih vrednosti biohemijskih analiza pacijenata dobijenih po prijemu i po otpustu iz bolnice, utvrđeno je da postoji statistički značajna razlika ($p < 0,01$) koja ukazuje na smanjenje vrednosti laboratorijskih parametara kao što su sedimentacija eritrocita, C-reaktivni protein, ukupan broj leukocita i procenat segmentiranih leukocita.

Zaključak: U posmatranom uzorku sepse se, kao etiološki faktor nejasnog febrilnog stanja, sreće relativno često (11,9%). I pored značajnog napretka i razvoja sofisticiranih dijagnostičkih postupaka, u diferencijalnoj dijagnozi nejasnog febrilnog stanja treba uvek razmišljati o potencijalnoj sistemskoj infekciji kao mogućem uzroku u sklopu koje septično stanje zauzima važno mesto, čak i kada nas inicijalna ispitivanja ne navode na takav zaključak.

Ključne reči: sepsa, SIRS, nejasno febrilno stanje, infektivne bolesti

SUMMARY

Introduction: In the modern world, fever of unknown origin is becoming an increasingly common entity with varied etiologies. Septic condition has a significant role as an etiological factor of fever of unknown origin, often being overlooked or treated late.

Objective: To determine the frequency of sepsis, to establish demographic characteristics, clinical presentation of the disease, to identify the proportion of proven pathogens and their distribution by type, and to present laboratory analyses of patients diagnosed with sepsis upon admission and discharge from the hospital.

Materials and Methods: The study included patients treated at the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, from December 1, 2014, to December 31, 2017, with documented sepsis during the investigation of the etiology of FUO.

Results: Among 420 patients studied, sepsis was documented in 50 (11.9%). The study included 29 (58%) women and 21 (42%) men, with an average age of 63.76 ± 13.6 (24-90) years. The causative agent of the disease was detected in blood cultures in 40 (80%) patients, while not in 10 (20%). Elevated body temperature occurred in 49 (98%) patients, whilst 24 (47%) experienced chills and shivering, 13 (25.5%) nausea, and 16 (31.4%) vomiting. Headache occurred in 8 (16%) patients, while diarrhea, urinary symptoms, and altered consciousness were observed in 11 (21.6%) patients. By comparing the median values of biochemical analyses of patients obtained upon admission and discharge from the hospital, a statistically significant difference ($p < 0,01$) was found, indicating a decrease in laboratory parameter values such as erythrocyte sedimentation rate, C-reactive protein, total leukocyte count, and percentage of segmented leukocytes.

Conclusion: In the observed sample, sepsis occurs relatively frequently (11.9%) as an etiological factor of FUO. In the differential diagnosis of fever of unknown origin, despite significant progress and development of sophisticated diagnostic procedures, one should always consider potential systemic infection as a possible cause, among which septic condition occupies an important place, even when initial examinations do not lead to such a conclusion.

Keywords: sepsis, SIRS, fever of unknown origin, infectious diseases

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UVOD

Febrilno stanje nejasnog porekla označava prisustvo telesne temperature $>38,3^{\circ}\text{C}$ registrovane u više mahova koja traje duže od 3 nedelje, a dijagnoza nije postavljena uprkos adekvatnom ispitivanju koje obuhvata osnovna biohemijska ispitivanja, radiološka snimanja pluća, ultrazvučni pregled abdomena, bris grla, urinokulturu, kao i ginekološki pregled kod žena, odnosno urološki kod muškaraca sprovedenom u toku tri posete lekaru, odnosno nakon tri dana boravka u bolnici [1-3].

Septično stanje označava sistemski inflamatorni odgovor (SIRS – “systemic inflammatory response syndrome”) dokazane ili verovatne mikrobne etiologije, bez obzira da li se mikroorganizmi raznose krvlju, što se najčešće dešava, ili ostaju u lokalnom žarištu. SIRS je imunsko-metabolička reakcija organizma na različite, pa i biološke agense koji ga napadaju, a kog karakterišu najmanje dva od sledećih kliničkih znakova:

- ♦ febrilnost ($> 38^{\circ}\text{C}$) ili hipotermija ($< 36^{\circ}\text{C}$)
- ♦ tahipneja (> 24 udaha/min)
- ♦ tahikardija (>90 otkucaja/min)
- ♦ leukocitoza ($> 12 \times 10^9/\text{l}$), leukopenija ($<4 \times 10^9/\text{l}$) ili više od 10% nezrelih formi leukocita

Kako se radi o disregulaciji imunskog odgovora na infektivni agens i kako se on često karakteriše poremećajem telesne temperature, od izuzetnog je značaja pravovremeno pomisliti na ovo stanje [4-6].

U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznolikom etiologijom. Sepsa značajno participira kao etiološki faktor nejasnog febrilnog stanja, a često se previdi tj. lečenje se započinje kasno. Cilj ovog rada je bio da se utvrdi učestalost sepse, da se predstave demografske karakteristike, klinička prezentacija oboljenja, proporcija dokazanih izazivača i njihova raspodela po vrstama, kao i da se predstave laboratorijske analize pacijenata sa dijagnozom sepse po prijemu i po otpustu iz bolnice.

MATERIJAL I METODE

Ispitivanjem su obuhvaćeni pacijenti lečeni na Klinici za infektivne i tropske bolesti Kliničkog centra Srbije, na Odeljenju kliničke farmakoterapije u periodu od 1.12.2014. do 31.12.2017. godine, a kod kojih je u toku ispitivanja etiologije nejasnog febrilnog stanja dokazana sepsa. U posmatranom periodu je ispitivano 420 pacijenata tokom kojeg je sepsa dokazana kod 50 ispitanika. U ispitivanje nisu uključene osobe mlađe od 18 godina, jer Odeljenje kliničke farmakoterapije u sklopu Klinike za infektivne i tropske bolesti Kliničkog centra Srbije ne leči pedijatrijsku populaciju. U dijagnostici su korišćene standardne biohemijske metode

INTRODUCTION

Fever of unknown origin denotes the presence of body temperature $>38.3^{\circ}\text{C}$ recorded on multiple occasions lasting longer than 3 weeks, with no diagnosis established despite adequate investigation including basic biochemical tests, chest radiographs, abdominal ultrasound examination, throat swab culture, urine culture, and gynecological examination in women, or urological examination in men, conducted during three visits to the doctor or after three days of hospital stay [1-3].

Septic condition signifies a systemic inflammatory response (SIRS – “systemic inflammatory response syndrome”) of proven or probable microbial etiology, regardless of whether microorganisms are disseminated in the blood, which commonly occurs, or remain in a local focus. SIRS is the immune-metabolic reaction of the body to various, including biological, agents attacking it, characterized by at least two of the following clinical signs:

- ♦ fever ($> 38^{\circ}\text{C}$) or hypothermia ($< 36^{\circ}\text{C}$)
- ♦ tachypnea (> 24 breaths/min)
- ♦ tachycardia (> 90 beats/min)
- ♦ leukocytosis ($> 12 \times 10^9/\text{L}$), leukopenia ($< 4 \times 10^9/\text{L}$), or more than 10% immature forms of leukocytes

Given that it involves dysregulation of the immune response to infectious agents and is often characterized by disturbances in body temperature, timely consideration of this condition is of utmost importance [4-6].

In the modern world, fever of unknown origin is an increasingly common entity with diverse etiology. Sepsis significantly participates as an etiological factor of fever of unknown origin, often overlooked, i.e., treatment is initiated late. This study aimed to determine the frequency of sepsis, present demographic characteristics, clinical presentation of the disease, proportion of proven pathogens, and their distribution by types, and to present laboratory analyses of patients diagnosed with sepsis upon admission and discharge from the hospital.

MATERIALS AND METHODS

The study included patients treated at the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, from December 1, 2014, to December 31, 2017, who were diagnosed with sepsis during the investigation of the etiology of fever of unknown origin. During the observation period, 420 patients were examined, among whom sepsis was confirmed in 50 individuals. Persons under 18 years old were not included in the study, as the Department of Clinical Pharmacotherapy within the

koje uključuju nespecifične faktore inflamacije (CRP, SE), kompletnu krvnu sliku (*Leu*, % granulocita, *Er*, *Tr*, *Hgb*), ispitivanje enzima od značaja (AST, ALT, LDH, CPK) i mikrobiološke metode koje podrazumevaju uzimanje uzoraka krvi i urina radi izolacije i kultivisanja potencijalnog infektivnog agensa, kao i izrade antibiograma prema kome bi se uvela tj. korigovala terapija.

Statističke metode

Za statističko analiziranje podataka korišćeni su programi SPSS-a (*Statistical Package for the Social Sciences*) i EZR (*Easy R*). U cilju ispitivanja statističke značajnosti razlike srednjih vrednosti dva nezavisna uzorka korišćeni su Studentov t-test i Wilcoxon-ov test. Kao kriterijum statističke značajnosti razlike primenjene su vrednosti $p < 0,01$.

REZULTATI

Rezultati ovog istraživanja pokazali su da je među 420 ispitivanih pacijenta u datom periodu kod 50 (11,9%) dokazana sepsa (Grafikon 1).

Među pacijentima koji su bili uključeni u istraživanje bilo je 29 (58%) žena i 21 (42%) muškarac (Grafikon 2). Prosečna starost pacijenata bila je $63,76 \pm 13,6$ (24–90) godina.

Kod 40 (80%) pacijenata je iz hemokulture dokazan uzročnik oboljenja, dok kod 10 (20%) pacijenata nije (Tabela 1).

Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia does not treat pediatric patients. Standard biochemical methods were used in the diagnosis, including non-specific inflammation factors (CRP, ESR), complete blood count (WBC, % granulocytes, RBC, platelets, Hgb), examination of significant enzymes (AST, ALT, LDH, CPK), and microbiological methods involving blood and urine sampling for isolation and cultivation of potentially infectious agents, as well as antibiotic susceptibility testing to guide or adjust therapy.

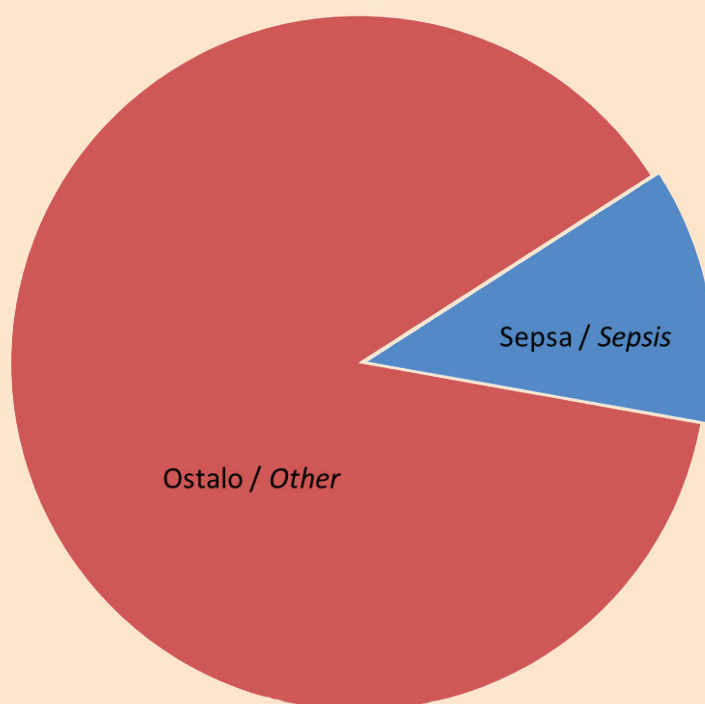
Statistical Methods

SPSS (Statistical Package for the Social Sciences) and EZR (Easy R) programs were used for statistical analysis of the data. Student's t-test and Wilcoxon's test were used to assess the statistical significance of the difference in mean values of two independent samples. A criterion of statistical significance was applied with $p < 0.01$.

RESULTS

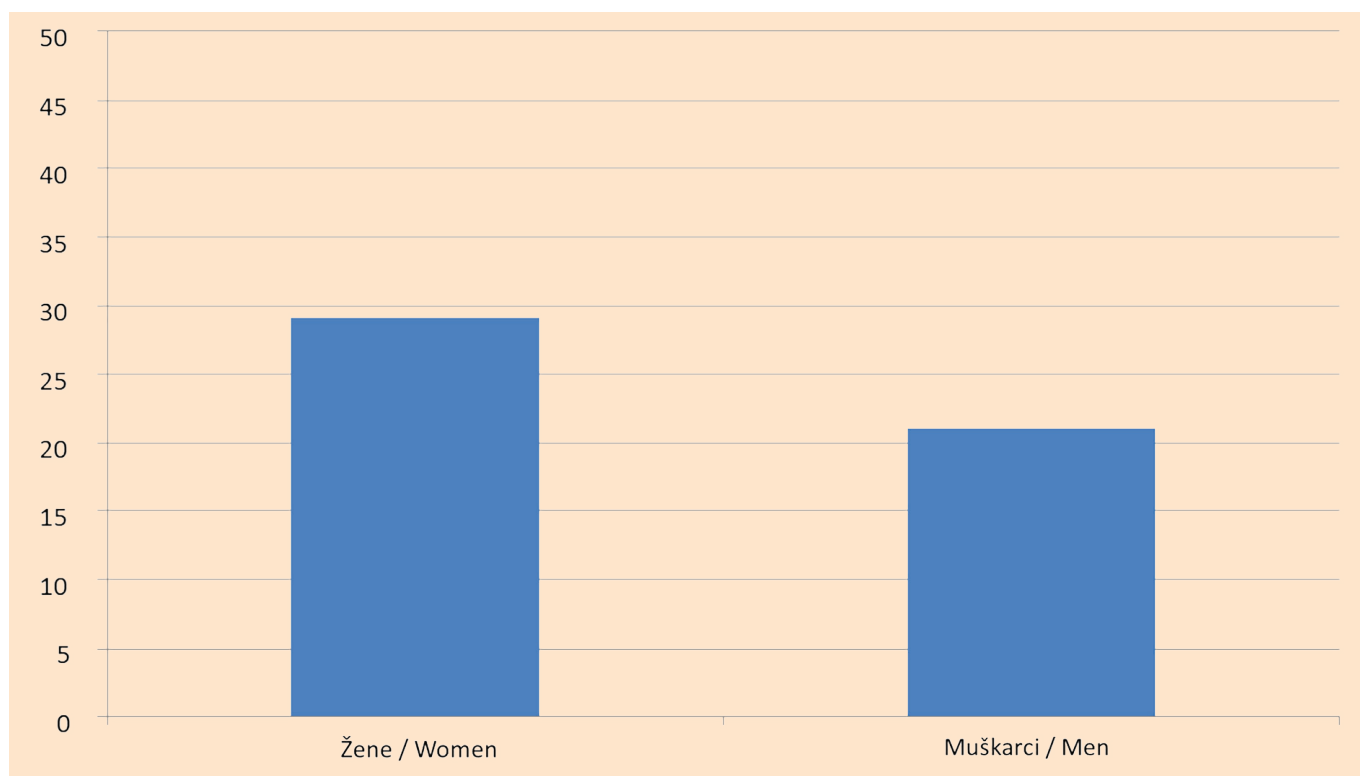
The results of this study showed that among the 420 examined patients during the given period, sepsis was confirmed in 50 (11.9%) cases (Graph 1).

Among the patients included in the study, there were 29 (58%) females and 21 (42%) males (Graph 2). The average age of the patients was 63.76 ± 13.6 (24–90) years.



Grafikon 1. Učestalost sepe u ispitivanoj grupi pacijenata

Figure 1. The frequency of sepsis within the examined group of patients



Grafikon 2. Demografski prikaz bolesnika sa dijagnozom sepe

Figure 2. Demographic display of patients diagnosed with sepsis

Kod pacijenata sa pozitivnom hemokulturom, najveći broj njih imao je izolovane bakterijske uzročnike među kojima dominiraju izazivači urosepse kao što su *Escherichia coli* koja se javila kod 17 (34%) i *Klebsiella* spp. kod 8 (16%) ispitanika. Svi ostali infektivni agensi prikazani su u sklopu priloga (Tabela 2).

In 40 (80%) patients, the causative agent of the disease was identified from blood culture, while in 10 (20%) patients it was not (Table 1).

Praćenjem osnovnih kliničkih manifestacija oboljenja i glavnih tegoba koje su pacijenti navodili po prijemu u bolnicu, rezultati prikazanog istraživanja pokazuju da se povišena telesna temperatura javila kod 49 (98,04%) pacijenata. Takođe, kod njih 24 (47%) postojala je jeza i drhtavica, 13 (25,5%) pacijenata imalo je mučninu kao jedan od simptoma bolesti, 16 (31,4%) je imalo povraćanje. Glavobolja se javila kod 8 (16%) pacijenata, dok su dijareja, dizurične tegobe, kao i poremećaj svesti registrovani kod 11 (21,6%) obolelih (Tabela 3).

Tabela 2. Prikaz uzročnika septičnog stanja prema učestalosti javljanja

Table 2. Display of pathogens of septic condition according to frequency of occurrence

	Učestalost / Frequency	%
<i>E. coli</i>	17	34
<i>K. pneumoniae</i>	8	16
<i>Staphylococcus aureus</i>	3	6
<i>Enterococcus spp.</i>	3	6
<i>Streptococcus gallolyticus</i>	2	4
<i>Bacteroides spp.</i>	1	2
<i>Streptococcus pneumoniae</i>	1	2
<i>Streptococcus viridans</i>	1	2
<i>Streptococcus dysgalactiae</i>	1	2
<i>Coagulase-negative staphylococcus</i>	1	2
<i>Candida parapsilosis</i>	1	2
<i>Listeria monocytogenes</i>	1	2
Nepoznato / Unknown	10	20
Ukupno / Total	50	100

Tabela 1. Proporcija dokazanih i nedokazanih mikrobioloških uzročnika septičnog stanja

Table 1. Proportion of proven and unproven microbiological pathogens of septic conditions

	Učestalost / Frequency	%
Dokazani / Proven	40	80
Nedokazani / Unproven	10	20
Ukupno / Total	50	100

Tabela 3. Kliničke karakteristike bolesnika sa dijagnozom sepsa**Table 3.** Clinical characteristics of patients diagnosed with sepsis

	Ukupno / Total	%
Povišena temperatura / Elevated temperature	49	98.04
Jeza i drhtavica / Chills and shivering	24	47.06
Mučnina / Nausea	13	25.49
Povraćanje / Vomiting	16	31.37
Dijareja / Diarrhea	11	21.57
Dizurične tegobe / Dysuric disorders	11	21.57
Poremećaj svesti / Altered consciousness	11	21.57
Glavobolja / Headache	8	16

Upoređivanjem srednjih vrednosti rutinskih biohemijskih analiza pacijenata sa dijagnozom sepsa dobijenih po prijemu i po otpustu iz bolnice, utvrđeno je da postoji statistički značajna razlika ($p < 0,01$) koja ukazuje na smanjenje vrednosti sledećih laboratorijskih parametara: sedimentacija eritrocita (78,6 / 55,16), C-reaktivni protein (344,6 / 30,6), ukupan broj leukocita (13,77 / 7,56), procenat segmentiranih leukocita (82,6 / 67,2) (Tabela 4).

DISKUSIJA

Na osnovu dostupnih podataka američkog Centra za kontrolu i prevenciju bolesti (CDC – “Centers for Disease Control and Prevention”) na teritoriji Sjedinjenih Američkih Država registruje se više od 1.5 miliona slučajeva septičnog stanja na godišnjem nivou, sa oko 250.000 smrtnih ishoda, a kod jednog od tri hospitalizovana pacijenta sa letalnim ishodom dokazana je sepsa. U odraslih pacijenata najčešća ishodišta infekcije koja dovode do razvoja septičnog stanja su: infekcije respiratornog sistema (35%), infekcije urinarnog sistema i bubrega (25%), infekcije digestivnog trakta (11%) i kožne infekcije (11%) [7-8].

Prema podacima dobijenim na osnovu velikih kohortnih studija koje su sprovedene u 5 razvijenih zemalja (Velika Britanija, Francuska, SAD, Australija i Novi Zeland) pokazano je da godišnja incidencija sepsa značajno varira u rasponu od 51 (Velika Britanija) do 300 (SAD) obolelih na 100.000 stanovnika, a beleži se i rast incidencije (8-13%) u odnosu na prethodne dve decenije. Ovaj trend pripisuje se starenju stanovništva, produženju života bolesnika sa hroničnim bolestima i infekcijama (tumori, diabetes mellitus tip 2, AIDS), širokoj upotrebi antimikrobnih lekova, glukokortikoida, trajnih katetera, mehaničkih naprava i mehaničke ventilacije [9-13].

Tabela 4. Srednje vrednosti rutinskih biohemijskih analiza pacijenata sa dijagnozom sepsa dobijenih po prijemu i po otpustu iz bolnice**Table 4.** Median values of routined biochemical analyses of patients diagnosed with sepsis upon admission and discharge from the hospital

	Pre prijema / Before admission	Po otpustu / After discharge	$p (< 0,01)$
SE (mm/h)	78.66	55.16	$<0.001^{**}$
CRP (mg/l)	344.578	30.581	$<0.001^{**}$
ALT (IU/l)	48.35	29.11	0.002^{**}
AST (IU/l)	41.35	23.97	0.001^{**}
LDH (IU/l)	325.98	252.29	$<0.001^{**}$
CPK (IU/l)	234.96	41.00	0.001^{**}
HgB ($\times 10^{12}/l$)	118.02	112.28	0.079^*
Tr ($\times 10^{12}/l$)	213.34	256.08	$<0.001^{**}$
Le ($\times 10^{12}/l$)	13.767	7.556	$<0.001^{**}$
Segmentirani / Segmented %	82.65	67.16	$<0.001^*$

*Studentov t-test / *Student's t-test

**Wilcoxon-ov test / **Wilcoxon's test

Among patients with positive blood cultures, the majority had isolated bacterial pathogens, with urosepsis-causing agents such as *Escherichia coli* occurring in 17 (34%) and *Klebsiella* spp. in 8 (16%) subjects. All other infectious agents are presented in the appendix (Table 2).

Monitoring the basic clinical manifestations of the disease and the main complaints reported by patients upon admission to the hospital, the results of the presented study show that elevated body temperature occurred in 49 (98.04%) patients. Additionally, 24 (47%) experienced chills and shivering, 13 (25.5%) had nausea as a symptom of the disease, and 16 (31.4%) experienced vomiting. Headache occurred in 8 (16%) patients, while diarrhea, urinary symptoms, and altered consciousness were reported in 11 (21.6%) patients (Table 3).

By comparing the median values of routine biochemical analyses of patients diagnosed with sepsis upon admission and upon discharge from the hospital, a statistically significant difference ($p < 0.01$) was found, indicating a decrease in the values of the following laboratory parameters: erythrocyte sedimentation rate (78.6 / 55.16), C-reactive protein (344.6 / 30.6), total leukocyte count (13.77 / 7.56), percentage of segmented leukocytes (82.6 / 67.2) (Table 4).

DISCUSSION

Based on available data from the Centers for Disease Control and Prevention (CDC) in the United States, over 1.5 million cases of septic conditions are registered an-

Ukoliko posmatramo samo pojedinačne oblasti Evrope, kao značajnu izdvajamo veliku retrospektivnu analizu sprovedenu na tlu Katalonije, autonomne oblasti Španije, u kojoj se navodi incidencija sepse tj. septičnog stanja od 1,72% na godišnjem nivou. Od ukupnog broja obolelih, 56,1% činili su pripadnici muškog pola, dok je prosečna starost pacijenata sa dijagnozom sepse bila $71,2 \pm 19,7$ godina. U najčešća ishodišta infekcije koja su dovela do razvoja septičnog stanja navode se infekcije urinarnog trakta (37,2%) i infekcije respiratornog sistema (32,5%). Rezultati studije pokazuju da je iz hemokulture dokazan uzročnik kod 84,2% pacijenta, a kod 15,8% ispitanika nije. Kao najčešće izolovani infektivni agensi navode se *Escherichia coli* (8%), *Streptococcus* spp. (7%), koagulaza-negativni *Staphylococcus* spp. (6%) i *Staphylococcus aureus* (6%) [14,15].

Na Klinici za infektivne i tropske bolesti KCS-a, na Odeljenju kliničke farmakoterapije, među 420 ispitivanih pacijenata, u periodu od 1.12.2014. do 31.12.2017., kod 50 (11,9%) pacijenata se javila sepsa; od čega je njih 29 (58%) pripadalo ženskoj populaciji i 21 (42%) muškoj populaciji, a prosečna starost ispitanika bila je $63,76 \pm 13,6$ (24-90) godina. Rezultati studije takođe su pokazali da su kod pacijenata sa pozitivnom hemokulturom najčešće izolovani etiološki agensi bile bakterije i to: *Escherichia coli* koja se javila kod 17 (34%) i

Klebsiella spp. kod 8 (16%) ispitanika. Ostali izolati, kao što su na primer *Staphylococcus aureus* (6%), *Streptococcus gallolyticus* (6%) i *Streptococcus pneumoniae* (2%), govore u prilog bakterijskih mikroorganizama kao najčešćih uzročnika ovog stanja. Kod jednog pacijenta (2%) dokazana je gljivična etiologija (*Candida parapsilosis*).

Upoređivanjem ovih rezultata sa rezultatima prethodnih studija, registruju se veća učestalost septičnog stanja i niža prosečna starost bolesnika. Značajnije odstupanje vezano za procenat pozitivnih hemokultura, kao i izolovanih uzročnika se ne zapaža.

Sepsa može biti odgovor na infekciju uzrokovanu bilo kojom vrstom mikroorganizama. Premda gram-negativne i gram-pozitivne bakterije čine najčešće infektivne agense koji su u osnovi SIRS-a, sepsa može biti uzrokovana gljivicama, mikobakterijama, protozoama [16].

Na sepsu se lako posumnja kod bolesnika sa lokalnom infekcijom koji naglo dobije povišenu telesnu temperaturu, groznicu, tahikardiju, tahipneju, poremećaj svesti i hipotenziju. Međutim, septički odgovor se može razvijati mnogo sporije i imati suptilnije manifestacije. U jednom proučavanju 36% bolesnika sa sepsom bilo je afebrilno, 44% je imalo uredno stanje svesti, 60% eupnoično, 10% je imalo broj srčanih otkucaja u okviru fizioloških granica. Odsustvo febrilnosti najčešće je u starijih osoba i bolesnika sa uremijom, ili kod alkoholičara [17-19].

nually, resulting in approximately 250,000 fatalities. Sepsis is proven in one out of three hospitalized patients with a fatal outcome. The most common sources of infection leading to the development of septic conditions in adults include respiratory infections (35%), urinary tract and kidney infections (25%), gastrointestinal infections (11%), and skin infections (11%) [7-8].

According to data obtained from large cohort studies conducted in five developed countries (the United Kingdom, France, the United States, Australia, and New Zealand), the annual incidence of sepsis significantly varies from 51 (the United Kingdom) to 300 (the United States) cases per 100,000 population, with an increasing incidence trend (8-13%) over the past two decades. This trend is attributed to population aging, prolonged lifespan of patients with chronic diseases and infections (such as tumors, type 2 diabetes mellitus, AIDS), widespread use of antimicrobial drugs, glucocorticoids, indwelling catheters, mechanical devices, and mechanical ventilation [9-13].

If we focus solely on individual regions of Europe, a significant retrospective analysis conducted in Catalonia, an autonomous region of Spain, reports an incidence of sepsis or septic conditions of 1.72% annually. Of the total number of cases, 56.1% were male, with an average age of 71.2 ± 19.7 years among patients diagnosed with sepsis. The most common sources of infection leading to the development of septic conditions include urinary tract infections (37.2%) and respiratory system infections (32.5%). The study results indicate that the causative agent was identified from blood culture in 84.2% of patients, while it was not in 15.8% of subjects. The most frequently isolated infectious agents include *Escherichia coli* (8%), *Streptococcus* spp. (7%), coagulase-negative *Staphylococcus* spp. (6%), and *Staphylococcus aureus* (6%) [14,15].

At the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, among the 420 examined patients from December 1, 2014, to December 31, 2017, sepsis occurred in 50 (11.9%) patients. Among them, 29 (58%) were female and 21 (42%) were male, with an average age of 63.76 ± 13.6 (24-90) years. The study results also showed that the most commonly isolated etiological agents in patients with positive blood cultures were bacteria, namely *Escherichia coli* occurring in 17 (34%) and *Klebsiella* spp. in 8 (16%) subjects. Other isolates, such as *Staphylococcus aureus* (6%), *Streptococcus gallolyticus* (6%), and *Streptococcus pneumoniae* (2%), support bacterial microorganisms as the most common causative agents of this condition. A fungal etiology (*Candida parapsilosis*) was confirmed in one patient (2%).

Osnovne kliničke manifestacije oboljenja i glavne tegobe koje su pacijenti navodili po prijemu u bolnicu bili su povišena telesna temperatura koja se javila kod 98% ispitanika, jeza i drhtavica 47%, mučnina 25,5%, povraćanje 31,4%, glavobolja 16%, dok su dijareja, dizurične tegobe i poremećaj svesti registrovani kod 21,6% bolesnika.

Povišen ili snižen broj leukocita, kao i pojava mladih formi granulocita, deo je definicije SIRS-a u okviru kojeg se nalazi i sepsa. Leukocitoza, sa izrazitom predominacijom polimorfonukleara se najčešće sreće u ranoj fazi sepse izazvane gram-pozitivnim bakterijama, dok je leukopenija karakterističnija za sepsu izazvanu gram-negativnim bakterijama. Ubrzana sedimentacija eritrocita, povišen nivo fibrinogena, C-reaktivnog proteina, alfa 2- globulina nespecifični su pokazatelji zapaljenja i po pravilu su prisutni i u sepsi [6-9].

Tokom ispitivanja pacijenata po prijemu u ustanovu, kod većine je zabeležena leukocitoza sa porastom procenta segmentiranih leukocita, kao i ubrzana sedimentacija eritrocita i povišen nivo C-reaktivnog proteina. Kontrolnim biohemijskim analizama po otpustu pacijenata iz bolnice ustanovljeno je statistički značajno sniženje ovih parametara.

U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznovrsnom etiologijom. Septično stanje značajno participira kao etiološki faktor nejasnog febrilnog stanja, a često se previdi tj. lečenje se započinje kasno.

Na osnovu rezultata možemo zaključiti da je procenat obolelih od ovog infektivnog stanja veći među učesnicima prikazane studije zbog lošijih socijalno-ekonomskih uslova naše zemlje i zdravstvenog sistema uopšte, koji dovode do slabijih rezultata primarne dijagnostike u odnosu na zdravstvene sisteme razvijenih zemalja. Takođe, ovo se može opravdati većom zastupljenošću infektivnih bolesti u našem okruženju, kao i većim procentom radno aktivnih koji zbog loše medicinske kulture kasnije dolaze u medicinske ustanove.

ZAKLJUČAK

U posmatranom uzorku sepsa se kao etiološki faktor nejasnog febrilnog stanja sreće relativno često (11,9%). Na osnovu rezultata ovog istraživanja zaključuje se da češće obolevaju pripadnice ženskog pola (58%), starije životne dobi, a da u najčešće izolovane uzročnike spadaju *Escherichia coli* (34%) i *Klebsiella* spp. (16%) što ukazuje na to da je najčešće ishodište infekcije urinarni trakt. Glavne tegobe ne moraju obavezno biti specifične, te kod svake produžene febrilnosti u razmatranje treba uključiti i sistemsku infekciju.

U diferencijalnoj dijagnozi nejasnog febrilnog stanja, i pored značajnog napretka i razvoja sofisticiranih dija-

Comparing these results with those of previous studies, a higher frequency of septic conditions and a lower average patient age are observed. Significant deviations regarding the percentage of positive blood cultures and isolated pathogens are not noted.

Sepsis can be a response to an infection caused by any type of microorganism. Although gram-negative and gram-positive bacteria are the most common infectious agents underlying SIRS, sepsis can also be caused by fungi, mycobacteria, protozoa [16].

Sepsis can be easily suspected in patients with a local infection who suddenly develop elevated body temperature, fever, tachycardia, tachypnea, altered consciousness, and hypotension. However, the septic response can develop much more slowly and have subtler manifestations. In one study, 36% of patients with sepsis were afebrile, 44% had normal consciousness, 60% were eupneic, and 10% had heart rates within physiological limits. Absence of fever is most common in older individuals, patients with uremia, or alcoholics [17-19].

Basic clinical manifestations of the disease and main complaints reported by patients upon hospital admission included elevated body temperature in 98% of respondents, chills and shivering in 47%, nausea in 25.5%, vomiting in 31.4%, headache in 16%, while diarrhea, urinary symptoms, and altered consciousness were reported in 21.6% of patients.

Elevated or decreased leukocyte count, as well as the presence of young forms of granulocytes, are part of the definition of SIRS, within which sepsis is encompassed. Leukocytosis, with a marked predominance of polymorphonuclear cells, is most commonly encountered in the early stage of sepsis caused by gram-positive bacteria, while leukopenia is more characteristic of sepsis caused by gram-negative bacteria. Elevated erythrocyte sedimentation rate, increased fibrinogen level, C-reactive protein, and alpha 2-globulin are non-specific indicators of inflammation and are typically present in sepsis [6-9].

During the examination of patients upon admission to the institution, leukocytosis with an increase in segmented leukocyte percentage, accelerated erythrocyte sedimentation rate, and elevated C-reactive protein level were recorded in most cases. Statistical analysis of biochemical parameters upon discharge from the hospital revealed a significant decrease in these parameters.

In the modern world, fever of unknown origin becoming increasingly common entities with diverse etiologies. Septic conditions significantly contribute as an etiological factor in fever of unknown origin, often overlooked, i.e. leading to delayed treatment.

gnostičkih postupaka, treba uvek razmišljati o potencijalnoj sistemskoj infekciji kao mogućem uzroku u sklopu koje septično stanje zauzima važno mesto, čak i kada nas inicijalna ispitivanja ne navode na takav zaključak.

Sukob interesa: Nije prijavljen.

LITERATURA / REFERENCES

1. Arnow PM, Flaherty JP. Fever of unknown origin. *Lancet*. 1997 Aug 23;350(9077):575-80. doi: 10.1016/S0140-6736(97)07061-X.
2. Gelfand J. A. Fever of unknown origin. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. editors. *Harrison's Principles of Internal Medicine*, 15th edition. New York, NY: McGraw-Hill; 2001. p. 125.
3. Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. *J Intern Med*. 2003 Mar;253(3):263-75. doi: 10.1046/j.1365-2796.2003.01120.x.
4. Astiz ME, Rackow EC. Septic shock. *Lancet*. 1998 May 16;351(9114):1501-5. doi: 10.1016/S0140-6736(98)01134-9.
5. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013 Mar 2;381(9868):774-5. doi: 10.1016/S0140-6736(12)61815-7.
6. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003 Apr;29(4):530-8. doi: 10.1007/s00134-003-1662-x.
7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287.
8. Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al; CDC Prevention Epicenter Program. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. *JAMA*. 2017 Oct 3;318(13):1241-9. doi: 10.1001/jama.2017.13836.
9. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003 Apr 17;348(16):1546-54. doi: 10.1056/NEJMoa022139.
10. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. *Expert Rev Anti Infect Ther*. 2012 Jun;10(6):701-6. doi: 10.1586/eri.12.50.
11. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med*. 2003 Sep;31(9):2332-8. doi: 10.1097/01.CCM.0000085141.75513.2B.
12. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med*. 2004 Apr;30(4):589-96. doi: 10.1007/s00134-004-2157-0.
13. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001 Jul;29(7):1303-10. doi: 10.1097/00003246-200107000-00002.
14. Ferrer R, Artigas A, Levy MM, Blanco J, González-Díaz G, Garnacho-Montero J, et al; Edusepsis Study Group. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA*. 2008 May 21;299(19):2294-303. doi: 10.1001/jama.299.19.2294.
15. Yébenes JC, Ruiz-Rodríguez JC, Ferrer R, Clèries M, Bosch A, Lorenzo C, Rodríguez A, et al; SOCMIC (Catalonian Critical Care Society) Sepsis Working Group. Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. *Ann Intensive Care*. 2017 Dec;7(1):19. doi: 10.1186/s13613-017-0241-1.

Based on the results, we can conclude that the percentage of individuals affected by this infectious condition is higher among the participants in the present study due to the poorer socio-economic conditions of our country and the healthcare system in general. These conditions lead to poorer primary diagnostic results compared to healthcare systems in developed countries. Additionally, this can be justified by a higher prevalence of infectious diseases in our environment, as well as a higher percentage of working individuals who, due to poor medical culture, tend to seek medical attention later.

CONCLUSION

In the observed sample, sepsis emerges relatively frequently as an etiological factor in a fever of unknown origin (11.9%). Based on the results of this study, it is concluded that females are more often affected (58%), particularly those of older age, with *Escherichia coli* (34%) and *Klebsiella* spp. (16%) being the most commonly isolated pathogens, indicating that the most common origin of infection is the urinary tract. The main symptoms may not necessarily be specific, thus systemic infection should be considered in the differential diagnosis of prolonged fever.

Despite significant advancements and the development of sophisticated diagnostic procedures, differential diagnosis of fever of unknown origin should always include the consideration of potential systemic infection, among which septic conditions hold a significant position, even when initial investigations do not suggest such a conclusion.

Conflict of interest: None declared.

16. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013 Feb;41(2):580-637. doi: 10.1097/CCM.0b013e31827e83af.
17. Parrillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med*. 1990 Aug 1;113(3):227-42. doi: 10.7326/0003-4819-113-3-227.
18. Marx JA, Hockberger RS, Walls RM. *Rosen's emergency medicine: concepts and clinical practice*. 7th edition. Philadelphia, PA: Mosby/Elsevier; 2010.
19. Rumbus Z, Matics R, Hegyi P, Zsiborás C, Szabo I, Illes A, et al. Fever Is Associated with Reduced, Hypothermia with Increased Mortality in Septic Patients: A Meta-Analysis of Clinical Trials. *PLoS One*. 2017 Jan 12;12(1):e0170152. doi: 10.1371/journal.pone.0170152.

UZROK PREVREMENOG POROĐAJA KAO PROGNOŠTIČKI FAKTOR NEONATALNOG ISHODA I NAČINA ZAVRŠAVANJA POROĐAJA

ORIGINALNI RAD

ORIGINAL ARTICLE

CAUSE OF PREMATURE BIRTH AS A PROGNOSTIC FACTOR OF NEONATAL OUTCOME AND TYPE OF DELIVERY

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SAŽETAK

Uvod: Prevremeni porođaj je porođaj pre 37. nedelje gestacije. Prevremeni porođaji su najčešće uzrokovani pojavom regularnih uterinskih kontrakcija, prevremenim prsnućem plodovih ovojaka ili abrupcijom posteljice. U 20% – 30% slučajeva kada postoje maternalne ili fetalne komplikacije, prevremeni porođaj može biti indukovani. Najčešći razlog za to su preeklampsija, zastoj u rastu ploda, te teška srčana oboljenja majke.

Cilj rada: Cilj rada jeste utvrđivanje povezanosti uzroka i vremena nastanka prevremenog porođaja sa neonatalnim ishodom.

Materijali i metode: Retrospektivnom studijom smo analizirali prevremeno porođene pacijentkinje u Ginekološko-akušerskoj klinici „Narodni front“ tokom 2020. kao i uzrok njihovog prevremenog porođaja, stanje ploda nakon porođaja. Komparirali smo neonatalni ishod kod spontanog i indukovano prevremenog porođaja.

Rezultati: Od ukupnog broja porođaja ($n = 4,211$), od jula do decembra 2020. godine, 498 je bilo pretermijskih, što čini 11,83%. Na osnovu podataka o vitalnom statusu prematurusa, procenat mrtvih nedonoščadi iznosio je 8,9%, dok je procenat živih iznosio 91,1%. Apgar skor je bio najviši kod novorođenčadi iz vaginalnog porođaja, nakon 34. nedelje gestacije, sa intaktnim plodovim opnama i spontanom uspostavljanjem kontrakcija. Prema datoj studiji, 54,1%, pretermijskih porođaja je završeno carskim rezom, što je uzrokovano gestacijskom starošću trudnoće mlađom od 28 nedelja gestacije i dominantno karličnom prezentacijom ploda.

Zaključak: Značajna učestalost prevremenog porođaja, u odnosu na ukupan broj porođaja, ukazuje na ozbiljnost problema i dalju tendenciju rasta broja prevremenih porođaja i pored primenjenih svih preventivnih mera. Bolji ishod trudnoće se uočava kod porođaja u kasnijoj gestaciji, nakon 34. nedelje, sa intaktnim plodovim opnama, bez znakova infekcije. Viši Apgar skor kod dece iz spontanog u odnosu na indukovani prevremeni porođaj govori o boljem neonatalnom ishodu.

Ključne reči: prevremeni porođaj, prematurus, Apgar skor

ABSTRACT

Introduction: Premature birth, occurring before the 37th gestational week, is commonly attributed to uterine contractions, premature rupture of the amniotic sac, or placental abruption. In 20% – 30% cases involving maternal or fetal complications, premature birth may be induced, often due to conditions such as preeclampsia, fetal growth retardation, or severe maternal heart disease.

Aim: The study aims to determine whether the cause and time of preterm birth affect the neonatal outcome.

Material and methods: This retrospective study analyzes patients prematurely born at the Obstetrics and Gynecology Clinic *Narodni Front* in 2020, the cause of their premature birth, as well as the status of the fetus after birth. In the study, we compared the neonatal outcome in spontaneously induced preterm birth.

Results: Among all the births ($n = 4,211$), in the period between July and December 2020, there were 498 preterm births, i.e., 11.83%. Based on the data on the status of the premature infants' vital signs, the percentage of stillborn preterm infants was 8.9% while the percentage of live births was 91.1%. The Apgar score was the highest in neonates born by vaginal birth after the 34th week of gestation, with intact fetal membranes and spontaneous contractions. According to the study, 54.1% of preterm births ended in cesarean section due to gestational age younger than 28 weeks and with a predominantly pelvic presentation of the fetus.

Conclusion: The high rate of premature births highlights a serious problem and suggests a continued rising trend, despite preventive efforts. Improved outcomes are seen in pregnancies reaching later gestational weeks, particularly after the 34th week of gestation, with intact fetal membranes and no signs of infection. Spontaneously born premature infants tend to have higher Apgar scores and better neonatal outcomes, as compared to induced births.

Keywords: preterm birth, premature infant, Apgar score

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UVOD

Pretermijski porođaj je jedan od najaktuelnijih problema perinatalne medicine danas. Predstavlja potencijalno vrlo opasan perinatalni događaj, prvenstveno sa stanovišta perinatalnog morbiditeta i mortaliteta. Po definiciji, to je porođaj koji nastupi pre 37. gestacijske nedelje [1]. Prema podacima Svetske zdravstvene organizacije (SZO), na osnovu gestacijske starosti, prevremeni porođaj može biti ekstremno rani – pre 28. nedelje gestacije, rani – između 28. i 32. nedelje gestacije, umereno rani – između 32. i 34. nedelje gestacije, te kasni – između 34. i 37. nedelje gestacije. Novorođenče iz pretermijskog porođaja se naziva nedonoščetom ili prematurusom. Dugo se definicija pretermijskog porođaja vezivala za telesnu masu novorođenčeta, ali danas se zna da je za preživljavanje mnogo značajnija gestacijska starost trudnoće i zrelost prematurusa nego sama telesna masa na rođenju [1].

Prematuritet je najvažniji pojedinačni faktor neonatalnog morbiditeta, mortaliteta i kasnih posledica na preživelim. Ishod i tok prevremenog porođaja zavise i od ekonomske razvijenosti zemlje. Na našim prostorima učestalost pretermijskog porođaja iznosi oko 8% [1].

Prematurusi su ugroženi nezrelošću svih organskih sistema, ali pluća i centralni nervni sistem su posebno osetljivi. Komplikacije kod prevremeno rođene dece mogu se javiti neposredno nakon rođenja. Najčešće i najozbiljnije su: intraventrikularna hemoragija, respiratorni distres sindrom, sepsa i nekrotizirajući enterokolitis. Kasne komplikacije se uočavaju tokom odrastanja i predstavljaju trajne sekvele: retinopatija, cerebralna paraliza, psihomotorni i kognitivni poremećaji. Prematurusi predstavljaju veliki problem, ne samo za pojedince i porodicu, već i za društvo uopšte [1].

Etiologija prevremenog porođaja je multifaktorijska, neretko ne možemo utvrditi tačan uzrok njegovog nastanka. Uzroke možemo podeliti na promenljive i nepromenljive, kao i na uzroke maternalnog ili fetalnog porekla. Najčešći uzroci su infekcija, multiparitet, anomalije materice, kratak vremenski period između dve trudnoće, te raniji prevremeni porođaji u anamnezi. Na povećanje rizika utiču stil života, pušenje, loša ishrana, konzumiranje lekova, alkohola i droga (posebno kokaina), stres, loši socioekonomski uslovi. Uopšteno posmatrajući etiološke faktore, jedna trećina pretermijskih porođaja je uzrokovana infekcijom i prevremenim prsnućem plodovih ovojaka (engl. *preterm premature rupture of membranes -PPROM*), druga trećina je posledica maternalnih i fetalnih faktora, a kod preostale trećine, koja je po nekim podacima i do 50% nepoznate etiologije, govorimo o idiopatskom prevremenom porođaju. Najznačajniji faktori rizika koji su u vezi sa majkom su

INTRODUCTION

Preterm birth is one of the most relevant problems of perinatal medicine today. It represents a potentially very dangerous perinatal event, primarily from the point of view of perinatal morbidity and mortality. By definition, it is a birth that occurs before the 37th week of gestation [1]. According to World Health Organization (WHO) data, based on gestational age, premature birth can be extremely preterm – before the 28th week of gestation, very preterm – between the 28th and 32nd weeks of gestation, moderate preterm – between the 32nd and 34th weeks of gestation, and late preterm – between the 34th and 37th weeks of gestation. A newborn baby born prematurely is called a premature or preterm infant. For a long time, the definition of preterm delivery was linked to the body weight of the newborn, but today it is known that the gestational age of the pregnancy and the maturity of the preterm infant are much more important for survival than the body weight at birth [1].

Prematurity is the single most important factor in neonatal morbidity, mortality, and subsequent effects on surviving infants. The outcome and course of premature birth also depend on the economic development of the country. In our region, the frequency of preterm birth is about 8% [1].

Premature babies are threatened by the immaturity of all organ systems, but the lungs and central nervous system are particularly sensitive. Complications in premature babies can occur immediately after birth. The most common and most serious are the following: intraventricular hemorrhage, respiratory distress syndrome, sepsis, and necrotizing enterocolitis. Late complications are observed during adulthood and represent permanent sequelae: retinopathy, cerebral palsy, and psychomotor and cognitive disorders. Premature babies are a significant problem, not only for individuals and families but also for society in general [1].

The etiology of premature birth is multifactorial, and we often cannot determine the exact cause of its occurrence. The causes can be categorized as variable and non-variable, as well as causes of maternal or fetal origin. The most common causes are infection, multiparity, uterine anomalies, a short period between two pregnancies, and previous premature births in the anamnesis. Lifestyle, smoking, poor diet, consumption of medicines, alcohol and drugs (especially cocaine), stress, and poor socioeconomic conditions increase the risk of premature birth. Looking at the etiological factors in general, one third of preterm births are caused by infection and premature rupture of membranes (PPROM), another third is the result of maternal and fetal factors, and the remaining third, which ac-

sledeći: pozitivna prethodna anamneza pretermanskog porođaja, životno doba trudnice (ispod 20 ili preko 35 godina), višerotke, rađanje dece male telesne mase, hipertenzivna bolest u trudnoći, urinarne infekcije, infektivne bolesti, febrilna stanja majke, maligna oboljenja, anemija, *diabetes mellitus*, razvojne anomalije uterusa, inkompetentan i insuficijentan donji uterusni segment, povećana količina plodove vode, krvarenja iz uterusa (abrupcija placente, *placenta previa*, placenta insuficijencija), kao i druga hronična oboljenja majke [1].

Kod intaktnih plodovih ovojaka, preterminski porođaj može biti uzrokovan ascendentnim širenjem infekcije iz vagine i cerviksa. To je stanje neme infekcije, kada postoji intrauterina infekcija, ali nema kliničkih znakova koji ukazuju na njeno prisustvo. Od fetalnih faktora na prvom mestu su višeploidne trudnoće, zatim fetalne anomalije, intrauterini zastoj u rastu, intrauterino ugnuće ploda, anomalije položaja i prezentacije [1].

Cilj rada je da se utvrdi da li uzrok i vreme nastanka prevremenog porođaja utiče na neonatalni ishod.

MATERIJALI I METODE

Iz baze podataka porođaja obavljenih tokom 2020. godine u Ginekološko-akušerskoj klinici „Narodni front“, u studiju su uključeni samo preterminski porođaji u vremenskom periodu od 1. 07. 2020. do 31. 12. 2020. godine. Iz studije su isključene sve višeploidne trudnoće, kao i prevremeni porođaji indukovani zbog anomalija ploda. Metodama deskriptivne statistike opisali smo makroskopski izgled plodove vode, pol, vitalni status novorođenčeta, način završetka porođaja, intaktnost plodovih opni, položaj ploda, Apgar ocenu u prvom i petom minutu, te prepartalno primenjenu terapiju deksametazonom kod trudnica.

Statistička analiza

Podaci su uneti u bazu podataka i obrađeni korišćenjem programa *IBM SPSS 25*. U radu su korišćene metode deskriptivne i analitičke statistike. Od metoda deskriptivne statistike korišćene su: mere centralne tendencije, mere varijabiliteta i relativni brojevi. Od metoda analitičke statistike korišćene su metode za procenu značajnosti razlike, hi-kvadratni test i Men Vitnijev test, kao i metode za procenu značajnosti povezanosti, Spirmanov koeficijent korelacije ranga. Vrednost $p < 0,05$ je smatrana statistički značajnom.

REZULTATI

Od ukupnog broja porođaja ($n = 4.211$), od jula do decembra 2020. godine, bilo je 498 preterminskih, što čini 11,83% (Grafikon 1). Na osnovu podataka o vitalnom statusu prematurusa, procenat mrtvih nedonoščadi iznosio je 8,9%, a živih 91,1%.

According to some data is up to 50% of unknown etiology, is idiopathic premature birth. The most significant risk factors related to the mother are the following: positive previous history of preterm birth, age of the pregnant woman (below 20 or over 35 years), multiple births, birth of children with low body weight, hypertensive disease in pregnancy, urinary infections, infectious diseases, febrile maternal conditions, malignant diseases, anemia, diabetes mellitus, developmental anomalies of the uterus, incompetent and insufficient lower uterine segment, increased amount of amniotic fluid, bleeding from the uterus (abruption of the placenta, placenta previa, placental insufficiency), as well as other chronic maternal diseases [1].

In the case of intact fetal membranes, preterm delivery can be caused by an ascending infection from the vagina and cervix. It is a state of silent infection, when there is an intrauterine infection, but there are no clinical signs indicating its presence. Of the fetal factors, multiple pregnancies are the most common cause of premature birth, followed by fetal anomalies, intrauterine growth retardation, intrauterine death of the fetus, and anomalies of position and presentation [1].

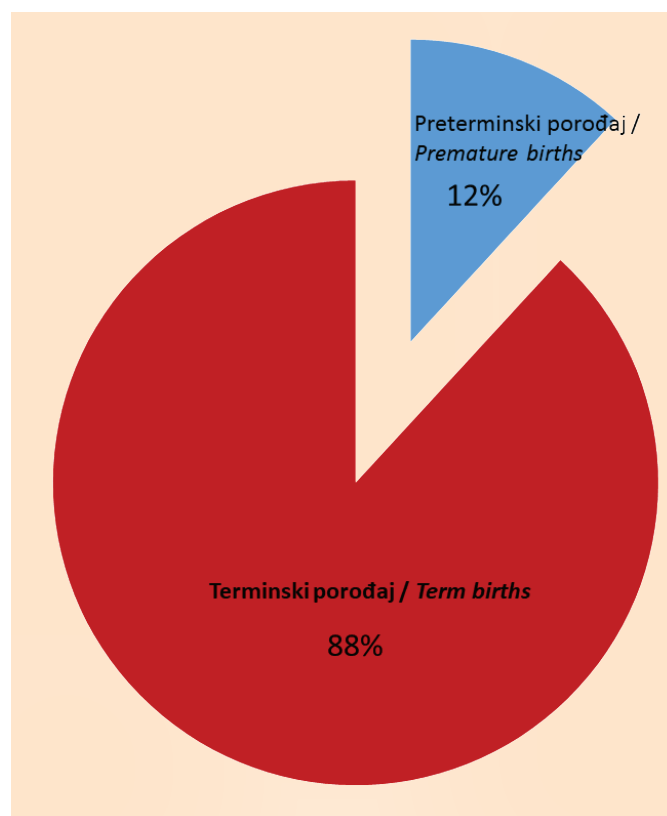
The study aims to determine whether the cause and time of premature birth affect the neonatal outcome.

MATERIALS AND METHODS

From the database of deliveries performed during 2020 at the Obstetrics and Gynecology Clinic *Narodni Front*, only preterm births occurring in the period between July 1, 2020, and December 31, 2020, were included in the study. All multiple pregnancies, as well as premature births induced due to fetal anomalies, were excluded from the study. Using the methods of descriptive statistics, we described the macroscopic appearance of the amniotic fluid, the sex, the status of the newborn's vitals, the way the delivery was completed, the structural integrity of the fetal membranes, the position of the fetus, the Apgar score at one and five minutes after birth, and noted prepartum dexamethasone therapy administered in the expectant mothers.

Statistical analysis

The data were entered into the database and processed using the *IBM SPSS 25* software. Methods of descriptive and analytical statistics were applied in the study. The following methods of descriptive statistics were used: measures of central tendency, measures of variability, and relative numbers. The following methods of analytical statistics were used: methods for assessing the significance of difference, the Chi-square test, and the Mann-Whitney test, as well as methods for assessing



Grafikon 1. Prikaz odnosa pretermijskih porođaja u odnosu na sve porođaje u Ginekološko-akušerskoj klinici „Narodni front“ u vremenskom periodu od 1. 07. 2020. do 31. 12. 2020. godine

Figure 1. Overview of preterm births compared to all births at the Obstetrics and Gynecology Clinic Narodni Front in the period between July 1, 2020 and December 31, 2020

Prema datoj studiji, 54,1%, pretermijskih porođaja je završeno carskim rezom, što je uzrokovano gestacijskom starošću trudnoće mlađom od 28 nedelja gestacije i dominantno karličnom prezentacijom ploda. Vaginalnim putem je bilo završeno 46% porođaja.

Najčešće je plod bio u prezentaciji glavom (41,9%), dok je prezentacija zatkom bila prisutna u 3,4% slučajeva. Akušerske intervencije, vakum i unutrašnji okret, urađene su u samo 0,6% slučajeva. Spontano prsnuće vodenjaka, kao uzrok prevremenog porođaja, zabeleženo je u 39,7% slučajeva, dok su plodove opne bile intaktne kod 60,3% svih prevremenih porođaja. Metoda analitičke statistike ($p = 0,075$) uočeno je da ne postoji značajna diskrepancija između načina rupture vodenjaka i vitalnog statusa prematurusa.

Plod, kao porođajni objekat, utiče na tok i ishod porođaja svojim položajem [1]. U našoj studiji, podaci u vezi sa položajem ploda (385) govore da je bilo 313 (79,2%) uzdužnih položaja glavom, 41 (10,4%) uzdužni karlični, 19 (4,8%) nožnih, 11 (2,8%) poprečnih, 8 (2%) karličnih, dva (0,5%) zadnja potiljačna, te jedan (0,3%) kosi.

the significance of association, Spearman's rank correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Of the total number of births ($n = 4,211$), in the period between July and December 2020, there were 498 preterm births, which is 11.83% (Figure 1). Based on the data on the status of the premature infants' vital signs, the percentage of stillborn preterm infants was 8.9% while the percentage of live births was 91.1%.

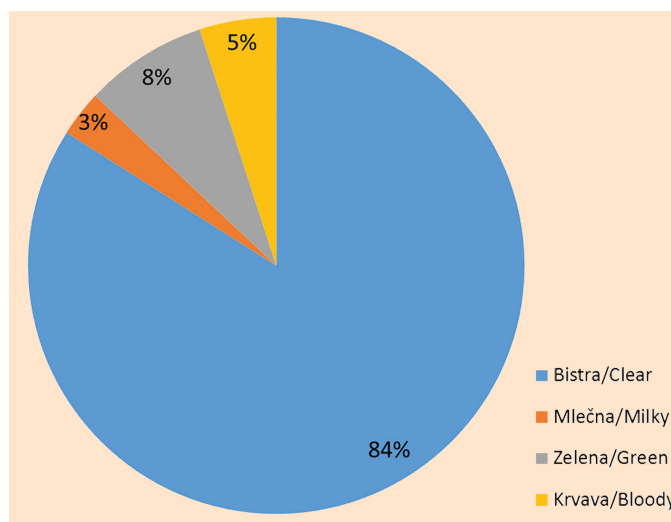
According to the study, 54.1% of preterm births ended in cesarean section due to gestational age younger than 28 weeks and with a predominantly pelvic presentation of the fetus. A total of 46% of births were completed vaginally.

Most often, the fetal presentation was cephalic (41.9%), while the pelvic presentation was present in 3.4% of cases. Obstetric interventions, vacuum and internal rotation, were performed in only 0.6% of cases. Spontaneous rupture of the amniotic sac, as a cause of premature birth, was recorded in 39.7% of cases, while the amniotic sac was intact in 60.3% of all premature births. Methods of analytical statistics ($p = 0.075$) revealed no significant discrepancy between the mechanism of amniotic sac rupture and the status of the preterm infants' vital signs.

The fetus, as the object of the delivery, affects the course and outcome of childbirth with its position [1]. In our study, data related to fetal position (385) indicate that there were 313 (79.2%) cases of longitudinal cephalic position, 41 (10.4%) cases of longitudinal pelvic position, 19 (4.8%) cases of breech presentation, 11 (2.8%) cases of transverse lie, 8 (2%) cases of pelvic presentation, two (0.5%) cases of occiput posterior position, and one case of (0.3%) oblique position.

First-time mothers included in the study made up 61.5% (294) of the sample, 24.9% (119) of the subjects were second-time mothers, 8.6% (41) had delivered their third baby, 3.6% (17) of the mothers had given birth for the fourth time, 1% (5) had delivered a baby for the fifth time, while for 0.4% of the subjects this was their sixth or seventh delivery.

Amniotic fluid is an incredibly complex and dynamic milieu that changes as pregnancy progresses. It contains nutrients and growth factors, which facilitate the growth of the fetus, it provides mechanical movements of the fetus and antimicrobial effects that protect the fetus, and it allows assessment of fetal maturity and disease [2]. Of the available data for 390 preterm births, 327 (83.8%) had clear amniotic fluid, in 18 (4.6%) cases it was bloody, in 12 (3.1%) instances it was milky, and in 33 (8.5%) it had green discoloration (Figure 2).



Grafikon 2. Učestalost različitog makroskopskog izgleda plodove vode kod pretermijskih porođaja (bistra, zelena, krvava, mlečna)

Figure 2. The frequency of different forms of amniotic fluid macroscopic appearance in preterm births (clear, green, bloody, milky)

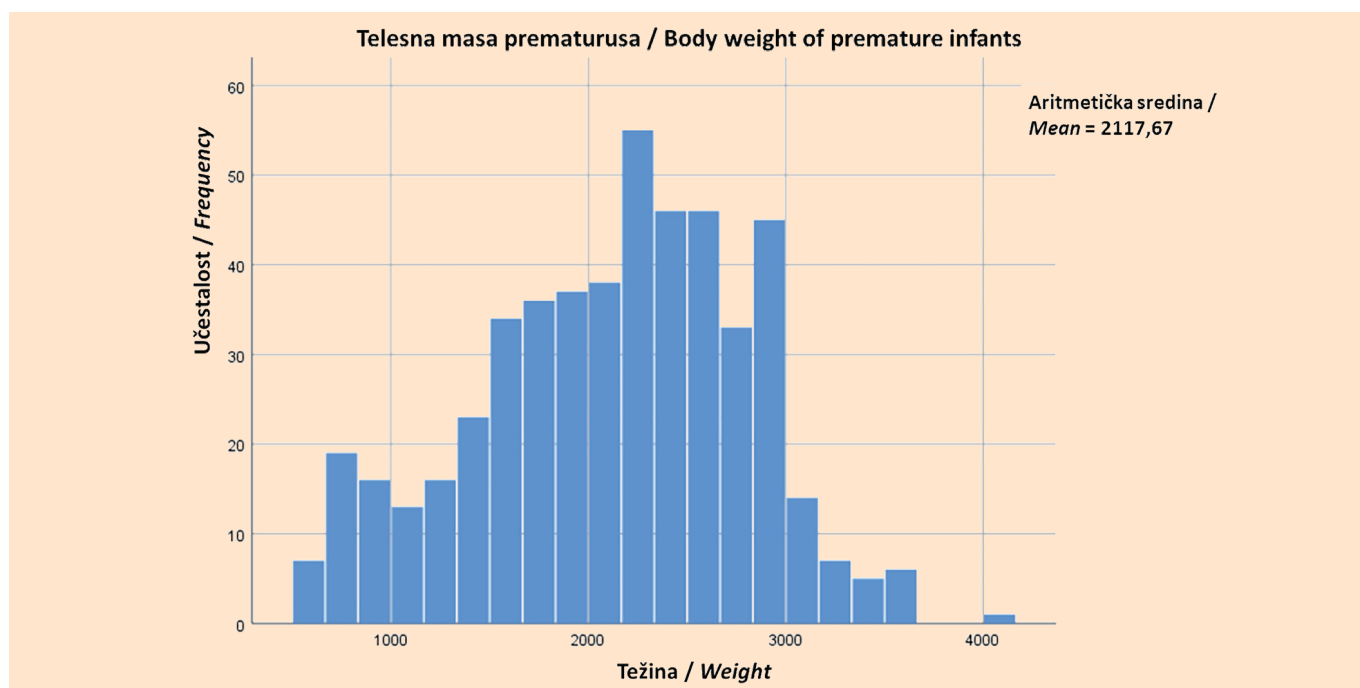
Prvorotke uključene u istraživanje su činile 61,5% (294), drugorotki je bilo 24,9% (119), trećerotki 8,6% (41), četvororotki 3,6% (17), petorotki 1% (5), dok je šestorotki i sedmorotki bilo 0,4%.

Plodova voda je neverovatno složen i dinamičan milje koji se menja kako trudnoća napreduje. Sadrži hranljive materije i faktore rasta, koji olakšavaju rast fetusa, obezbeđuje mehaničke pokrete fetusa i antimikrobne efekte koji štite fetus, te omogućava procenu zrelosti i bolesti fetusa [2]. Od postojećih podataka za

Despite technological progress and efforts made by doctors to preserve the health of newborns in recent years, extremely preterm infants (born before the 28th week of gestation) or with an extremely low birth weight (< 1,000 g) remain at high risk of death and disability, while female preterm infants, on average, have a better survival rate, as compared to the male sex [3]. Based on the data for 397 preterm births, 200 (50.4%) preterm males and 197 (49.6%) females were born. Using the chi-square test ($p = 0.617$), no statistically significant difference in the vital status of newborns was found between the male and female sex. The average weight of the total number of premature babies was 2117.67 ± 684.22 g, the average length was 44.17 ± 5.47 cm, and the mean value of head circumference was 31.05 ± 3.44 cm (Figure III). The highest frequency of premature births was in the 33rd week of gestation.

The Apgar score is a clinical assessment of the newborn's ability to survive based on vital parameters such as skin color, heart rate, breathing, muscle tone, and reflex response. It is determined at one and five minutes after childbirth. The score can range from 0 to 10. An Apgar score of 8 – 10 is considered normal, a score of 4 – 7 indicates moderate, and a score of 0 – 3 indicates severe neuromuscular depression, which most often occurs as the result of perinatal asphyxia [1,4].

The total number of available data regarding the Apgar score at one minute after birth is for 474 preterm infants. Of the given number, 39 (8.2%) preterm infants had a score of 0, 2 (0.4%) preterm infants had a score of 1, a score of 2 was found in 7 (1, 5%) premature babies,



Grafikon 3. Prikaz telesne mase prematurusa uključenih u studiju, u gramima

Figure 3. Body weight of premature infants included in the study, in grams

390 pretermijskih porođaja, 327 (83,8%) je imalo bistru plodovu vodu, 18 (4,6%) krvavu, 12 (3,1%) mlečnu i 33 (8,5%) zelenu prebojenost (**Grafikon II**).

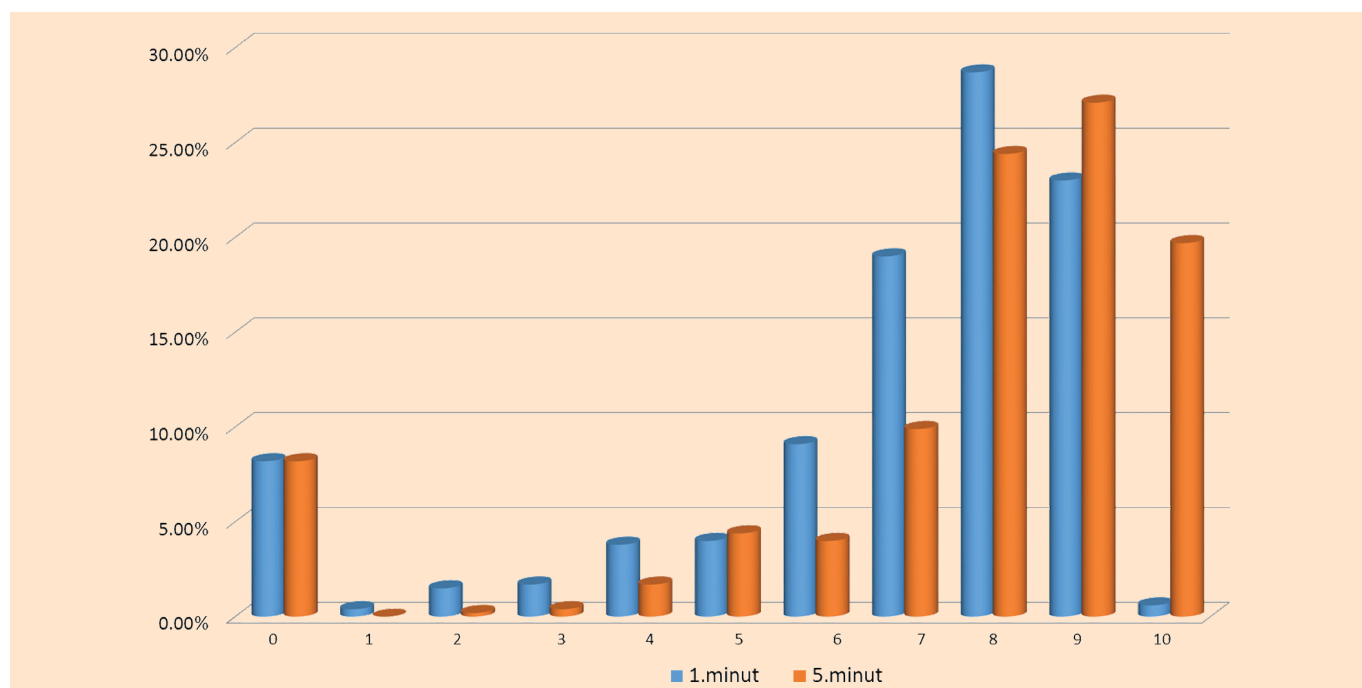
Uprkos tehnološkom napretku i naporima lekara da očuvaju zdravlje novorođenčadi tokom poslednjih godina, ekstremni prematurusi (rođeni pre 28. nedelje gestacije) ili sa ekstremno malom porođajnom težinom (< 1.000 g) ostaju pod visokim rizikom od smrti i invaliditeta, dok ženska nedonoščad, u proseku, imaju bolju stopu preživljavanja u odnosu na muški pol [3]. Na osnovu podataka za 397 pretermijskih porođaja, rođeno je 200 (50,4%) prematurusa muškog pola i 197 (49,6%) ženskog pola. Korišćenjem hi-kvadratnog testa ($p = 0,617$) nije pronađena statistički značajna razlika vitalnog statusa novorođenčadi između muškog i ženskog pola. Prosečna težina totalnog broja prematurusa je bila $2117,67 \pm 684,22$ g, dužina $44,17 \pm 5,47$ cm, dok je srednja vrednost obima glave iznosila $31,05 \pm 3,44$ cm (**Grafikon III**). Najveća frekvencija prevremenih porođaja bila je u 33. nedelji gestacije.

Apgar skor predstavlja kliničku procenu životne sposobnosti novorođenčeta na osnovu vitalnih parametara kao što su boja kože, srčana radnja, disanje, mišićni tonus, refleksni odgovor. Određuje se u prvom i petom minutu nakon porođaja. Skor se može kretati u rasponu od 0 do 10. Normalnim se smatra Apgar skor 8 – 10, skor 4 – 7 ukazuje na umerenu, a skor od 0 – 3 na tešku neuromišićnu depresiju, do koje najčešće dolazi usled perinatalne asfiksije [1,4].

Ukupan broj podataka o Apgar skoru u prvom minutu iznosi 474. Od datog broja, zbir 0 je imalo 39

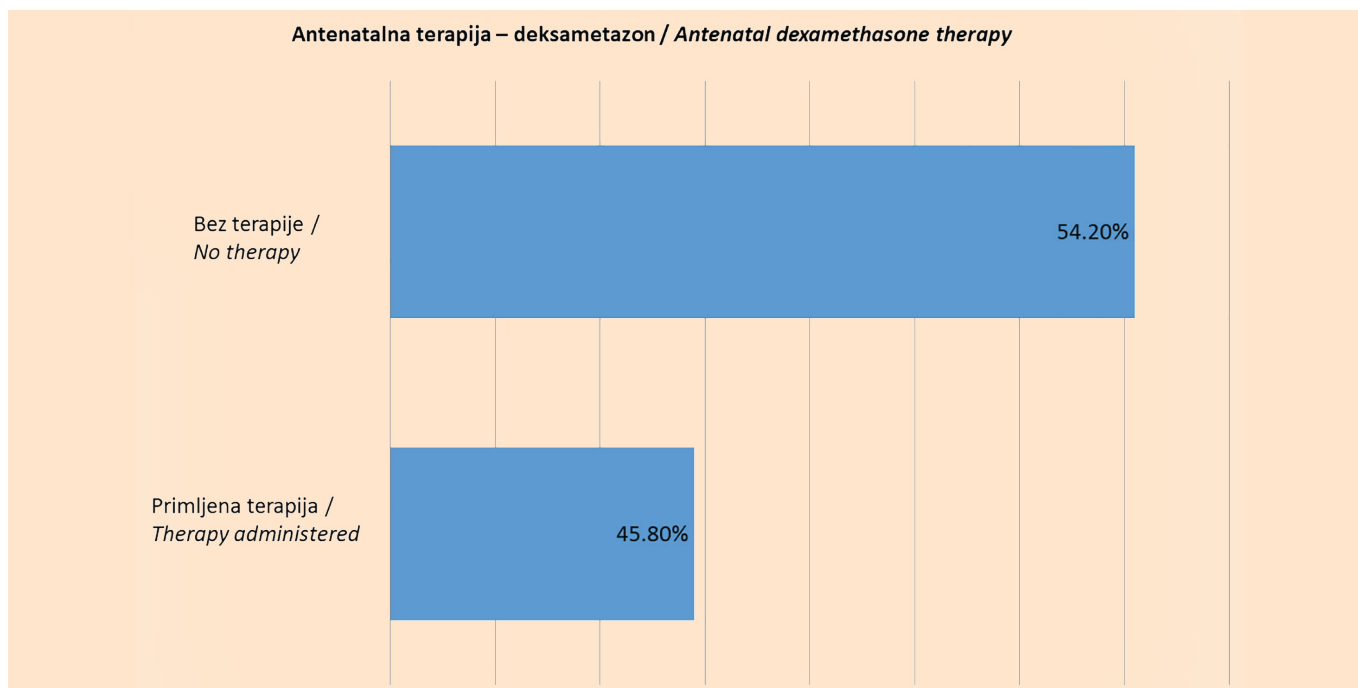
a score of 3 was registered in 8 (1.7%) preterm infants, 18 (3.8%) premature babies had a score of 4, a score of 5 was found in 19 (4%) premature newborns, a score of 6 was registered in 43 (9.1%) premature babies, a total of 90 (19.0%) preterm infants had a score of 7, 136 (28.7%) preterm newborns had a score of 8, 109 (23.0%) of them had a total of 9, while 3 (0.6%) premature babies scored a 10.

Today, greater importance is attached to the score at five minutes after birth, as it indicates the speed of adaptation of a healthy newborn, or the dynamics of recovery of an asphyxiated one [4]. From the database of 476 Apgar scores at five minutes after birth, a score of 0 was found in 39 (8.2%) premature babies, a score of 1 does not exist in the database, a score of 2 was recorded in one (0.2%) premature baby, a sum of 3 was found in 2 (0.4%) preterm infants, a score of 4 was determined in 8 of them (1.7%), a score of 5 was registered in 21 (4.4%) premature babies, a score of 6 was found in 19 (4.0%) premature infants, a score of 7 was registered in 47 (9.9%) cases, 116 (24.4%) premature babies had a score of 8, 129 (27.1%) of them had a score of 9, while 94 (19.7%) preterm infants scored a 10 (**Figure IV**). The Apgar score was the highest in newborns delivered vaginally, after the 34th week of gestation, with intact fetal membranes, and spontaneous onset of contractions. This data shows that the outcome of pregnancy is better in childbirth occurring later in gestation, after the 34th week, with intact fetal membranes and without signs of infection. A higher Apgar score in children from spontaneous



Grafikon 4. Vrednost Apgar skora u prvom i petom minutu, u rasponu od 0 do 10

Figure 4. The value of Apgar scores at one and five minutes after birth, ranging from 0 to 10



Grafikon 5. Učestalost porodilja koje nisu primale deksametazon i onih koje jesu primale deksametazon

Figure 5. The frequency of mothers who did not receive dexamethasone therapy and those who did receive dexamethasone therapy

(8,2%) prematurusa, zbir 1 je imalo 2 (0,4%) prematurusa, zbir 2 je imalo 7 (1,5%) prevremeno rođenih beba, zbir 3 je imalo 8 (1,7%) njih, zbir 4 je imalo 18 (3,8%) beba, zbir 5 je imalo 19 (4%) novorođenčadi, zbir 6 je imalo 43 (9,1%) prematurusa, zbir 7 je imalo 90 (19,0%) beba, zbir 8 je imalo 136 (28,7%) novorođenčadi, zbir 9 je imalo 109 (23,0%) njih, dok je zbirom 10 ocenjeno 3 (0,6%) prematurusa.

Danas se veći značaj pridaje skor u petom minutu, koji označava brzinu adaptacije zdravog, odnosno dinamiku oporavka asfiktičnog novorođenčeta [4]. Iz baze 476 podataka o Apgar skor u petom minutu rođenja imamo zbir 0 kod 39 (8,2%) prematurusa, zbir 1 ne postoji u bazi, zbir 2 je zabeležen kod jednog (0,2%) prematurusa, zbir 3 je dobilo 2 (0,4%) novorođenčeta, zbir 4 je utvrđen kod njih 8 (1,7%), zbir 5 kod 21 (4,4%) prematurusa, zbir 6 kod njih 19 (4,0%), zbir 7 kod njih 47 (9,9%), zbir 8 kod 116 (24,4%) beba, zbir 9 kod njih 129 (27,1%), dok je zbir 10 imalo njih 94 (19,7%), (Grafikon IV). Apgar skor je bio najviši kod novorođenčadi iz vaginalnog porođaja, nakon 34. nedelje gestacije, sa intaktnim plodovim opnama i spontanijem uspostavljanjem kontrakcija. Ovaj podatak nam ukazuje da je bolji ishod trudnoća kod porođaja u kasnijoj gestaciji, nakon 34. nedelje, sa intaktnim plodovim opnama, bez znakova infekcije. Viši Apgar skor kod dece iz spontanog u odnosu na indukovani prevremeni porođaj govori i o boljem neonatalnom ishodu.

Kortikosteroidi se upotrebljavaju u cilju povećanja produkcije surfaktanta i ubrzanja fetalne plućne maturacije kod pretećeg prevremenog porođaja [1]. U

versus induced premature birth also indicates a better neonatal outcome.

Corticosteroids are administered in order to increase the production of surfactant and accelerate fetal lung maturation in case of threat of premature birth [1]. It has been proven in numerous studies that antenatal dexamethasone treatment of parturients results in a significantly lower risk of neonatal death, without any evidence of harm to the patient or the newborn [5]. A total of 228 (45.8%) parturients included in the study received dexamethasone, while 270 (54.2%) did not (Figure V). A statistically significant difference was observed in the status of the vitals in preterm infants whose mothers received dexamethasone, as compared to those who did not receive this treatment, using the chi-square test ($p < 0.001$). According to our study, premature babies whose mothers received antenatal therapy had higher Apgar scores at one minute ($p = 0.004$) and five minutes ($p = 0.046$) after birth.

DISCUSSION

A study conducted by Goldenberg et al., in 2008, in the United States of America (USA), indicates that the frequency of preterm births is about 12% - 13% in the United States and 5% - 9% in many other developed countries. However, the rate of premature birth also depends on the geographical location, mainly due to increased risk factors, as well as due to premature births resulting from multiple IVFs [6]. Common causes of preterm delivery include preeclampsia or eclampsia

brojnim studijama je dokazano da antenatalna terapija porodilja deksametazonom rezultira značajno manjim rizikom od neonatalne smrti, bez ikakvih dokaza o šteti po pacijentkinje ili novorođenčad [5]. Ukupno 228 (45,8%) porodilja uključenih u studiju je primilo deksametazon, dok 270 (54,2%) nije (Grafikon V). Uočena je statistički značajna razlika u vitalnom statusu prematurusa čije su majke primile deksametazon u odnosu na one koje nisu, primenom hi-kvadratnog testa ($p < 0,001$). Prema našoj studiji, viši Apgar skor u prvom ($p = 0,004$) i petom minutu ($p = 0,046$) su imali prematurusi čije su majke primile antenatalnu terapiju.

DISKUSIJA

Istraživanje, koje su sproveli Goldenberg i saradnici u Sjedinjenim Američkim Državama (SAD) 2008. godine ukazuje na to da je učestalost prevremenih porođaja oko 12% – 13% u Sjedinjenim Američkim Državama i 5% – 9% u mnogim drugim razvijenim zemljama, međutim stopa prevremenog porođaja zavisi i od geografske lokacije, uglavnom zbog povećanja faktora rizika i zbog prevremenih porođaja usled višeplođnih vantelesnih oplodnji [6]. Česti razlozi uključuju preeklampsiju ili eklampsiju i intrauterini zastoj rasta ploda. Od ukupnog broja pretermijskih porođaja, učestalost indukovanih porođaja iznosi 30 – 35%, spontani prevremeni porođaj ima učestalost 40% – 45%, dok je učestalost PPRM-a 25% – 30% [6]. Spontani porođaj i PPRM su zajedno označeni kao spontani prevremeni porođaji [6]. U našoj studiji je učestalost pretermijskih porođaja, tokom posmatranog perioda od šest kalendarskih meseci, iznosila 11,83%, dok se spontano započeti porođaj uočava kod 39,7% a indukovani porođaj kod 60,3% slučajeva.

Rizici se smanjuju sa porastom gestacijskog doba [1]. Pre 34. nedelje više od polovine pretermijskih neonatusa ima neku komplikaciju, dok se nakon 36. nedelje komplikacije sreću kod oko 16% njih.

Prema studiji koju su sproveli Mejo i saradnici 2017. godine u Sjedinjenim Američkim Državama, izuzetno mlade nulipare su u većem riziku od prevremenog porođaja, ali mehanizam nije jasno utvrđen [7]. Retrospektivnom kohortnom studijom su obuhvaćene nulipare starosti od 13 do 20 godina kod kojih je prevremeno završena pojedinačna trudnoća, u vremenskom periodu od 2007. do 2011. godine [7]. Rezultati govore da je najveća prevalencija, odnosno 14,5% pretermijskih porođaja kod najmlađih nulipara starosti 13 godina, a najniža upravo kod najstarijih, iz posmatrane grupe, odnosno kod dvadesetogodišnjakinja (6,7%) [7]. Naime, značajno je povećan rizik od spontanog prevremenog porođaja kod subjekata mlađih od 16 godina [7].

Naše istraživanje korelira sa dokazima koji upućuju na povećani rizik od prevremenog porođaja kod

and intrauterine growth retardation. Of the total number of preterm births, the frequency of induced births is 30% – 35%, the frequency of spontaneous preterm births is 40% – 45%, and the frequency of PPRM is 25% – 30% [6]. Spontaneous labor and PPRM are collectively referred to as spontaneous preterm labor [6]. In our study, the frequency of preterm births, during the observed period of six calendar months, was 11.83%, while spontaneous births were observed in 39.7%, and induced births in 60.3% of cases.

The risks decrease with increasing gestational age [1]. Before the 34th week, more than half of preterm neonates have some complication, while after the 36th week, complications occur in about 16% of preterm infants.

According to a study conducted by Mayo et al., in 2017, in the United States of America, extremely young nulliparous women are at higher risk of preterm birth, but the mechanism has not been clearly established [7]. A retrospective cohort study included nulliparae aged 13 to 20 years who had a single pregnancy terminated prematurely, in the period between 2007 and 2011 [7]. The results show that the highest prevalence, i.e. 14.5% of preterm births, is among the youngest nulliparae, aged 13, while the lowest prevalence of preterm deliveries was among the oldest in the observed group, i.e. among twenty-year-old women (6.7%) [7]. Namely, the risk of spontaneous preterm birth is significantly higher in subjects younger than 16 years [7].

Our study correlates with the evidence pointing to an increased risk of premature delivery in nulliparous women, who account for as many as 61.5% (294) cases, while women giving birth for the second time make up 24.9% (119) of the cases, women delivering their third child account for 8.6% (41) of preterm deliveries, those delivering their fourth child make up 3.6% (17) of cases, women having their fifth child constitute 1% (5) of all cases, and those delivering their sixth or seventh child contribute with only 0.4%, but we do not have data on the age of the mothers.

A 2017 UK study by Roberts et al. supports evidence that antenatal corticosteroids accelerate fetal lung development in case of the threat of premature birth [5]. The study included 7,774 parturients and 8,158 preterm infants [5]. Antenatal corticosteroid therapy, as compared to placebo or no treatment, clearly reduces some of the most serious complications in preterm infants, such as perinatal mortality, neonatal mortality, respiratory distress syndrome, intravascular hemorrhage, necrotizing enterocolitis, the need for mechanical ventilation, and systemic infection in the first 48 hours of life [5]. Based on the available data, we compared the status of the vitals of neonates with the use

nulipara, koje čine čak 61,5% (294) slučajeva, dok drugorotke čine 24,9% (119), trećerotke 8,6% (41), četvororotke 3,6% (17), petorotke 1% (5), a šestorotke i sedmorotke samo 0,4% prevremenih porođaja, ali ne posedujemo podatke o starosti porodilja.

Studija koju su sprovedi Roberts i saradnici 2017. godine u Velikoj Britaniji podržava dokaze da primena antenatalnih kortikosteroida ubrzava razvoj fetalnih pluća kod pretećih preterminskih porođaja [5]. U studiju je uključeno 7.774 porodilje i 8.158 prematurusa [5]. Terapija antenatalnim kortikosteroidima, u poređenju sa placebom ili bez tretmana, jasno redukuje neke od najozbiljnijih komplikacija kod nedonoščadi, kao što su perinatalni mortalitet, neonatalni mortalitet, respiratorni distres sindrom, intravaskularna hemoragija, nekrotizirajući enterokolitis, potreba za mehaničkom ventilacijom i sistemska infekcija u prvih 48 sati života [5]. Prema dostupnim informacijama, uporedili smo vitalni status neonatusa sa primenom deksametazona kod porodilja u 394 slučajeva. U grupi pacijentkinja koje su primile terapiju deksametazonom (172), smrtnost je zabeležena kod samo 1 neonatusa što čini 0,6%, dok je 171 (99,4%) neonatus ostao živ. Sa druge strane, u grupi pacijentkinja koje nisu primile terapiju (222), bilo je 34 (15,3%) preminulih neonatusa i 188 (84,7%) živih.

U studiji koju su sprovedi Li i saradnici 2013. godine u Kini dokazano je da sistem Apgar skora ima kontinuiranu, značajnu vrednost za predviđanje neonatalnih ishoda, kako za terminsku novorođenčad tako i za preterminsku [8]. Prevremeni porođaji su imali oko 10 do 20 puta veću incidenciju niskog Apgar skora tokom petog minuta (< 7) nego terminski porođaji, iako je velika većina prevremenih porođaja imala rezultat veći od 7 [8]. Neonatalna stopa mortaliteta se smanjivala sa povećanjem Apgar skora. Analizirani su preterminski porođaji od 24. do 36. gestacijske nedelje [8]. Vrednosti Apgar skora u petom minutu bile su: 1 kod 0,43 % prematurusa sa stopom neonatalnog mortaliteta od 581,86; 2 kod 0,293% prematurusa sa stopom mortaliteta koja je iznosila 334,68; 3 kod 0,38% prematurusa sa stopom mortaliteta od 192,42; 4 kod 0,57% prematurusa kod kojih je stopa mortaliteta bila 121,28; 5 kod 1% prematurusa sa stopom mortaliteta od 74,58; 6 kod 2,31% prematurusa koji su imali stopu mortaliteta od 43,47; 7 kod 5,2% prematurusa sa stopom mortaliteta od 18,91; 8 kod 16% prematurusa kod kojih je stopa mortaliteta iznosila 4,39; 9 kod 69,60% prematurusa sa stopom mortaliteta od 0,59; te 10 kod 4,23% prematurusa koji su imali stopu neonatalnog mortaliteta od 0,37 [8].

Međutim, Apgar skor ima svoja ograničenja [8]. Brojni faktori mogu uticati na Apgar rezultat kao što su

of dexamethasone in parturients, in 394 cases. In the group of patients who received dexamethasone therapy (172), mortality was recorded in only 1 neonate, which is 0.6%, while 171 (99.4%) neonates survived. On the other hand, in the group of female patients who did not receive this treatment (222), there were 34 (15.3%) deceased neonates while 188 (84.7%) survived.

In a study conducted by Li et al., in 2013, in China, it was demonstrated that the Apgar score system has a continuous, significant value for predicting neonatal outcomes, both for term and preterm infants [8]. Preterm births had about a 10 to 20 times higher incidence of low 5-minute Apgar scores (< 7) than term births, although a vast majority of preterm births had a score greater than 7 [8]. The neonatal mortality rate decreased with the increase of the Apgar score. The analysis included preterm births occurring between the 24th and the 36th gestational week [8]. Apgar score values at five minutes after birth were as follows: a score of 1 in 0.43% of premature infants with a neonatal mortality rate of 581.86; a score of 2 in 0.293% of premature babies with a mortality rate of 334.68; a score of 3 in 0.38% of premature babies with a mortality rate of 192.42; a score of 4 in 0.57% of premature infants, whose mortality rate was 121.28; a score of 5 in 1% of premature babies with a mortality rate of 74.58; a score of 6 in 2.31% of premature babies who had a mortality rate of 43.47; a score of 7 in 5.2% of premature babies with a mortality rate of 18.91; a score of 8 in 16% of premature babies with the mortality rate of 4.39; a score of 9 in 69.60% of premature babies with a mortality rate of 0.59; and a score of 10 in 4.23% of premature infants who had a neonatal mortality rate of 0.37 [8].

However, the Apgar score has its limitations [8]. Numerous factors can affect the Apgar score, such as drugs, trauma, congenital anomalies, infections, hypoxia, and hypovolemia, especially in premature births [8]. To date, there are but several consistent data on the significance of the Apgar score in preterm infants [8]. Because score components such as tone, color, and reflex excitability depend in part on the physiological maturity of infants, this situation may cause a healthy preterm infant without evidence of asphyxia to score lower, simply because of its current immaturity [8].

In our study, at five minutes after birth, we recorded an Apgar score of 0 in 8.2% of premature babies, a score of 1 does not exist in the database, a score of 2 was found in 0.2% of the cases, a score of 3 was recorded in 0.4% of premature babies, a score of 4 was registered in 1.7% of preterm infants, a score of 5 was recorded in 4.4% of the babies, a score of 6 occurred in 4.0% of cases, a score of 7 was observed in 9.9% of preterm infants, a score of 8 occurred in 24.4 % of cas-

lekovi, traume, urođene anomalije, infekcije, hipoksija, hipovolemija, naročito kod prevremenih porođaja [8]. Do danas, postoji nekoliko konzistentnih podataka o značaju Apgar skora kod nedonoščadi [8]. Pošto elementi skora kao što su tonus, boja i refleksna razdražljivost delimično zavise od fiziološke zrelosti odojčadi, ova situacija može dovesti do toga da zdravo prevremeno rođeno dete bez dokaza o asfiksiji dobije niži rezultat samo zbog trenutne nezrelosti [8].

U našem istraživanju, u petom minutu rođenja, imamo Apgar zbir 0 kod 8,2% prematurusa, zbir 1 ne postoji u bazi, zbir 2 se javlja kod 0,2% prematurusa, zbir 3 je zabeležen kod 0,4% prematurusa, zbir 4 je utvrđen kod 1,7% prematurusa, zbir 5 je zabeležen kod 4,4% njih, zbir 6 se javlja kod 4,0% prematurusa, zbir 7 uočavamo kod 9,9% prematurusa, zbir 8 se javlja kod 24,4% prematurusa, zbir 9 je prisutan kod 27,1% njih, dok je zbir 10 zabeležen kod 19,7% preautrusa. Ograničenja istraživanja su nedovoljan broj ispitanika i kratak vremenski period posmatranja.

ZAKLJUČAK

Značajna učestalost prevremenog porođaja (11,8%) u ukupnom broju porođaja, ukazuje na ozbiljnost problema i dalju tendenciju rasta broja prevremenih porođaja i pored primenjenih svih preventivnih mera. Visoka učestalost vitalne novorođenčadi (91%) ukazuje na to da se, uz adekvatnu i pravovremenu terapiju, kao i uz adekvatan izbor u načinu završavanja ranih prevremenih porođaja, poboljšava perinatalni ishod novorođenčeta.

Visoka zastupljenost carskog reza (54,1%) pretermiskih porođaja je uzrokovana gestacijskom starošću trudnoće mlađom od 28. nedelje gestacije i dominantno karličnom prezentacijom ploda.

Intaktne plodove opne u više od polovine prevremenih porođaja govore da je najčešći uzrok prevremenih porođaja spontano započeta uterusna aktivnost kod prvorotki, što nam sugeriše na potrebu bolje informisanosti, kao i rasprostranjenosti preventivnih mera.

Bistra plodova voda (83,8%) ukazuje na to da infekcija nije bila dominantni uzrok prevremenog porođaja u našoj studiji.

Apgar skor je bio najviši kod novorođenčadi iz vaginalnog porođaja, nakon 34. nedelje gestacije, sa intaktnim plodovim opnama i spontanim uspostavljanjem kontrakcija. Ovaj podatak nam ukazuje na to da je bolji ishod trudnoća kod porođaja u kasnijoj gestaciji, nakon 34. nedelje, sa intaktnim plodovim opnama i bez znakova infekcije. Viši Apgar skor kod dece iz spontanog, u odnosu na indukovani prevremeni porođaj, govori o boljem neonatalnom ishodu. Bolji Apgar skor kod novorođenčadi čije su majke primile deksameta-

es, a score of 9 was present in 27.1% of premature infants, while a score of 10 was recorded in 19.7% of cases. Limitations of the research include the insufficient number of subjects and the short observation period.

CONCLUSION

A significant frequency of premature births (11.8%) in the total number of births indicates the seriousness of the problem and the further tendency of the number of premature births to increase despite the implementation of all preventive measures. The high frequency of vital newborn infants (91%) indicates that, with adequate and timely therapy, as well as with an appropriate choice in the way that early premature delivery is completed, the perinatal outcome of the newborn improves.

A high incidence of cesarean section (54.1%) in preterm births is caused by the gestational age of the pregnancy that is younger than the 28th week as well as the predominant pelvic presentation of the fetus.

Intact fetal membranes in more than half of premature births indicate that the most common cause of premature deliveries is spontaneously initiated uterine activity in primiparous mothers, which suggests the need for better information dissemination and wider implementation of preventive measures.

Clear amniotic fluid (83.8%) indicates that infection was not the dominant cause of preterm birth in our study.

The Apgar score was the highest in newborns delivered vaginally, after the 34th week of gestation, with intact fetal membranes and spontaneous onset of contractions. This data indicates that the pregnancy outcome is better in late gestation, after the 34th week, with intact fetal membranes and no signs of infection. A higher Apgar score in children from spontaneous, compared to induced premature birth, indicates a better neonatal outcome. A better Apgar score in newborns whose mothers received dexamethasone indicates that we significantly improve the perinatal outcome with its application.

The frequency of preterm births is still increasing and is therefore a challenge for perinatologists and neonatologists. We emphasize the importance of implementing preventive measures at the level of primary health care in order to establish control over premature births.

Conflict of interest: None declared.

zon ukazuje na to da njegovom primenom značajno poboljšavamo perinatalni ishod.

Učestalost prevremenih porođaja je i dalje u porastu i stoga predstavlja izazov za perinatologe i neonatologe. Napominjemo značaj implementacije preventivnih mera na nivou primarne zdravstvene zaštite kako bi se uspostavila kontrola nad prevremenim porođajima.

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LITERATURA / REFERENCES

1. Plećaš D, Stanimirović B, Stanković A, Vasiljević M. Pretermiski porođaj i posttermiski porođaj. Ginekologija i akušerstvo - Udžbenik za studente medicine, 5. izdanje, Beograd: Medicinski fakultet u Beogradu; 2019. p. 256-258.
2. Underwood MA, Gilbert WM, Sherman MP. Amniotic Fluid: Not Just Fetal Urine Anymore. J Perinatol. 2005; 25, p. 341-348.
3. Glass HC, Costantino AT, Stayer SA, Brett CM, Cladis F, Davis PJ. Outcomes for Extremely Premature Infants. Anesth Analg. 2015; 120(6):1337-51.
4. Perišić V, Janković B. Neonatologija. Pedijatrija - Udžbenik za studente medicine, 3. izdanje, Beograd: Medicinski fakultet u Beogradu; 2019. p. 109-115.
5. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev, 2017;(3): CD004454.
6. Goldendenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008; 371(9606): 75-84.
7. Mayo JA, Shachar BZ, Stevenson DK, Shaw GM. Nulliparous teenagers and preterm birth in California, J Perinatal Med. 2017; 45(8):959-967.
8. Li T, Wu T, Lei X, Zhang H, Mao M, Zhang J. The Apgar Score and Infant Mortality, PLoS One. 2013; 8(7):e69072.

ISHRANA RADNIKA KOJI RADE U NOĆNOJ SMENI – RAZLOG ILI IZGOVOR ZA NEPRAVILNU ISHRANU

PREGLEDNI RAD

REVIEW ARTICLE

DIETARY HABITS OF NIGHT SHIFT WORKERS – A REASON OR AN EXCUSE FOR POOR NUTRITION

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SAŽETAK

Dostupnost veštačkog svetla i uređaja koji emituju svetlost promenili su ljudski život u smislu vremena, omogućavajući 24-časovnu zdravstvenu zaštitu, trgovinu i proizvodnju, kao i širenje društvenog života na dan i noć. U Evropi oko 21% radno aktivnog stanovništva čine radnici koji rade u smenama. 10% radne snage ima večernji ili noćni raspored, a 7% radnika u Evropi redovno radi noćnu smenu. Prema Birou za statistiku rada, više od 15 miliona Amerikanaca radi noćne smene. Smenski, a naročito noćni rad, ozbiljno utiče na ponašanje u vezi sa ishranom.

Zna se da noćni rad izaziva konflikt između društveno određenog ritma obedovanja i cirkardijalnih bioloških ritmova vezanih za osećaj gladi, sitosti, kao i za sam metabolizam. Noćni obroci izazivaju poremećaje intestinalnog motiliteta, utiču na digestiju, apsorpciju, ali i na iskoristljivost nutrijenata i eventualne medikamentozne terapije (ako je pojedinac uzima). Sa gledišta hronobiologije, ljudska vrsta je diurnalna, što unekoliko objašnjava zašto noćni radnici imaju smanjen apetit u toku noći, kada je ljudski organizam zapravo programiran za odmaranje, i gladovanje, kao i za endogenu mobilizaciju glikoze. Sa psihosocijalnog aspekta, smenski radnici obično doživljavaju razmimoilaženje između svojih dnevnih rutina (uključujući i raspored obroka), kao i onih sa porodicom i prijateljima, što dalje dovodi do još težih poremećaja navika u ishrani.

Međutim, teško je dati dijetarne preporuke u vezi sa ishranom. Prvo, nema jasnog stava po pitanju toga da li noćni radnici treba da jedu u toku noćnih sati ili ne. Drugo, čak i da se podstakne noćno obedovanje, nedostaje krajnji dokaz o tome koja vrsta hrane treba da se konzumira, a koja da se izbegava. Treće, nutritivno vredna hrana možda neće biti dostupna u to doba noći. Najzad, ishrana u toku noći sigurno utiče na metabolizam. Imajući u vidu sve navedeno, pokušali smo da damo neke korisne smernice u vezi sa ovim pitanjima.

Ključne reči: cirkardijalni biološki ritam, hronobiologija, metabolizam

ABSTRACT

The availability of artificial light and light-emitting devices has changed human life in relation to time, enabling 24-hour health care, trade, and production, as well as the expansion of social life around the clock. In Europe, about 21% of the labor force consists of shift workers. 10% of the employed population work evening shifts or the night shift, and 7% of employees in Europe regularly work the night shift. According to the Bureau of Labor Statistics, more than 15 million Americans work the night shift. Shift work, especially night-time work, seriously affects dietary habits.

It is known that night-time work produces a conflict between the socially determined rhythm of eating and the circadian biological rhythms related to the feeling of hunger, satiety, as well as the metabolism itself. Night meals cause disorders of intestinal motility, affect digestion, absorption, but also the utilization of nutrients and possible medical therapy (if the individual has one). From the point of view of chronobiology, humans belong to diurnal species, which to a certain extent explains why night shift workers have a decreased appetite at night, when the human body is programmed for rest and fasting, as well as for endogenous mobilization of glucose. From the psychosocial aspect, shift workers usually experience a discrepancy between their daily routines (including the meal schedule) and those they have with family and friends, which further leads to even more severe disorders of dietary habits.

However, it is difficult to give dietary recommendations regarding nutrition. Firstly, there are no clear views on whether night shift workers should eat during the night hours or not. Secondly, even if night eating is encouraged, definitive evidence is lacking on which types of food should be consumed and which should be avoided. Thirdly, the most nutritious foods may not be available at that time of night. Finally, eating at night certainly has an impact on the metabolism. With all the above in mind, we have tried to provide some useful guidelines regarding these issues.

Keywords: circadian biological rhythm, chronobiology, metabolism

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UVOD

U protekle tri do četiri milijarde godina, život na Zemlji je evoluirao prema predvidivom obrazcu solarnih dana, tj. izlaganju relativno jakoj svetlosti tokom dana i mraku tokom noći. Odavno je poznato da svi živi organizmi imaju unutrašnji biološki sat koji im pomaže da se prilagode ritmu dana. Takve ciklične promene nazivaju se bioritmovi. Najznačajniji primer bioritma je ljudski cirkadijalni ritam. Procesi i strukture koje stvaraju cirkadijalne ritmove nazivaju se cirkadijalni satovi. Primarni cirkadijalni sat kod ljudi je upareni skup od oko 20,000 nervnih ćelija u hipotalamusu u bazi mozga, nazvan suprahijazmatično jezgro (SCN) [1-2]. Dostupnost veštačkog svetla i uređaja koji emituju svetlost promenili su ljudski život i omogućili nam da budemo aktivni 24 h dnevno, 7 dana u nedelji, što dovodi do cirkadijalne neusklađenosti, a to sve u krajnjoj liniji dovodi do poremećaja u fiziološkom i bihevioralnom funkcionisanju pojedinca. Noćna smena je neophodan deo redovnog radnog dana u mnogim delatnostima (pekar, lekar, policajac, noćni čuvar), ali i u mnoštvu drugih zanimanja često ne postoji „normalno“ radno vreme, već se rad obavlja i u sitne sate. Kod nekih od ovih zanimanja, poput lekara i medicinskog osoblja, postoje rotacije, dok su kod nekih radnici „zaglavljani“ radeći tokom noći sve do jutra. U Evropi oko 21% radno aktivnog stanovništva čine radnici koji rade u smenama. 10% radne snage ima večernji ili noćni raspored, a 7% radnika u Evropi redovno radi noćnu smenu. Prema Birou za statistiku rada, više od 15 miliona Amerikanaca radi noćnu smenu. [3,4].

Rad u smenama Savet Evropske unije definiše [5] kao „bilo koji metod organizovanja rada u smenama pri čemu radnici smenjuju jedni druge na istim radnim mestima prema određenom šablonu“. Tradicionalno, samo je ograničeni deo radne snage bio angažovan da radi u smenama. Međutim, poslednjih godina mnogi sektori su svoj rad organizovali na ovaj način.

U Republici Srbiji noćni rad je definisan Članom 62 Zakona o radu [6], prema kojem se „svaki rad koji se obavlja u vremenu od 22 časa do 6 časova narednog dana smatra radom noću“. Zaposlenom koji radi noću najmanje tri časa svakog radnog dana ili trećinu punog radnog vremena u toku jedne radne nedelje poslodavac je dužan da obezbedi obavljanje poslova u toku dana ako bi, po mišljenju nadležnog zdravstvenog organa, takav rad doveo do pogoršanja njegovog zdravstvenog stanja. Poslodavac je dužan da pre uvođenja noćnog rada zatraži mišljenje sindikata o merama bezbednosti i zaštite života i zdravlja na radu zaposlenih koji rad obavljaju noću.

Sa hronobiološkog stajališta, ljudska vrsta je diurnalna (aktivna u toku dana), što objašnjava činjenicu

INTRODUCTION

Over the past three to four billion years, life on Earth has evolved according to a predictable solar day pattern, i.e., being exposed to relatively bright light during the day and to darkness during the night. It has been known for quite some time that all living organisms have an internal biological clock that helps them adjust to the rhythm of the day. Such cyclic changes are called biorhythms. Human circadian rhythm is the most significant example of a biorhythm. The processes and structures that make up circadian rhythms are called circadian clocks. The master biological clock in humans is a cluster of about 20,000 nerve cells based in the hypothalamus and it is called suprachiasmatic nucleus (SCN) [1-2]. The availability of artificial light and light-emitting devices has changed human life by enabling us to be active 24/7, which leads to circadian misalignment and, eventually, to disturbances in physiological and behavioral functioning of an individual. In many professions (a baker, a doctor, a police officer, a night guard), the night shift is a necessary part of a regular working day, but many other occupations do not have regular hours either, but the work is done in the wee hours as well. In some professions, such as doctors or medical staff, there are rotation schedules, but in some other cases employees are "stuck" working at night, until the morning hours. In Europe, around 21% of the labor force consists of shift workers. 10% of all employees work evening shifts or the night shift, and 7% of European employees regularly work the night shift. According to the Bureau of Labor Statistics, more than 15 million Americans work the night shift [3,4].

According to the Council of the European Union, shift work is defined [5] as "any method of organizing work in shifts so that employees take turns on same job positions according to a determined schedule". In the past, only a limited number of employees were engaged in shift work. However, in recent years, many sectors have organized their work that way.

In the Republic of Serbia, night-time work is defined by Article 62 of the Employment Act [6], according to which "each work performed between 10 PM and 6 AM of the following day is deemed to be night-time work". An employer is bound to provide an employee who works at night for at least three hours every workday or one third of the full-time working hours in course of one working week, with the performance of jobs during daytime, should such work, according to the opinion of a competent health-service agency, cause deterioration of the employee's health condition. Before introducing night-time work, an employer is obliged to request an opinion of the trade union about the measures of safety and protection of life and health of employees who work during night-time.

da raspored rada u smenama, a naročito noćni rad, zahteva od ljudi da rade tokom biološke noći (kada cirkadijalni satovi podstiču san) i spavaju tokom biološkog dana (kada cirkadijalni satovi podstiču aktivnost), što može dovesti do promene u načinu ishrane, te menjaju nutritivne vrednosti hrane zahvaljujući širokom spektru bioloških, socijalnih i kulturoloških faktora. Na primer, zapaženo je da noćni rad dovodi do konflikta između utvrđenog rasporeda obroka i cirkadijalnih ritmova koji se odnose na osećaj gladi, sitosti i metabolizam [7,8]. Pitanje ishrane uvek je uticalo na kvalitet rada i zdravlja zaposlenih radnika, uzimajući u obzir sledeće: različito fizičko opterećenje, različite energetske potrebe, i različite potrebe za gradivnim i energetskim materijalom. Međutim, teško je dati smernice za ishranu radnika koji rade u noćnoj smeni. Prvo, ne znamo da li radnici koji rade noću uopšte treba da jedu u toku noći ili ne. Drugo, nedostaje definitivni dokaz na koji bismo se pozvali u vezi sa tim šta treba jesti, a šta izbegavati. Treće, nutritivno vredna i kvalitetna hrana možda neće biti dostupna u toku noćnih radnih sati. Najzad, ishrana tokom noći može poboljšati blagostanje, ali oštetiti metabolizam.

Cirkadijalni ritam i enzimaska sekrecija

Centralni sat tela koji se nalazi u suprahijazmatskom jezgri kontroliše metabolizam kružeći tokom 24 sata, dok su periferni satovi smešteni u tkivima širom tela sinhronizovani sa centralnim satom kada spoljni faktori (izloženost svetlosti, fizička aktivnost i unos hrane) prate dnevne obrasce.

Cirkadijalni procesi noću podstiču san i post kroz regulatorne hormone kao što su melatonin i insulin, dok hranjenje i aktivnost dominiraju dnevnim satima uz optimizaciju metaboličkih procesa za potrošnju energije, lučenje insulina i sintezu holesterola i glikogena koji se dešavaju tokom ranog dela dana. Noćno jedenje i izmenjeno vreme spavanja, što je tipično za radnike koji rade u smenama, ometaju sinhronizaciju centralnog i perifernog sata i utiču na hormone na koje utiče pogrešno spavanje i unos hrane.

Svakom stimulusu odgovara pokretanje enzimске sekrecije, koja je u savršenoj harmoniji sa energetskim i kalorijskim potrebama ljudskog bića, koje pak odgovaraju potrebama funkcionisanja njegovog organizma.

U jutarnjim časovima dešava se sekrecija proteaza da bi se metabolisali proteini, kao i jaka sekrecija lipaze kako bi se metabolisale masti, koje će biti korišćene tokom naredne noći za izgradnju ćelijskih zidova. Na metabolizam lipida utiču i cirkadijalne oscilacije. Studije pokazuju da mnogi proteini povezani sa metabolizmom lipida (npr. ApoB, ApoA1 i ApoA4), intestinalni mikrozomalni transportni protein triglicerida i protein

From a chronobiological point of view, the human species is diurnal (i.e., active during the day), which means that shift work, especially night-time work, requires people to work during the biological night (when circadian clocks promote sleep) and to sleep during the biological day (when circadian clocks promote activity), which may lead to a change in dietary habits and in the nutritive value of food owing to a broad spectrum of biological, social and cultural factors. For example, it was found that night-time work caused a conflict between the determined meal schedule and circadian biological rhythms related to the feeling of hunger, satiety, as well as the metabolism itself [7,8]. The issue of nutrition has always affected the quality of work and health of employees, taking the following into consideration: different workload, different energy requirements, and different nutrient requirements. However, it is difficult to provide dietary guidelines for night shift workers. Firstly, we do not know whether employees who work at night should eat at all when at work or not. Secondly, there is no definitive proof we would rely on concerning the food they should eat or avoid. Thirdly, the most nutritious foods may not be available at that time of night. Finally, eating at night may improve one's well-being, but damage their metabolism.

Circadian rhythm and enzyme secretion

The central biological clock based in the suprachiasmatic nucleus controls the metabolism by cycling over the period of 24 hours, whereas peripheral body clocks located in tissues throughout the body are synchronized with the master clock when external factors (exposure to light, physical activity, and food intake) follow daily patterns.

At night, circadian processes promote sleep and fasting by means of regulatory hormones such as melatonin and insulin, while feeding and activity dominate daytime hours with the optimization of metabolic processes for energy expenditure, insulin secretion, and cholesterol and glycogen synthesis that occur during the early part of the day. Nocturnal eating and altered sleep time, which are typical of night shift workers, disrupt the synchronization of the central clock and peripheral clocks and impact on the hormones that are affected by poor sleep and food intake.

Each stimulus corresponds to the initiation of enzyme secretion which is in perfect harmony with energy and caloric requirements of a human being, which in turn corresponds to the needs of functioning of their organism.

In the morning, protease secretion occurs to metabolize proteins, as well as lipase secretion which is of importance for metabolizing lipids that will be used

koji vezuje masne kiseline creva pokazuju promene tokom dana [25-27]. Pored toga, studije na miševima pokazuju da je apsorpcija holesterola i lipida u tamnoj fazi veća nego u svetloj fazi. Neki proizvodi metabolizma lipida takođe pokazuju cirkadijalni ritam. Na primer, cirkulišuće neesterifikovane masne kiseline kod ljudi su više noću zbog povećane lipolitičke aktivnosti [9]. Ovim dvema sekercijama predhodi lučenje kortizola koji je takođe pod kontrolom suprahijazmatskog jedra (SCN) koje je smešteno u hipotalamusu. Kortizol je steroidni hormon koji se luči iz nadbubrežnih žlezda. Reguliše mnoge metaboličke procese kao što su glikogenoliza, lipoliza i proteoliza. Količina i učestalost lučenja kortizola regulišu se preko cirkadijalnog ritma [10,11]. Koncentracija kortizola u cirkulaciji dostiže najviši nivo neposredno pre jutarnjeg buđenja (između 7 i 8 časova). Kortizol postepeno opada tokom dana. Najniži nivo dostiže tokom sna posle ponoći, između 2 i 4 časa ujutru. Kortizol je glavni hormon koji reguliše metaboličke događaje u telu. Visok nivo kortizola funkcioniše kao katabolički hormon koji smanjuje čistu telesnu i mišićnu masu i povećava potrošnju energije.

Potom dolazi do lučenja insulina, koji pred kraj sna, omogućava početak korišćenja sporih šećera kako bi se omogućio priliv energije potrebne za funkcionisanje svih organa koji rade, i to za ceo dan. Pored toga, tolerancija na glukozu i lučenje insulina variraju tokom dana. U prirodnom toku metabolizma, osetljivost na insulin i lučenje insulina se smanjuju noću (naročito između 3 i 5 časova ujutru) u poređenju sa jutarnjim satima. Ovaj metabolički proces, „fenomen zore“, naglašava uticaj cirkadijalne kontrole na metabolizam glukoze. U prirodnim fiziološkim procesima u telu, hormoni koji rade kao antagonisti insulina (posebno hormona rasta) ispoljavaju hiperinsulinemičnu aktivnost zbog smanjenja lučenja insulina između 3 i 5 časova ujutru, tako da se nivo šećera u krvi vraća u normalu. Ovo se suprotstavlja dodatnom fiziološkom lučenju insulina kod nedijabetičara ili insulin zavisnih osoba. Nasuprot tome, kada je poremećeno oslobađanje insulina, efekat hormona rasta koji se oslobađa tokom noći, posebno kod pacijenata sa dijabetesom, možda neće biti ublažen. Ovo dovodi do patološkog cirkadijalnog ritma, koji može dovesti do jutarnje hiperglikemije nezavisno od načina ishrane [12]. U podne dolazi do sekrecija proteaza i amilaza [13,14] kako bi se obezbedila asimilacija namirnica. Popodne se javlja pojava višeg kortizola, nekih pet sati od prethodnog obroka, što izaziva sekreciju insulina, koji pak zahteva korišćenje brzih i polubrzih šećera kako bi se izbeglo oslobađanje uskladištenih proteina i kompenzovao zamor povezan sa funkcionisanjem organa.

U večernjim satima praktično više nema digestivne sekrecije, što znatno usporava asimilaciju namirnica,

during the following night for building cell walls. Circadian oscillations affect lipid metabolism as well. It has been concluded that many proteins associated with lipid metabolism (e.g., ApoB, ApoA1, and ApoA4), intestinal microsomal triglyceride transfer protein and intestinal fatty acid binding protein undergo changes during the day [25-27]. Moreover, mouse studies show that the absorption of cholesterol and lipids is greater in the dark phase than in the light phase. Some products of lipid metabolism also exhibit a circadian rhythm. For example, the level of circulating non-esterified fatty acids in humans is higher at night due to increased lipolytic activity [9]. These two secretions are preceded by cortisol secretion which is also controlled by the suprachiasmatic nucleus (SCN) located in the hypothalamus. Cortisol is a steroid hormone secreted by the adrenal glands. It regulates many metabolic processes such as glycogenolysis, lipolysis, and proteolysis. The amount and frequency of cortisol secretion are regulated by the circadian rhythm [10,11]. Circulating cortisol levels are at their highest immediately before waking (between 7 AM and 8 AM). Cortisol level gradually declines during the day, and it is at its lowest during sleep, after midnight (between 2 AM and 4 AM). Cortisol is the key hormone which regulates metabolic events in the body. Elevated levels of cortisol act as a catabolic hormone which reduces lean body mass and increases energy expenditure.

Then there is insulin secretion towards the end of sleep which enables the start of using slow-digested sugars in order to enable the flow of energy necessary for the functioning of all organs throughout the day. Besides, glucose tolerance and insulin secretion vary during the day. In the natural course of metabolism, insulin sensitivity and insulin secretion decrease at night (especially between 3 AM and 5 AM) in comparison with the morning hours. This metabolic process, "the dawn phenomenon", emphasizes the impact of circadian control on glucose metabolism. In natural physiological processes in the body, hormones that function as insulin antagonists (especially growth hormone) exert hyperinsulinemic activity due to a decrease in insulin secretion between 3 AM and 5 AM, so blood sugar levels return to normal. This is in contrast with the additional physiological insulin secretion in non-diabetics or in insulin-dependent individuals. On the other hand, when insulin release is impaired, the effect of growth hormone released at night, especially in patients with diabetes, may not be attenuated. This leads to a pathological circadian rhythm which may lead to hyperglycemia in the morning regardless of the dietary habits [12]. At noon, proteases and amylases are secreted [13,14] to ensure the assimilation of food. In the after-

odnosno organizam više neće moći da metaboliše prevelik unos hrane, kako kvalitativno tako i kvantitativno. Noću mora biti prisutna katabolička aktivnost vezano za potrebu mobilizacije endogene energije za vreme spavanja i gladovanja, ali su takođe prisutni i anabolički restorativni procesi. Tokom noći, hormon rasta (oslobođen u ovoj fazi dubokog sna) i kortizol [15-17] dovode do interne energetske mobilizacije serumske glikoze. Dostupni nivoi glikoze su smanjeni tokom noći i glukoza se „štedi“ tako da obezbedi energiju za CNS, što dovodi do rezistentnosti za noćnu energiju u mišićnim tkivima. To se smatra razlogom za oštećenu toleranciju glikoze kod radnika koji rade u noćnoj smeni.

Nespavanje i noćni rad takođe utiču na metabolizam dva važna hormona u našem telu i to na hormon gladi i sitosti (leptin i grelin) koji zavise od cirkadijalnog ritma, tako da pospešuju noćno gladovanje i spavanje. Ovo može uticati na poremećaj apetita koji se često zapaža kod radnika koji rade noću.

Leptin ima endokrine i parakrine efekte i učestvuje u regulaciji telesne mase, metabolizma i reproduktivnih funkcija. Porast nivoa leptina daje informaciju da je organizam sit i apetit se smanjuje, i obrnuto. Leptin je hormon koji se proizvodi u masnom tkivu; nakon što se leptin izluči iz adipocita, on prelazi krvno-moždanu barijeru, odlazi do mozga i vezuje se za njegov receptor LepR. Disregulacija ili disfunkcija receptora (nedostatak receptora za leptin) može dovesti do prejedanja i debljanja. Cirkadijalni ritam utiče na nivo koncentracije leptina, pa je najniža koncentracija u ranim jutarnjim satima, a tokom dana se povećava i na svom je najvišem nivou kasno uveče. Ono što utiče na nivo leptina tokom 24 sata jeste gubitak sna ili produženi san, cirkadijalna faza, prekomerni unos hrane, ili ograničenje kalorija. Leptin i insulin utiču na osetljivost mozga na signale sitosti [18,19].

Grelin ima strukturu peptida, sastoji se od 28 aminokiselina i naziva se hormonom gladi, jer ima jako važnu ulogu u regulaciji apetita. Grelin proizvode P/D1 ćelije u stomaku i to je hormon koji povećava apetit. Prazan želudac luči grelin koji informiše endokrine žlezde mozga o nedostatku hrane u sistemu za varenje i javlja se osećaj gladi. Grelin deluje kratkoročno i utiče na svakodnevni osećaj gladi. Kod zdravih odraslih, 24-časovni obrazac se javlja u cirkulišućim nivoima grelina u uslovima energetske ravnoteže, tako da se nivoi grelina povećavaju između obroka, smanjuju posle obroka, povećavaju pre i tokom prvih nekoliko sati sna i smanjuju tokom druge polovine epizode spavanja. U stalnim rutinskim uslovima, cirkadijalni ritam grelina se povećava tokom biološkog dana i smanjuje tokom biološke noći [20,21]. U uslovima kontrolisanog unosa energije ili energetske ravnoteže kod zdravih odraslih

noon, high levels of cortisol occur, approximately five hours after the last meal, which causes insulin secretion, which in turn requires the use of fast-acting and medium-acting sugars in order to avoid the release of stored proteins and compensate the fatigue associated with the functioning of the organs.

In the evening there is practically no digestive secretion, which significantly slows down the assimilation of food, or in other words, the body will no longer be able to metabolize excessive food intake, both qualitatively and quantitatively. At night, catabolic activity must be present related to the need to mobilize endogenous energy during sleep and fasting, but restorative anabolic processes are also present. During the night, growth hormone (released in this deep sleep phase) and cortisol [15-17] lead to internal energy mobilization of serum glucose. Available glucose levels are reduced at night and glucose is "spared" so as to provide energy for CNS, which leads to the resistance to nocturnal energy in muscle tissues. This is considered to be the reason for impaired glucose tolerance in night shift workers.

A lack of sleep and night-time work also influence the metabolism of two important hormones in our body – hunger and satiety hormones (leptin and ghrelin) which depend on the circadian rhythm promoting nocturnal fasting and sleep. This may affect appetite disturbance, which is often the case in employees who work the night shift.

Leptin has endocrine and paracrine effects, and it takes part in the regulation of body mass, metabolism and reproductive functions. Increased leptin provides the information that the organism is full, and appetite thus decreases, and vice versa. Leptin is a hormone produced in the adipose tissue; after leptin has been secreted from adipocytes, it crosses the blood-brain barrier, goes to the brain, and is bound to its receptor LEPR. Dysregulation or dysfunction of the receptor (leptin receptor deficiency) may lead to overeating and gaining weight. The circadian rhythm affects leptin levels, so its concentration is lowest in the morning, and it increases during the day being at its highest late in the evening. What affects the 24-hour leptin levels is as follows: a lack of sleep or prolonged sleep, circadian phase, excessive food intake, or calorie restriction. Leptin and insulin affect the brain's sensitivity to satiety signals [18,19].

Ghrelin has the structure of a peptide; it consists of 28 amino acids and it is called hunger hormone as it plays an important role in the regulation of appetite. Ghrelin is produced by P/D1 cells in the stomach, and it is an appetite-increasing hormone. An empty stomach secretes ghrelin which informs endocrine glands of

osoba, prijavljeno je da cirkadijalna neusklađenost ima minimalan uticaj na ukupne cirkulišuće nivoe grelina. Hormon grelin je povezan sa hormonom rasta pa tako podstiče telo na fizički razvoj, a takođe je dokazano da visoka koncentracija grelina pojačava memoriju i koncentraciju [22].

Homocistein je pseudo-aminokiselina koja u našem telu učestvuje u izgradnji tkiva. Viši nivoi homocisteina su nađeni kod radnika koji rade u smenama, koji su stariji od 40 godina i koji imaju probleme sa spavanjem. Homocistein pokazuje cirkadijalni noćni pik koji je povišen usled konzumiranja proteina životinjskog porekla u obroku tokom noći i smatra se vodećim uzrokom srčanih i moždanih udara [23,24].

Ishrana radnika koji rade u smenama

Imajući u vidu kako cirkadijalni ritam utiče na naš metabolizam, još 1960. godine počelo je da raste interesovanje za ishranu radnika koji rade u smenama. Studija koju je sproveo Derbi sa saradnicima [25] bila je jedna od prvih koja je pokazala da ukupni energetske unos kod zaposlenih koji rade u smenama jeste sličan onom kod radnika koji rade danju, ali da se značajno razlikuju po distribuciji/dinamici tih obroka tokom 24 časa. Međutim, ishrana radnika koji rade po smenama pokazala se bogatijom životinjskim mastima i proteinima. U istraživanjima koja su kasnije sprovedena takođe je uočeno da unos energije nije veći kod radnika koji rade u smenama i koji već imaju cirkadijalnu neusklađenost u odnosu na radnike koji ne rade u smenama. Međutim, izbor hrane može biti manje zdrav, a stopa gojaznosti je veća. Ovi rezultati upućuju na to da, čak i bez promena u unosu energije, može doći do povećanja telesne težine kada se energija troši u neodgovarajuće cirkadijalno vreme. Potrošnja energije raste nakon jutarnjeg obroka, i tada dolazi do većeg sagorevanja kalorija i veće iskoristljivosti hranljivih materija u odnosu na noćno obrokovanje [26,27]. Iako je u okviru sistematskih pregleda i u meta-analizama ranije prijavljivano da je ukupni energetske unos radnika koji rade u smenama sličan onom kod radnika koji rade danju i ovde su se pojavile nedoumice oko dokazivanja ove tvrdnje. Razlog za to je najpre ograničen broj studija, tj. mali broj studija koje se fokusiraju isključivo na radnike koji menjaju smene (kao na vrstu rasporeda smena) i na rotirajući unos energije u „noćnoj” smeni, a ne na unose koji su reprezentativniji za promenu rasporeda smena. Ono što je manje poznato je kako individualni rasporedi smena, posebno rotirajući rad u smenama, mogu uticati na unos energije i obrasce ishrane. Do danas, studije retko razlikuju tipove radnog rasporeda osim „dnevne smene” ili „noćne smene” i često u analizama kombinuju raspored smena sa rotacijom i bez rotacije.

the brain about the lack of food in the digestive system and the feeling of hunger occurs. Ghrelin has a short-term effect, and it affects the daily feeling of hunger. In healthy adults, a 24-hour pattern occurs in circulating ghrelin levels if there is energy balance – ghrelin levels increase between meals, decrease after meals, increase before and during the first few hours of sleep, and decrease during the second half of the sleep episode. Under constant routine conditions, the circadian rhythm of ghrelin increases during the biological day and decreases during the biological night [20,21]. Under conditions of controlled energy intake or energy equilibrium in healthy adults, circadian misalignment has been reported to have a minimal effect on total circulating ghrelin levels. The hormone ghrelin is related to growth hormone, so it encourages physical development, and high concentrations of ghrelin have been proven to enhance memory and concentration [23].

Homocysteine is a pseudo-amino acid which participates in tissue building in our body. Elevated homocysteine levels are found in night shift workers, those who are over 40 years of age, and who have sleep problems. Homocysteine has circadian nocturnal peak that is elevated due to animal protein consumption in a night-time meal and is considered to be a leading cause of myocardial infarction and stroke [23,24].

Dietary habits of night shift workers

Bearing in mind the impact of the circadian rhythm on our metabolism, as early as 1960 an interest in dietary habits of night shift workers was increased. The study conducted by Derby et al. [25] was among the first to show that the total energy intake in employees who worked shifts was similar to that of employees who worked daytime shifts, but that they differed significantly in distribution/dynamics of meals over the course of 24 hours. However, the diet of shift workers was found to be richer in animal fats and proteins. Subsequent studies also found that energy intake was not higher in shift workers who already suffered from circadian misalignment compared to those who did not work shifts. However, they may choose less healthy foods, and obesity rates could be higher. These results suggest that, even with no changes in energy intake, weight gain may occur if energy is expended at an inappropriate circadian time. Energy expenditure increases after the morning meal and this is when more calories are burnt and more nutrients are used compared to night-time eating [26,27]. Although it was previously reported in regular medical check-ups and meta-analyses that the total energy intake in shift workers was similar to that of daytime workers, doubts have arisen concerning this claim. The primary reason for this is

Dakle, uticaj rotirajućeg rasporeda smena na obrasce ishrane nije dobro utvrđen. Ovo je veoma važno s obzirom na rotaciju radnika u smenama koji menjaju sate rada iz dana u noć i povezanost sa lošijim metaboličkim zdravstvenim rezultatima i jedenjem noću [28].

S druge strane, primećena je i razlika u unosu mikronutrijenata [29-31] između radnika koji rade noću i radnika koji rade u dnevnoj smeni. Od desetak studija koje su ispitivale unos makronutrijenata, sedam studija je prijavilo značajnu razliku u unosu proteina kod radnika koji rade noćnu smenu uključujući niži unos proteina kod žena u odnosu na muškarce. Što se tiče unosa masti postoje oprečna mišljenja, ali je dokazano da se ipak značajno više masti unese tokom noćne smene, kao i da postoji značajno viši unos ugljenih hidrata u noćnoj smeni u odnosu na dnevnu.

Knutson i saradnici [32] su 90-ih godina ustanovili da radnici koji rade noću unose manje dijetalnih vlakana 6 meseci nakon početka rada u noćnoj smeni. Takođe, u studijama koje su sprovedene kasnije primećeno je da radnici koji rade u smenama, a naročito noću, unose manje dijetetskih vlakana. Za to se uglavnom krivi smanjen unos zelenog povrća, veća konzumacija krompira, manji unos voća i povećan unos glukoze zahvaljujući većem unosu gaziranih i energetske pića, kofeina, kao i većem unosu zasićenih masti [33-35]. Linseisen i saradnici [36] ustanovili su da je unošenje dijetetskih vlakana, cinka i vitamina A i D bilo manje i ispod dnevnih preporučenih vrednosti u grupi radnika koji stalno rade u noćnoj smeni. Pored toga, u studiji Przeora i saradnika [37] ukazano je na to da radnici koji rade u smenama unose hranu koju karakteriše nizak nivo hranljivih materija kao što su vlakna, Ca, Mg, Fe, vitamin D, folna kiselina. Pored toga, hrana kod žena koje su učestvovala u studiji, kao i kod muškaraca, imala je nepovoljno visok sadržaj natrijuma i fosfora. Razlog za visok unos gore navedenih materija možda leži u tome što su ovi radnici unosili veću količinu prerađevina od mesa [38,39]. Poslednjih godina sprovode se ispitivanja koncentracije vitamina D u ishrani kod radnika koji rade noću. Došlo se do zaključka da radnici koji rade u smenama, a naročito noću, imaju niži nivo vitamina D nego radnici koji rade u dnevnoj smeni. Uzrok je taj što su noćni radnici manje izloženi sunčevoj svetlosti u odnosu na radnike koji nemaju smenski rad [40,41]. Pored toga, radnici u noćnoj smeni pokazuju tendenciju ka neredovnom rasporedu obroka, jedenju noću i većem unosu nezdrave hrane, što sve može dovesti do smanjenog unosa vitamina D. Takođe je poznato da radnici koji rade u smenama, a naročito oni koji rade noću imaju tendenciju ka većem BMI (indeksu telesne mase) od opšte populacije, što je faktor koji može dovesti do povećane sekvestracije vitamina D u

the limited number of studies, i.e., a small number of studies focusing exclusively on shift workers (as in shift schedule) and the rotating energy intake in the night shift rather than intakes that are more representative of shift work. What is not well known is how individual shift schedules, especially shift rotations, may affect energy intake and dietary patterns. To date, studies have rarely distinguished between the types of work schedule other than "the day shift" and "the night shift" and they have often mixed rotating and non-rotating shift schedule in their analyses. So, the impact of rotating shift schedules on dietary patterns has not been well established. This is very important considering the fact that some shift workers change work hours from day-time to night-time and that it is associated with poorer metabolic health results and night-time eating [28].

On the other hand, there is a difference between micronutrient intake [29-31] between employees who worked during the night-time and those who worked the day shift. Seven out of a dozen studies that explored macronutrient intake reported a significant difference in protein intake in night shift workers, including a lower protein intake in women compared to men. Regarding fat intake, there are conflicting opinions, but it has been proven that significantly more fat is consumed during the night shift, as well as that there is significantly higher intake of carbohydrates during the night shift in comparison with the day shift.

In the 1990s, Knutson et al. [32] found that night shift workers consumed less dietary fiber 6 months after they had started working the night shift. Also, in studies conducted later, it was noticed that night shift workers consumed less dietary fiber especially at night. This is mainly due to reduced intake of green vegetables, higher potato consumption, lower fruit intake and increased glucose intake because of higher intake of carbonated and energy drinks and caffeine and higher intake of saturated fats [33-35]. Linseisen et al. [36] found that the intake of dietary fiber, zinc and vitamins A and D was lower and below the recommended values in a group of workers who constantly worked the night shift. Moreover, in a study conducted by Przeor et al. [37] it was pointed out that shift workers consumed foods characterized by a low level of nutrients such as fiber, Ca, Mg, Fe, vitamin D, folic acid. In addition, the diets of the women who participated in the study, as well as those of the men who participated in it, were unfavorably high in sodium and phosphorus. The reason behind the high intake of the abovementioned substances may lie in the fact that these workers consumed a larger amount of meat products [38,39]. In recent years, tests have been conducted on the concentration of vitamin D in the diets of night shift work-

masnom tkivu i posledično do niže vrednosti vitamina D u cirkulaciji [42]. Usled smanjenog unosa vitamina D dolazi do poremećaja metabolizma kostiju i nastanka osteoporoze. Rizik od povećanog preloma kostiju kod radnika koji rade noćnu smenu nisu istraživana sve do Bukovske-Damske i saradnika [43] koji su sprovedli studiju koja je pokazala veću stopu naprsnuća i preloma kostiju kod radnica koje rade noćnu smenu u odnosu na radnice koje rade danju, što ukazuje na potencijalnu vezu između osteoporoze i smenskog rada. Pored toga, nekoliko studija je pokazalo povezanost između niskog nivoa vitamina D i nastanka drugih bolesti, kao što su autoimuni poremećaji, kardiovaskularne bolesti, dijabetes melitus tip 2, zarazne bolesti, rak, neurološki i neuropsihijatrijski poremećaji, kao što su šizofrenija, demencija i depresija [44]. Na osnovu dosadašnjih saznanja o unosu vitamina D kod radnika koji rade noću otvara se čitav niz pitanja. Heterogenost među studijama bila je visoka, nije objašnjena godinama, polom, BMI i metodama merenja nivoa 25-OH-D u serumu i veći broj studija sprovedli su Koreanci, pa je potrebno sprovesti veće epidemiološke studije u drugim populacijama, kako bi se ove tvrdnje dokazale. Verovatno je da karakteristike smenskog rada, posebno broj odrađenih noći na mesečnom nivou, igraju ključnu ulogu u koncentraciji vitamina D kod ovih radnika, pa bi iz tog razloga bilo poželjno da se u okviru periodičnih pregleda određuje i koncentracija vitamina D i na osnovu rezultata sprovede brza korekcija nedostataka vitamina D radi sprečavanja rizika od preloma [45].

Nekoliko studija je takođe izvestilo da radnici u noćnim smenama imaju tendenciju da jedu češće [46,47], jednu manje sa više užina nego što je uobičajeno („faktor grickanje“) tokom noćnih smena umesto jednog većeg obroka, što se može opisati kao konzumiranje „mnogo hrane putem nekoliko obroka“.

Pored toga, ostaje da se utvrdi da li ponovljena izloženost cirkadijalnoj neusklađenosti (na primer, tokom rada u noćnoj smeni) i usklađivanju (slobodni dani) hronično menja hormone apetita i unos energije, odnosno treba istražiti san kod ovih radnika jer postoje studije koje pokazuju štetne efekta lošeg kvaliteta sna i kratkog trajanja sna jer ova uloga još uvek nije kvantifikovana. Potrebne su dalje studije koje bi ispitalle individualne razlike između polova i potvrdile vezu između obrazaca spavanja i buđenja i faktora načina života, kao što su navike u ishrani, fizička aktivnost i navika pušenja [48,49].

Efekat rada u smenama na zdravlje zaposlenih

Svako prisilno narušavanje normalnih obrazaca spavanja, kao što je rad u smenama, a naročito rad noću, može dovesti do cirkadijalne neusklađenosti i veruje se da je

ers. It has been concluded that shift workers, especially those who work the night shift, have a lower level of vitamin D compared to those who work the day shift. This is because night shift workers are less exposed to sunlight than those who do not work shifts [40,41]. In addition, night shift workers tend to adopt irregular meal schedules, eat at night, and consume more unhealthy food, which can lead to reduced vitamin D intake. It is also known that shift workers, especially those who work the night shift, tend to have a higher BMI (body mass index) than the general population, which may lead to increased sequestration of vitamin D in adipose tissue and consequently to lower levels of circulating vitamin D [42]. Due to reduced intake of vitamin D bone metabolism disorders and osteoporosis occur. The risk of increased incidence of bone fractures had not been researched until Bukowska-Damska et al. [43] conducted a study which showed a higher rate of fissures and fractures in female night shift workers compared to those female workers who worked the day shift, suggesting a potential link between osteoporosis and shift work. In addition, several studies have showed a link between low levels of vitamin D and the occurrence of other diseases, such as autoimmune disorders, cardiovascular disease, diabetes mellitus type 2, infectious diseases, cancer, neurological and neuropsychiatric disorders (e.g. schizophrenia, dementia, and depression) [44]. Based on the current knowledge about vitamin D intake in night shift workers, a series of questions opens. There was high heterogeneity not explained by age, gender, BMI, and methods of measuring 25-OH-D levels and a large number of studies were conducted by Koreans, so it is necessary to conduct larger epidemiological studies in order to prove the statements. It is likely that the characteristics of shift work, especially the number of working nights on a monthly basis, play a vital role in vitamin D concentrations in these workers, and for this reason it would be desirable to determine vitamin D concentration as part of check-ups and based on the results carry out a rapid correction of vitamin D deficiency in order to prevent the risk of bone fractures [45].

Several studies have also reported that night shift workers have a tendency to eat more frequently [46,47], eat less with more snacks than usual ("snacking factor") during the night shift instead of a single large meal, which can be described as consuming "a lot of food in several meals".

Apart from this, it remains to be determined whether repeated exposure to circadian misalignment (for example, when working the night shift) and alignment (days off) chronically alters appetite hormones and energy intake, i.e., sleep should be examined in these

to delimično odgovorno za nastanak metaboličkog sindroma i hroničnih bolesti [50]. Metabolički sindrom karakteriše istovremna pojava hipertenzije, dijabetesa, gojaznosti i dislipidemije, i utvrđen je kao glavni uzročnik morbiteteta i mortaliteta od kardiovaskularnih bolesti. Hronični metabolički poremećaj predstavlja veliki zdravstveni problem širom sveta. U poređenju sa osobama koje rade danju, radnici koji rade noću imaju veći rizik od niza metaboličkih poremećaja i bolesti, kao posledice poremećenog cirkadijalnog ritama i spavanja, izloženosti psihosocijalnom stresu, fizičke neaktivnosti i nedovoljno vremena za odmor i revitalizaciju. Uprkos tome što imaju isti dnevni unos energije kao radnici koji rade danju, radnici koji rade noću imaju za 23% povećan rizik od razvoja prekomerne težine/gojaznosti i 35% povećan rizik od razvoja abdominalne gojaznosti u poređenju sa dnevnim radnicima. Pored toga, kod ovih radnika dolazi do upalnih reakcija, kao i do narušene tolerancije na glukozu i osetljivosti na insulin [51,52].

Cirkadijalni ritmovi imaju važnu ulogu u regulaciji kardiovaskularne fiziologije i zdravlja. Periferni satovi su prisutni u svakom od tipova kardiovaskularnih ćelija, regulišući njihovu funkciju, krvni pritisak, rad srca, cirkulišuće kateholamine, markere koagulacije krvi i funkciju vaskularnog endotela. Rizik od koronarne bolesti srca može biti povećan izlaganjem noćnom svetlu zbog poremećaja cirkadijalnih ritmova, koji utiču na funkciju endotela, što dovodi do aterosklerotičnih promena na krvnim sudovima, formiranja tromba i izazivanja inflamatornih odgovora [53,54].

Usled metaboličkih poremećaja, naročito u odnosu na lipidnu i glikoznu intoleranciju, imaju 9% veću mogućnost za razvoj dijabetesa tipa 2, 23% povećan rizik od infarkta miokarda i 5% povećan rizik od moždanog udara [55]. Javlja se problem sa uspavlivanjem i dolazi do razvoja mentalnih bolesti poput anksioznosti i depresije, kao i do uticaja na kognitivne performanse (smanjenje pažnje i otežano izvršavanje zadataka), promenu raspoloženja i budnost [56].

Svetska zdravstvena organizacija i Međunarodna agencija za istraživanje raka [57] zaključuju da je noćni rad verovatno kancerogen za ljude. Smanjenje nivoa lučenja melatonina dovodi do imunosupresije uključujući smanjenu aktivnost prirodnih ćelija ubica što može dovesti do kolorektalnog karcinoma, karcinoma dojke i karcinoma prostate [58]. Analizom 31 kohortne studije dolazi se do saznanja da izloženost noćnom radu značajno povećava rizik od oboljevanja od raka dojke za 2,9%, a za 8,6% za grupu radnika koja radi više od 10 godina u noćnoj smeni i 5,3% za radnike kod kojih se smene rotiraju. [59]. Međutim, rezultati istraživanja su kontroverzni, jer 26 meta-studija koje su prihvaćene

workers as there are studies showing harmful effects of poor sleep quality and short sleep duration considering this role has not been quantified yet. Further studies are needed to examine individual differences between the sexes and confirm the relationship between sleep-wake patterns and lifestyle factors, such as dietary habits, physical activity and smoking habit [48,49].

The effect of shift work on workers' health

Any forced disruption of normal sleep patterns, such as shift work (especially working at night), can lead to circadian misalignment and it is believed that this is partly to be blamed for the development of metabolic syndrome and chronic diseases [50]. Metabolic syndrome is characterized by the simultaneous occurrence of hypertension, diabetes, obesity, and dyslipidemia, and it has been marked as the leading cause of cardiovascular morbidity and mortality. Chronic metabolic disorder is a major health problem worldwide. Compared to people who work the day shift, night shift workers have a higher risk of a number of metabolic disorders and diseases as a consequence of disturbed circadian rhythm and sleep, exposure to psychosocial stress, physical inactivity and insufficient time for rest and revitalization. Despite having the same daily energy intake as people who work the day shift, night shift workers have a 23% increased risk of becoming overweight/obese and a 35% increased risk of developing abdominal obesity compared to daytime workers. Moreover, inflammatory reactions occur in these workers, as well as impaired glucose tolerance and insulin sensitivity [51,52].

Circadian rhythms play an important role in the regulation of cardiovascular physiology and health. Peripheral clocks are present in each type of cardiovascular cells, and they regulate their functioning, blood pressure, the functions of the heart, circulating catecholamines, blood coagulation markers, and the vascular endothelium. The risk of coronary heart disease may be increased by exposure to light during the night due to the disruption of circadian rhythms, which affects the endothelial function leading to atherosclerotic changes in blood vessels, thrombus formation and the induction of inflammatory responses [53,54].

Due to metabolic disorders, especially in relation to lipid and glucose intolerance, they are 9% more likely to develop diabetes type 2, they have a 23% increased risk of myocardial infarction, and a 5% increased risk of stroke [55]. There are problems with falling asleep and with the development of mental disorders such as anxiety and depression, and there is an impact on cognitive performances (decreased attention span and difficulty completing tasks), mood swings and alertness [56].

nije otkrilo povećanje oboljevanja od raka kod radnika koji dugo rade u noćnoj smeni [60] tako da predstoje dalja istraživanja u ovom smeru.

Saveti za zdraviju ishranu tokom noćne smene

Radnici koji rade noću suočeni su sa brojnim izazovima, naročito kada je u pitanju njihovo zdravlje i način ishrane. Za njih zdrava ishrana predstavlja pravi izazov. Postoje brojne preporuke kako da radnici koji rade noću obezbede svom telu uravnoteženu i zdravu ishranu [61], što smo mi u ovom preglednom članku pokušali da predstavimo.

Posle smene i pre spavanja treba izbegavati kofein najmanje 6 sati, a 1-2 sata pre spavanja treba doručkovati, pri čemu treba izbegavati „velike/obilne obroke“. Doručak je neophodan kako ne bi dolazilo do preranog buđenja zbog gladi.

Nakon spavanja sledi ručak koji bi trebao da obiluje povrćem, posnim mesom i obaveznom salatam, kako bi se obezbedila energija za ceo dan.

Nekoliko sati pre odlaska na posao, savetuje se glavni obrok (večera u krugu porodice ili prijatelja). Hrana koja se teško vari sigurno nije pogodna za noćne obroke, kao na primer gotovo sve prženo, ali zato lako svarljivi obroci poput supe, čorbe, jogurta i pirinča neće opteretiti stomak. Kako ne bi dolazilo do prejedanja jako je bitna i veličina tanjira. Naime, jelo iz manjeg tanjira može da prevari naš mozak da pomisli da je obrok veći nego što jeste. Tanjir treba popuniti tako da polovina tanjira sadrži raznobojno povrće (povrće spremi na pari, isitniti i preliti sosom), a jedna četvrtina tanjira treba da bude popunjena niskokaloričnim belančevinama (najbolje je izabrati posna (mršava) mesa bez kože, uključujući i biljne proteine od mahunarki i tofua). Preostala četvrtina tanjira može se ispuniti škrobnim povrćem ili integralnom hranom.

Odlaskom na posao (treća smena podrazumeva rad od 22h do 6h) rano u smeni neminovno će se osetiti glad koju treba zavarati malim obrokom ili užinom. Ovaj obrok bi trebalo da sadrži, na primer, kuvana jaja, tunjevinu, pečeno ćureće ili pileće belo meso, badem i kikiriki (može i u obliku putera). Može se napraviti sendvič od navedenog i svemu tome dodati neko voće. Kasno u smeni slede dopunski obroci (mali zalogaji na svakih nekoliko sati kako bi se očuvala koncentracija i energija), otprilike na svaka 3 sata. Savetuje se izbegavanje obrokovanja ili ako se baš mora, unositi hranu koja je energetska siromašna i to između ponoći i 6 sati ujutru, ili probati da se jede na početku i na kraju smene.

Mnogo je zdravije ako hranu ponesemo sa sobom (zdrava hrana i zdrave grickalice). Mnogi zaposleni nemaju organizovane restorane (kantine) za ishranu, a

The World Health Organization and the International Agency for Research on Cancer [57] have concluded that night work is probably carcinogenic to humans. Decreased levels of melatonin secretion lead to immunosuppression including decreased activity of natural killer cells which can in turn lead to colorectal cancer, breast cancer and prostate cancer [58]. An analysis of 31 cohort studies revealed that exposure to light during the night significantly increased the risk of breast cancer by 2.9%, in the group of workers who had been working the night shift for more than 10 years by 8.6%, and in workers who rotated shifts by 5.3% [59]. However, the research results are controversial as 26 accepted meta-studies did not notice an increase in cancer incidence in workers who had been working the night shift for a long time [60], so further research in this field is expected.

Tips for healthier dietary habits in the night shift

Night shift workers face many challenges, especially concerning their health and dietary habits. To them, healthy eating is a real challenge. There are numerous recommendations on how night shift workers may have a balanced and healthy diet [61], which we have tried to present in this review article.

Caffeine should be avoided for at least 6 hours after the night shift and before going to sleep, and it is recommended to have breakfast 1–2 hours before going to bed avoiding "large/extra large meals". It is necessary to have breakfast to avoid waking up too early due to hunger.

After sleeping it is lunch time and lunch should be rich in vegetables, lean meat and inevitable salad in order to provide the organism with energy for the entire day.

A few hours before going to work it is recommended to have the main meal (dinner with family or friends). Foods that are difficult to digest are certainly not suitable for night meals (e.g., almost anything fried), but easy-to-digest foods such as soups, cream soups, yogurt, and rice will not cause stomach heaviness. In order to avoid overeating, it is also important to pay attention to the size of the plate. In other words, eating from a smaller plate can trick our brain into thinking that the meal is bigger than it really is. The plate should be filled in the following way: a half of the plate should contain vegetables in different colors (the vegetables should be steamed, cut, and seasoned with a dressing), and a quarter of the plate should be filled with low-calorie proteins (it is best to choose lean meat with no skin, including protein-rich vegetables such as legumes or tofu). The remaining quarter of the plate should be filled with starchy vegetables or whole-grain food.

i ako ih imaju one nude brzu nezdravu hranu. Većina radnika na poslu nema pristup frižideru gde bi mogli da ostave svoju hranu. Zato radnici treba da budu kreativni u načinu pripremanja i čuvanja hrane [62].

Savetuje se da se tokom noćnog rada izbegava konzumacija slatkih grickalica. Hrana sa visokim sadržajem šećera kao što je čokoladica ili bezalkoholno piće može obezbediti kratak nalet energije, ali kasnije se može javiti osećaj usporenosti. Kada počne da se javlja osećaj umora i gladi, užina sa malo proteina obezbediće dovoljnu energiju.

Često pitanje koje se javlja među radnicima u noćnoj smeni je: "Šta treba konzumirati od napitaka?". Osnovna životna namirnica je voda. Bez nje organizam ne može da funkcioniše pravilno i zato je neophodno unositi dovoljnu količinu vode. Potrebno je piti svakog dana od 1,5–2 litra tečnosti. U vodu se može dodati sveže začinsko bilje poput nane ili voće. Unos tečnosti može biti i veći u zavisnosti od potreba organizma, npr. kod intenzivnih fizičkih napora ili kad su velike vrućine. Vodu treba uzimati između obroka, a ne u toku obroka kada uzimanje vode razređuje želudačnu kiselinu neophodnu za normalno varenje hrane.

Treba smanjiti unos kofeina. Kako bi ostali budni, radnici u noćnoj smeni često posežu za napicima koji su bogati kofeinom (kafa i energetske napici). Male količine kofeina, deluju kao stimulans i mogu pomoći mentalnoj budnosti. Tokom noćne smene preporučene su dve manje šoljice kafe (200 mg), 30–60 minuta pre početka smene. Međutim, ne sme se konzumirati više od 600 mg kofeina dnevno i treba prekinuti sa unosom 4–6 sati pre planiranog spavanja. Previše kofeina može prekinuti san i učiniti da se osoba oseća anksiozno ili mrzovoljno. Zato se radnicima koji rade noću savetuje da izbegavaju napitke bogate kofeinom i da pređu na čaj ili kafu bez kofeina [63].

Takođe je važno razmotriti ulogu koju ima socijalni kontekst u ishrani, pa se preporučuje da se radnicima obezbedi adekvatan prostor za večeru (obedovanje u opuštenoj atmosferi koja promovise aktivaciju anti-stres sistema) i da se obrok pojede daleko od radnog mesta sa kolegama, u prijatnom okruženju ukoliko je to moguće.

Pored toga, radnicima koji rade noću savetuje se da prave aktivne pauze. Tokom pauze pored ishrane savetuje se da se ostavi deo vremena kako bi se sprovele vežbe istezanja, otišlo u brzu šetnju ili vodio opuštajući razgovor sa kolegama. Sve ovo doprineće tome da radnik dobije dodatnu energiju kako bi mogao da završi smenu, poboljšaće njegovo raspoloženje i doprineće boljem snu nakon smene [64].

Da bi radnici koji rade noću ostali zdravi trebalo bi da praktikuju zdrav način života van radnog mesta: do-

Once at work (the night shift means working from 10 PM to 6 AM), early through the shift you will certainly feel hunger which you should deceive with a small meal or snack. For example, this meal should contain boiled eggs, tuna fish, grilled turkey or chicken meat, almond and peanuts (even as peanut butter). A sandwich can be made with the listed ingredients and some fruit could be added to it. Late in the shift, there are additional meals (small bites every few hours to maintain concentration and energy), approximately every 3 hours. It is recommended to avoid food completely, but if there is a need for food then food that is low in energy should be taken between midnight and 6 AM, or food should be consumed at the very beginning and the very end of the shift.

It is much healthier to take food with us (healthy food and healthy snacks). Many employees do not have access to organized restaurants (canteens), or even if they do these restaurants offer fast food. Most employees cannot use a refrigerator at work where they could keep their food. This is why employees should be creative when preparing and keeping food [62].

It is advised to avoid the consumption of sweets on the night shift. Foods that are high in sugar, such as a chocolate bar or a soft drink, could provide a short burst of energy, but later you may feel sluggish. When there are feelings of fatigue and hunger, a snack containing a small portion of proteins will provide enough energy.

A question that is frequently posed by night shift workers is: "Which drinks should I consume?" Water is the basic foodstuff. The organism cannot function properly without water, so it is necessary to take in a sufficient amount of it. It is necessary to drink 1.5–2 liters of liquid every day. Herbs such as mint or fruit can be added to water. Fluid intake can be even higher depending on the needs of the body, e.g., during intense physical efforts or when it is very hot. Water should be taken between meals, not during meals when water that is taken dilutes gastric acid that is necessary for normal digestion.

Caffeine intake should be reduced. In order to stay awake, night shift workers often choose drinks that are rich in caffeine (coffee and energy drinks). Small amounts of caffeine have a stimulating effect and can help mental alertness. During the night shift, it is recommended to consume two small cups of coffee (200 mg), 30–60 minutes before the shift. However, no more than 600 mg a day should be consumed, and the intake should be stopped 4–6 hours before going to sleep. Too much caffeine can disrupt sleep and make a person feel anxious or ill-humored. This is why night shift workers are advised to avoid caffeine-rich drinks and to take tea or decaffeinated coffee instead [63].

voljno odmora i sna, dobro izbalansiranu ishranu, fizičku aktivnost, održavanje zdrave telesne težine, izbegavanje pušenja, ograničavanje ili izbegavanje alkohola i očuvanje mentalnog zdravlja.

ZAKLJUČAK

Radnici koji rade noću suočavaju se sa jedinstvenim izazovima po svoje zdravlje na biološkom, psihološkom i socijalnom nivou. Hrana i piće koje se biraju tokom rada igraju važnu ulogu u održavanju nivoa zdravlja i energije, pa u tom smislu treba raditi na podizanju svesti o pravilnoj ishrani kako kod radnika tako i kod njihovih poslodavaca u smislu promocije zdravlja na radnom mestu. Poslodavci bi trebalo da preuzmu odgovornost za edukaciju radnika o prednostima zdrave ishrane jer bi to uticalo na bolje zdravlje zaposlenih i smanjilo troškove zdravstvene zaštite, dovelo do smanjenja izostanaka sa posla i do povećanja produktivnosti i bolje koncentracije zaposlenih, što u krajnjoj liniji dovodi do povećanja prihoda. Sam poslodavac umnogome može uticati na način ishrane radnika tako što bi noćna smena počinjala pre ponoći i ne bi trebalo da traje duže od 11 sati u kontinuitetu. Poželjno bi bilo da se u okviru fabrika naprave kantine (gde će se prodavati zdravi obroci i zdrave grickalice), te da poslodavac angažuje nutricionistu koji bi na radnom mestu održao seminar o ishrani. Nutricionista može zaposlenima da pruži dragocene savete o tome kako ishrana može da spreči zdravstvene probleme i poboljša njihov kvalitet života. Bolja kultura kompanije i bolje radno okruženje (kultura zdravlja na radnom mestu) može privući najbolje kandidate i pomoći poslodavcu da zadrži najbolje zaposlene.

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LITERATURA / REFERENCES

1. Bell-Pedersen D, Cassone VM, Earnest DJ, Golden SS, Hardin PE, Thomas TL, et al. Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nat Rev Genet.* 2005 Jul;6(7):544-56. doi: 10.1038/nrg1633.
2. Kumar V, Sharma A. Common features of circadian timekeeping in diverse organisms. *Current Opinion in Physiology.* 2018 Oct 1;5:58-67. doi: 10.1016/j.cophys.2018.07.004.
3. https://ec.europa.eu/eurostat/product?mode=view&code=lfsa_ewpnig doi:10.2908/lfsa_ewpnig
4. <https://redline.digital/shift-work-statistics/>
5. The Council of the European Union. Directive 2000/34/EC of the European Parliament and of the Council of 22 June 2000 amending Council Directive 93/104/EC 'concerning certain aspects of the organisation of working time to cover sectors and activities excluded from that Directive.'. *Official Journal* 1993;L195:41-5. <https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32000L0034>
6. Zakon o radu ("Sl. glasnik RS", br. 24/2005, 61/2005, 54/2009, 32/2013, 75/2014, 13/2017 - odluka US, 113/2017 i 95/2018-autentično tumačenje) https://www.paragraf.rs/propisi/zakon_o_radu.html

It is also important to consider the role of the social context in nutrition, so it is recommended to provide employees with an adequate dining space (dining in a relaxed atmosphere which promotes the activation of the anti-stress system) and to dine away from the workplace with colleagues, in a pleasant environment, if possible.

In addition, night shift workers are advised to take active breaks. During the break, besides nutrition, it is advisable to leave some time for stretching, a quick walk or a relaxed conversation with colleagues. This will contribute to some extra energy that will enable the employee to round the shift, improve their mood and sleep better after the shift [64].

To stay healthy, night shift workers should have a healthy lifestyle outside work – they should have enough rest and sleep, eat well-balanced food, have physical activity, maintain healthy body weight, avoid smoking, reduce or avoid alcohol consumption and preserve mental health.

CONCLUSION

Night shift workers face unique challenges to their health on the biological, psychological, and social level. The food and drink choices they make at work play an important role in maintaining health and energy levels, so awareness should be raised of proper nutrition in both employees and their employers in terms of health promotion at work. Employers should take responsibility for educating employees about the benefits of a healthy diet as this would lead to better health of employees and a decrease in healthcare costs, reduce absenteeism, increase productivity and bring about better concentration in employees, which ultimately leads to increased income. Employers could greatly influence their employees' dietary habits by deciding to start the night shift before midnight and make it last for not more than 11 hours continuously. It would be desirable to organize canteens within factories (where healthy meals and healthy snacks would be sold) and for the employer to hire a nutritionist who would organize a seminar on nutrition. A nutritionist can provide employees with valuable advice on how nutrition may prevent health problems and improve the quality of life. Better company culture and work environment (a culture of health at the workplace) may attract the best candidates and help the employer keep the best employees.

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7. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)*. 2003 Mar;53(2):103-8. doi: 10.1093/occmed/kqg048.
8. Bonnell EK, Huggins CE, Huggins CT, McCaffrey TA, Palermo C, Bonham MP. Influences on dietary choices during day versus night shift in shift workers: a mixed methods study. *Nutrients*. 2017 Feb 26;9(3):193. doi: 10.3390/nu9030193.
9. Pan X, Hussain MM. Clock is important for food and circadian regulation of macronutrient absorption in mice. *J Lipid Res*. 2009 Sep;50(9):1800-13. doi: 10.1194/jlr.M900085-JLR200.
10. Mohd Azmi, N.A.S.; Juliana, N.; Azmani, S.; Mohd Effendy, N.; Abu, I.F.; Mohd Fahmi Teng, N.I.; Das, S. Cortisol on Circadian Rhythm and Its Effect on Cardiovascular System. *Int. J. Environ. Res. Public Health* 2021, 18, 676. <https://doi.org/10.3390/ijerph18020676>.
11. O'Byrne NA, Yuen F, Butt WZ, Liu PY. Sleep and Circadian Regulation of Cortisol: A Short Review. *Curr Opin Endocr Metab Res*. 2021 Jun;18:178-186. doi: 10.1016/j.coemr.2021.03.011.
12. Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance REVIEW ARTICLES | APRIL 23 2019 *Ann Nutr Metab* (2019) 74(4):322–330 <https://karger.com/anm/article/74/4/322/51852/Effect-of-Circadian-Rhythm-on-Metabolic-Processes> <https://doi.org/10.1159/000500071>.
13. Digestive Enzymes: Amylase, Protease, And Lipase <https://integrativepro.com/blogs/articles/digestive-enzymes-amylase-protease-lipase>.
14. Digestive Enzymes: Types and Function A Necessary Part of Digestion By Barbara Bolen, PhD Updated on September 06, 2022 Medically reviewed by Jay N. Yepuri, MD <https://www-verywellhealth-com.translate.goog/what-are-digestive-enzymes>.
15. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab*. 1971 Jul;33(1):14-22. doi: 10.1210/jcem-33-1-14.
16. Selmaoui B, Touitou Y. Reproducibility of the circadian rhythms of serum cortisol and melatonin in healthy subjects: a study of three different 24-h cycles over six weeks. *Life Sci*. 2003 Nov 14;73(26):3339-49. doi: 10.1016/j.lfs.2003.05.007.
17. Kuo T, McQueen A, Chen TC, Wang JC. Regulation of glucose homeostasis by glucocorticoids. *Adv Exp Med Biol*. 2015;872:99-126. doi: 10.1007/978-1-4939-2895-8_5.
18. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000 Apr 6;404(6778):661-71. doi: 10.1038/35007534.
19. ŞAHİN, T., & TOZCU, D. (2022). Circadian rhythm and obesity. *International Journal of Science Letters*, 4(1), 202-219. <https://doi.org/10.38058/ijsl.1053393>
20. Hashiguchi H, Sheng Z, Routh V, Gerzanich V, Simard JM, Bryan J. Direct versus indirect actions of ghrelin on hypothalamic NPY neurons. *PLoS One*. 2017 Sep 6;12(9):e0184261. doi: 10.1371/journal.pone.0184261.
21. Rynders CA, Morton SJ, Bessesen DH, Wright KP Jr, Broussard JL. Circadian Rhythm of Substrate Oxidation and Hormonal Regulators of Energy Balance. *Obesity (Silver Spring)*. 2020 Jul;28 Suppl 1(Suppl 1):S104-S113. doi: 10.1002/oby.22816.
22. Hashiguchi H, Sheng Z, Routh V, Gerzanich V, Simard JM, Bryan J. Direct versus indirect actions of ghrelin on hypothalamic NPY neurons. *PLoS One*. 2017 Sep 6;12(9):e0184261. doi: 10.1371/journal.pone.0184261.
23. Antoniadis C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: from folate fortification to the recent clinical trials. *Eur Heart J*. 2009 Jan;30(1):6-15. doi: 10.1093/eurheartj/ehn515.
24. Lim JW, Kim CW, Park HO, Chung EY, Chae C, Son J, Shin YH, Park SH, Choi SM. Association between shift work and serum homocysteine level in female electronic manufacturing services workers. *Ann Occup Environ Med*. 2023 Mar;35(1):e4. <https://doi.org/10.35371/aoem.2023.35.e4>.
25. Debry G, Girault P, Lefort J, Thiébault J. Enquête sur les habitudes alimentaires des travailleurs "à feux continus" [Survey of the food habits of workers on shift work]. *Bull Inst Natl Sante Rech Med*. 1967 Nov-Dec;22(6):1169-202.
26. Boege HL, Bhatti MZ, St-Onge MP. Circadian rhythms and meal timing: impact on energy balance and body weight. *Curr Opin Biotechnol*. 2021 Aug;70:1-6. doi:10.1016/j.copbio.2020.08.009.
27. Qian J, Morris CJ, Caputo R, Wang W, Garaulet M, Scheer FAJL. Sex differences in the circadian misalignment effects on energy regulation. *Proc Natl Acad Sci U S A*. 2019 Nov 19;116(47):23806-23812. doi: 10.1073/pnas.1914003116.
28. Cayanan EA, Eyre NAB, Lao V, Comas M, Hoyos CM, Marshall NS, Phillips CL, Shiao JSC, Guo YL, Gordon CJ. Is 24-hour energy intake greater during night shift compared to non-night shift patterns? A systematic review. *Chronobiol Int*. 2019 Dec;36(12):1599-1612. doi: 10.1080/07420528.2019.1666865.
29. Ulusoy HG, Sanlier N, Rakıcıoğlu N. Do Rotating Night Shifts Change Nurses' Nutritional Status? A Cross-Sectional Study. *J Am Nutr Assoc*. 2022 Aug;41(6):608-616. doi: 10.1080/07315724.2021.1947413.
30. Kosmadopoulos A, Kervezee L, Boudreau P, Gonzales-Aste F, Vujovic N, Scheer FAJL, Boivin DB. Effects of Shift Work on the Eating Behavior of Police Officers on Patrol. *Nutrients*. 2020 Apr 4;12(4):999. doi: 10.3390/nu12040999.
31. Fradkin L, Raz O, Boaz M. Nurses who work rotating shifts consume more energy, macronutrients and calcium when they work the night shift versus day shift. *Chronobiol Int*. 2019 Feb;36(2):288-295. doi: 10.1080/07420528.2018.1538155.
32. Knutson A, Andersson H, Berglund U. Serum lipoproteins in day and shift workers: a prospective study. *Br J Ind Med*. 1990 Feb;47(2):132-4. doi: 10.1136/oem.47.2.132.
33. Balieiro LC, Rossato LT, Waterhouse J, Paim SL, Mota MC, Crispim CA. Nutritional status and eating habits of bus drivers during the day and night. *Chronobiol Int*. 2014 Dec;31(10):1123-9. doi: 10.3109/07420528.2014.957299.
34. Souza RV, Sarmiento RA, de Almeida JC, Canuto R. The effect of shift work on eating habits: a systematic review. *Scand J Work Environ Health*. 2019 Jan 1;45(1):7-21. doi: 10.5271/sjweh.3759.
35. Nakamura M, Miura A, Nagahata T, Toki A, Shibata Y, Okada E, Ojima T. Dietary intake and dinner timing among shift workers in Japan. *J Occup Health*. 2018 Nov 27;60(6):467-474. doi: 10.1539/joh.2018-0070-OA.
36. Linseisen J, Wolfram G. Nährstoffzufuhr bei Dauernachtschicht-Arbeitern [Nutrient intake in permanent night shift workers]. *Z Ernährungswiss*. 1994 Dec;33(4):299-309. German. doi: 10.1007/BF01614435.
37. Przeor M, Goluch-Koniuszy Z. [Evaluation of nutrition and diet of nurses during perimenopause while working in a shift system]. *Probl Hig Epidemiol*. 2013;94(4):797-801. Polish.
38. Katarzyna Daria Gołębek, Anna Chmielewska, Ewa Karoluk, Bożena Regul-ska-Iłlow A multifaceted assessment of the nutritional status, diet and eating habits of midwives working on a shift schedule in Wrocław, Poland: evaluation of macronutrients, vitamins and minerals in the diets of midwives participating in the study.
39. *International Journal of Occupational Medicine and Environmental Health* 2023;36(5):618–631 <https://doi.org/10.13075/ijom.1896.02117>.
40. Lee H.J., Choi H., Yoon I.Y. Impacts of serum Vitamin D levels on sleep and daytime sleepiness according to working conditions. *J. Clin. Sleep Med*. 2020;16:1045–1054. doi: 10.5664/jcsm.8390.

41. Martelli M, Salvio G, Santarelli L, Bracci M. Shift Work and Serum Vitamin D Levels: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2022 Jul 22; doi:10.3390/ijerph19158919.
42. Doğan Y., Kara M., Culha M.A., Özçakar L., Kaymak B. The relationship between vitamin D deficiency, body composition, and physical/cognitive functions. *Arch. Osteoporos*. 2022;17:66. doi: 10.1007/s11657-022-01109-6.
43. Bukowska-Damska A., Skowronska-Jozwiak E., Kaluzny P., Lewinski A. Night shift work and osteoporosis-bone turnover markers among female blue-collar workers in Poland. *Chronobiol. Int*. 2022;39:818–825. doi: 10.1080/07420528.2022.2037626.
44. Wassif G A, Alrehely M S, Alharbi D M, et al. (October 26, 2023) The Impact of Vitamin D on Neuropsychiatric Disorders. *Cureus* 15(10): e47716. doi:10.7759/cureus.47716.
45. Clark AB, Coates AM, Davidson ZE, Bonham MP. Dietary Patterns under the Influence of Rotational Shift Work Schedules: A Systematic Review and Meta-Analysis. *Adv Nutr*. 2023 Mar;14(2):295–316. doi: 10.1016/j.adv-nut.2023.01.006.
46. Takagi K. Influence of shift work on time and frequency of meal taking. *J Hum Ergol (Tokyo)*. 1972 Dec;1(2):195–205.
47. D. van de Langenberg, J.J. Vlaanderen, M.E. Dollé, M.A. Rookus, L.W. van Kerkhof, R.C. Vermeulen Diet, physical activity, and daylight exposure patterns in night-shift workers and day workers *Ann. Work. Expo. Health.*, 63 (1) (2019), pp. 9–21.
48. Bahinipati J, Sarangi R, Pathak M, Mohapatra S. Effect of night shift on development of metabolic syndrome among health care workers. *J Family Med Prim Care*. 2022 May;11(5):1710–1715. doi: 10.4103/jfmpc.jfmpc_375_21.
49. Mentzelou M, Papadopoulou SK, Papandreou D, Spanoudaki M, Dakanalis A, Vasios GK, et al. Evaluating the Relationship between Circadian Rhythms and Sleep, Metabolic and Cardiovascular Disorders: Current Clinical Evidence in Human Studies. *Metabolites*. 2023 Mar 1;13(3):370. doi: 10.3390/meta-bio13030370.
50. Khosravipour M, Khanlari P, Khazaie S, Khosravipour H, Khazaie H. A systematic review and meta-analysis of the association between shift work and metabolic syndrome: The roles of sleep, gender, and type of shift work. *Sleep Med Rev*. 2021 Jun;57:101427. doi: 10.1016/j.smr.2021.101427.
51. Sun M, Feng W, Wang F, Li P, Li Z, Li M, et al. Meta-analysis on shift work and risks of specific obesity types. *Obes Rev*. 2018 Jan;19(1):28–40. doi: 10.1111/obr.12621.
52. Chaput, JP., McHill, A.W., Cox, R.C. et al. The role of insufficient sleep and circadian misalignment in obesity. *Nat Rev Endocrinol* 19, 82–97 (2023). <https://doi.org/10.1038/s41574-022-00747-7>.
53. Sun S, Cao W, Ge Y, Ran J, Sun F, Zeng Q, Guo M, Huang J, Lee RS, Tian L, Welle-nius GA. Outdoor light at night and risk of coronary heart disease among older adults: a prospective cohort study. *Eur Heart J*. 2021 Feb 21;42(8):822–830. doi: 10.1093/eurheartj/ehaa846.
54. Kervezee L, Kosmadopoulos A, Boivin DB. Metabolic and cardiovascular consequences of shift work: The role of circadian disruption and sleep disturbances. *Eur J Neurosci*. 2020 Jan;51(1):396–412. doi: 10.1111/ejn.14216.
55. Gan Y, Yang C, Tong X, Sun H, Cong Y, Yin X, et al. Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occup Environ Med*. 2015 Jan;72(1):72–8. doi: 10.1136/oemed-2014-102150.
56. Moreno CRC, Marqueze EC, Sargent C, Wright KP, Jr, Ferguson SA, Tucker P. Working time society consensus statements: evidence-based effects of shift work on physical and mental health. *Ind Health*. 2019;57(2):139–157. doi: 10.2486/indhealth.SW-1.
57. IARC Monographs Vol 124 group. Carcinogenicity of night shift work. *Lancet Oncol*. 2019 Aug;20(8):1058–9. doi: 10.1016/S1470-2045(19)30455-3.
58. Dun A., Zhao X., Jin X., Wei T., Gao X., Wang Y., Hou H. Association between Night-Shift Work and Cancer Risk: Updated Systematic Review and Meta-Analysis. *Front. Oncol*. 2020;10:1006. doi: 10.3389/fonc.2020.01006.
59. Wei F., Chen W., Lin X. Night-shift work, breast cancer incidence, and all-cause mortality: An updated meta-analysis of prospective cohort studies. *Sleep Breath. Schlaf Atm*. 2022;26:1509–1526. doi: 10.1007/s11325-021-02523-9.
60. Manouchehri E., Taghipour A., Ghavami V., Ebadi A., Homaei F., Latifnejad Roudsari R. Night-shift work duration and breast cancer risk: An updated systematic review and meta-analysis. *BMC Women's Health*. 2021;21:89. doi: 10.1186/s12905-021-01233-4.
61. <https://www.henryford.com/blog/2022/05/tips-for-healthy-eating-while-working-the-night-shift> Tips For Healthy Eating While Working The Night Shift Posted on May 16, 2022 by Henry Ford Health Staff.
62. Add these low-calorie snacks to fill you up for hours! https://www-mynet-diary-com.translate.google/low-calorie-snacks-that-fill-you-up.html?_x_tr_sl=en&_x_tr_tl=sr&_x_tr_hl=sr&_x_tr_pto=sc.
63. How can I eat to optimize my performance on night shift? <https://www.hprc-online.org/nutrition/unique-nutrition-needs/how-can-i-eat-optimize-my-performance-night-shift>.
64. Easton, D.F., Gupta, C.C., Vincent, G.E. et al. Move the night way: how can physical activity facilitate adaptation to shift work?. *Commun Biol* 7, 259 (2024). <https://doi.org/10.1038/s42003-02>.

PERIOPERATIVNO ZBRINJAVANJE PACIJENATA SA KARDIOVASKULARNIM RIZIKOM U ABDOMINALNOJ HIRURGIJI

PRIKAZ SLUČAJA

CASE REPORT

PERIOPERATIVE MANAGEMENT OF HIGH-RISK CARDIOVASCULAR PATIENTS IN ABDOMINAL SURGERY

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SAŽETAK

Uvod: Priprema kardiovaskularnih bolesnika za različite vrste hirurških intervencija predstavlja svakodnevni izazov u radu anesteziologa. Kompleksnost se ogleda u težini osnovnog oboljenja pacijenta, efektima medikamentozne terapije, urgentnosti i vrsti hirurške intervencije. U proceni kardiovaskularnog rizika hirurškog pacijenta na raspolaganju su različiti scoring sistemi, među njima Revised Cardiac Risk Index (RCRI/Lee kriterijum) koji se zbog svoje sveobuhvatnosti i jednostavnosti procene najčešće koristi. Cilj rada je da kroz primer dva pacijenta sa kardiovaskularnim oboljenjima, pokaže kako se multidisciplinarnim pristupom, uz individualizovanu strategiju i primenu savremenih vodiča, rizik od perioperativnih komplikacija može redukovati.

Prikaz slučaja: U prvom slučaju reč je o pacijentu sa kliničkom slikom akutnog apendicitisa. Zbog angine pektoris, mesec dana pre hirurške intervencije kod pacijenta je plasiran stent, i propisana dvojna antiagregaciona terapija.

U drugom primeru reč je o pacijentu sa kliničkom slikom akutnog kalkuloznog holecistitisa. Pacijent ima tešku formu ishemijske kardiomiopatije, zbog čega je planirana revaskularizacija miokarda, unutar mesec dana od abdominalne hirurške intervencije. Oba pacijenta su pod povišenim perioperativnim rizikom za razvoj miokardnog oštećenja, dok u slučaju prvog pacijenta postoji i povišen rizik od krvarenja, usled primene redovne terapije.

Zaključak: Prava ravnoteža u perioperativnom zbrinjavanju ove kategorije pacijenta može se postići multidisciplinarnim pristupom, kao i prilagođavanjem savremenih smernica individualnim potrebama pacijenta.

Ključne reči: kardiovaskularni pacijent, abdominalna hirurgija, Lee kriterijum, miokardno oštećenje

ABSTRACT

Introduction: The preparation of cardiovascular patients for different types of surgical interventions represents a challenge in an anesthesiologist's everyday practice. Its complexity depends on the severity of the underlying disease, the effects of the drug treatment, urgency, and the type of surgical intervention. Different types of scoring systems are available when it comes to the assessment of cardiovascular risk in patients during surgery. One of them, Revised Cardiac Risk Index (RCRI/Lee criteria), stands out due to its comprehensiveness and simplicity, and is thus applied most frequently. Using the example of two patients with cardiovascular disease, the aim of this paper is to show how the risk of perioperative complications can be reduced by applying a multidisciplinary approach, along with an individualized strategy and modern guidelines.

Case reports: In the first case, we presented a patient with acute appendicitis. Because of angina pectoris, one month prior to the planned abdominal surgery, Percutaneous Coronary Intervention was performed placing one stent, after which dual antiplatelet drugs were prescribed.

A patient with acute cholecystitis is presented in the second case. Coronary artery bypass grafting is planned within a month upon the abdominal surgery, due to a severe form of ischemic cardiomyopathy. Both patients are at high risk of myocardial damage during surgery, the first patient being at high risk of hemorrhage as well.

Conclusion: The appropriate balance in the perioperative care of such patients can be achieved by a multidisciplinary approach, as well as by adapting modern guidelines to patients' individual needs.

Keywords: cardiovascular patient, abdominal surgery, Lee Criteria, myocardial injury

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UVOD

U svakodnevnoj kliničkoj praksi, priprema pacijenata za operativno lečenje nije nimalo lak zadatak. Prisustvo komorbiditeta, urgentnost hirurške intervencije, i potreba za dodatnim dijagnostičkim pretragama mogu uticati na tok lečenja pacijenta. Broj kardiovaskularnih oboljenja u svetu sa godinama se povećava. Na to utiču način života, hronična izloženost stresnim situacijama, kao i starenje populacije. Novine u farmakoterapiji prate trend porasta obolelih.

Smatra se da se oko 5% svetske populacije svake godine podvrgne nekoj vrsti hirurške intervencije, sa tendencijom procentualnog povećanja broja pacijenata iz godine u godinu [1,2]. Od toga čak 85% nije iz oblasti kardiovaskularne hirurgije [2].

Šta onda raditi kada se susretnete sa pacijentom sa kardiovaskularnim oboljenjem, koji je na terapiji poslednjom generacijom antikoagulatnih lekova, a kod koga je neophodna hirurška intervencija? Da li pacijenta sa povišenim kardiološkim rizikom treba dodatno pripremati za elektivnu hiruršku intervenciju?

Pokušaćemo da, kroz dva primera, predstavimo problematiku pacijenata sa povišenim kardiovaskularnim rizikom i njihovim perioperativnim zbrinjavanjem, te kako pravilna i pravovremena procena rizika, poštovanje smernica i vodiča, i multidisciplinarni pristup ovim pacijentima smanjuju rizik od perioperativnih komplikacija. U proceni pacijenata koristili smo RCRI, kao metod procene kardiološkog rizika, a kao temelj za preoperativnu pripremu pacijenata vodič Evropskog udruženja anesteziologa (Preoperative evaluation of adults undergoing elective noncardiac surgery) objavljen 2018. godine, kao i vodič Evropskog udruženja kardiologa (ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery) objavljen 2022. godine.

PRIKAZ SLUČAJA

Slučaj 1

Muškarac starosti 49 god, BMI=25,7 kg/m², primljen je na Kliniku za urgentnu hirurgiju UKCS-a zbog akutnog apendicitisa. U ličnoj anamnezi negira alergije, dok od hroničnih bolesti navodi hipertenziju (HTA), anginu pectoris (AP), hiperlipoproteinemiju (HLP), i giht, zbog čega je na redovnoj terapiji ACE inhibitorima, beta blokatorima, statinima, urikostaticima. Pacijentu je mesec dana pre prijema, nakon koronarografije, učinjeno plasiranje jednog stenta (PCI LAD proximal Resolute Onyx 4,0x22mm), nakon čega je u terapiju uvedena i dvojnna antiagregaciona terapija acetilsalicilnom kiselinom (ASA) i ticagrelorom (P2Y12 ADP receptor inhibitorom trombocita).

INTRODUCTION

In everyday clinical practice, preparing a patient for surgical treatment is not an easy task. The presence of comorbidities, the urgency of surgical intervention, and the need for additional diagnostic procedures can affect the course of the treatment. There is a constant increase in the number of individuals suffering from cardiovascular disease worldwide due to lifestyle, chronic exposure to stressful situations, as well as aging populations. Achievements in pharmacotherapy follow the trend of an ever-increasing number of patients.

It is believed that around 5% of the world population undergoes some sort of surgical intervention every year, with a tendency of a constant increase in the number of patients [1,2]. Of these, 85% of interventions do not belong to the field of cardiovascular surgery [2].

So, what should be done with a patient who suffers from cardiovascular disease, who is treated with the latest generation of anticoagulant drugs and who needs surgical intervention? Should a high-risk cardiovascular patient be additionally prepared for elective surgery?

Using two examples, we will try to present problems related to high-risk cardiovascular patients and their perioperative care, as well as the impact of adequate and timely risk assessment, adherence to guidelines and a multidisciplinary approach to such patients on reduced risk of perioperative complications. RCRI, a method for cardiac risk assessment, was used for patient evaluation, while the guide of the European Association of Anesthesiologists (Preoperative evaluation of adults undergoing elective noncardiac surgery) published in 2018 and the guide of the European Association of Cardiologists (ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery) published in 2022 were used as the basis of preoperative preparation of patients.

CASE PRESENTATION

Case 1

A 49-year-old male, BMI=25,7 kg/m², was admitted to the Emergency Room of the University Clinical Centre of Serbia for acute appendicitis. He denies any previous history of allergies and reports the following chronic diseases: arterial hypertension (HTA), angina pectoris (AP), hyperlipoproteinemia (HLP), and gout, which is why he is on regular therapy with ACE inhibitors, beta blockers, statins, and uricostatics. One month prior to admission, after coronary angiography, one stent (PCI LAD proximal Resolute Onyx 4,0x22mm) was placed, after which dual antiplatelet therapy with acetylsalicylic acid (ASA) and ticagrelor (P2Y12 ADP receptor platelet inhibitor) was introduced.

U laboratorijskim analizama preoperativno, izdava se povišena vrednost inflamatornih parametara Le $16,0 \times 10^9/L$, CRP 142mg/L, PCT 0,12ng/ml, dok je vrednost trombocita iznosila $301 \times 10^9/L$. Efekat antiagregacione terapije procenjen je point-of-care metodom, ispitivanjem funkcije agregabilnosti trombocita, Multiplate testom. Vrednosti ASPI 947; ADPhs 201, ukazale su na pozitivan terapijski efekat ticagrelora na funkciju trombocita, a efekat ASA je bio odsutan. RCRI skor kod pacijenta je bio 1.

Pacijent je u sklopu preoperativne pripreme pregledan od strane kardiologa, a u dogovoru sa kliničkim transfuziologom napravljena je strategija perioperativnog tretmana krvarenja, i to primenom sistemskih i lokalnih antifibrinolitika, kao i transfuzije trombocita u slučaju aktivnog krvarenja.

Šest sati od prijema, nakon preoperativne pripreme kod pacijenta je učinjena apendektomija, laparoskopskom hirurškom metodom, u uslovima balansirane opšte endotrahealne anestezije (OETA). Korišćen je osnovni respiratorni i hemodinamski monitoring (SpO_2 , $EtCO_2$, EKG, NIBP), i tokom operacije nisu zabeležene epizode hemodinamske nestabilnosti. Neposredno preoperativno ordinirana je traneksamična kiselina (TXK), u dozi od 30mg/kg TT, a kako je tokom operacije bilo minimalnih gubitaka krvi, odustalo se od predloga za primenu lokalnih hemostatika (fibrinskog lepka, TXK) na mestima hirurških incizija.

Laparoskopska operacija je protekla bez komplikacija, pacijent je ekstubiran, hemodinamski stabilan, prevenen u sobu za buđenje, a potom na odeljenje hirurgije.

Nakon urađenih laboratorijskih analiza, multiplate nalaza kao i praćenjem abdominalnih drenova, koji su bili bez sadržaja, u konsultaciji sa kardiologom, 12h nakon operacije kod pacijenta je uvedena ASA u dozi od 100mg jednom dnevno, a nakon 24h i ticagrelol u dozi od 90mg dva puta na dan. Kod pacijenta u postoperativnom toku nije zabeležena epizoda hemodinamske nestabilnosti, kao ni akutnog koronarnog dešavanja. Opušten je iz bolnice drugog postoperativnog dana, nakon započetog per os unosa i uspostavljene pasaže gastrointestinalnog trakta.

Slučaj 2

Muškarac, starosti 67 godina, BMI= $27,8 \text{ kg/m}^2$, primljen je na Kliniku za urgentnu hirurgiju UKCS zbog akutnog holecistitisa. Šest dana pre prijema, pacijent je otpušten sa Klinike za kardiologiju, gde je postavljena indikacija, od strane kardiohirurškog konzilijuma za hiruršku revaskularizaciju miokarda. Tokom hospitalizacije na Klinici za kardiologiju, u sklopu kardiološke procene rađena je selektivna koronarografija, kao i ehokardiografija srca.

In preoperative laboratory analyses, high levels of inflammatory markers were present (WBC $16.0 \times 10^9/L$, CRP 142mg/L, PCT 0.12ng/ml), whereas the platelet count was $301 \times 10^9/L$. The effect of the antiplatelet therapy was evaluated using point-of-care testing to examine platelet aggregation (the Multiplate test). The values of ASPI (947) and ADPHS (201) indicated a positive therapeutic effect of ticagrelor on platelet functions, whereas there was no effect of ASA. The RCRI score in this patient was 1.

As part of the preoperative preparation, the patient was examined by a cardiologist, and in cooperation with a clinical transfusion specialist a perioperative bleeding treatment strategy was developed including systemic and local antifibrinolytics, as well as platelet transfusion in case of acute bleeding.

Six hours upon hospital admission, after preoperative preparation, appendectomy was performed using the laparoscopic surgical technique and balanced general anesthesia (BGA). Basic respiratory and hemodynamic monitoring (SpO_2 , $EtCO_2$, ECG, NIBP) was used and no hemodynamic instability was recorded during the operation. Shortly before surgery, tranexamic acid had been prescribed (TXA), in a dose of 30 mg/kg, and since blood loss during surgery was minimal, the proposal to apply local hemostatics (fibrin sealant, TXA) at the sites of surgical incisions was abandoned.

There were no complications during the laparoscopic surgery, and the patient who was extubated and hemodynamically stable was first transferred to the recovery room and then to the surgery department.

Following lab analyses, multiplate findings and monitoring of abdominal drains (which were empty), and in cooperation with a cardiologist, the patient was prescribed 100 mg of ASA per day 12 hours upon surgery, and 90 mg of ticagrelol twice a day 24h later. No episodes of hemodynamic instability or acute coronary events were recorded during the postoperative course. He was discharged from the hospital on the second postoperative day, after oral intake was introduced and normal peristalsis established.

Case 2

A 67-year-old male, BMI= $27,8 \text{ kg/m}^2$, was admitted to the Clinic for Emergency Surgery of the University Clinical Centre of Serbia for acute cholecystitis. Six days before the admission, the patient had been discharged from the Clinic for Cardiology where the Cardiosurgical council had found indications for surgical myocardial revascularization. During his stay at the Clinic for Cardiology, selective coronary angiography and echocardiography were performed as part of a cardiac evaluation.

Koronarografija je pokazala sledeće: okluziju RCA u proksimalnom delu, Cx stenozu od 90-99%, dok je stenozu u LAD u proksimalnom segmentu iznosila 50%, i medijalnom od 50%-70%. Ehokardiografijom utvrđena je vrednost EF 40% sa znacima dijasolne disfunkcije leve komore (LK), hipo- do akinezija ½ donjeg zida LK, ožiljak bazalne ½ donjeg zida LK. U ličnoj anamnezi pacijent negira alergije. Od komorbiditeta navodi dijabetes melitus, pri čemu je 15 godina na terapiji oralnim antidijabetičima, zatim hipertenziju (HTA) i kardiomiopatiju (CMP), tretiranu ACE inhibitorima, beta blokatorima, diureticima, antianginoznim lekovima (trimetazidin), acetilsalicilnom kiselinom (ASA). Zbog hiperlipoproteinemije (HLP) na redovnoj je terapiji statinima, dok terapiju za hroničnu opstruktivnu bolest pluća (HOBP) neredovno koristi.

S obzirom na učinjene preoperativne preglede i dijagnostiku, najveća pažnja je usmerena na rizik od perioperativne ishemije miokarda, tako da je rađen monitoring kardiospecifičnih enzima za vreme hospitalizacije pacijeta. Preoperativni RCRI skor je iznosio 3.

Klasična holecistektomija je učinjena u uslovima opšte endotrahealne anestezije (OETA), uz osnovni respiratorni i hemodinamski monitoring. Operacija je protekla uredno, uz minimalne gubitke krvi, dok je intraoperativna hipertenzija kupirana infuzijom gliceriltrinitrata. Pacijent je nakon operacije ekstubiran, hemodinamski stabilan, preveden u sobu za buđenje, a potom na odeljenje poluintenzivne nege. Vrednost troponina preoperativno iznosio je 15ng/L, a trend vrednosti troponina praćen je 24h i 48h nakon operacije, i iznosio je 19ng/L, odnosno 11ng/L. Pacijent je u postoperativnom toku bio dobrog opšteg stanja, te je šestog postoperativnog dana otpušten iz bolnice.

DISKUSIJA

Revised Cardiac Risk Index (RCRI) je jednostavan metod za procenu kardiološkog rizika, upotrebom šest parametara: 1) hirurgije visokog rizika, 2) istorije ishemijske bolesti srca, 3) kongestivne srčane slabosti, 4) cerebrovaskularnih bolesti, 5) dijabetesa melitusa – terapije insulinom, 6) bubrežne slabosti ($Cr \geq 2,0\text{mg/dL}$) (Tabela 1). Svaki parametar nosi po jedan poen, a smatra se da zbirna vrednost parametara ≥ 2 , predstavlja povišen rizik od postoperativnog kardiološkog dešavanja [2,3] (Tabela 2). Iako postoje različiti scoring sistemi za procenu kardiovaskularnog rizika, odlučili smo se za RCRI kao najsveobuhvatniji u proceni rizika kardiovaskularnih pacijenata u abdominalnoj hirurgiji.

Niz faktora utiče na povećanje kardiološkog rizika tokom operativnog lečenja pacijenta. Hitnost hirurške intervencije, vrsta hirurške tehnike, medikamentozna terapija, procenjeni funkcionalni kapaciteti pacijenta,

The results of coronary angiography were as follows: RCA occluded proximally, Cx with 90-99% stenosis, 50% stenosis in the proximal LAD, and 50-70% in its mid portion. Echocardiography revealed EF of 40% with signs of left ventricular (LV) diastolic dysfunction, hypokinesia/akinesia of ½ left ventricular inferior wall (LVIW) and scarring in the basal part of LVIW. The patient denies any previous history of allergies. He reports the following comorbidities: diabetes mellitus (he has been on oral antidiabetic therapy for 15 years), hypertension (HTA), and cardiomyopathy (CMP) treated with ACE inhibitors, beta blockers, diuretics, antianginal drugs (trimetazidine), and acetylsalicylic acid (ASA). Due to hyperlipoproteinemia (HLP), he has been on regular statin therapy, whereas he uses his therapy for chronic obstructive pulmonary disease (COPD) irregularly.

Considering the performed preoperative examinations and diagnostics, the greatest attention was focused on the risk of perioperative myocardial ischemia, so monitoring of cardiospecific enzymes was done during the patient's hospitalization. The preoperative RCRI score was 3.

Classical cholecystectomy was performed in general endotracheal anesthesia (GETA), with basic respiratory and hemodynamic monitoring. The surgery was uneventful, with minimal blood loss, and intraoperative hypertension was controlled by intravenous glyceryl trinitrate solution. The patient was extubated after the surgery, he was hemodynamically stable and first transferred to the recovery room and then to the semi-intensive care unit. Pre-operative troponin level was 15ng/L, its trend was followed for 24h and 48h after surgery and it was 19 ng/L and 11 ng/L, respectively. The patient's condition was good during the postoperative course, so he was discharged from the hospital on the sixth day upon surgery.

DISCUSSION

Revised Cardiac Risk Index (RCRI) is a simple method for cardiac risk assessment which relies on six parameters: 1) high-risk surgery, 2) history of ischemic heart disease, 3) congestive heart failure, 4) cerebrovascular diseases, 5) diabetes mellitus – insulin therapy, 6) renal failure ($Cr \geq 2.0\text{mg/dL}$) (Table 1). Each parameter is worth one point, and it is considered that the overall value of all parameters ≥ 2 represents an increased risk of postoperative cardiac events [2,3]. (Table 2). Although there are various scoring systems for cardiovascular risk assessment, we have decided on the RCRI as the most comprehensive system in assessing high-risk cardiovascular patients in abdominal surgery.

A number of factors influence an increase in cardiac risk during the surgical treatment of a patient – the

Tabela 1. Revised Cardiac Risk Index-Lee kriterijumi

Table 1. Revised Cardiac Risk Index-Lee Criteria

Klinička slika / Clinical variable	Poeni / Points
Hirurgija visokog rizika / High-risk surgery	1
Ishemijska bolest srca / Ischemic heart disease	1
Kongestivna srčana slabost / Congestive heart failure	1
Cerebrovaskularna bolest / Cerebrovascular disease	1
Šećerna bolest-terapija insulinom / Diabetes mellitus-insulin treatment	1
Hronična bubrežna slabost, Cr ≥ 2,0 mg/dL / Chronic kidney disease, Cr ≥ 2.0 mg/dL	1

*Cr – creatinine

itd. Prema vrsti hirurške intervencije, kod ne-kardio-hirurških operacija, operacije su podeljene na one sa niskim, srednjim i visokim rizikom od perioperativnog krvarenja. Abdominalne operacije spadaju u grupu operacija srednjeg rizika [2].

Primeru radi, pacijente sa plasiranim PCI karakteriše primena dvojne antiagregacione terapije. Ukoliko je neophodna hirurška intervencija, takav pacijent je pod povišenim rizikom za neželjena koronarna dešavanja u prvih mesec dana od plasiranog PCI [2,4]. Zlatni standard u proceni efekta antiagregacione terapije ogleda se u primeni standardnih laboratorijskih analiza, prateći vremenski profil od poslednje doze leka do vremena operativnog lečenja. Poluživot ASA u plazmi je samo 20min, ali je efekat leka prisutan 7-10 dana nakon poslednje primenjene doze leka. Što se ticagrelola tiče, kao terapije kod jednog od naših pacijenta, vreme poluživota u plazmi iznosi 6-12h, a efekat leka je prisutan 3 do 5 dana od poslednje doze [2]. U stanjima u kojima je aktiviran inflamatorni odgovor organizma, efekat leka na funkcionalnost trombocita može biti narušen. Tada nam u proceni može poslužiti i point-of-care metoda, Multiplate test. Kombinacijom standardnih laboratorijskih testova i point-of-care metoda, može se dobiti dobra procena perioperativnog krvarenja, kao i rezidualni efekat primenjene terapije. U današnje vreme, Multiplate test se rutinski koristi, ali u slučajevima kada nije dostupan, kliničari se najčešće oslanjaju na standardne analize i "terapijski prozor" od poslednje doze leka. U slučajevima neodložne hirurške intervencije, prema proceni stepena perioperativnog krvarenja, vođeni dostupnim podacima o frekvenci upotrebe redovne terapije, rukovodimo se primenom terapije transfuzijom kao i dostupnom lepezom hemostatskih lekova (desmopresin, antifibrinolitički, rekombinantni aktivni faktor VII, koncentrat fibrinogena, protrombinski kompleks koncentrat, aktivirani protrombinski kompleks, itd).

Tabela 2. Tumačenje risk skora

Table 2. Interpretation of risk score

Klasa Rizika / Risk class	Bodovi / Points	Rizik od komplikacija (%) / Complication risk (%)
Veoma nizak / Very low	0	0.4%
Nizak / Low	1	0.9%
Umeren / Moderate	2	7.0%
Visok / High	3+	11.0%

urgency of surgical intervention, the type of surgical technique, drug therapy, the evaluated functional capacities of the patient, etc. When it comes to the category of noncardiac surgery, according to the type of surgical intervention, interventions can be classified as those with low, intermediate, and high risk of perioperative bleeding. Abdominal surgeries belong to the group of intermediate-risk procedures [2].

For example, it is typical that patients who have undergone percutaneous coronary intervention (PCI) with stent placement are prescribed dual antiplatelet therapy. In case of a necessary surgical intervention, such a patient is at an increased risk of adverse coronary events in the first month upon the performed PCI [2,4]. The gold standard in evaluating the effect of antiplatelet therapy is reflected in the application of standard laboratory analyses, and following the time profile from the last taken dose of the drug to the time of the surgical intervention. ASA's plasma half-life is only 20 minutes, but the effect of the medication is present for 7-10 days after the last dose. When it comes to ticagrelol, which is one of our patient's prescribed medications, its plasma half-life is 6-12h, and its effect is present for 3 to 5 days after the last dose [2]. In conditions where the inflammatory response of the organism is activated, the effect of a drug on platelet functions may be impaired. This is when the point-of-care method, Multiplate test, can be of help in the assessment. By combining standard laboratory tests and the point-of-care method, a good assessment of perioperative bleeding can be obtained, as well as the residual effect of the applied therapy. Nowadays, Multiplate test is routinely applied, but in cases where it is not available, clinicians most often rely on standard laboratory analyses and the "therapeutic window" since the last dose of the drug. In cases of urgent surgical interventions, according to the assessment of the degree of perioperative bleeding and guided by the available data on how often regular therapy is used, we are governed by the application of transfusion therapy, as well as the available range of hemostatic drugs (desmopressin, antifibrinolytics, recom-

Oštećenje miokarda tokom nekardiohirurških operacija (MINS) predstavlja perioperativnu ishemiju miokarda, izazvanu neravnotežom između potreba miokarda za kiseonikom i isporuke kiseonika miokradu, tj. tip 2 miokardnog oštećenja [2,5,6].

Stepen oštećenja korelira sa porastom high sensitive (hs) troponina-T u serumu. VISION studijom je pokazano da je porast vrednosti hsT preko 20ng/L, tj. porast od 5ng/L, od preoperativnih vrednosti, praćenih tokom tri dana nakon operacije dobar prediktor 30-dnevnog moratliteta nakon nekardiohirurških operacija [2,7].

Vrsta hirurške tehnike, klasična ili laparoscopska, kao i vrsta anestezije, OETA ili regionalna anestezija, utiču na kardiovaskularni status tokom perioperativnog perioda. Laparoscopska hirurgija, vezana je za česte promene položaja pacijenta na operacionom stolu, a sama tehnika podrazumeva „kreiranje“ pneumoperitoneuma insuflacijom CO₂. Usled tranzitornog jatrogenog abdominalnog kompartment sindroma, prilikom laparoskopije, dolazi do smanjenjena priliva krvi u srce (pre-load), porasta sistemske vaskularne rezistence, centralnog venskog pritiska, što može uticati na smanjenu perfuziju kroz koronarne krvne sudove [8]. Stoga, kod pacijenta koji ima prethodno verifikovanu bolest koronarnih krvnih sudova ovo nije najpopularnija tehnika.

ZAKLJUČAK

Tretman hirurškog pacijenta sa kardiovaskularnim bolestima može biti za kliničara posebno izazovan. Rizik od potencijalnog krvarenja, procena kardiološkog rizika, i strategija primene kardiološke terapije tokom perioperativnog perioda problemi su sa kojima se anesteziolog svakodnevno susreće.

Prava ravnoteža može se postići multidisciplinarnim pristupom hirurga, kardiologa, kliničkog transfuziologa i anesteziologa, a u današnje vreme veliki akcenat stavlja se i na prilagođavanje savremenih smernica individualnim potrebama pacijenta.

Sukob interesa: Nije prijavljen.

binant activated factor VII, fibrinogen concentrate, prothrombin complex concentrate, activated prothrombin complex, etc.).

Myocardial injury during noncardiac surgery (MINS) is perioperative myocardial ischemia caused by an imbalance between myocardial oxygen needs and the delivery of oxygen to the myocardium, i.e., type 2 myocardial damage [2,5,6].

The degree of damage correlates with an increase in high-sensitive (hs) serum troponin-T. The VISION study showed that an increase in the levels of hsT >20ng/L, i.e., a 5ng/L-increase compared to preoperative levels followed for three days upon surgery, was a good predictor of 30-day mortality after noncardiac surgery [2,7].

The type of surgical technique (classical open surgery or laparoscopic surgery), and the type of anesthesia (GETA or regional anesthesia) affect the cardiovascular status during the perioperative period. Laparoscopic surgery is related to frequent changes in the patient's position on the operating table, and the technique itself involves "creating" the pneumoperitoneum by CO₂ insufflation. Due to transient iatrogenic Abdominal Compartment Syndrome, during laparoscopy, there is a decrease of blood flow to the heart (pre-load), an increase in systemic vascular resistance, and central venous pressure, which can affect reduced perfusion through the coronary blood vessels [8]. Therefore, this is not the most popular technique in a patient with previously verified coronary artery disease.

CONCLUSION

Treating a surgical patient who suffers from cardiovascular disease may be highly challenging for a clinician. The risk of potential bleeding, cardiac risk assessment, and the strategy of applying cardiovascular therapy during the postoperative period are some of the problems an anesthesiologist faces on a daily basis.

A real balance may be achieved by a multidisciplinary approach of a surgeon, a cardiologist, a clinical transfusion specialist, and an anesthesiologist, and nowadays a great emphasis is also placed on adapting modern guidelines to individual patient needs.

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LITERATURA / REFERENCES

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet*. 2015 Apr 27;385 Suppl 2:S11. doi: 10.1016/S0140-6736(15)60806-6.
2. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al; ESC Scientific Document Group. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J*. 2022 Oct 14;43(39):3826-924. doi: 10.1093/eurheartj/ehac270.
3. Roshanov PS, Walsh M, Devereaux PJ, MacNeil SD, Lam NN, Hildebrand AM, et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. *BMJ Open*. 2017 Jan 9;7(1):e013510. doi: 10.1136/bmjopen-2016-013510.
4. De Hert S, Staender S, Fritsch G, Hinkelbein J, Afshari A, Bettelli G, et al. Pre-operative evaluation of adults undergoing elective noncardiac surgery: Updated guideline from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2018 Jun;35(6):407-65. doi: 10.1097/EJA.0000000000000817.
5. Ruetzler K, Smilowitz NR, Berger JS, Devereaux PJ, Maron BA, Newby LK, et al. Diagnosis and management of patients with myocardial injury after noncardiac surgery: a scientific statement from the American Heart Association. *Circulation*. 2021 Nov 9;144(19):e287-e305. doi: 10.1161/CIR.0000000000001024.
6. Ellenberger C, Schorer R, Diaper J, Jeleff A, Luise S, Hagermann A, et al. Myocardial injury after major noncardiac surgery: A secondary analysis of a randomized controlled trial. *Surgery*. 2022 Jun;171(6):1626-34. doi: 10.1016/j.surg.2021.10.029.
7. Devereaux PJ, Biccadd BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, et al; Writing Committee for the VISION Study Investigators. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2017 Apr 25;317(16):1642-51. doi: 10.1001/jama.2017.4360.
8. Atkinson TM, Giraud GD, Togioka BM, Jones DB, Cigarroa JE. Cardiovascular and ventilatory consequences of laparoscopic surgery. *Circulation*. 2017 Feb 14;135(7):700-10. doi: 10.1161/CIRCULATIONAHA.116.023262.

VEZANI MUSKULOKUTANI REŽANJ TRAPEZIUSA U REKONSTRUKCIJI DEFEKTA U REGIJI RAMENA NAKON RESEKCIJE MEKOTKIVNOG SARKOMA – PRIKAZ SLUČAJA I PREGLED LITERATURE

PRIKAZ SLUČAJA

CASE REPORT

PEDICLED TRAPEZIUS MUSCULOCUTANEOUS FLAP IN THE RECONSTRUCTION OF A SHOULDER DEFECT AFTER THE RESECTION OF SOFT TISSUE SARCOMA – CASE REPORT AND LITERATURE REVIEW

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SAŽETAK

Uvod: Mekotkivni sarkomi (MTS) na ekstremitetima zahtevaju kompleksno lečenje koje podrazumeva hirurgiju očuvanja ekstremiteta uz adjuvantnu terapiju. Lečenje uključuje resekciju tumora sa širokim granicama uz dodatnu zračnu i/ili hemioterapiju. Pored resekcije tumora, važan segment predstavlja i rekonstrukcija nastalog mekotkivnog defekta. Za obimne rekonstruktivne procedure na gornjim ekstremitetima literatura sugerše upotrebu slobodnih ili vezanih reznjeva. U regiji ramena, zbog složene regionalne anatomije, odabir adekvatnog reznja je hirurški imperativ. U poslednje vreme postoji veliko interesovanje za upotrebu vezanog muskulokutanog reznja *m. trapezius-a*, koji ima određene prednosti u odnosu na ostale reznjeve.

Prikaz slučaja: Pacijentkinja (31 godina) sa MTS-om u predelu levog ramena, tri puta je operativno lečena. Prvi put je učinjena intraleziona procedura – R2 resekcija, kada je ustanovljen pleomorfni dermalni sarkom. Nakon pet meseci, na osnovu nalaza nuklearne magnetne rezonance (NMR) konstatovan je rest-recidiv u predelu operativnog ožiljka. Učinjena je resekcija tumora, a mekotkivni defekt pokriven je slobodnim kožnim transplantatom parcijalne debljine kože po Tiršu. Patohistološki je dijagnostikovao visokogradusni leiomyosarkom. Nakon dva meseca od druge operacije NMR-om je potvrđen recidiv. Sprovedena je široka resekcija tumora, a mekotkivni defekt je pokriven vezanim donjim muskulokutanom reznjem trapezastog mišića.

Zaključak: Literatura oskudeva radovima koji opisuju rezultate primene reznja trapezastog mišića u rekonstrukciji defekata u regiji ramena nakon resekcije MTS-a. Takođe, ne postoji jednoglasni zvanični stav o širini granica resekcije koje se smatraju sigurnim. Ishod lečenja naše pacijentkinje ukazuje na veliki potencijal i prednosti reznja trapezastog mišića u poređenju sa drugim reznjevima iz te regije.

Ključne reči: leiomyosarkom, resekcija tumora, granice resekcije, rekonstruktivna hirurgija

ABSTRACT

Introduction: Soft tissue sarcomas (STS) in the extremities require complex treatment involving limb-sparing surgery with adjuvant therapy. The treatment involves tumor resection with wide margins along with additional radiation and/or chemotherapy. In addition to tumor resection, an important aspect is the reconstruction of the resulting soft tissue defect. For extensive reconstructive procedures in the upper extremities, literature suggests the use of free or pedicled flaps. In the shoulder region, due to its complex regional anatomy, selecting an appropriate flap is the surgical imperative. Recently, there has been significant interest in the use of the pedicled trapezius musculocutaneous flap, which offers certain advantages over other flaps.

Case report: A female patient (31 years old) with STS in the left shoulder region, was surgically treated three times. The first surgery involved an intralesional procedure – R2 resection when a pleomorphic dermal sarcoma was diagnosed. After five months, a recurrence of the disease was detected based on magnetic resonance imaging (MRI) findings at the site of the surgical scar. Tumor resection was performed, and the soft tissue defect was covered with a free Thiersch partial-thickness skin graft. Histopathological analysis revealed a high-grade leiomyosarcoma. Two months after the second surgery, MRI findings confirmed a recurrence of the disease. Wide tumor resection was conducted, and the soft tissue defect was covered with a pedicled lower trapezius musculocutaneous flap.

Conclusion: The literature lacks studies describing the outcomes of the use of trapezius flaps in the reconstruction of defects in the shoulder region following STS resection. Additionally, there is no unanimous official opinion on the resection margin width that is considered safe. The treatment outcome of our patient indicates the significant potential and advantages of the trapezius flap, as compared to other flaps of that region.

Keywords: leiomyosarcoma, tumor resection, resection margins, reconstructive surgery

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UVOD

Mekotkivni sarkomi (MTS) predstavljaju heterogenu grupu tumora i čine oko 1% svih tumora kod odraslih, a čak i do 15% tumora kod dece starosti do četiri godine [1,2]. U Evropi ukupna incidenca za sve lokalizacije iznosi 4 - 5/100.000 na godišnjem nivou [3,4]. Kod odraslih, 60% ovih tumora je lokalizovano na ekstremitetima, od toga 45% na donjim i 15% na gornjim [5]. Kada je tumor na ruci, u oko 50% slučajeva je lokalizovan u regiji ramena, u 30% - 40% u regiji lakta i podlaktice, a kod 10% - 20% slučajeva javlja se na šaci [6,7].

Savremeni standard u lečenju MTS-a podrazumeva hiruriju očuvanja ekstremiteta što se postiže resekcijom tumora sa što širim granicama uz dodatnu adjuvantnu zračnu i/ili hemioterapiju. Ovaj terapijski pristup pokazuje dobre rezultate, s obzirom da se primenom ovakvog protokola u oko 95% slučajeva može izbeći amputacija [8-10].

U nekim slučajevima, pokušaj postizanja dobrih resekcionih margina ostavlja značajne defekte koji zahtevaju obimne rekonstruktivne procedure. Adekvatna rekonstrukcija ovih defekata ima neprocenljiv klinički značaj jer pruža mogućnost da se brzo primeni adjuvantna onkološka terapija i da se na taj način uspostavi bolja lokalna i sistemska kontrola bolesti. Literatura sugeriše da su u ovom smislu najefikasniji oni pristupi koji koriste slobodne i vezane mišićno-kožne režnjeve, posebno kada je reč o gornjem ekstremitetu [8,11].

Najbolji izbor za rekonstrukciju velikih defekata su slobodni mišićno-kožni režnjevi, uzeti sa udaljenog donorskog mesta. Nedostatak ovih režnjeva je što su tehnički komplikovani za uzimanje i presađivanje, zahtevaju više vremena pri intervenciji, kao i mikrohirusko iskustvo, uz rizik od neuspeha [11-13].

Zbog anatomske specifičnosti regije ramena najbolju alternativu predstavlja upotreba vezanih režnjeva sa vaskularnom peteljkom, kako lokalnih, tako i udaljenih. Lokalni režnjevi sa vaskularnom peteljkom su tehnički manje izazovni, ali su ograničeni po veličini i nisu adekvatni za pokrivanje većih defekata. Najbolji izbor za defekte u ovoj regiji predstavlja upotreba udaljenih vaskularnih režnjeva. Njihove glavne prednosti su pouzdanost i univerzalnost, jednostavnija hirurška tehnika u poređenju sa slobodnim režnjevima i mogućnost brže postoperativne rehabilitacije [14].

Kada je reč o defektima u ramenom pojasu, najčešće se koriste mišićno-kožni režnjevi bazirani na najširem leđnom mišiću (lat. *m. latissimus dorsi*) i velikom prsnom mišiću (lat. *m. pectoralis major*, mada u poslednjih nekoliko godina postoji povećano interesovanje za upotrebu vezanog mišićno-kožnog režnja trapeziusa [12]. Literatura je oskudna u radovima koji opisuju

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of tumors and account for about 1% of all tumors in adults, and as many as up to 15% of tumors in children aged four years and younger [1,2]. In Europe, the total incidence for all localizations is 4 - 5/100,000, annually [3,4]. In adults, 60% of these tumors are localized in the extremities, of which 45% in the legs and 15% in the arms [5]. When the tumor is in the arm, in about 50% of the cases it is localized in the shoulder region, in 30% - 40% of the cases it is in the region of the elbow and forearm, and in 10% - 20% of the cases it can be found in the hand [6,7].

The modern standard in STS treatment involves limb-sparing surgery, which is achieved by tumor resection with the widest possible margins, with additional adjuvant radiation and/or chemotherapy. This therapeutic approach shows good results, considering that the application of this protocol can avoid amputation in about 95% of cases [8-10].

In some cases, the attempt to achieve good resection margins leaves significant defects that require extensive reconstructive procedures. Appropriate reconstruction of these defects is of invaluable clinical importance because it provides the possibility of quickly applying adjuvant oncological therapy and thus establishing better local and systemic control of the disease. Literature suggests that, in this sense, the approaches that use free and pedicled musculocutaneous flaps are the most effective, especially when it comes to the arm [8,11].

Free musculocutaneous flaps taken from a distant donor site are the best choice for the reconstruction of large defects. The disadvantage of these flaps is that they are technically complicated to harvest and transplant, they require a longer surgical procedure, as well as microsurgical experience, at the same time carrying a risk of failure [11-13].

Due to the complex anatomy of the shoulder region, the best alternative is the use of vascular pedicled flaps, both local and distant. Local flaps with a vascular pedicle are technically less challenging but are limited in size and are not sufficient to cover larger defects. The best choice for defects in this particular region is the use of distant vascular flaps. Their main advantages are reliability and universality, a simpler surgical technique compared to free flaps, as well as the possibility of faster postoperative recovery [14].

When it comes to defects in the shoulder girdle, musculocutaneous flaps based on the latissimus dorsi muscle and the pectoralis major muscle are most commonly used, although in recent years there has been an increased interest in the use of the pedicled trapezius musculocutaneous flap [12]. There are few studies

rezultate primene ovog režnja u rekonstrukciji defekata u regiji ramena nakon resekcije MTS-a.

U ovom radu će biti prikazan slučaj recidiva MTS-a ramenog pojasa sa primenom široke resekcije i rekonstrukcijom defekta tkiva korišćenjem udaljenog vezanog mišićno-kožnog režnja trapeziusa. Takođe, biće predstavljeni onkološki i funkcionalni rezultati lečenja, uz dodatni pregled literature.

PRIKAZ PACIJENTA

Prikazujemo pacijentkinju staru 31 godinu, koja je u tri navrata operisana zbog MTS-a u predelu levog ramena. Prvi put je učinjena intraleziona procedura – R2 resekcija, gde je patohistološkom analizom utvrđeno da je reč o pleomorfnom dermalnom sarkomu.

Pet meseci posle prve intervencije, nakon kliničkog pregleda, utvrđena je mekotkivna promena u predelu operativnog ožiljka, koja je odgovarala rest-recidivu, što je i potvrđeno na osnovu snimanja nuklearnom magnetnom rezonancom (NMR). Isplanirana je i učinjena resekcija tumora, što je uključivalo kožu, potkožu i deo mišića u predelu levog ramena. Za rekonstrukciju mekotkivnog defekta korišćen je slobodni kožni transplantat parcijalne debljine kože po Tiršu. U narednim nedeljama slobodni transplantat kože je zarastao u potpunosti. Pacijentkinja nije imala subjektivne tegobe u vidu bolova, pokreti u levom ramenu su bili pune amplitude. Patohistološki nalaz pokazao je da se radi

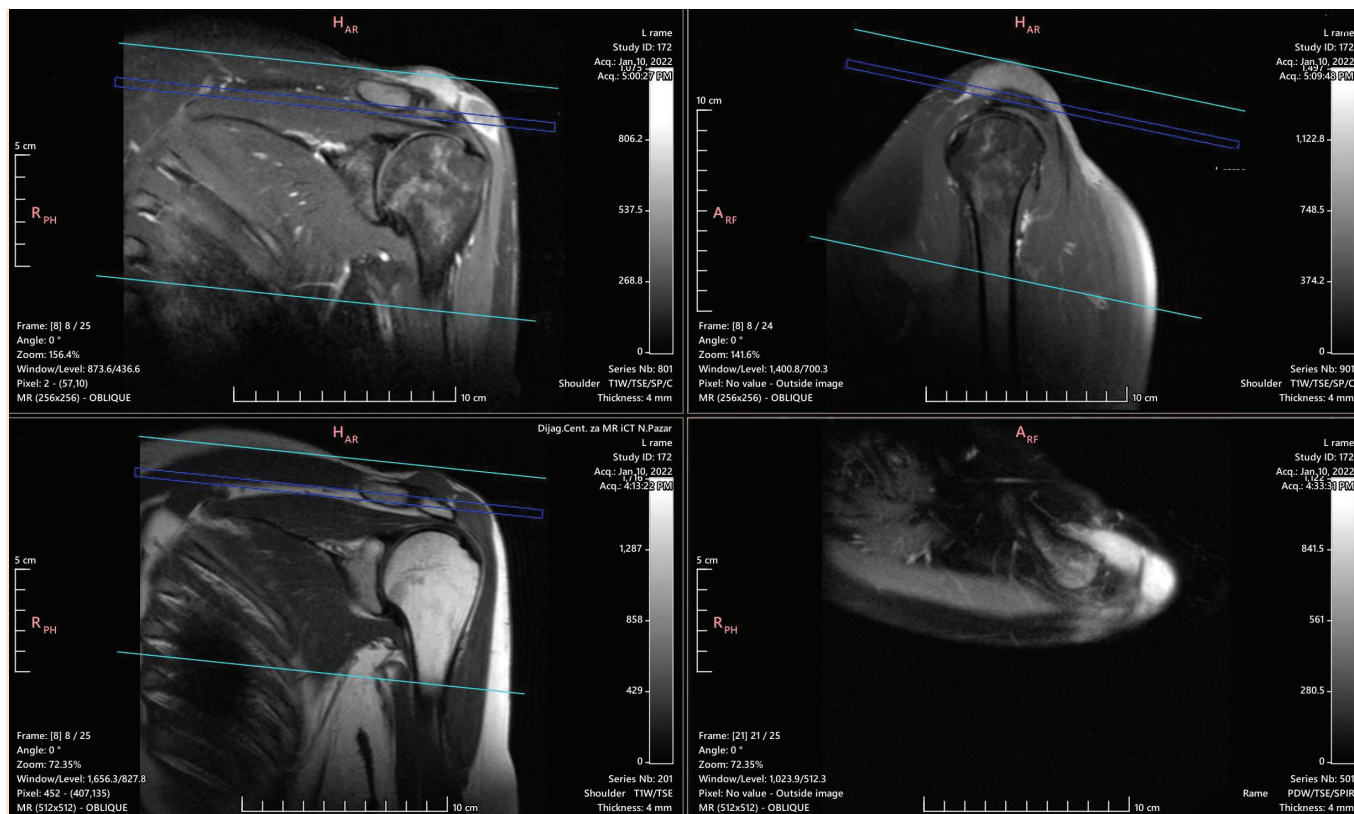
describing the results of the application of this flap in the reconstruction of defects in the shoulder region after STS resection.

This paper will present a case of a recurrence of STS in the shoulder girdle with the application of wide resection and reconstruction of the tissue defect using a distant pedicled trapezius musculocutaneous flap. Also, oncological and functional treatment results will be presented, with an additional review of the available literature.

PATIENT CASE REPORT

We present a 31-year-old female patient who was surgically treated three times for STS in the region of the left shoulder. An intralesional procedure – R2 resection was performed for the first time, wherein pathohistological analysis confirmed a pleomorphic dermal sarcoma.

Five months after the first procedure, upon clinical examination, a soft tissue lesion was found in the area of the surgical scar, corresponding to a "rest" recurrence of the tumor, which was confirmed with nuclear magnetic resonance imaging (NMRI). Resection of the tumor was planned and performed, which included the skin, subcutaneous tissue, and part of the muscle in the left shoulder area. For the reconstruction of the soft tissue defect, a free Thiersch partial-thickness skin graft was used. In the following weeks, the free skin graft healed completely. The patient had no subjec-



Slika 1. Recidiv mekotkivnog tumora - leiomyosarkoma

Figure 1. Recurrence of soft tissue tumor - leiomyosarcoma



Slika 2. (a-b-c-d). a – široka resekcija mekotkivnog sarkoma iz regije ramena; b – vaskularna peteljka dorzalne skapularne arterije za donji mišićno-kožni režanj trapeziusa; c – recipijentna regija ramena sa donjim mišićno-kožnim režnjem trapeziusa; d – donorska regija donjeg mišićno-kožnog režnja trapeziusa

Figure 2. (a-b-c-d). a – wide resection of soft tissue sarcoma in the shoulder region; b – vascular pedicle of the dorsal scapular artery for the lower trapezius musculocutaneous flap; c – recipient site of the shoulder with the lower trapezius musculocutaneous flap; d – donor site of the lower trapezius musculocutaneous flap

o visokogradusnom lejomiosarkomu, sa linijom resekcije udaljenom tri milimetra od tumorske mase. Done-ta je odluka da se kod pacijentkinje sprovede lokalna zračna terapija.

Dva meseca nakon operativnog zahvata, kontrolni snimak nuklearnom magnetnom rezonancom je poka-zao recidiv (Slika 1) i indikovana je nova operacija. Pla-nirana je i sprovedena široka resekcija tumora. Ovom prilikom granice resekcije su bile udaljene od ivica tumora oko 30 mm na koži i 20 mm u dubokim struk-turama, što je uključivalo resekciju kože, potkože, dela deltoidnog mišića i dela lateralne klavikule (Slika 2 a-b). Tako nastali mekotkivni defekt nakon resekcije (Slika 2 c-d) pokriven je vezanim muskulokutanim režnjem tra-peziusa. Kao adjuvantna terapija, sprovedena je hemi-oterapija u vidu tri ciklusa Mono ADM (Adriablastin 75 mg/m²), a nakon toga lokalna zračna terapija.

tive complaints in the form of pain and had full move-ment in the left shoulder. The pathohistological find-ings confirmed high-grade leiomyosarcoma, with the resection line three millimeters away from the tumor mass. A decision was made to perform local radiation therapy on the patient.

Two months after the operation, follow-up NMRI showed a recurrence of the tumor (Figure 1), and a new surgical procedure was indicated. A wide resection of the tumor was planned and performed. On this occa-sion, the resection margins were about 30 mm from the tumor margins on the skin and 20 mm from the tumor margins in the underlying deep structures. The resection included the skin, subcutaneous tissue, part of the deltoid muscle, and part of the lateral clavicle (Figure 2 a-b). The resulting soft tissue defect after re-section (Figure 2 c-d) was covered with a pedicled tra-pezius musculocutaneous flap. Chemotherapy in the

DISKUSIJA I REZULTATI LEČENJA

MTS na gornjem ekstremitetu, posebno u regiji rame-na, predstavljaju veliki izazov u hirurškom lečenju, s obzirom na složenu anatomiju. U ranijoj medicinskoj praksi, ovi pacijenti su, u velikom broju slučajeva, lečeni amputacijom ekstremiteta. Razvoj novih i sofisticiranih dijagnostičkih metoda, napredak hirurške tehnike i formulisanje novih protokola za adjuvantnu terapiju, omogućili su, u većini slučajeva, očuvanje ekstremiteta [15,16].

Lečenje pacijenata sa MTS-om ramena je multidisciplinarno i zahteva formiranje individualnih terapijskih algoritama za svakog pacijenta. Početni deo tog protokola je resekcija tumora sa odgovarajućim širokim granicama. U poslednjih nekoliko decenija postoji tendencija sužavanja resekcionih granica, ali i dalje postoji kontinuirana naučna kontroverza o njihovoj tačnoj širini [17-19].

Aktuelna naučna literatura ne samo da nema konkretne smernice za širinu resekcionih granica, već ni standardnu definiciju negativnih granica kod resekcije MTS-a [19]. Iako većina objavljenih serija slučajeva zaključuje da resekciju MTS-a sa pozitivnim granicama prati neprihvatljivo visok procenat lokalnih recidiva [20-23], nekoliko studija je pokazalo da pozitivna linija resekcije nema uticaja na stopu lokalnog recidiva bolesti [24,25].

King i saradnici su pokazali da je incidencija lokalnog recidiva slična, bez obzira na to da li je širina resekcionih granica bila manja od 1 mm ili veća od 1 mm [26]. Ovakav nalaz je u suprotnosti sa studijom Dickinsona i saradnika, koja je pokazala da su pozitivne ili granice manje od 1 mm potpuno neadekvatne, ali da nema značajne razlike ukoliko su granice u opsegu od 1 do 4 mm, 5 do 9 mm ili 10 do 19 mm [27]. S druge strane, postoji značajan broj studija koje ističu potrebu za širim granicama resekcije od 1 mm [19]. Neki autori navode da minimalno prihvatljiva negativna granica resekcije ne sme biti manja od 2 mm [28,29]. Brojne studije podržavaju stav da negativne resekcione granice treba da budu barem 5 mm, ukoliko plan lečenja ne uključuje adjuvantnu radioterapiju, dok se, ukoliko je planirana ovakva terapija, one mogu suziti na 1 mm [18,30]. S obzirom da postizanje adekvatnih resekcionih granica može biti izuzetno izazovno, mikroskopska udaljenost od tumora od 1 mm smatra se zadovoljavajućom, dok se operativno granice resekcije postavljaju dosta šire, odnosno 20 do 30 mm [31,32].

Mogućnost rekonstrukcije mekih tkiva ostavlja prostora za postizanje „sigurne“ široke resekcije. Da bi se tumor u celosti uklonio nekada je potrebno napraviti relativno velika oštećenja okolnih tkivnih struktura, što može ostaviti funkcionalne i estetske defekte. Iz opisa-

form of three cycles of Mono ADM (Adriablastin 75 mg/m²) was performed as adjuvant therapy, followed by local radiation therapy.

DISCUSSION AND TREATMENT RESULTS

STS in the arm, especially in the shoulder region, represents a great challenge in surgical treatment, given the complex anatomy of this region. In earlier medical practice, these patients were, in a large number of cases, treated by limb amputation. The development of new and sophisticated diagnostic methods, the advancement of surgical techniques, and the formulation of new protocols for adjuvant therapy have enabled, in most cases, the preservation of limbs [15,16].

The treatment of patients with STS of the shoulder is multidisciplinary and requires individual therapeutic algorithms for each patient. The initial part of that protocol is the resection of the tumor with appropriate wide margins. In the last few decades, there has been a tendency to narrow the resection margins, however, scientific controversy about their exact width remains ongoing [17-19].

Current scientific literature not only lacks specific guidelines for the width of resection margins but also lacks a standard definition of negative margins in STS resection [19]. Although most published case series conclude that the resection of STS with positive margins is accompanied by an unacceptably high rate of local recurrence [20-23], several studies have shown that a positive resection margin does not affect the rate of local disease recurrence [24,25].

King et al. demonstrated that the incidence of local recurrence was similar whether the width of the resection margins was less than 1 mm or greater than 1 mm [26]. This finding contrasts with the study by Dickinson et al., which showed that positive margins or margins of less than 1 mm are completely inadequate, but that there is no significant difference if the margins are in the range between 1 mm and 4 mm, 5 mm and 9 mm, or 10 mm and 19 mm [27]. On the other hand, a significant number of studies have stressed the need for resection margins wider than 1 mm [19]. Some authors state that the minimum acceptable negative margin of resection must not be less than 2 mm [28,29]. Numerous studies support the position that negative resection margins should be at least 5 mm wide, if the treatment plan does not include adjuvant radiotherapy, while, if such therapy is planned, they can be decreased to 1 mm [18,30]. Given that achieving appropriate resection margins can be extremely challenging, a microscopic distance from the tumor of 1 mm is considered satisfactory, while operative resection margins are set much wider, i.e., at 20 to 30 mm [31,32].

nog razloga rekonstrukcija mekih tkiva ima ogroman značaj jer omogućava da se postigne šira resekcija tumora, čime se ostvaruju bolja kontrola lokalne bolesti i rezultati lečenja.

Na drugoj operaciji kod prikazane pacijentkinje, urađena je resekcija kojom su dobijene granice od 3 mm. Tom prilikom, mesto resekcije je pokriveno Tiršovim transplantatom, te je došlo do dominantno sekundarnog zarastanja, što je spor proces koji je rezultirao probijanjem vremenskog okvira za zračnu terapiju. U međuvremenu je došlo do pojave recidiva, što je indikovalo primenu radikalne hirurgije, tako da je urađena široka resekcija, usled čega je nastao veliki mekotkivni defekt koji je pokriven vezanim muskulokutanim režnjem trapeziusa. Uprkos primeni radikalne hirurgije, dobijena je granica resekcije od 1 mm, ali je upotreba ovog transplantata omogućila brzo zarastanje, čime je napravljen prostor za blagovremenu primenu hemioterapije, a zatim je ciljano na mestu resekcije sprovedena lokalna zračna terapija.

Veliki tkivni defekti nakon resekcije MTS-a zahtevaju imedijantnu rekonstrukciju kako bi se rana zatvorila i obnovila anatomska funkcija, čime se olakšava rehabilitacija i omogućava blagovremena primena adjuvantnih terapijskih protokola [17]. Kada je u pitanju specifična lokacija MTS-a u regiji ramena, neophodno je da ovi defekti budu zatvoreni otpornim režnjem koji neće ograničavati pokrete u zglobovima [33]. Jedan od najpogodnijih režnjeva za rekonstrukciju srednjih do velikih defekata u regiji ramena jeste udaljeni vezani kožno-mišićni režanj trapeziusa. Kompozitni režanj trapeziusa prvi put je opisao i popularizovao Demergas, 1979. godine [34]. Najvažnije prednosti ovog režnja su pristupačnost, lako uzimanje, dobra vaskularizacija, relativno mala debljina i mogućnost dobijanja željenog oblika i veličine. Njegova glavna mana je varijabilnost vaskularizacije i ne baš jednostavno prepoznavanje glavnih krvnih sudova za snabdevanje. Zbog ovih mana se ovaj režanj svrstava u II klasu i zbog toga retko koristi u kliničkoj praksi [35].

Imajući u vidu da se defekt tkiva nakon resekcije MTS-a kod prikazane pacijentkinje nalazio u zadnjem delu ramena, za rekonstrukciju je odabran donji mišićno-kožni režanj trapeziusa. Jedna od značajnijih prednosti korišćenja režnja trapeziusa je očuvanje najšireg leđnog mišića (lat. *m. latissimus dorsi*), čije premeštanje ostavlja veći defekt u mišićnoj masi sa lošijim estetskim rezultatima i potencijalno značajnim funkcionalnim oštećenjem. S druge strane, trapezasti mišić je manji, ali se može preneti sa značajnim kožnim režnjem što ostavlja manji defekt na donorskom mestu, istovremeno omogućavajući veću slobodu pri pokrivanju mekih tkiva. Nije zanemarljiva ni prednost upotrebe ovog re-

The possibility of soft tissue reconstruction leaves room for achieving a “safe” wide resection. To completely remove the tumor, it is sometimes necessary to cause relatively large damage to the surrounding tissue structures, which can leave functional and aesthetic defects. This is why the reconstruction of soft tissues is of great importance as it enables wider tumor resection, thereby achieving better local disease control and treatment results.

During the second surgical procedure performed on the patient presented in this case report, resection was carried out, which resulted in three-millimeter margins. On that occasion, the resection site was covered with a Tirsch graft, and predominantly secondary intention healing occurred, which is a slow process that caused the time limit for radiation therapy to be broken. In the meantime, a recurrence occurred, which indicated the application of radical surgery, so wide resection was performed, resulting in a large soft tissue defect that was covered by a pedicled trapezius musculocutaneous flap. Despite the application of radical surgery, a resection margin of 1 mm was achieved, and the use of this graft enabled rapid healing, which made room for the timely application of chemotherapy, and then targeted local radiation therapy, at the resection site.

Large tissue defects after STS resection require immediate reconstruction to close the wound and restore anatomical function, thus facilitating rehabilitation and enabling timely application of adjuvant therapeutic protocols [17]. When it comes to the particular location of STS in the shoulder region, these defects must be closed with a durable flap that will not limit movement in the joint [33]. One of the most suitable flaps for the reconstruction of medium to large defects in the shoulder region is the distant pedicled trapezius musculocutaneous flap. The composite trapezius flap was first described and popularized by Demergass in 1979 [34]. The most important advantages of this flap are its accessibility, easy harvesting, good vascularization, relatively small thickness, and the possibility of obtaining the desired shape and size. Its main disadvantage is the variability of vascularization and rather difficult identification of the main blood vessels for blood supply. Due to these disadvantages, this flap is classified as class II and is therefore rarely used in clinical practice [35].

Bearing in mind that the tissue defect after STS resection in the patient presented in this case study was in the back of the shoulder, the lower trapezius musculocutaneous flap was selected for reconstruction. One of the most significant advantages of using the trapezius flap is the preservation of the latissimus dorsi

žnja u očuvanju najšireg leđnog mišića za potencijalne kasnije operacije u slučaju lokalnog recidiva bolesti.

Navedene prednosti upotrebe ovog režnja su se potvrdile i u aktuelnom ishodu lečenja prikazane pacijentkinje. Tokom dve godine nakon opisanog hirurškog lečenja pacijentkinja je redovno kontrolisana snimanjem operisane regije nuklearnom magnetnom rezonancom, te kompjuterskom tomografijom pluća, abdomena i male karlice, pri čemu nisu konstatovani ni lokalni recidiv ni sekundarni depoziti. Na funkcionalnom nivou, pacijentkinja ima punu amplitudu pokreta, nema neuroloških ispada niti bolnih senzacija. Sa estetskog aspekta, ožiljak je na zadovoljavajućem nivou.

Iz svega navedenog se izvodi zaključak da je trapezasti mišić gotovo idealan za pokrivanje defekata na ramenu, jer je sam mišić relativno mali, a sa sobom nosi značajan kožni pokrivač koji je dovoljan za zatvaranje srednjih, pa čak i nekih većih defekata. Uz to se štedi najširi leđni mišić, koji je veći mišić i čija transpozicija ostavlja estetski nedostatak i potencijalno funkcionalno ograničenje, a koji bi se mogao iskoristiti u slučaju recidiva i potrebe za ponovnom resekcijom.

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LITERATURA / REFERENCES

1. Fenzl L, Mehrmann M, Kremp K, Schneider G. Weichteiltumoren: Epidemiologie, Klassifikation und Stadieneinteilung. *Radiol.* 2017;57(11):973-986. doi:10.1007/s00117-017-0320-1.
2. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CDM, Devesa SS. Incidence patterns of soft tissue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978–2001: An analysis of 26,758 cases. *Int J Cancer.* 2006;119(12):2922-2930. doi:10.1002/ijc.22239.
3. Casali PG, Abecassis N, Aro HT, Bauer S, Biagioni R, Bielack S, et al; ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018 Oct 1;29(Suppl 4):iv51-iv67. doi: 10.1093/annonc/mdy096.
4. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirilaque MD, et al; RARECARE Working Group. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer.* 2013 Feb;49(3):684-95. doi: 10.1016/j.ejca.2012.09.011.
5. Lahat G, Lazar A, Lev D. Sarcoma Epidemiology and Etiology: Potential environmental and genetic factors. *Surg Clin North Am.* 2008;88(3):451-481. doi:10.1016/j.suc.2008.03.006.
6. Gustafson P, Arner M. Soft tissue sarcoma of the upper extremity: descriptive data and outcome in a population-based series of 108 adult patients. *J Hand Surg.* 1999;24(4):668-674. doi:10.1053/jhsu.1999.0668.
7. Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, et al. The influence of anatomic location on functional outcome in lower-extremity soft-tissue sarcoma. *Ann Surg Oncol.* 2004 May;11(5):476-82. doi: 10.1245/ASO.2004.07.016.
8. Lucattelli E, Luseti IL, Cipriani F, Innocenti A, De Santis G, Innocenti M. Reconstruction of upper limb soft-tissue defects after sarcoma resection with free flaps: A systematic review. *J Plast Reconstr Aesthet Surg.* 2021;74(4):755-767. doi:10.1016/j.bjps.2020.10.065.

muscle, whose displacement leaves a larger defect in the muscle mass with worse aesthetic results and potentially significant functional damage. On the other hand, the trapezius muscle is smaller but can be transplanted with a significant skin flap leaving a smaller defect at the donor site while allowing greater freedom in soft tissue coverage. The advantage of using this flap in preserving the latissimus dorsi muscle for potential subsequent surgical procedures, in case of local recurrence of the disease, is also not negligible.

The abovementioned advantages of using this particular flap have been confirmed in the current treatment outcome of the patient presented in this case report. During two years after the described surgical treatment, the patient was regularly monitored with NMRI of the surgically treated region, and with CT scans of the lungs, abdomen, and pelvis, wherein neither local recurrence nor secondary deposits were detected. At the functional level, the patient has full range of motion, and no neurological symptoms or painful sensations. From an aesthetic point of view, the scar is satisfactory.

All of the above leads to the conclusion that the trapezius muscle is almost ideal for covering defects in the shoulder, because the muscle itself is relatively small, and it carries with it a significant skin covering that is sufficient to close medium and even some larger defects. In addition, the latissimus dorsi muscle is spared, which is a larger muscle whose transposition results in an aesthetic defect and potential functional limitation, and which could be used in case of recurrence and the need for re-resection.

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9. Smith HG, Thomas JM, Smith MJF, Hayes AJ, Strauss DC. Major amputations for extremity soft-tissue sarcoma. *Ann Surg Oncol.* 2018;25(2):387-393. doi:10.1245/s10434-017-5895-2.
10. Duran-Moreno J, Kontogeorgakos V, Koumariannou A. Soft tissue sarcomas of the upper extremities: Maximizing treatment opportunities and outcomes. *Oncol Lett.* 2019;18(3):2179-2191. doi:10.3892/ol.2019.10575.
11. Krijgh DD, Mureau MAM. Reconstructive options in patients with late complications after surgery and radiotherapy for head and neck cancer: remember the deltopectoral flap. *Ann Plast Surg.* 2013;71(2):181-185. doi:10.1097/SAP.0b013e3182414612.
12. Can A, Orgill DP, Dietmar Ulrich JO, Mureau MAM. The myocutaneous trapezius flap revisited: A treatment algorithm for optimal surgical outcomes based on 43 flap reconstructions. *J Plast Reconstr Aesthet Surg.* 2014;67(12):1669-1679. doi:10.1016/j.bjps.2014.07.044.
13. Naalla R, Murthy V, Chauhan S, Chinta K, Singhal M. Revisiting the trapezius flap as a reconstructive option for cervico-occipital and thoracic spine regions. *Indian J Plast Surg.* 2019;52(03):322-323. doi:10.1055/s-0039-3400677.
14. Benanti E, De Santis G, Leti Acciaro A, Colzani G, Baccarani A, Starnoni M. Soft tissue coverage of the upper limb: A flap reconstruction overview. *Ann Med Surg.* 2020;60:338-343. doi:10.1016/j.amsu.2020.10.069.

15. Brennan MF, Casper ES, Harrison LB, Shiu MH, Gaynor J, Hajdu SI. The role of multimodality therapy in soft-tissue sarcoma: Ann Surg. 1991;214(3):328-338. doi:10.1097/0000658-199109000-00015.
16. Nichter L, Menendez L. Reconstructive considerations for limb salvage surgery. *Orthop Clin North Am*. 1993;24(3):511-521.
17. Koulaxouzidis G, Simunovic F, Bannasch H. Soft tissue sarcomas of the arm — oncosurgical and reconstructive principles within a multimodal, interdisciplinary setting. *Front Surg*. 2016;3. [Internet]. [Pristupljeno: 14. oktobar, 2022.]. Dostupno:
18. Cates MM, Cates JMM. Surgical resection margin classifications for high-grade pleomorphic soft tissue sarcomas of the extremity or trunk: definitions of adequate resection margins and recommendations for sampling margins from primary resection specimens. *Mod Pathol*. 2019;32(10):1421-1433. doi:10.1038/s41379-019-0278-9.
19. Sambri A, Caldari E, Fiore M, Zucchini R, Giannini C, Pirini MG, et al. Margin Assessment in Soft Tissue Sarcomas: Review of the Literature. *Cancers (Basel)*. 2021 Apr 2;13(7):1687. doi: 10.3390/cancers13071687.
20. Bilgeri A, Klein A, Lindner LH, Nachbichler S, Knösel T, Birkenmaier C, et al. The Effect of Resection Margin on Local Recurrence and Survival in High Grade Soft Tissue Sarcoma of the Extremities: How Far Is Far Enough? *Cancers (Basel)*. 2020 Sep 8;12(9):2560. doi: 10.3390/cancers12092560.
21. Kawaguchi N, Ahmed AR, Matsumoto S, Manabe J, Matsushita Y. The concept of curative margin in surgery for bone and soft tissue sarcoma: *Clin Orthop*. 2004;419:165-172. doi:10.1097/00003086-200402000-00027.
22. Vodanovich DA, Spelman T, May D, Slavin J, Choong PFM. Predicting the prognosis of undifferentiated pleomorphic soft tissue sarcoma: a 20-year experience of 266 cases. *ANZ J Surg*. 2019;89(9):1045-1050. doi:10.1111/ans.15348.
23. Chen Y, Hao J, Yang Y, Yang J, Hao X. Tumor rupture predicts early metastasis and poor prognosis in stage III soft tissue sarcomas. *World J Surg*. 2011;35(5):1002-1009. doi:10.1007/s00268-011-0995-9.
24. Kamat NV, Million L, Yao DH, Donaldson SS, Mohler DG, van de Rijn M, et al. The Outcome of Patients With Localized Undifferentiated Pleomorphic Sarcoma of the Lower Extremity Treated at Stanford University. *Am J Clin Oncol*. 2019 Feb;42(2):166-171. doi: 10.1097/COC.0000000000000496.
25. Kim YB, Shin KH, Seong J, Roh JK, Kim GE, Hahn SB, et al. Clinical significance of margin status in postoperative radiotherapy for extremity and truncal soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys*. 2008 Jan 1;70(1):139-44. doi: 10.1016/j.ijrobp.2007.05.067.
26. King DM, Hackbarth DA, Kirkpatrick A. Extremity soft tissue sarcoma resections: How wide do you need to be? *Clin Orthop*. 2012;470(3):692-699. doi:10.1007/s11999-011-2167-5.
27. Dickinson IC, Whitwell DJ, Battistuta D, Thompson B, Strobel N, Duggal A, et al. Surgical margin and its influence on survival in soft tissue sarcoma. *ANZ J Surg*. 2006 Mar;76(3):104-9. doi: 10.1111/j.1445-2197.2006.03615.x.
28. Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS, Sim FH. Do surgical margin and local recurrence influence survival in soft tissue sarcomas? *Clin Orthop*. 2010;468(11):3003-3011. doi:10.1007/s11999-010-1471-9.
29. Willeumier J, Fiocco M, Nout R, Dijkstra S, Aston W, Pollock R, et al. High-grade soft tissue sarcomas of the extremities: surgical margins influence only local recurrence not overall survival. *Int Orthop*. 2015 May;39(5):935-41. doi: 10.1007/s00264-015-2694-x.
30. Cates JMM. Modeling continuous prognostic factors in survival analysis: Implications for tumor staging and assessing chemotherapy effect in osteosarcoma. *Am J Surg Pathol*. 2018;42(4):485-491. doi:10.1097/PAS.0000000000000995.
31. O'Donnell PW, Griffin AM, Eward WC, Sternheim A, Catton CN, Chung PW, et al. The effect of the setting of a positive surgical margin in soft tissue sarcoma. *Cancer*. 2014 Sep 15;120(18):2866-75. doi: 10.1002/cncr.28793.
32. Ramu EM, Houdek MT, Isaac CE, Dickie CI, Ferguson PC, Wunder JS. Management of soft-tissue sarcomas; treatment strategies, staging, and outcomes. *SICOT-J*. 3:20. doi:10.1051/sicotj/2017010.
33. Kim JS, Lee JS, Yoon JO, Park JB. Reconstruction of the shoulder region using a pedicled latissimus dorsi flap after resection of soft tissue due to sarcoma. *J Plast Reconstr Aesthet Surg*. 2009;62(9):1215-1218. doi:10.1016/j.bjps.2007.12.079.
34. Ulrich D, Fuchs P, Pallua N. Preexpanded vertical trapezius musculocutaneous flap for reconstruction of a severe neck contracture after burn injury: *J Burn Care Res*. 2008;29(2):386-389. doi:10.1097/BCR.0b013e31816677d9.
35. Behr B, Wagner JM, Wallner C, Harati K, Lehnhardt M, Daigeler A. Reconstructive options for oncologic posterior trunk defects: a review. *Front Oncol*. 2016 Mar 8;6:51. doi: 10.3389/fonc.2016.00051.

ANAFILAKTIČKI ŠOK IZAZVAN SUBKUTANOM IMUNOTERAPIJOM ALERGENOM *AMBROSIA ELATIOR* – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

ANAPHYLACTIC SHOCK CAUSED BY SUBCUTANEOUS IMMUNOTHERAPY WITH THE ALLERGEN *AMBROSIA ELATIOR* – CASE REPORT

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SAŽETAK

Uvod: Sensibilizacija na polen ambrozije može dovesti do simptoma alergijskog rinitisa, konjuktivitisa i alergijske astme. Alergenska imunoterapija (AIT) je imunomodulatorna terapijska procedura koja pored kratkoročnog kurativnog (smanjenje simptoma bolesti) ima i dugoročni preventivni efekat (sprečavanje progresije alergijskog rinitisa u alergijsku astmu i/ili sprečavanje razvoja teže forme bolesti). Dva glavna modaliteta primene alergenske imunoterapije koja se koriste u kliničkoj praksi su subkutana imunoterapija alergenom (engl. *subcutaneous allergen immunotherapy* – SCIT) i sublingvalna imunoterapija alergenom (engl. *sublingual allergen immunotherapy* – SLIT). Oba modaliteta imaju podjednaku efikasnost u smanjenju simptoma bolesti, ali je primena SCIT-a povezana sa većim rizikom od ispoljavanja lokalnih i sistemskih neželjenih reakcija.

Prikaz slučaja: U ovom radu prikazan je pacijent koji je razvio kliničku sliku anafilaktičkog šoka u toku indukcionog faze SCIT-a ekstraktom polena *Ambrosia-elatior*. Opisan je klinički tok kao i brzo i efikasno terapijsko zbrinjavanje ovog životno ugrožavajućeg stanja.

Zaključak: Kada se primenjuje pravilno doziranje, u medicinskoj ustanovi i pod lekarskim nadzorom, SCIT ambrozijom je veoma bezbedna i dobro tolerisana opcija lečenja alergijskog rinitisa. Lokalne reakcije na mestu subkutane primene javljaju se češće u odnosu na sistemske neželjene reakcije. Anafilaktički šok je najteži oblik sistemske alergijske reakcije koji zahvata više organskih sistema i može se završiti smrtnim ishodom, najčešće zbog opstrukcije disajnih puteva i kardiovaskularnog kolapsa. Neophodna je edukacija medicinskog osoblja kao i pacijenata o pravilnom lečenju ovog teškog stanja. Na osnovu procene faktora rizika kod svakog pacijenta, teške reakcije na SCIT se mogu predvideti i izbeći odgovarajućim merama predostrožnosti, kao i profilaktičkim merama. Očekuje se da buduće inovacije u alergenskoj imunoterapiji dodatno poboljšaju efikasnost i bezbednost ovakvog vida lečenja alergijskih bolesti.

Ključne reči: alergenska imunoterapija, SCIT, anafilaktički šok, ambrozija

ABSTRACT

Introduction: Sensitization to ragweed pollen can lead to symptoms of allergic rhinitis, conjunctivitis, and allergic asthma. Allergen immunotherapy (AIT) is an immunomodulatory therapeutic procedure that, in addition to short-term curative effect (reduction of disease symptoms), also has a long-term preventive effect (preventing the progression of allergic rhinitis into allergic asthma and/or preventing the development of a more severe form of the disease). The two main AIT administration modalities used in clinical practice are subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Both modalities are equally effective in reducing disease symptoms, but the use of SCIT is associated with a higher risk of local and systemic adverse reactions.

Case report: A patient who developed a clinical picture of anaphylactic shock during the induction phase of SCIT with *Ambrosia elatior* pollen extract is presented in this article. The clinical course is described as well as the quick and effective therapeutic management of this life-threatening condition.

Conclusion: When properly dosed, in a medical facility and under medical supervision, SCIT with *Ambrosia elatior* is a very safe and well-tolerated treatment option for allergic rhinitis. Local reactions at the site of subcutaneous administration occur more often than systemic adverse reactions. Anaphylactic shock is the most severe form of a systemic allergic reaction that affects multiple organ systems and can end in death, usually due to airway obstruction and cardiovascular collapse. It is necessary to educate the medical staff as well as the patients regarding the proper treatment of this difficult condition. Based on the assessment of risk factors in each patient, severe reactions to SCIT can be predicted and avoided with appropriate precautions and prophylactic measures. Future innovations in AIT are expected to further improve the efficacy and safety of this form of treatment for allergic diseases.

Keywords: allergen immunotherapy, SCIT, anaphylactic shock, ambrosia

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UVOD

Alergija na polen ambrozije je poslednjih godina postala važan zdravstveni problem. Ambrozija (rod *Ambrosia* iz porodice *Asteraceae*) je biljka koja je izvorno poreklom iz Severne Amerike. U svetu su dve vrste najrasprostranjenije, obična (ili kratka) ambrozija (*A. artemisiifolia* ili *A. elatior*) i velika ambrozija (*A. trifida*), koje su i klinički najrelevantnije zbog visokog potencijala da izazovu simptome alergijskog rinitisa i alergijske astme [1].

Ambrosia elatior je najinvazivnija korovska jednogodišnja biljka, u smislu zahvatanja velikih područja [2]. Danas je široko rasprostranjena na području cele Republike Srbije kao i u okruženju. Polen *Ambrosia*-e *elatior* je dobro poznat po svom velikom potencijalu da izazove reakcije preosetljivosti tipa I u periodu cvetanja, koji vrhunac dostiže u avgustu i septembru, a uočen je sve duži period polinacije [2]. Jedna stabljika ambrozije proizvede do 45 grama polena godišnje, a jedan gram polena sadrži oko 30 miliona polenovih zrna. Dovoljno je od 8 do 10 polenovih zrna ambrozije po kubnom metru da bi se ispoljile alergijske manifestacije. Oko 50% polenskih alergija izazvano je polenom ambrozije. U Evropi postoji prosečna prevalencija senzibilizacije na alergene polena ambrozije od 14%; sa rasponom od najveće vrednosti zabeležene u Mađarskoj od 54% do 3,5% u Italiji. Pretpostavlja se da će klimatske promene i sve veće zagađenje vazduha u narednim godinama povećati alergenski potencijal polena [2].

Senzibilizacija na polen ambrozije može dovesti do tegoba u vidu alergijskog rinitisa, alergijskog konjuktivitisa i alergijske astme. Brojne studije ukazuju na to da velika izloženost polenu ili povećana koncentracija polena u određenom vremenskom periodu rezultira visokom stopom senzibilizacije i pojavom simptoma. U Evropi, najmanje jedan od petoro ljudi pati od respiratorne alergije na ambroziju. Smatra se da će do 2050. godine koncentracija ambrozije biti povećana do četiri puta. Istrajnost u iskorenjivanju ambrozije jedini je način da se smanji veliki broj respiratornih alergija [2].

Prvi korak u lečenju alergijskih respiratornih bolesti podrazumeva primenu konvencionalne terapije (antihistaminici, lokalna i sistemska primena glikokortikoida, stabilizatori mastocita, antagonisti leukotrijenskih receptora). Alergenska imunoterapija (AIT) je jedini modalitet lečenja koji može da menja tok bolesti i modifikuje imunski odgovor preusmeravanjem sa patološkog *T helper 2* (TH2) ka *T helper 1* (TH1). Ovakav vid lečenja primenjuje se unazad više od 100 godina. Dva glavna modaliteta alergenske imunoterapije koja se koriste u kliničkoj praksi su subkutana imunoterapija alergenom (engl. *subcutaneous allergen immunotherapy* – SCIT) i sublingvalna imunoterapija alergenom (engl. *sublingual allergen immunotherapy* – SLIT). Iako

INTRODUCTION

Allergy to ragweed pollen has become a significant health problem in recent years. *Ambrosia* (genus *Ambrosia* of the *Asteraceae* family) is a plant originally from North America. Worldwide, two species are the most widespread, common (or short) ragweed (*A. artemisiifolia* or *A. elatior*) and giant ragweed (*A. trifida*), which are also the most clinically relevant due to their high potential to cause symptoms of allergic rhinitis and allergic asthma [1].

Ambrosia elatior is the most invasive annual weed, in terms of covering large areas [2]. At present, it is widespread throughout the Republic of Serbia as well as in the surrounding region. *Ambrosia elatior* pollen is well known for its high potential to cause type I hypersensitivity reactions during the flowering season, which peaks in August and September, and an increasingly long pollination period has been observed [2]. One stalk of ragweed produces up to 45 grams of pollen per year, and one gram of pollen contains about 30 million pollen grains. Between 8 and 10 ragweed pollen grains per cubic meter is sufficient to provoke allergic manifestations. About 50% of pollen allergies are caused by ragweed pollen. In Europe, there is an average prevalence of sensitization to ragweed pollen allergens of 14%; with a range between the highest value recorded in Hungary of 54% to 3.5% in Italy. It is believed that climate change and increasing air pollution will also increase the allergenic potential of pollen in the coming years [2].

Sensitization to ragweed pollen can lead to complaints in the form of allergic rhinitis, allergic conjunctivitis, and allergic asthma. Numerous studies indicate that high exposure to pollen or an increased concentration of pollen over a period of time results in a high rate of sensitization and the onset of symptoms. In Europe, at least one in five people suffer from a respiratory allergy to ragweed. It is believed that by 2050, the concentration of ragweed will increase up to four times. Persistent eradication of ragweed is the only way to reduce a large number of respiratory allergies [2].

The first step in the treatment of allergic respiratory diseases involves the use of conventional therapy (antihistamines, local and systemic application of glucocorticoids, mast cell stabilizers, leukotriene receptor antagonists). Allergen immunotherapy (AIT) is the only treatment modality that can alter the course of the disease and modify the immune response by redirecting it from pathological *T helper 2* (TH2) to *T helper 1* (TH1). This type of treatment has been in use for more than 100 years. The two main modalities of allergen immunotherapy applied in clinical practice are subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Although

je utvrđeno da su oba pristupa efikasna u smanjenju simptoma bolesti, SCIT je povezan sa povećanim rizikom od nastanka sistemskih neželjenih efekata [3].

Anafilaktički šok je najteži oblik alergijske reakcije koji zahvata više organskih sistema i ukoliko se ne primeni hitna i neodložna medicinska pomoć, može se završiti smrtnim ishodom, najčešće zbog opstrukcije disajnih puteva i kardiovaskularnog kolapsa. Nastaje usled reakcije specifičnog alergena sa IgE antitelima na površini mastocita i bazofila, nakon čega dolazi do njihove aktivacije i oslobađanja medijatora, u prvom redu histamina, i nastanka kožnih, respiratornih, kardiovaskularnih, gastrointestinalnih i neuroloških simptoma. Tri najčešća pokretača anafilakse su hrana, venomi insekata i lekovi. Simptomi se uglavnom javljaju unutar jednog sata od izlaganja specifičnom alergenu [4,5].

PRIKAZ SLUČAJA

Pacijent starosti 40 godina prvi put je pregledan u alergološkoj ambulanti Klinike za alergologiju i imunologiju Univerzitetskog kliničkog centra Srbije (UKCS), juna 2021. godine. Anamnestički podaci ukazivali su na to da godinama unazad pacijent u proleće i kasno leto ima tegobe u vidu kihanja u seriji, nazalne opstrukcije, učestale bistro sekrecije iz nosa, uz prisustvo svraba nosa i grla. Povremeno se javljao i osećaj kratkog daha uz neproduktivni kašalj. U ličnoj anamnezi negirao je postojanje drugih hroničnih oboljenja kao i uzimanje redovne terapije. U detinjstvu je lečen zbog čestih bronhitisa. Poslednjih 5 godina povremeno je imao blaže epizode otežanog disanja koje je uspešno kupirao primenom kratkododelujućeg beta2 agonista (engl. *short-acting beta2 agonist* – SABA). Avgusta 2021. godine imao je epizodu težeg oblika bronhospazma zbog čega je lečen intravenskom primenom kortikosteroida. U sklopu dijagnostike su urađene PRICK kožne probe na panel inhalacionih alergena kojima je dokazana polisenzibilizacija na grinje, kućnu prašinu i sva tri tipa polena (drveće, trava, korov). Kod pacijenta je urađen nespecifični bronhoprovokacioni test sa metaholinom, koji je bio negativan (detektovan pad FEV1 za 6,2 %). Određivan je nivo specifičnih IgE antitela (*radioallergosorbent test* – RAST) na panel inhalacionih alergena: *Ambrosia elatior* – klasa 3, poleni trava – klasa 4, raž – klasa 4; ostali alergeni nisu dali značajniju pozitivnost.

Objektivnim pregledom nije utvrđeno postojanje bronhoopstrukcije. U redovnu terapiju uveden je antihistaminik (levocetirizin), intranazalni kortikosteroid (mometazon furoat), antagonist leukotrijenskih receptora (montelukast), kao i, po potrebi, inhalaciona fiksna kombinacija kortikosteroida i dugodelujućeg beta2 agonista (budesonid/formoterol), imajući u vidu prethodne epizode bronhospazma i mogućnost da

both approaches have been found to be effective in reducing symptoms of disease, SCIT is associated with an increased risk of systemic side effects [3].

Anaphylactic shock is the most severe form of allergic reaction that affects multiple organ systems and if urgent and immediate medical assistance is not provided, it can end in death, most often due to airway obstruction and cardiovascular collapse. It is caused by the reaction of a specific allergen with IgE antibodies on the surface of mast cells and basophils, after which their activation and the release of mediators, primarily histamine, occurs, as well as the appearance of skin, respiratory, cardiovascular, gastrointestinal and neurological symptoms. The three most common triggers of anaphylaxis are food, insect venom, and medication. Symptoms generally appear within one hour of exposure to a specific allergen [4,5].

CASE REPORT

A 40-year-old patient was examined for the first time at the allergology unit of the Clinic of Allergology and Immunology of the University Clinical Center of Serbia (UCCS), in June 2021. The anamnestic data indicated that for a number of years the patient had been experiencing complaints in spring and late summer in the form of continuous sneezing, nasal obstruction, frequent discharge of a clear secretion from the nose, accompanied by an itchy nose and throat. Occasionally, there was also a sensation of shortness of breath with a non-productive cough. In his personal history, he denied the existence of other chronic diseases as well as taking any regular therapy. In childhood, he was treated for frequent bronchitis. For the previous five years, he occasionally had mild episodes of difficulty breathing, which he successfully managed with the use of a short-acting beta2 agonist (SABA). In August 2021, he had an episode of severe bronchospasm, for which he was treated with intravenous corticosteroids. As part of the diagnosis, prick skin tests were performed for a panel of inhalation allergens, which proved polysensitization to dust mites, house dust and all three types of pollen (trees, grass, weeds). A non-specific bronchoprovocation test with methacholine was performed on the patient, which was negative (a 6.2% drop in FEV1 was detected). The level of specific IgE antibodies (radioallergosorbent test - RAST) for a panel of inhalation allergens was determined: *Ambrosia elatior* – class 3, grass pollen – class 4, rye – class 4; other allergens did not show significant positivity.

Objective examination did not establish the presence of broncho-obstruction. An antihistamine (levocetirizine), intranasal corticosteroid (mometasone furoate), leukotriene receptor antagonist (montelukast)

pacijent u određenom periodu sezone polinacije ima indukovanu bronhijalnu hiperreaktivnost.

Novembra 2021. godine započeta je AIT (SCIT) sa ekstraktima polena *A. elatior* i mešavinom polena trava.

Januara 2022. godine pacijent je u ambulanti Klinike za alergologiju i imunologiju UKCS-a primio redovnu indukcionu dozu SCIT-a, koju je dobijao u nedeljnim intervalima (II rastvor – 1.000 proteinskih jedinica (PNU), 0,3 ml SC, sa ekstraktima *A. elatior* i mešavinom polena trava). Nakon 10 minuta od subkutane aplikacije ekstrakata, kod pacijenta se razvija gigantska urtika nadlaktice, na mestu dobijanja ekstrakta *A. elatior*, uz difuzni eritem kože sa hiperemijom konjunktiva, te subjektivnim osećajem otežanog disanja i gutanja. Nije bilo lokalne reakcije na mestu davanja ekstrakta mešavine polena trava (nadalaktica druge ruke). Objektivnim pregledom auskultacijski se konstatuje sviranje (engl. *wheezing*), a inspekcijski se uočava blaži otok uvule kao i pad arterijskog pritiska na 85/60 mmHg.

Na osnovu kompletne kliničke slike, postavlja se dijagnoza teške sistemske reakcije – anafilaktičkog šoka, i odmah se pristupa primeni hitnih terapijskih mera. Prvi terapijski postupak je bilo davanje epinefrina intramuskularno (*m. deltoideus*) u dozi od 0,5 ml u nerazblaženom obliku (koncentracija epinefrina u ampuli je 1:1,000). Nakon ove primarne terapijske mere, intravenski se ordiniraju kortikosteroidi (metilprednizolon u dozi od 2 mg/kg telesne težine), kristaloidni rastvori (0,9% NaCl, 1,000 ml iv u brznoj infuziji), i vrši se intramuskularna primena hloropiramina u dozi od 20 mg, daje se inhibitor protonске pumpe (pantoprazol 40 mg iv), i vrši intravenska primena infuzije aminofilina (500 mg u 250 ml 0,9% NaCl).

Primenjena terapija imala je povoljan efekat uz brzo (unutar nekoliko minuta) povlačenje kliničkog nalaza. Izmereni kontrolni TA iznosio je 115/70 mmHg, auskultacijski je detektovan normalan disajni šum, inspekcijski se pokazalo povlačenje eritema kože, hiperemije konjunktiva i edema uvule.

Naredna 24 časa, pacijent je bio opserviran u hospitalnim uslovima uz nastavak intravenske primene kortikosteroida (metilprednizolon, ukupno još 2 mg po kilogramu telesne težine, podeljeno na tri doze, u roku od 24 sata), rehidraciju izotoničnim fiziološkim rastvorom i *per os* primenu antihistaminika (četvorostruka doza levocetirizina). Odložene sistemske reakcije se nisu javljale, kao ni potreba za naknadnim ordiniranjem epinefrina.

U daljem toku, obustavljena je subkutana primena alergenske imunoterapije. Pacijent nije bio motivisan za prevođenje na SLIT. Nastavljeno je lečenje konvencionalnom terapijom, odnosno antihistaminicima, intranazalnim kortikosteroidima, inhalacionim korti-

and, when necessary, an inhalation of a fixed combination of corticosteroids and a long-acting beta2 agonist (budesonide/formoterol) were introduced into regular therapy, taking into account previous episodes of bronchospasm and the possibility of the patient having induced bronchial hyperreactivity during a certain period of the pollination season.

In November 2021, the patient was started on AIT (SCIT) with *A. elatior* pollen extracts and a grass pollen mixture.

In January 2022, the patient received a regular induction dose of SCIT at weekly intervals, at the outpatient unit of the Clinic of Allergology and Immunology of the UCCS (solution II - 1,000 protein units (PNU), 0.3 ml SC, with extracts of *A. elatior* and a mixture of grass pollen). After 10 minutes of subcutaneous application of the extract, the patient developed giant urticaria on the upper arm, at the site where the *A. elatior* extract was administered, with diffuse erythema of the skin and with hyperemia of the conjunctiva, as well as subjective feeling of difficulty breathing and swallowing. There was no local reaction at the site of grass pollen mixture extract administration (other upper arm). Objective examination revealed the following: wheezing was detected with auscultation, while slight swelling of the uvula was observed on inspection. A drop in arterial pressure (85/60 mmHg) was also detected.

Based on the overall clinical presentation, a diagnosis of severe systemic reaction - anaphylactic shock was established and immediate therapeutic measures were applied. The first therapeutic procedure was the administration of epinephrine intramuscularly (*m. deltoideus*) at a dose of 0.5 ml in undiluted form (the concentration of epinephrine in the vial is 1:1,000). After this primary therapeutic measure, intravenous corticosteroids (methylprednisolone at a dose of 2 mg/kg body weight), crystalloid solutions (0.9% NaCl, 1,000 ml iv in rapid infusion) were administered, intramuscular administration of chloropyramine at a dose of 20 mg was performed, a proton pump inhibitor (pantoprazole 40 mg iv) was given, and an intravenous infusion of aminophylline (500 mg in 250 ml 0.9% NaCl) was administered.

The applied therapy had a beneficial effect with a rapid (within a few minutes) withdrawal of the clinical findings. Repeated measurement of blood pressure detected a BP of 115/70 mmHg, normal breathing sounds were detected by auscultation, while inspection showed that the skin erythema, conjunctival hyperemia, and uvular edema had receded.

During the following 24 hours, the patient was under observation in hospital with a continuation of intravenous corticosteroid therapy (methylprednisol-

kosteroidima u kombinaciji sa dugodelujućim beta2 agonistima (engl. *long-acting beta2 agonist* – LABA), kao i antagonistima leukotrijenskih receptora.

DISKUSIJA

Reakcije preosetljivosti tipa I (rani tip) na polen ambrozije mogu se manifestovati kao simptomi alergijskog rinitisa, rinokonjunktivitisa i alergijske astme.

Alergijski rinitis je najčešća atopijska manifestacija, globalni zdravstveni problem koji pogađa 10% do 40% populacije. Alergijski rinitis klinički karakterišu paroksizmalne epizode kihanja, rinoreje, nazalnog svraba i nazalne opstrukcije. Alergijski rinitis je glavni faktor rizika za razvoj alergijske astme [2].

Alergijska astma je hronična inflamatorna bolest donjih disajnih puteva uzrokovana IgE antitelima, posredovanom senzibilizacijom na inhalacione alergene. Glavna karakteristika bolesti je inflamacija i bronhijalna hiperreaktivnost sa reverzibilnom opstrukcijom disajnih puteva. Klinički se prezentuje ponavljanim epizodama sviranja i stezanja u grudima, suvim kašljem i kratkim dahom.

Dijagnostikovanje alergijskog rinitisa, kao i alergijske astme, koji su izazvani polenom ambrozije, obuhvata detaljnu anamnezu (simptomatologija ima sezonski karakter), *in vivo* (kožni PRICK testovi, nazalni test provokacije alergenom i nespecifični bronhoprovokacioni test), kao i *in vitro* dijagnostiku (određivanje koncentracije specifičnih IgE antitela u serumu) [1].

Standardni protokoli lečenja alergijskog rinitisa i astme podrazumevaju lokalnu i sistemsku primenu glikokortikoida (intranazalna, inhalaciona, *per os* i parenteralna primena), intranazalnu i sistemsku primenu antihistaminika, primenu antagonista leukotrijenskih receptora, antiholinergika, teofilinskih preparata, bioloških lekova i alergenske imunoterapije.

Pacijent prikazan u ovom radu je imao tipične simptome sezonskog alergijskog rinitisa. U sezoni polena ambrozije je imao nekoliko epizoda bronhospazma, koje su zahtevale kratkotrajnu parenteralnu primenu glikokortikoida. Nespecifični bronhoprovokacioni test sa metaholinom, koji je urađen izvan sezone polena, bio je negativan uz uredan spirometrijski nalaz. Imajući u vidu kliničku sliku, zaključeno je da pacijent može imati simptomatsku bronhijalnu hiperreaktivnost (intermitentnu astmu) u sezoni polena korova. Iz tog razloga je, izvan sezone polenacije korova, lečen prema prvom koraku GINA protokola za lečenje astme, kombinovanom inhalacionom terapijom po potrebi (budesonid 160 mcg/formoterol 9 mcg).

Alergenska imunoterapija može se sprovoditi kao SCIT ili SLIT. Oba načina primene su bezbedna,

lone, a total of 2 mg per kilogram of body weight, divided into three doses, within 24 hours), rehydration with isotonic saline, and *per os* administration of antihistamines (quadruple dose of levocetirizine). Delayed systemic reactions did not occur nor did the need for subsequent administration of epinephrine arise.

Subsequently, the subcutaneous application of allergen immunotherapy was discontinued. The patient was not willing to transfer to SLIT. Treatment continued with conventional therapy, i.e. antihistamines, intranasal corticosteroids, inhalation of corticosteroids in combination with long-acting beta2 agonists (LABA), as well as leukotriene receptor antagonists.

DISCUSSION

Type I (immediate reaction) hypersensitivity reactions to ragweed pollen can manifest as symptoms of allergic rhinitis, rhinoconjunctivitis, and allergic asthma.

Allergic rhinitis is the most common atopic manifestation, a global health problem affecting 10% to 40% of the population. Allergic rhinitis is clinically characterized by paroxysmal episodes of sneezing, rhinorrhea, nasal itching, and nasal obstruction. Allergic rhinitis is the main risk factor for the development of allergic asthma [2].

Allergic asthma is a chronic inflammatory disease of the lower respiratory tract caused by IgE antibodies, through mediated sensitization to inhaled allergens. The main characteristic of the disease is inflammation and bronchial hyperreactivity with reversible airway obstruction. Clinically, it presents with repeated episodes of wheezing and tightness in the chest, dry cough, and shortness of breath.

Diagnosing allergic rhinitis and allergic asthma caused by ragweed pollen includes detailed anamnesis (symptomatology is seasonal), *in vivo* (skin prick tests, nasal allergen provocation test, and non-specific bronchoprovocation test), as well as *in vitro* diagnostics (determining the concentration of specific IgE antibodies in the serum) [1].

Standard protocols for the treatment of allergic rhinitis and asthma include local and systemic administration of glucocorticoids (intranasal, inhalation, oral, and parenteral administration), intranasal and systemic administration of antihistamines, administration of leukotriene receptor antagonists, anticholinergics, theophylline preparations, biologic medications, and allergen immunotherapy.

The patient presented in this paper had typical symptoms of seasonal allergic rhinitis. During the ragweed pollen season, he had several episodes of bronchospasm, which required short-term parenteral administration of glucocorticoids. A non-specific bron-

efikasna i mogu dovesti do indukcije tolerancije na senzibilisani alergen, koja se održava više godina nakon prestanka lečenja. I urođeni i adaptivni imunski odgovori koji doprinose alergijskoj inflamaciji su potisnuti AIT-om. Urođeni imunski odgovor je modulisan smanjenjem broja mastocita, bazofila, eozinofila i cirkulišućih urođenih limfoidnih ćelija grupe 2. Indukcija blokirajućih antitela specifičnih za alergene, imunosupresivnih citokina i regulatornih T i B ćelijskih fenotipova, ključni su pro-tolerogeni adaptivnog imunskog odgovora [6]. Inhibicija oslobađanja medijatora iz mastocita i bazofila delimično je zavisna od IL10, koji direktno inhibira IgE zavisnu aktivaciju mastocita i proizvodnju njihovih citokina. Rezultat toga je značajno smanjenje nakupljanja inflamatornih ćelija, kao što su eozinofilni i neutrofilni granulociti, u šoknim tkivima (sluznica nosa i bronhija) [7].

SCIT dovodi do smanjenja proizvodnje imunoglobulina E (IgE) specifičnog za alergen i povećanja proizvodnje imunoglobulina G (IgG) specifičnog za alergen (IgG4). Indukovana IgG antitela se takmiče sa IgE antitelima za epitope na antigenima, čime ispoljavaju efekat blokiranja. Nakon izlaganja alergenu, antigen prezentujuće ćelije su u stanju da usmere imunski odgovor ka TH1, a time i prema imunotoleranciji, i verovatno su ključne za efekat SCIT-a [7]. Kao nosači aeroalergena kod SCIT-a služe aluminijum ili tirozin, i na taj način se odlaže oslobađanje alergena [7]. U okviru SCIT-a se mogu se primenjivati nemodifikovani ekstrakti sa nativnim alergenima kao i hemijski modifikovani ekstrakti alergena (alergoidi) [8].

Tokom sprovođenja SCIT-a postoje dve faze, indukcija i održavanje. U toku faze indukcije postepeno povećanje doze alergena, odnosno njegove koncentracije, vrši se na nedeljnom nivou, a nakon postizanja doze održavanja terapija se daje u intervalima od 4 do 6 nedelja tokom 3 do 5 godina [7]. Doza održavanja je ona doza kojom se klinički postiže tolerogeni efekat [3].

Naš pacijent je sistemsku neželjenu reakciju razvio u fazi indukcije, nakon dobijanja II rastvora (1.000 proteinskih jedinica - PNU) u dozi od 0,3 ml.

Uvođenje alergenske imunoterapije u lečenju alergijske astme generalno se vrši sa većim oprezom i ne može se koristiti kao zamena za konvencionalnu antiastmatičnu terapiju. AIT se preporučuje kod astme koja je dobro kontrolisana, kao dodatna (engl. *add on*) terapija farmakološkoj. Kod takvih pacijenata ovakav vid terapije može značajno da smanji bronhijalnu hiperreaktivnost, simptome bronhijalne opstrukcije kao i potrebu za korišćenjem drugih terapijskih opcija, pre svega kortikosteroida [8].

SCIT, kao terapijska opcija lečenja alergijskog rinitisa ima i preventivni uticaj na razvoj alergijske astme.

choprovocation test with methacholine, which was performed outside the pollen season, was negative with normal spirometry findings. Bearing in mind the clinical presentation of the patient, the conclusion was that the patient may have symptomatic bronchial hyperreactivity (intermittent asthma) in the weed pollen season. This is why, outside the weed pollination season, he was treated according to the first step of the GINA protocol for the treatment of asthma, with combined inhalation therapy as needed (budesonide 160 mcg/formoterol 9 mcg).

Allergen immunotherapy can be administered as SCIT or SLIT. Both methods of administration are safe, effective and can induce tolerance to the sensitized allergen, which is then maintained for many years after treatment is discontinued. Both innate and adaptive immune responses contributing to allergic inflammation are suppressed by AIT. The innate immune response is modulated by reducing the number of mast cells, basophils, eosinophils, and circulating group 2 innate lymphoid cells. Induction of allergen-specific blocking antibodies, immunosuppressive cytokines and regulatory T and B cell phenotypes are key pro-tolerogens of the adaptive immune response [6]. Inhibition of mediator release from mast cells and basophils is partially dependent on IL10, which directly inhibits IgE-dependent activation of mast cells and their cytokine production. The result is a significant reduction in the accumulation of inflammatory cells, such as eosinophilic and neutrophilic granulocytes, in the nasal mucosa and bronchial tissue [7].

SCIT leads to a decrease in the production of allergen-specific immunoglobulin E (IgE) and an increase in the production of allergen-specific immunoglobulin G (IgG4). Induced IgG antibodies compete with IgE antibodies for epitopes on antigens, thereby exerting a blocking effect. After allergen exposure, antigen-presenting cells can direct the immune response towards TH1, and thus towards immunotolerance, and are probably key in achieving the effect of SCIT [7]. Aluminium or tyrosine are used as carriers of aeroallergens in SCIT, and in this way the release of allergens is delayed [7]. Within SCIT, unmodified extracts with native allergens as well as chemically modified allergen extracts (allergoids) can be applied [8].

During the implementation of SCIT there are two phases, induction and maintenance. During the induction phase, the allergen dose, i.e. its concentration, is gradually increased on a weekly basis, and after reaching the maintenance dose, the therapy is given at intervals of 4 to 6 weeks for a period of 3 to 5 years [7]. The maintenance dose is the dose that clinically achieves a tolerogenic effect [3].

Dodatna prednost primene SCIT-a u odnosu na drugu konvencionalnu terapiju odnosi se i na mogućnost modifikacije toka bolesti kao i na prevenciju razvoja astme i novih senzibilizacija [9].

Primer prave indikacije za alergensku imunoterapiju sa ekstraktima ambrozije bio bi pacijent sa alergijskim rinitisom (AR) izazvanim senzibilizacijom na ambroziju, poželjno bi bilo monosenzibilisan, čiji simptomi nisu dobro kontrolisani uobičajenom farmakoterapijom [8]. Većina pacijenata sa AR-om je polisenzibilisana, ali postoje dokazi da je primena alergenske imunoterapije i kod ovih pacijenata efikasna, i da polisenzibilizacija nije kontraindikacija za AIT. Dokazi iz randomizovanih kliničkih studija sugerišu da je efekat terapije veći kod pacijenata kod kojih su simptomi izraženi [8].

Naš pacijent je bio polisenzibilisan (poleni trava i korova) i kod njega je uvedena SCIT istovremeno sa alergenima *Ambrosia-e elatior* i mešavinom polena trava.

Faktore rizika treba pratiti kod svih pacijenata pre započinjanja SCIT-a (razmotriti prekid terapije beta blokatorima, sprovoditi redovne spirometrijske kontrole astme, izbegavati injekcije imunoterapije kod pacijenata sa aktuelnom kliničkom slikom respiratorne infekcije ili teškim pogoršanjem alergijskog rinitisa ili astme, izbegavati neadekvatno doziranje, lošu tehniku primene, izbegavati naporno vežbanje ili konzumiranje alkohola) [10].

Nijedan od navedenih faktora rizika nije bio zabeležen kod našeg pacijenta.

Uzimajući u obzir faktore rizika od nastanka neželjenih reakcija, teške reakcije na SCIT se mogu predviđeti i izbeći odgovarajućim merama predostrožnosti, kao i profilaktičkim merama. Moguća je premedikacija antihistaminicima kako bi se smanjila učestalost i težina potencijalnih sistemskih reakcija, ali ova mera ne eliminiše mogućnost javljanja sistemskih reakcija [8].

Kada se primenjuje na pravilan način, uz pravilno doziranje, u medicinskoj ustanovi i pod lekarskim nadzorom, SCIT je veoma bezbedna i dobro tolerisana opcija lečenja. U slučaju SCIT-a sa alergenima ekstraktima koji sadrže adjuvanse na bazi aluminijuma, određeni neželjeni efekti, kao što su kontaktni dermatitis, reakcije tipa vaskulitisa ili granuloma, mogu se javiti usled reakcije na strano telo, iako je to veoma retko. Lokalne reakcije na mestu injekcije uključuju otok, svrab i crvenilo. Ove reakcije se pojavljuju relativno često, uglavnom prolaze spontano ili primenom H1-antihistaminika ili topikalnih kortikosteroida. U slučaju pojave intenzivnijih lokalnih reakcija (crvenilo i/ili otok preko 1 cm u prečniku) na mestu injekcije, neophodno je pažljivo isplanirati dalji nastavak alergenske imunoterapije (prekidanje terapije, korekcija doze i intervala davanja terapije) [8].

Our patient developed a systemic adverse reaction during the induction phase, after receiving solution II (1,000 protein units - PNU) at a dose of 0.3 ml.

The introduction of allergen immunotherapy in the treatment of allergic asthma is generally done with greater caution and cannot be used as a substitute for conventional antiasthmatic therapy. AIT is recommended in well-controlled asthma as an add-on to pharmacological therapy. In such patients, this type of therapy can significantly reduce bronchial hyper-reactivity, symptoms of bronchial obstruction, as well as the need to use other therapeutic options, primarily corticosteroids [8].

SCIT, as a therapeutic option for the treatment of allergic rhinitis, also has a preventive effect on the development of allergic asthma. An additional advantage of using SCIT, as compared to other conventional therapy, is in connection with the possibility of modifying the course of the disease as well as preventing the development of asthma and new sensitizations [9].

An example of a true indication for allergen immunotherapy with ragweed extracts would be a patient with allergic rhinitis (AR) caused by sensitization to ragweed, preferably monosensitized, whose symptoms are not well controlled by conventional pharmacotherapy [8]. Most patients with AR are polysensitized, but there is evidence that allergen immunotherapy is also effective in these patients and that polysensitization is not a contraindication to AIT. Evidence from randomized clinical trials suggests that the effect of therapy is greater in patients with more severe symptoms [8].

Our patient was polysensitized (grass and weed pollen) and SCIT was introduced simultaneously with *Ambrosia elatior* allergens and a grass pollen mixture.

Risk factors should be monitored in all patients before starting SCIT (discontinuation of beta-blocker therapy should be considered, regular spirometry follow-ups of asthma should be performed, immunotherapy injections in patients with ongoing clinical presentation of respiratory infection or severe exacerbation of allergic rhinitis or asthma should be avoided, as well as inadequate dosing, poor application technique, strenuous exercise, and alcohol consumption) [10].

None of the abovementioned risk factors were noted in our patient.

Bearing in mind the risk factors for the occurrence of adverse reactions, severe reactions to SCIT can be predicted and avoided by using appropriate precautions and prophylactic measures. Premedication with antihistamines is possible to reduce the frequency and severity of potential systemic reactions, but this measure does not eliminate the possibility of systemic reactions [8].

Do pojave teške sistemske reakcije naš pacijent nije imao ispoljene značajnije lokalne reakcije (papula i/ili eritem > 3 mm) na mestima subkutanog aplikovanja oba alergena.

Rizik od teških alergijskih reakcija izazvanih SCIT-om je nizak, a i blage sistemske reakcije (urtikarija, laringealni ili bronhijalni spazam) poslednjih godina pokazuju tendenciju opadanja, zahvaljujući dobrom monitoringu tokom sprovođenja terapije. Međutim, kod malog broja pacijenata može doći do skoro fatalnih i fatalnih anafilaktičkih reakcija. Kliničari koji primenjuju alergensku imunoterapiju treba da prođu specijalizovanu obuku i da budu svesni faktora rizika i preventivnih mera kako bi izbegli teške alergijske reakcije izazvane SCIT-om [11]. Prepoznavanje pacijenata sa većim rizikom od sistemske reakcije (SR) predstavlja suštinski deo donošenja odluke da se započne SCIT. U tabeli 1 i 2 prikazane su apsolutne i relativne kontraindikacije za alergensku imunoterapiju [12]. Nekontrolisana astma je glavni faktor rizika za razvoj sistemske reakcije [13]. Nakon započinjanja alergenske imunoterapije važno je kontinuirano procenjivati rizik u odnosu na korist kod pacijenata koji se leče i oprezno povećavati dozu do postizanja doze održavanja [11]. Neželjene alergijske reakcije na SCIT se klasifikuju kao lokalne, sistemske i fatalne, rane ili kasne reakcije. Lokalne reakcije se javljaju kod 26% – 86% pacijenata koji primaju SCIT [3]. Sistemske reakcije mogu biti u rasponu težine od blagog rinitisa do fatalnog kardiopulmonalnog zastoja [14]. Stopa sistemskih reakcija različite težine je relativno niska i iznosi 0,1% – 0,2%. Većina odloženih sistemskih reakcija, koje se javljaju nakon 30 minuta, blage su do umerene po stepenu ozbiljnosti [3]. Obavezna je opservacija svih pacijenata u trajanju od najmanje 30 minuta nakon aplikacije alergenskog ekstrakta.

When administered correctly, at a proper dosage, in a medical facility, and under medical supervision, SCIT is a very safe and well-tolerated treatment option. In the case of SCIT with allergenic extracts containing aluminum-based adjuvants, certain side effects, such as contact dermatitis, vasculitis-type or granuloma-type reactions, may occur due to reaction to a foreign body, although this is very rare. Local reactions at the injection site include swelling, itching and redness. These reactions appear relatively often, they usually resolve spontaneously or with the use of H1-antihistamines or topical corticosteroids. In the event of more intense local reactions (redness and/or swelling over 1 cm in diameter) at the injection site, it is necessary to carefully plan further continuation of allergen immunotherapy (discontinuation of therapy, correction of the dose and interval of therapy administration) [8].

Before the development of a severe systemic reaction, our patient had no significant local reactions (papules and/or erythema > 3 mm) at the sites of subcutaneous application of both allergens.

The risk of severe allergic reactions caused by SCIT is low, and even mild systemic reactions (urticaria, laryngeal or bronchial spasm) have shown a decreasing tendency in recent years, thanks to good monitoring during therapy. However, near-fatal and fatal anaphylactic reactions may occur in a small number of patients. Clinicians administering allergen immunotherapy should receive specialized training and be aware of risk factors and preventive measures to avoid severe allergic reactions caused by SCIT [11]. Identifying patients at higher risk of systemic reaction (SR) is an essential part of making the decision to initiate SCIT. Tables 1 and 2 show absolute and relative contraindications for allergen immunotherapy [12]. Uncontrolled asthma is a major risk factor for the development of a systemic reaction [13]. After starting aller-

Tabela 1. Apsolutne kontraindikacije za alergensku imunoterapiju

Table 1. Absolute contraindications for allergen immunotherapy

**APSOLUTNE KONTRAINDIKACIJE ZA ALERGENSKU IMUNOTERAPIJU /
ABSOLUTE CONTRAINDICATIONS FOR ALLERGEN IMMUNOTHERAPY**

Nekontrolisana astma / *Uncontrolled asthma*

Aktivna autoimunska bolest / *Active autoimmune disease*

Aktivna maligna bolest / *Active malignancy*

Deca ispod 2 godine / *Children below two years of age*

Započinjanje tokom trudnoće / *Introduction of treatment in pregnancy*

SIDA / *AIDS*

Tabela 2. Relativne kontraindikacije za alergen specifičnu imunoterapiju

Table 2. Relative contraindications for allergen-specific immunotherapy

**RELATIVNE KONTRAINDIKACIJE ZA ALERGEN SPECIFIČNU IMUNOTERAPIJU /
RELATIVE CONTRAINDICATIONS FOR ALLERGEN-SPECIFIC IMMUNOTHERAPY**

Autoimunska bolest u remisiji / *Autoimmune disease in remission*

Terapija beta blokatorima i ACE inhibitorima /
Treatment with beta blockers and ACE inhibitors

Kardiovaskularne bolesti / *Cardiovascular disease*

Imunodeficijencije / *Immunodeficiency*

Psihijatrijske bolesti / *Psychiatric illnesses*

Trudnoća (nije kontraindikacija za nastavak terapije održavanja) /
Pregnancy (not a contraindication for continuing maintenance therapy)

U prikazanom slučaju, pacijent je tešku sistemsku reakciju razvio nakon 10 minuta od dobijanja SCIT-a.

Kod pacijenata koji su razvili sistemsku reakciju je potrebno smanjiti dozu SCIT-a, odnosno nastaviti terapiju prethodnom dozom koja je dobro tolerisana. Kod pacijenata sa jednom teškom sistemskom reakcijom ili tri i više blažih sistemskih reakcija, potrebno je razmotriti potpuni prekid imunoterapije [11]. Prilagođavanje doze tokom sezone polena za visoko osetljive pacijente može smanjiti rizike od sistemskih reakcija [15].

Incidencija anafilakse je 21 na 100.000 ljudi godišnje, sa smrtnim ishodom u oko 0,65% slučajeva [4]. PRICK kožni testovi na alergene i *in vitro* testovi za određivanje serumskog specifičnog imunoglobulina E ne predviđaju pouzdano rizik od razvoja anafilakse [5]. Unutar dva sata od početka sistemske anafilakse od koristi može biti određivanje nivoa triptaze u serumu, što potvrđuje dijagnozu, a odraz je degranulacije mastocita [16].

Prvi farmakološki tretman anafilaktičkog šoka podrazumeva intramuskularnu primenu epinefrina. Sekundarne mere uključuju nadoknadu tečnosti, davanje H1 i H2 antagonista, primenu bronhodilatatora i kortikosteroidnih preparata [4].

Epinefrin je vazokonstriktor, smanjuje oslobađanje medijatora i edem sluzokože (preko α_1 -adrenergičkog receptora); ublažava bronhokonstrikciju (α_1 - i β_2 -adrenergički receptor), i ispoljava pozitivno inotropno i hronotropno dejstvo (β_1 -adrenergički receptor). Epinefrin bi trebalo primeniti intramuskularno u sredinu anterolateralne butine (lat. *vastus lateralis*), što dovodi do bolje apsorpcije od intramuskularne (IM) ili subkutane (engl. *subcutaneous* – SC) injekcije u deltoidni mišić. Ne postoje apsolutne kontraindikacije za primenu epinefrina [17].

Podaci ukazuju na to da se H1-antihistaminici češće koriste za lečenje pacijenata sa anafilaksom. Iako je histamin ključan u nastanku anafilakse, lečenje H1-antihistaminicima ne ublažava niti sprečava sve patofiziološke mehanizme anafilakse, uključujući i ozbiljnije komplikacije kao što su opstrukcija disajnih puteva, hipotenzija i šok. Pored toga, H1-antihistaminici ne deluju tako brzo kao epinefrin. Maksimalne koncentracije u plazmi se postižu u periodu između jednog i tri sata za H1-antihistaminike, u poređenju sa manje od 10 minuta za intramuskularnu primenu epinefrina. Ovo ukazuje na potrebu za dodatnom edukacijom lekara u zbrinjavanju anafilakse, kao i pacijenata u vezi sa odgovarajućim merama samopomoći kod anafilakse [18].

Prema podacima iz literature, dvofazna anafilaksa se javlja kod oko 20% odraslih sa simptomima koji se ponavljaju u roku od 1 h – 72 h (obično 8 h – 10 h) nakon što je početna reakcija nestala. Ne postoje jasni prediktori razvoja druge faze anafilakse [17]. Pošto se po život opasne manifestacije mogu ponoviti tokom druge faze, neophodno je posmatranje pacijenata u

gen immunotherapy, it is important to continuously assess the risk versus benefit in patients being treated, and cautiously increase the dose until the maintenance dose is reached [11]. Adverse allergic reactions to SCIT are classified as local, systemic, and fatal, early or late reactions. Local reactions occur in 26% - 86% of patients receiving SCIT [3]. Systemic reactions can range in severity from mild rhinitis to fatal cardiopulmonary arrest [14]. The rate of systemic reactions of varying severity is relatively low and amounts to 0.1% - 0.2%. Most delayed systemic reactions occurring after 30 minutes are mild to moderate in severity [3]. All patients must be observed for at least 30 minutes after the application of the allergenic extract.

In the case presented in this article, the patient developed a severe systemic reaction 10 minutes upon receiving SCIT.

In patients who have developed a systemic reaction, it is necessary to reduce the dose of SCIT, i.e., continue therapy with the previous dose that was well tolerated. In patients with one severe systemic reaction or three or more milder systemic reactions, complete discontinuation of immunotherapy should be considered [11]. Dose adjustment during the pollen season for highly sensitive patients may reduce the risks of systemic reactions [15].

The incidence of anaphylaxis is 21 per 100,000 people per year, with a fatal outcome in about 0.65% of cases [4]. Prick skin tests for allergens and *in vitro* tests for verifying serum specific IgE do not reliably predict the risk of developing anaphylaxis [5]. Within two hours of the onset of systemic anaphylaxis, determining serum tryptase levels can be useful, thus confirming the diagnosis and reflecting mast cell degranulation [16].

The first-line pharmacological treatment for anaphylactic shock involves the intramuscular administration of epinephrine. Secondary measures include fluid replacement, administration of H1 and H2 antagonists, use of bronchodilators and corticosteroid preparations [4].

Epinephrine is a vasoconstrictor, it reduces the release of mediators and mucosal edema (via the α_1 -adrenergic receptor); relieves bronchoconstriction (α_1 - and β_2 -adrenergic receptor), and exhibits a positive inotropic and chronotropic effect (β_1 -adrenergic receptor). Epinephrine should be administered intramuscularly in the middle of the anterolateral thigh (Lat. *vastus lateralis*), which leads to better absorption than intramuscular (IM) or subcutaneous (SC) injection into the deltoid muscle. There are no absolute contraindications for the use of epinephrine [17].

Data indicate that H1-antihistamines are more commonly used to treat patients with anaphylaxis. Although histamine is key in the development of anaphylaxis, treatment with H1-antihistamines does not

bolničkim uslovima 24 sata nakon očiglednog oporavka od anafilaktičke epizode [4]. Svi pacijenti sa rizikom od ponovne anafilakse treba da budu edukovani o odgovarajućoj upotrebi autoinjektora epinefrina [5].

Prikazani pacijent je ubrzo nakon dobijanja epinefrina (1:1.000) 0,5 ml intramuskularno, razvio dobar terapijski odgovor sa porastom arterijske tenzije i bronhodilatacijom. Uz ostale terapijske mere (intravenski glikokortikoidi, antihistaminici, infuzioni rastvori), koje su primenjivane tokom naredna 24 sata, došlo je do potpunog oporavka, bez razvoja odložene anafilakse.

Kod prikazanog pacijenta dalje lečenje alergijskog rinitisa i intermitentne alergijske astme nastavljeno je konvencionalnom terapijom, imajući u vidu da nije bio motivisan za prelazak na SLIT. Takođe, obustavljena je i SCIT sa mešavinom polena trava.

Alergenska imunoterapija je bezbedan vid lečenja alergijskog rinitisa sa malom incidencijom sistemskih reakcija. Individualni pristup, adekvatni odabir pacijenta, rana identifikacija faktora rizika, primena odgovarajućeg alergenskog ekstrakta i protokola minimiziraju sistemske reakcije. SLIT ima bolji bezbedonosni profil od SCIT-a i ova formulacija odobrena je za samoprime-nu u Evropi i Severnoj Americi [3].

AIT trenutno prolazi kroz velika poboljšanja i inovacije, u smislu povećanja imunogenosti uz manju alergogenost, posebno sa novim adjuvansima, rekombinantnim ili modifikovanim alergenima, sintetičkim peptidima i novim putevima primene (epidermalni ili intralimfatički). Ovakav napredak je osnov veće efikasnosti i bezbednosti alergenske imunoterapije u budućnosti, sa većom zastupljenošću ovog modaliteta lečenja u svakodnevnoj kliničkoj praksi [8].

SPISAK SKRAĆENICA

AIT – alergenska imunoterapija

SCIT – subkutana imunoterapija (engl. *subcutaneous immunotherapy*)

SLIT – sublingvalna imunoterapija (engl. *sublingual immunotherapy*)

TH2 – T helper 2 limfociti

TH1 – T helper 1 limfociti

SABA – kratkododelujući beta2 agonist (engl. *short acting beta2 agonist*)

RAST – engl. *radioallergosorbent test*

LABA – dugodelujući beta2 agonist (engl. *long acting beta2 agonist*)

IPP – inhibitori protonске pumpe

AR – alergijski rinitis

IM – intramuskularni

SC – subkutani (engl. *subcutaneous*)

LR – lokalne reakcije

SR – sistemske reakcije

PNU – engl. *protein nitrogen units*

Sukob interesa: Nije prijavljen.

alleviate or prevent all pathophysiological mechanisms of anaphylaxis, including more serious complications such as airway obstruction, hypotension, and shock. In addition, H1-antihistamines do not act as quickly as epinephrine. Peak plasma concentrations are reached between one and three hours for H1-antihistamines, as compared to less than 10 minutes for intramuscular epinephrine. This indicates the need for additional training of physicians in the management of anaphylaxis, as well as the education of patients regarding appropriate self-help measures for anaphylaxis [18].

According to literature data, biphasic anaphylaxis occurs in about 20% of adults with symptoms that recur within 1 h – 72 h (usually 8 h – 10 h) after the initial reaction has disappeared. There are no clear predictors of the development of the second phase of anaphylaxis [17]. Since life-threatening manifestations may recur during the second phase, it is necessary to keep patients under observation in hospital for a period of 24 hours after apparent recovery from an anaphylactic episode [4]. All patients at risk of recurrent anaphylaxis should be educated on the appropriate use of epinephrine autoinjectors [5].

The patient presented in this article developed a good therapeutic response shortly after receiving 0.5 ml of epinephrine (1:1,000) intramuscularly, demonstrating an increase in arterial blood pressure and bronchodilation. With other therapeutic measures (intravenous glucocorticoids, antihistamines, infusion solutions), which were applied during the following 24 hours, there was a complete recovery, without the development of delayed anaphylaxis.

In the patient presented in this article, further treatment of allergic rhinitis and intermittent allergic asthma continued with conventional therapy as he was not willing to switch to SLIT. Also, SCIT with grass pollen mixture was discontinued.

Allergen immunotherapy is a safe form of treatment and North America [3].

AIT is currently undergoing major improvements and innovations, in terms of increased immunogenicity with less allergenicity, especially with new adjuvants, recombinant or modified allergens, synthetic peptides and new routes of administration (epidermal or intralymphatic). This progress is the basis for greater efficiency and safety of allergen immunotherapy in the future, with a greater prevalence of this treatment modality in daily clinical practice [8].

LIST OF ABBREVIATIONS AND ACRONYMS

AIT – allergen immunotherapy

SCIT – subcutaneous immunotherapy

SLIT – sublingual immunotherapy

LITERATURA / REFERENCES

- Ihler F, Canis M. Ragweed-induced allergic rhinoconjunctivitis: current and emerging treatment options. *J Asthma Allergy*. 2015 Feb 16;8:15-24. doi: 10.2147/JAA.S47789.
- Florinescu-Gheorghe NA, Popescu F, Alexandru DO, Popescu FD. The prevalence of allergic rhinitis to Ambrosia elatior in Oltenia area and the association with allergic conjunctivitis or asthma. *Curr Health Sci J*. 2019 Jan-Mar;45(1):66-72. doi: 10.12865/CHSJ.45.01.09.
- James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. *Curr Opin Allergy Clin Immunol*. 2017 Feb;17(1):55-9. doi: 10.1097/ACI.0000000000000335.
- Janwitayanujit S. Anaphylaxis. *J Med Assoc Thai*. 2007 Jan;90(1):195-200.
- Arnold JJ, Williams PM. Anaphylaxis: recognition and management. *Am Fam Physician*. 2011 Nov 15;84(10):1111-8.
- Drazdauskaitė G, Layhadi JA, Shamji MH. Mechanisms of allergen immunotherapy in allergic rhinitis. *Curr Allergy Asthma Rep*. 2020 Dec 12;21(1):2. doi: 10.1007/s11882-020-00977-7.
- Klimek L, Brehler R, Hamelmann E, Kopp M, Ring J, Treudler R, et al. Evolution of subcutaneous allergen immunotherapy (part 1): from first developments to mechanism-driven therapy concepts. *Allergo J Int*. 2019 Apr 15;28(3):78-95. doi: 10.1007/s40629-019-0092-4.
- Turkalj M, Banic I, Anzic SA. A review of clinical efficacy, safety, new developments and adherence to allergen-specific immunotherapy in patients with allergic rhinitis caused by allergy to ragweed pollen (*Ambrosia artemisiifolia*). *Patient Prefer Adherence*. 2017 Feb 14;11:247-57. doi: 10.2147/PPA.S70411.
- Klimek L, Brehler R, Hamelmann E, Kopp M, Ring J, Treudler R, et al. Development of subcutaneous allergen immunotherapy (part 2): preventive aspects and innovations. *Allergo J Int*. 2019 May 13;28(4):107-19. doi: 10.1007/s40629-019-0097-z.
- Aue A, Ho J, Zhu R, Kim H, Jeimy S. Systemic reactions to subcutaneous allergen immunotherapy: real-world cause and effect modelling. *Allergy Asthma Clin Immunol*. 2021 Jul 6;17(1):65. doi: 10.1186/s13223-021-00566-x.
- Sánchez-Borges M, Bernstein DI, Calabria C. Subcutaneous immunotherapy safety: incidence per surveys and risk factors. *Immunol Allergy Clin North Am*. 2020 Feb;40(1):25-39. doi: 10.1016/j.iac.2019.09.001.
- TH2 – T helper 2 lymphocytes
- TH1 – T helper 1 lymphocytes
- SABA – short acting beta2 agonist
- RAST – radioallergosorbent test
- LABA – long acting beta2 agonist
- PPI – proton pump inhibitors
- AR – allergic rhinitis
- IM – intramuscular
- SC – subcutaneous
- LR – local reactions
- SR – systemic reactions
- PNU – protein nitrogen units
- Conflict of interest: None declared.
- THE ANNUAL
- Pitsios C, Demoly P, Bilò MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015 Aug;70(8):897-909. doi: 10.1111/all.12638.
- Passalacqua G, Nowak-Węgrzyn A, Canonica GW. Local Side Effects of Sublingual and Oral Immunotherapy. *J Allergy Clin Immunol Pract*. 2017 Jan-Feb;5(1):13-21. doi: 10.1016/j.jaip.2016.06.020.
- Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. *J Allergy Clin Immunol*. 2010 Mar;125(3):569-74. doi: 10.1016/j.jaci.2009.10.060.
- Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). *Ann Allergy Asthma Immunol*. 2016 Apr;116(4):354-9.e2. doi: 10.1016/j.anai.2016.02.001.
- Pflipsen MC, Vega Colon KM. Anaphylaxis: Recognition and Management. *Am Fam Physician*. 2020 Sep 15;102(6):355-62.
- Rutkowski K, Dua S, Nasser S. Anaphylaxis: current state of knowledge for the modern physician. *Postgrad Med J*. 2012 Aug;88(1042):458-64. doi: 10.1136/postgradmedj-2011-130634.
- Fineman SM. Optimal treatment of anaphylaxis: antihistamines versus epinephrine. *Postgrad Med*. 2014 Jul;126(4):73-81. doi: 10.3810/pgm.2014.07.2785.

BOOK REVIEW: SELECTED CHAPTERS FROM PULMONOLOGY

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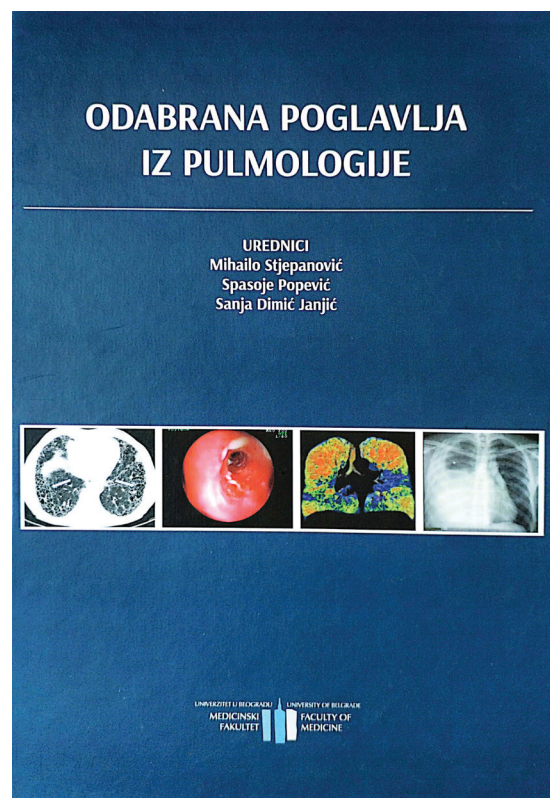
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Chief Editor: Sekulić S. Pulmonary Diseases. Medical Faculty in Belgrade, 2000.

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Prikazujem udžbenik „Odabrana poglavlja iz pulmologije” glavnih urednika Mihaila Stjepanovića, Spasoja Popevića i Sanje Dimić Janjić, koji je veće za specijalističku nastavu Medicinskog fakulteta u Beogradu namenilo postdiplomskom usavršavanju lekara na sednici održanoj 30.5.2022. godine. Izdavač je Medicinski fakultet Univerziteta u Beogradu, Centar za Izdavačku, Bibliotečku i Informatičku Delatnost Medicinskog fakulteta u Beogradu (CIBID). Svi recenzenti knjige su redovni profesori sa Medicinskih fakulteta u Srbiji: prof. dr Zorica Lazić, Medicinski fakultet u Kragujevcu, prof. dr Tatjana Pejčić, Medicinski fakultet u Nišu, prof. dr Arsen Ristić, Medicinski fakultet u Beogradu, i prof. dr Violeta Mihailović-Vučinić, Medicinski fakultet u Beogradu.

Knjigu odlikuje jedinstveni pristup problematiki dijagnostike i lečenja plućnih bolesti koji su predstavljeni kroz 39 tematske jedinice tj. poglavlja. Po

I present the textbook "Selected Chapters from Pulmonology" edited by Mihailo Stjepanović, Spasoje Popević, and Sanja Dimić Janjić, which was designated for specialist education at the Medical Faculty in Belgrade for the postgraduate training of physicians at a session held on May 30, 2022. The publisher is the Medical Faculty of the University of Belgrade, Center for Publishing, Library, and Information Activities of the Medical Faculty in Belgrade (CIBID). All reviewers of the book are regular professors from medical faculties in Serbia: Prof. Dr. Zorica Lazić, Medical Faculty in Kragujevac, Prof. Dr. Tatjana Pejčić, Medical Faculty in Niš, Prof. Dr. Arsen Ristić, Medical Faculty in Belgrade, and Prof. Dr. Violeta Mihailović-Vučinić, Medical Faculty in Belgrade.

The book is characterized by a unique approach to the diagnosis and treatment of pulmonary diseases, which are presented through 39 thematic units or

naslovima i redosledu poglavlja su: Rana dijagnostika neuromišićnih oboljenja na osnovu testova plućne funkcije, Značaj ergospirometrije u pulmologiji, Biomarkeri u dijagnostici pleuralnih izliva, Savremena dijagnostika i terapijski pristup netuberkuloznim mikobakterijskim infekcijama pluća, Značaj određivanja aktivirajućih mutacija u lečenju nesitnoćelijskog karcinoma pluća, Radiološka dijagnostika idiopatske plućne fibroze, Bronhoskopija u dijagnostici i lečenju endobronhijalne tuberkuloze, Savremena bronhoskopska dijagnostika sarkoidoze, Bronhoskopija u dijagnostici tumora pluća, Postintubacione stenoze traheje-dijagnostika i bronhoskopski tretman, Hemoptizije, Hronična opstruktivna bolest pluća- dijagnostički značaj novih saznanja, Komorbiditeti i hronična opstruktivna bolest pluća: prevalencija, uticaj na ishode bolesti i lečenje, Šećerna bolest kao jedan od komorbiditeta u hroničnoj opstruktivnoj bolesti pluća, Metabolički sindrom kod bolesnika sa hroničnom opstruktivnom bolesti pluća i povezanost sa sistemskom inflamacijom, Hronična opstruktivna bolest pluća (HOBP) u pandemiji COVID-19-šta smo naučili, Plućna hipertenzija u hroničnoj opstruktivnoj bolesti pluća, Hirurški aspekti lečenja hronične opstruktivne bolesti, Tuberkuloza-aktuelne teme, Imunopatogeneza sarkoidoze, Dijagnostika i lečenje neurosarkoidoze, Novine u lečenju sarkoidoze, Novi oralni antikoagulansi u prevenciji i lečenju plućne tromboembolije, Akutni edem pluća, Terapija plućne arterijske hipertenzije, Torakohirurške manifestacije limfangioleiomiomatoze, Inovativna terapija u lečenju cistične fibroze, Inovativni terapijski pristupi u lečenju NSCLC-a-imunoterapija, Kliničke manifestacije timoma, Maligni mezoteliom pleure, Farmakoterapija idiopatske plućne fibroze, Mehanička ventilacija, Savremeno lečenje opstruktivne sleep apneje, Da li post-COVID zaista postoji?, Fizička aktivnost nakon COVID-19 infekcije, Respiratorna rehabilitacija kod restriktivnih bolesti, Elektrokardiografske zamke u hroničnoj opstruktivnoj bolesti pluća, Kardiovaskularna razmatranja u vezi sa bronhoskopijom, "End of life care" – od jedinice intenzivnog lečenja do karcinoma pluća. Data poglavlja su rezultat rada i multidisciplinarnog pristupa 67 autora (doktora medicine); među njima su uvaženi univerzitetski profesori, docent i asistenti sa Medicinskog fakulteta u Beogradu. Pored najveće zastupljenosti pulmologa, uglavnom članova Katedre za pulmologiju Medicinskog fakulteta i doktora Klinike za pulmologiju Univerzitetskog kliničkog centra Srbije, tu su i doktori drugih specijalnosti koji su od posebnog interesa u dijagnostici i lečenju plućnih oboljenja kao što su: radiolozi, grudni hirurzi, kardiolozi, patolozi, fizijatri, mikrobiolozi, anesteziolog i imunolog [1].

chapters. The chapter titles and order are as follows: Early diagnosis of neuromuscular diseases based on pulmonary function tests, The importance of ergospirometry in pulmonology, Biomarkers in the diagnosis of pleural effusions, Contemporary diagnosis and therapeutic approach to non-tuberculous mycobacterial lung infections, The importance of determining activating mutations in the treatment of non-small cell lung carcinoma, Radiological diagnosis of idiopathic pulmonary fibrosis, Bronchoscopy in the diagnosis and treatment of endobronchial tuberculosis, Contemporary bronchoscopic diagnosis of sarcoidosis, Bronchoscopy in the diagnosis of lung tumors, Post-intubation tracheal stenosis-diagnosis and bronchoscopic treatment, Hemoptysis, Chronic obstructive pulmonary disease-diagnostic significance of new findings, Comorbidities and chronic obstructive pulmonary disease: prevalence, impact on disease outcomes, and treatment, Diabetes mellitus as one of the comorbidities in chronic obstructive pulmonary disease, Metabolic syndrome in patients with chronic obstructive pulmonary disease and its association with systemic inflammation, Chronic obstructive pulmonary disease (COPD) in the COVID-19 pandemic-what have we learned, Pulmonary hypertension in chronic obstructive pulmonary disease, Surgical aspects of treating chronic obstructive pulmonary disease, Tuberculosis-current topics, Immunopathogenesis of sarcoidosis, Diagnosis and treatment of neurosarcoidosis, Innovations in the treatment of sarcoidosis, New oral anticoagulants in the prevention and treatment of pulmonary thromboembolism, Acute pulmonary edema, Therapy of pulmonary arterial hypertension, Thoracic surgical manifestations of lymphangioleiomyomatosis, Innovative therapy in the treatment of cystic fibrosis, Innovative therapeutic approaches in the treatment of NSCLC-immunotherapy, Clinical manifestations of thymoma, Malignant pleural mesothelioma, Pharmacotherapy of idiopathic pulmonary fibrosis, Mechanical ventilation, Contemporary treatment of obstructive sleep apnea, Does post-COVID exist? Physical activity after COVID-19 infection, Respiratory Rehabilitation in Restrictive Lung Diseases, Electrocardiographic Pitfalls in Chronic Obstructive Pulmonary Disease, Cardiovascular Considerations Related to Bronchoscopy, "End of Life Care" – from Intensive Care Units to Lung Cancer. These chapters are the result of the work and multidisciplinary approach of 67 authors (medical doctors); among them are respected university professors, assistant professors, and assistants from the Medical Faculty in Belgrade. In addition to the predominant representation of pulmonologists, mostly members of the Department of Pulmonology at the Medical Faculty and doctors from the Clinic for

U srpskoj literaturi preko dve decenije nije bilo udžbenika iz oblasti pulmologije, što ovo izdanje čini dragocenim i dugo iščekivanim. Poslednji štampani udžbenik „Plućne bolesti“, glavnog urednika Srboljuba Sekulića je objavljen 2000. godine, i odobren kao udžbenik za postdiplomsko usavršavanje lekara sa preko 50 autora različitih specijalnosti [2]. Kako se razvoj pulmologije dešava jako brzo, kao i ostalih grana medicine, u domaćoj literaturi je bila velika potreba za ovakvim udžbenikom. Knjiga opisuje kroz poglavlja najnovija saznanja o etiologiji, dijagnostičkim procedurama, terapijskim saznanjima i najnovijim svetskim priznatim preporukama o lečenju plućnih bolesti. Glavni urednici su ovaj prvi udžbenik i nazvali odabrana poglavlja iz pulmologije, nepretenciozno, ostavljajući prostora za nova, dopunjena izdanja shodno promenama i razvoju pulmologije. Posebno je značajno da su autori u nekim poglavljima koristili originalne slike, sheme i tabele, što daje jedan poseban i jasan prikaz problematike plućnih bolesti (npr. u poglavlju Bronhoskopija u dijagnostici i lečenju endobronhijalne tuberkuloze, Savremena bronhoskopska dijagnostika sarkoidoze, Bronhoskopija u dijagnostici tumora pluća, Postintubacione stenoze traheje – dijagnostika i bronhoskopski tretman, Hirurški aspekti lečenja hronične opstruktivne bolesti pluća...).

I pored toga što je u pisanju knjige učestvovao veliki broj autora, knjiga je ukomponovana u jednu celinu s obzirom da su nosioci poglavlja eminentni stručnjaci iz oblasti kojima se bave. Knjiga je napisana jasnim jezikom, razumljiva, kako za subspecijaliste tako i za doktore medicine, studente, i sve one koje žele da prošire svoje znanje iz plućnih bolesti. Pre svega je namenjena kao udžbenik za postdiplomsko usavršavanje doktora specijalista interne medicine, subspecijalista pulmologa, doktoranata iz oblasti pulmologije, ali i svim lekarima koji rade i leče obolele od plućnih bolesti.

Čitanjem i detaljnim upoznavanjem sa udžbenikom „Odabrana poglavlja iz pulmologije“ može se reći da se radi o delu koji značajno doprinosi kako pulmologiji u Srbiji, tako i domaćoj medicinskoj literature uopšte.

Mihailo Stjepanović

Pulmonology of the University Clinical Center of Serbia, there are also doctors from other specialties who are of particular interest in the diagnosis and treatment of pulmonary diseases, such as radiologists, thoracic surgeons, cardiologists, pathologists, physiatrists, microbiologists, anesthesiologists, and immunologists [1].

For over two decades, there hasn't been a textbook on pulmonology in Serbian literature, making this edition valuable and long-awaited. The last printed textbook "Pulmonary Diseases," edited by Srboljub Sekulić, was published in 2000 and approved as a textbook for postgraduate training of physicians with over 50 authors from various specialties [2]. As the field of pulmonology, like other branches of medicine, is developing rapidly, there has been a great need in domestic literature for such a textbook. The book describes, through chapters, the latest knowledge on the etiology, diagnostic procedures, therapeutic insights, and the latest internationally recognized recommendations on the treatment of pulmonary diseases. The editors have modestly named this first textbook "Selected Chapters from Pulmonology," leaving room for new, updated editions in line with changes and developments in pulmonology. It is particularly noteworthy that in some chapters, the authors have used original images, diagrams, and tables, providing a unique and clear overview of the issues related to pulmonary diseases (for example, in the chapter on Bronchoscopy in the Diagnosis and Treatment of Endobronchial Tuberculosis, Contemporary Bronchoscopic Diagnosis of Sarcoidosis, Bronchoscopy in the Diagnosis of Lung Tumors, Post-intubation Tracheal Stenosis – Diagnosis and Bronchoscopic Treatment, Surgical Aspects of Treating Chronic Obstructive Pulmonary Disease...).

Despite the involvement of a large number of authors in writing the book, it is integrated into a cohesive whole as the chapter leaders are eminent experts in their respective fields. The book is written in clear language, and understandable for subspecialists as well as medical doctors, students, and anyone wishing to expand their knowledge of pulmonary diseases. It is primarily intended as a textbook for postgraduate training of specialist doctors in internal medicine, subspecialist pulmonologists, and doctoral students in the field of pulmonology, but also for all doctors who diagnose and treat patients with pulmonary diseases.

By reading and thoroughly familiarizing oneself with the textbook "Selected Chapters from Pulmonology," it can be said that it significantly contributes to pulmonology in Serbia as well as to domestic medical literature in general.

Mihailo Stjepanović

ZAHVALNICA RECENZENTIMA

Urednici Srpskog medicinskog časopisa Lekarske komore izražavaju iskrenu zahvalnost za izuzetnu pomoć u proceni naučne vrednosti rukopisa sledećim recenzentima angažovanim u 2023. godini:

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The paper should be submitted as a Microsoft Word document (.docx, .doc), using the Times New Roman font, size 12 pt. All four margins should be set to 25 mm and the page size to A4. The line spacing should be 1.5, with left alignment and 10 mm indentation of each paragraph. There should be no end-of-line hyphenation. The alignment tools should be used for aligning the text, not tabs or multiple spaces. Only the page-break should be used for a new page in the document. A single space should follow each punctuation mark. If special characters (symbols) are used in the text, use the font from the Symbol package. Use only generic names for drugs. Devices (equipment) should be identified using factory names, and the name and location of the manufacturer should be indicated in parentheses. If the text uses labels that are a combination of letters and numbers, it is necessary to appropriately write the number that appears in superscript or subscript (e.g. ⁹⁹Tc, IL-6, O₂, B12, CD8, etc.). If something is typically written in italic, it should be written so (e.g. gene names). International System of Units (SI) units should be used, with the exception of temperature (°C) and blood pressure (mmHg). If the paper is part of a master's thesis or doctoral dissertation, or was created within a scientific project, this should be specifically indicated in the Notes section, at the end of the text.

Graphics attachments should be created using standard graphics software for MS Windows, preferably from the MS Office suite (MS Excel, MS Word Graph). Use of colors should be avoided, especially gradients and shading.

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The sections of the paper are: the cover page, the abstract and keywords, the text of the paper, acknowledgements (optional), literature, and attachments.

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ABSTRACT should be up to 250 words, including acronyms (third page). For original papers, preliminary and short communications, meta-analyses and review papers, the abstract should have the following structure: Introduction, Aim, Methods, Results, Conclusion. Each of these segments should be written as a separate paragraph. For case report, the summary should have the following sections: Introduction, Case Report, Conclusion; each part should be written as a separate paragraph. For other types of papers, the abstract does not have a special structure. List three to six key words or phrases below the abstract. Words from the

ba da se ponavljaju reči iz naslova, a ključne reči treba da budu relevantne i opisne. U izboru ključnih reči koristiti *Medical Subject Headings* – MeSH (<http://www.nlm.nih.gov/mesh>). Sažetak treba da bude napisan na srpskom i engleskom jeziku.

Na četvrtoj **strani** treba da se nalazi prevod teksta koji je na trećoj strani (sažetak). Ova strana mora da ima identičnu strukturu trećoj strani.

Od pete strane broji se broj strana predviđen za odgovarajuću strukturu rada.

STRUKTURA RADA. Svi podnaslovi se pišu velikim masnim slovima (**bold**). Originalni rad, meta-analiza, prethodno i kratko saopštenje obavezno treba da imaju sledeće podnaslove: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Metode rada, Rezultati, Diskusija (koncizna, jasna, predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi), Zaključak (mora proisteci isključivo iz rezultata istraživanja rada, Spisak skraćenica (ukoliko su korišćene u tekstu), Zahvalnica, Literatura (navodi se arapskim brojevima redosledom kojim je u tekstu navedena u uglastim zagradama, vidi dalje). Struktura rada kod pregleda literature sastoji se od Uvoda, Većeg broja podnaslova, Zaključka, Literature. Autori preglednog rada treba da navedu bar tri rada (kao autori ili koautori) publikovanih u časopisima s recenzijom. Struktura rada kod prikaza jednog ili više slučajeva čine: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Prikaz bolesnika, Diskusija, Literatura. Ne treba koristiti imena bolesnika, inicijale, niti brojeve istorija bolesti, naročito u ilustracijama. Prikazi slučajeva ne smeju imati više od pet autora.

STATISTIČKE METODE, PRIKAZ I INTERPRETACIJA REZULTATA

Ukoliko je moguće, sve numeričke vrednosti zaokružiti na jedno decimalno mesto. Ne duplirati prikaz rezultata u tabelama i grafikonima. Za prikaz rezultata u tabelama i tekstu preporuka je da se: numerički podaci sa normalnom raspodelom i bez ekstremnih vrednosti prikazuju kao aritmetička sredina $\pm$ standardna devijacija; numerički podaci čija raspodela odstupa od normalnosti ili kada postoje ekstremne vrednosti, i ordinalni podaci prikazuju kao medijana i opseg (minimalna – maksimalna vrednost); nominalni podaci i ordinalni podaci sa malim brojem kategorija prikazuju kao n (%).

Prilikom opisa primenjenih statističkih metoda, prikaza i interpretacije rezultata u radu pridržavati se *SAMPL Guidelines* (Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines*. *Int J Nurs Stud* 2015;52(1):5-9.). Primenjene statističke metode treba opisati dovoljno detaljno da ih čitalac može ponoviti na svojim podacima. Navesti korišćeni statistički test i nivo značajnosti. Saopštiti tačnu *p*-vrednost na 3 decimalna mesta.

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(mol), a pritisak krvi u milimetrima živinog stuba (mm Hg). Sve rezultate hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).

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Information about the literature used in the paper is indicated in the text by Arabic numerals in square brackets, e.g. [1,2], in the order in which they appear in the text. References are cited according to the **Vancouver style** (Uniform Requirements for Manuscripts Submitted to Biomedical Journals), established by the International Committee of Medical Journal Editors (<http://www.icmje.org>), whose format is used by the U.S. National Library of Medicine and scientific publication databases. Examples of citations of publications (articles, books and other monographs, electronic, unpublished and other published material) are available at http://www.nlm.nih.gov/bsd/uniform_requirements.html. When citing literature, it is very important to abide by the mentioned standard, because it is one of the most important indexing factors when classifying scientific journals. Online data is cited with the date of access to that data.

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