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EDITORIJAL



Na završnici prve četvrtine 21. veka, uobičajena su preispitivanja o naučnim i stručnim dostignućima kao i izazovima u očuvanju i unapređenju zdravlja stanovnika, odnosno lečenju i rehabilitaciji pacijenata. Preispitivanja su neophodna, iako teška, a kada se rade na pravi način, uvek donose neophodnu snagu i kvalitet u promišljanjima o inovacijama. Period za nama odlikuju posledice finansijskih i javnozdravstvenih katastrofa, pojave novih oboljenja, ratovi u okruženju, migracije, društvena previranja i preispitivanje vrednosnih sistema, višestruka kriza zdravstvenih radnika, informatizacija i digitalizacija društva, i porast troškova života, kao i troškova za očuvanje zdravlja i okruženja. Period koji je pred nama, od nas, kao naučnih i stručnih ljudi, zahteva ponašanje i osećanja koja odlikuju znanje, veštine, mudrost i umetnost da se održe zdravstvena dostignuća, javna dobra i pravično unaprede uslovi života i rada za sve ljude, bez izuzetka. Autori članaka u ovoj svesci, u svojim naučno-stručnim promišljanjima, bave se i dostignućima i izazovima profesionalaca, čime se sveska preporučuje kao zanimljiv izvor za inoviranje znanja u medicini i zdravstvenoj zaštiti.

Autorka pisma uredniku, dr Mirjana Anđelić, objašnjava domete inovativne primene plazme bogate trombocitima u stanjima u ginekologiji, naglašavajući neophodnost rigoroznih istraživanja efikasnosti primene kod brojnih intrauterinih i intraovarijalnih stanja.

U našem fokusu je naučni rad tročlanog tima, dr Bosiljke Đikanović, dr Janka Jankovića, i dr Milene Čavić, kojim se otvara tema o smislenosti populacionog skrininga genoma kao opcije za rano otkrivanje rizika od onkoloških bolesti. Opisujući termin *precizno javno zdravlje*, autori objašnjavaju da korist od pravilne upotrebe veštačke inteligencije i profilisanja genoma postoji ukoliko se istovremeno radi na eliminaciji rizika za nastanak maligniteta, te čuvaju, održavaju i izgrađuju zdrava životna i radna okruženja.

Na analitički način, tim stručnjaka predvođen dr Ljubicom Dimitrijević kao prvim autorom originalnog rada, predstavlja kliničku sliku i ishode lečenja kod teških stanja sa intracerebralnim krvarenjem i konstruktivno objašnjava uspešnost primene različitih vrsta antikoagulanasa, na osnovu rezultata kohortne studije sprovedene 2024. godine u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava“.

U svom originalnom radu, Franciska da Karidade Feliš Čitanga, Selina Malakias kritički predstavlja upravljanje ljudskim resursima u namibskoj pokrajinskoj bolnici "N'Gola Kimbanda", u Angoli, ukazujući da nedostatak stručnjaka, loša raspodela funkcija, neadekvatni uslovi rada, te ograničenja u znanjima i veštinama, predstavljaju glavne prepreke da zdravstvene strategije uspešno odgovore na zdravstvene potrebe stanovništva.

EDITORIAL

As we reach the end of the first quarter of the 21st century, it is natural to reevaluate scientific and professional achievements as well as the challenges in maintaining and improving the health of the population, including the treatment and rehabilitation of patients. Although difficult, retrospection is necessary, and when done properly, it always brings the necessary strength and quality to considerations regarding innovations. The period behind us was characterized by the consequences of financial and public health disasters, the emergence of new diseases, warfare in our part of the world, migration, social turmoil and re-examination of value systems, a multiple crisis of health workers, computerization and digitalization of society, and an increase in the cost of living, as well as the costs of protecting health and the environment. The period ahead requires from us, as scientists and professionals, behavior and feelings founded in our knowledge, skills, wisdom, and the art of maintaining health achievements and public goods and fairly improving living and working conditions for all people, without exception. In their scientific and professional reflections, the authors of the articles in this issue deal with the achievements and challenges of professionals, which is why we recommend this issue as an interesting source that offers new insights into innovations in medicine and health care.

The author of the letter to the editor, Dr. Mirjana Anđelić, explains the scope of the innovative application of platelet-rich plasma in different conditions in gynecology, emphasizing the necessity of rigorous research into the effectiveness of the application of this method in numerous intrauterine and intraovarian conditions.

Our focus is on the research article of a three-member team, Dr. Bosiljka Đikanović, Dr. Janko Janković, and Dr. Milena Čavić, which delves into the topic of the meaningfulness of population genome screening as an option for early detection of the risk of oncological diseases. Describing the term *precise public health*, the authors explain that the proper use of artificial intelligence and genome profiling is beneficial provided that, at the same time, efforts are made to eliminate the risk of malignancy and preserve, maintain and build healthy living and working environments.

In an analytical manner, the team of experts led by Dr. Ljubica Dimitrijević as the first author of the original paper, describes the clinical presentation and treatment outcomes in severe conditions with intracerebral bleeding and constructively explains the success of the application of different types of anticoagulants, based on the results of a cohort study conducted in 2024 at the *Sveti Sava* Special Hospital for Cerebrovascular Diseases.

In her original article, Francisca da Caridade Felix Chitanga, Celina Malaquias critically presents the management of human resources in the Namibe Provincial Hospital “N’Gola Kimbanda”, indicating that

Dr Vesna Đorđević i saradnici, u svom originalnom radu opisuju primenu četiri nova prognostička sistema bodovanja („skoring“ sistema) primarne mijelofibroze u ispitivanju korelacije citogenetike i stepena fibroze koštane srži, i daju procenu značaja kliničkog praćenja stepena rizika hromozomskih aberacija i stepena fibroze koštane srži kod pacijenata sa primarnom mijelofibrozmom.

U svom originalnom radu, kroz prikaz serije slučajeva lekara sa Zapadnog Balkana, Sara Tintor analizira razloge njihovog iseljavanja iz matične zemlje, nemački pravni sistem, uspostavljanje profesionalnog statusa i profesionalni napredak u Nemačkoj, kao i opšte zadovoljstvo lekara.

Pregledni rad dr Predraga Đurđevića i dr Danijele Jovanović detaljno prikazuje kliničku manifestaciju veoma retke i agresivne forme plazmocitnih diskrazija. Opisujući i najnovije terapijske modalitete, autori ukazujući na potrebu nastavka ulaganja u istraživanja i inoviranje pristupa lečenja koji bi dali bolje ishode.

Zoonoze spadaju u najčešće novootkrivene bolesti. Dr Dolika D. Vasović, i saradnici opisuju redak slučaj zoonoze - dirofilariozu donjeg očnog kapka. Iako pravovremena hirurška intervencija često dovodi do potpunog izlečenja, komplikacije mogu da nastanu zbog neadekvatne dijagnostike i lečenja. Autori dodatno ističu da je dirofilarioza endemska bolest u Srbiji, mada se često povezuje sa putovanjima u zemlje Mediterana.

Prikaz slučaja, dr Miljane Vrhovac i koautora, postupno opisuje lečenje KOVID-19 primenom leka casirivimab/indevimab kod pacijenta sa povredom vratnog dela kičme, čime se dopunjuju nedostajuća znanja i pružaju odgovori na dileme sa kojima se suočavao stručni kadar u prethodnom periodu.

Kroz prikaz slučaja periferne paralize facijalnog nerva, kao retke manifestacije neuroendokrinog tumora srednjeg uva, dr Ana Miljković pruža sjajan primer neophodnosti integrisane zdravstvene zaštite u funkciji multidisciplinarnog upravljanja, kako bi se poboljšali ishodi i minimizirali rizici od recidiva. Ovakav pristup počinje ranim prepoznavanjem simptoma maligniteta na primarnom nivou zdravstvene zaštite, a na bolničkom nivou uključuje naprednu dijagnostiku i snimanja, histopatološke potvrde, i potom hirurške intervencije i pomoćne terapije.

Raznovrsnost opisanih studija pokazuje bogatstvo misli i delanja u našem profesionalnom okruženju i inspiriše nas da doprinesemo zdravijoj sadašnjosti i budućnosti. Iz tog razloga, svesku zaokružujemo novim pozivom za radove, koji objavljujemo u celini.

S poštovanjem,

*Prof. Dr Milena Šantrić Milićević
Glavni i odgovorni urednik
Srpski medicinski časopis Lekarske komore*

workforce shortages, inefficient role distribution, inadequate working conditions, and skill gaps are the main obstacles to health strategies successfully responding to the health needs of the population.

In their original article, Dr. Vesna Đorđević et al. describe the application of four new prognostic scoring systems of primary myelofibrosis in examining the correlation between cytogenetics and the degree of bone marrow fibrosis, and provide an assessment of the importance of clinical monitoring of the degree of risk of chromosomal aberrations and the degree of bone marrow fibrosis, in patients with primary myelofibrosis.

In her original article, by presenting a series of cases of doctors from the Western Balkans, Sara Tintor analyzes the physicians' motivation for emigration from their home countries, their professional status establishment and development in Germany, the German legal system, and overall satisfaction of the physicians.

The review paper by Dr. Predrag Đurđević and Dr. Danijela Jovanović presents in detail the clinical manifestation of a very rare and aggressive form of plasmacytic dyscrasia. Describing the latest therapeutic modalities, the authors highlight the need to continue investing in research and innovating treatment approaches that would yield better outcomes.

Zoonoses are among the most common newly discovered diseases. Dr. Dolika D. Vasović et al. describe a rare case of zoonosis - dirofilariasis of the lower eyelid. Although timely surgical intervention often leads to complete resolution of the condition, complications can arise due to inadequate diagnosis and treatment. The authors additionally point out that dirofilariasis is an endemic disease in Serbia, although it is often associated with trips to Mediterranean countries.

The case report, by Dr. Miljana Vrhovac et al., provides a step-by-step description of the treatment of COVID-19 with the drug casirivimab/indevimab in a patient with an injury to the cervical spine, thus providing the missing insights and answers to the dilemmas faced by health professionals in the previous period.

By presenting a case of peripheral facial nerve paralysis, as a rare manifestation of a neuroendocrine tumor of the middle ear, Dr. Ana Miljković provides an excellent example of the need for integrated health care and multidisciplinary management, in order to improve outcomes and minimize the risks of disease recurrence. This approach begins with the early recognition of symptoms of malignancy at the primary level of health care, and continues at the hospital level encompassing advanced diagnostics and imaging, as well as histopathological confirmation, followed by surgical interventions and adjuvant therapies.

The diversity of the studies described demonstrates the richness of thought and activity in our professional environment and inspires us to contribute to a healthier present and a healthier future. This is why we end our issue with a new call for papers, which we are publishing in its entirety.

Sincerely,

Prof. Milena Šantrić Milićević, PhD
Editor-in-Chief
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NEW APPLICATIONS OF PLATELET-RICH PLASMA IN GYNECOLOGY

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Poštovano uredništvo,

Obraćam Vam se sa ciljem da skrenem pažnju na nove primene plazme obogaćene trombocitima (engl. *platelet-rich plasma* – PRP) u ginekologiji – intrauterinu primenu i intraovarijalne injekcije.

Upotreba PRP-a privukla je značajnu pažnju u poslednjoj deceniji zahvaljujući sposobnosti da promoviše regeneraciju tkiva putem diferencijacije ćelija i stimulacije trofičkih aktivnosti. Plazma bogata trombocitima se široko koristi za promociju zarastanja i regeneracije u različitim oblastima medicine, kao što su ortopedija, stomatologija, dermatologija, plastična hirurgija, nega pacijenata sa komplikacijama dijabetesa, te tokom kardiohirurških operacija i carskog reza [1]. U oblasti ginekologije, PRP se koristi u tretmanu simptoma stres urinarne inkontinencije i genitalne rejuvenacije [2]. Posebno su zanimljive novije metode primene PRP-a u ginekologiji, kao što su intrauterina primena i intraovarijalne injekcije PRP-a [3].

Intrauterina primena PRP-a sreće se kod stanja kao što su Ašermanov sindrom, gde dolazi do oštećenja bazalnog sloja endometrija i formiranja intrauterinih adhezija, zatim kod hroničnog endometritisa, kao i kod pacijentkinja u procesu vantelesne oplodnje sa nereceptivnim endometrijumom. Aghajanova i saradnici u radu *Autologous Platelet-Rich Plasma Treatment for Moderate-Severe Asherman Syndrome: The First Experience* prvi su pokazali primenu intrauterinih PRP infuzija kod ljudi. Studija je uključivala grupu od 15 pacijentkinja koje su primile autologni PRP sa Ašermanovim sin-

Dear Editorial Board,

I am reaching out to draw attention to new applications of platelet-rich plasma (PRP) in gynecology, particularly its intrauterine application and intraovarian injections.

The use of PRP has gained significant attention over the past decade due to its ability to promote tissue regeneration by facilitating cell differentiation and stimulating trophic activity. Platelet-rich plasma is widely used to enhance healing and regeneration in various medical fields, such as orthopedics, dentistry, dermatology, plastic surgery, the care of patients with diabetes-related complications, cardiac surgery and cesarean sections [1]. In gynecology, PRP has been applied in the treatment of stress urinary incontinence and genital rejuvenation [2]. Particularly intriguing are the emerging PRP applications in gynecology, such as intrauterine administration and intraovarian injections [3].

Intrauterine PRP application has been used for conditions such as Asherman's syndrome, which involves damage to the basal endometrial layer and the formation of intrauterine adhesions, as well as for chronic endometritis and patients undergoing in vitro fertilization (IVF) with a non-receptive endometrium. Aghajanova et al., in their study **Autologous Platelet-Rich Plasma Treatment for Moderate-Severe Asherman's Syndrome: The First Experience**, were the first to report intrauterine PRP infusion in humans. The study included 15 patients with Asherman's syndrome

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dromom putem Wallace IUI katetera neposredno nakon adheziolize, i 15 pacijentkinja u kontrolnoj grupi. Nije zabeležena statistički značajna razlika među grupama kada je u pitanju uspeh u začeću, usled nedovoljno velikog uzorka, ali je uspešno ukazano na sigurnost i pristupačnost intrauterine primene PRP-a [3]. Liu i saradnici sprovedli su meta-analizu koja sugerise da intrauterina aplikacija autologne plazme bogate trombocitima (PRP) može biti efikasan terapijski pristup za tanak endometrijum, jer povećava debljinu endometrija kod pacijentkinja sa tankim endometrijumom, i poboljšava ishod trudnoće, uz odsustvo neželjenih efekata [4].

Intraovarijalne PRP injekcije primenjuju se kod preuranjene ovarijalne insuficijencije (POI) i u menopauzi, sa ciljem sprečavanja ovarijalne atrezije i podsticanja rasta primordijalnih i preantralnih folikula. Cakiroglu i saradnici regrutovali su 311 žena sa POI za primenu intraovarijalnih autoloških PRP injekcija. Nakon šest nedelja, spontana trudnoća razvila se kod 23 pacijentkinje (7,4%), dok je kod preostale 201 žene, 70% razvilo barem jedan antralni folikul nakon tretmana PRP-om [5]. Eliasova meta-analiza je pokazala da je na osnovu analize najšireg naučnog pregleda do sada, koji se uglavnom sastoji od opservacionih studija, PRP tretman jajnika doveo do statistički značajnog poboljšanja glavnih parametara plodnosti kod žena sa smanjenom ovarijalnom rezervom kao što su broj antralnih folikula, AMH (Antimilerov hormon), FSH (folikulostimulirajući hormon), i LH (luteinizirajući hormon) [6].

Upotreba PRP-a na ovarijumima i endometriju pokazala je obećavajuće rezultate kod pacijentkinja sa niskom ovarijalnom rezervom ili nereceptivnim endometrijuom, kao i kod postojećih indikacija u ginekologiji u sferi zarastanja rana, lichen sklerozusa, vulvodinije, i stres inkontinencije urina. Kod primene PRP-a, ipak, postoje brojni izazovi u standardizaciji metode, usled individualnih razlika u broju trombocita i sadržaju faktora rasta kod pacijenata, zatim varijabilnost indikacija, te veliki broj različitih protokola za pripremu PRP-a. Važno je napomenuti da postoje pacijenti koji nisu kandidati za ovu metodu – pacijenti sa malignim bolestima, akutnim infekcijama, zatim sa poremećajima koagulacije i autoimunim bolestima. Smatram da ove metode zaslužuju mnogo više pažnje u našoj zemlji, ali i da je potrebno dalje potvrđivanje efikasnosti kroz dodatna velika, multicentrična rigorozno izvedena istraživanja, uz praćenje tokom dužeg vremenskog perioda.

*Srdačan pozdrav,
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Sukob interesa: Nije prijavljen.

who received autologous PRP via a Wallace IUI catheter immediately upon adhesiolysis, along with a control group of 15 patients. While no statistically significant difference in conception success was observed due to the small sample size, the study effectively demonstrated the safety and feasibility of intrauterine PRP administration [3]. Liu et al. conducted a meta-analysis suggesting that intrauterine application of autologous PRP may be an effective therapeutic approach for thin endometrium, as it increases endometrial thickness in affected patients, improves pregnancy outcomes, and is free of adverse effects [4].

Intraovarian PRP injections are used for premature ovarian insufficiency (POI) and menopause, aiming to prevent ovarian atresia and stimulate the growth of primordial and preantral follicles. Cakiroglu et al. recruited 311 women with POI for intraovarian autologous PRP injections. After six weeks, spontaneous pregnancy occurred in 23 patients (7.4%), while among the remaining 201 women, 70% developed at least one antral follicle following PRP treatment [5]. Elias's meta-analysis, which represents the most extensive scientific review to date (primarily based on observational studies), demonstrated that ovarian PRP treatment led to a statistically significant improvement in key fertility parameters among women with diminished ovarian reserve, including antral follicle count, anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels [6].

Although PRP application to the ovaries and endometrium has shown promising results in patients with low ovarian reserve or a non-receptive endometrium, as well as in established gynecological indications such as wound healing, lichen sclerosus, vulvodynia, and stress urinary incontinence, several challenges remain in standardizing the method. These include individual variations in platelet counts and growth factor content, variability in indications, and a large number of different PRP preparation protocols. It is also important to note that certain patients are not suitable candidates for this method, including those with malignant diseases, acute infections, coagulation disorders, and autoimmune diseases. I believe these methods warrant greater attention in our country and require further validation through large, multicenter studies conducted with rigor and long-term follow-up to confirm their efficacy.

*Best regards,
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PRECIZNO JAVNO ZDRAVLJE: DA LI JE POPULACIONI SKRINING GENOMA SMISLENA OPCIJA ZA RANO OTKRIVANJE RIZIKA OD ONKOLOŠKIH BOLESTI? RAZMATRANJA IZ SRBIJE

U FOKUSU

IN THE SPOTLIGHT

PRECISION PUBLIC HEALTH PERSPECTIVE: IS GENOMIC POPULATION SCREENING A VIABLE OPTION FOR THE EARLY DETECTION OF RISKS FOR ONCOLOGICAL DISEASES? REFLECTIONS FROM SERBIA

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SAŽETAK

Ovaj rad ima za cilj da objasni termin *precizno javno zdravlje* i njegovu primenu u ranom otkrivanju onkoloških bolesti i genomske rizika za ove bolesti. Ukratko se razmatra upotreba veštačke inteligencije i profilisanje genoma, uključujući i uvide u trenutno stanje inovativnih pristupa u Republici Srbiji. Potrebno je stvoriti okruženje za skladištenje velikih genetičkih i zdravstvenih skupova podataka koje je zaštićeno i interoperabilno, u skladu sa principima nesmetanog pronalaza, pristupačnosti, interoperabilnosti i ponovne upotrebe (engl. *findability, accessibility, interoperability, and reusability - FAIR*). Šira upotreba genomike u ranom otkrivanju rizika od onkoloških bolesti mora da ispunji dobro utvrđene kriterijume za populacioni skrining, što trenutno nije slučaj. Faktori rizika koji mogu da izazovu ispoljavanje gena dovodeći do onkoloških bolesti su dobro poznati, a to su: nezdravo okruženje uključujući zagađenje vazduha, pušenje i izloženost duvanskom dimu, stres, neuravnotežena ishrana i drugi štetni faktori. Stoga bi nadležne zdravstvene institucije i donosioci odluka u oblasti zdravstvene politike trebalo da se fokusiraju na izgradnju zdravog okruženja isto koliko i na rad na tehničkoj i tehnološkoj zdravstvenoj infrastrukturi neophodnoj za dalji razvoj genomike i preciznog javnog zdravlja.

Ključne reči: precizno javno zdravlje, genomika, veštačka inteligencija, onkološke bolesti, skrining, zdravstvena politika

ABSTRACT

This paper aims to discuss the term *precision public health* and its application in the early detection of oncological diseases and genomic risks for these diseases. The use of artificial intelligence and genomic profiling are briefly elaborated on, including reflections on the current status of innovative approaches in the Republic of Serbia. An environment for big genetic and health data sets storage that is protected and interoperable needs to be created, in keeping with the findability, accessibility, interoperability, and reusability (FAIR) principles. Wider use of genomics in the early detection of risks for oncological diseases must meet the well-established criteria for population screening, which is currently not the case. The risk factors that can trigger the penetrance of genes, thus leading to oncological disease, are also well known, and are as follows: unhealthy environments including air pollution, smoking and exposure to second-hand smoke, stress, unbalanced diet, and other harmful factors. Therefore, health governance bodies and health policy decision-makers should focus on building a healthy environment as much as on working on the technical and technological health information infrastructure necessary for further development of genomics and precision public health.

Keywords: precision public health, genomics, artificial intelligence, oncological diseases, screening, health policy

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MALIGNA OBOLJENJA U SRBIJI

Maligna oboljenja predstavljaju značajan javnozdravstveni problem u Republici Srbiji. Starosno standardizovana stopa incidencije (engl. *age-standardized incidence rate - ASIR*) iznosi 250,4 na 100.000 stanovnika [1], dok je stopa mortaliteta za sve tipove karcinoma u 2022. godini iznosila 128,4 na 100.000 stanovnika, što Srbiju svrstava na četvrto mesto u Evropi [2]. Nekoliko faktora rizika doprinosi ovoj nepovoljnoj statistici, kao što su: visoka prevalencija pušenja među odraslima (36,6%) [3], visok stepen zagađenosti vazduha tokom cele godine (prosečna godišnja koncentracija PM_{2,5} od 19,4 mg/m³, u poređenju sa 14 mg/m³ u evropskom regionu) [4], ishrana u kojoj su bogato zastupljene masti i prerađevine a koja je siromašna u vlaknima, ali i starenje stanovništva (2022. godine udeo osoba starosti 65 i više godina bio je 22,0%) [6], u kombinaciji sa niskom stopom ukupnog fertiliteta (1,63 u 2022. godini) [7].

Visoke incidencije malignih bolesti i mortaliteta uzrokovanog ovim bolestima su uočene još pre 20 godina, a nacionalni kreatori politike najavljivali su programe prevencije i ranog otkrivanja karcinoma kao strategiju koja je trebalo da poboljša dužinu i kvalitet života. Shodno tome, 2012. godine pokrenuti su programi skrininga populacije za tri vrste karcinoma: rak dojke (mamografija praćena biopsijom), karcinom grlića materice (Papa test praćen biopsijom), i kolorektalni test (test fekalne okultne krvi – engl. *fecal occult blood test - FOBT*, praćen kolonoskopijom i biopsijom) [8-10]. Iako je Nacionalna kancelarija za skrining raka, osnovana da koordiniše proaktivni pristup u pozivanju zdravog stanovništva (preciznije, stanovništva za koje se pretpostavlja da je zdravo) da se podvrgne skriningu, stope odgovora su ostale na skromnom nivou, daleko ispod željenih ciljeva. Uprkos svim naporima i sprovođenju javnozdravstvenih kampanja kako bi se podigla svest o značaju ranog otkrivanja karcinoma, prema *Serbia: Health System Review 2019*, stope odgovora su bile 11,4%, 15,8% i 5,0% ciljane populacije, za rak dojke, grlića materice i kolorektalnog kancera, što je daleko ispod stope odgovora u drugim evropskim zemljama [11-13].

Kao stručnjaci za javno zdravlje koji sagledavaju sveobuhvatnu i široku društvenu perspektivu, moramo da razmotrimo da li se inovativni pristupi dostupni u 21. veku mogu smisleno primeniti u ranom otkrivanju onkoloških bolesti i proceni rizika kod pretpostavljeno zdrave populacije. Štaviše, trebalo bi da ispitamo da li ovi pristupi u zdravstvenom domenu mogu da smanje stope mortaliteta i poboljšaju preživljavanje i kvalitet života.

INOVATIVNI PRISTUPI

Živimo u eri četvrte industrijske revolucije, a dostupnost inovativnih tehnologija, veštačke inteligencije (engl.

MALIGNANT DISEASES IN SERBIA

Malignant diseases are a significant public health problem in the Republic of Serbia. The age-standardized incidence rate (ASIR) is 250.4 per 100,000 population [1], while the mortality rate for all cancer types, in 2022, was 128.4 per 100,000 population, which puts Serbia in fourth place in Europe [2]. Several risk factors contribute to these unfavorable statistics, such as a high prevalence of smoking among adults (36.6%) [3], high levels of air pollution during the entire year (an annual average PM_{2.5} concentration of 19.4 µg/m³, as compared to 14 µg/m³ in the European Region) [4], a national diet rich in fat and processed foods and depleted in fiber [5], but also an aging population (in 2022, the share of persons aged 65 and over was 22.0%) [6], in combination with a low total fertility rate (1.63 in 2022) [7].

The threat of a high incidence of malignant diseases and mortality caused by these diseases was observed as early as 20 years ago, and national policymakers announced programs for the prevention and early detection of cancers as the strategy which was supposed to improve the length and quality of life. Consequently, population screening programs were launched for three types of cancers in 2012: breast cancer (mammography followed by biopsy), cervical cancer (Papa test followed by biopsy), and colorectal test (fecal occult blood test - FOBT, followed by colonoscopy and biopsy) [8-10]. Although the National Cancer Screening Office was established to coordinate a proactive approach in inviting the population believed to be healthy (ostensibly healthy) to undergo screening, the response rates remained modest, far below the desired goals. Despite all efforts and the implementation of public health campaigns to raise awareness of the importance of early detection of cancers, according to *Serbia: Health System Review 2019*, the response rates were 11.4%, 15.8%, and 5.0% of the target population, for breast, cervical and colorectal cancer, respectively, which was far below the reported response rates for other European countries [11-13].

As public health professionals with a comprehensive societal perspective, we must consider whether the innovative approaches available in the 21st century can meaningfully be used in the early detection of oncological diseases and the assessment of risks within ostensibly healthy populations. Furthermore, we should examine whether these approaches can reduce mortality rates and enhance survival and health-related quality of life.

INNOVATIVE APPROACHES

We are living in the era of the fourth industrial revolution, and the availability of innovative technologies,

artificial intelligence – AI) i profilisanja genoma imaju revolucionaran uticaj na sve aspekte zdravstvene zaštite. Stoga se postavlja validno i opravdano pitanje: da li ovi inovativni pristupi mogu da unaprede rano otkrivanje i lečenje onkoloških bolesti? Dok aspekt onkoloških bolesti u vezi sa inovativnim dijagnostičkim metodama i terapijama ostavljamo na razmatranje kliničarima, patolozima i specijalistima molekularne biologije, mi možemo da razmotrimo prvi deo, odnosno rano otkrivanje onkoloških bolesti. U toku su inicijative i projekti programiranja AI modela koji će se koristiti u radiologiji za validno otkrivanje sumnjivih promena, posebno kod čitanje izveštaja sa mamografije [14-17]. Nekoliko studija je dokazalo da korišćenje veštačke inteligencije u prvom čitanju radioloških izveštaja može biti efikasno i isplativo. Može da prevaziđe važnu barijeru, kao što je nedostatak visoko kvalifikovanih radiologa, što je poznato kao jedno od najvažnijih uskih grla u zdravstvenim sistemima širom sveta. Ovo je posebno slučaj u zemljama u razvoju, zbog odliva mozgova i zbog opsežne obuke koju lekari moraju da prođu pre nego što postanu specijalisti [18]. Međutim, iako se u retrospektivnim evaluacijama pokazalo da AI obećava u domenu skrininga putem mamografije, malo je prospektivnih studija na ovu temu, zbog čega je obim primene veštačke inteligencije još uvek ograničen [19]. Očekuje se da bi u budućnosti veštačka inteligencija mogla da doprine ranom otkrivanju klinički relevantnih karcinoma i da na taj način smanji obim posla u čitanju snimaka, a bez povećanja broja lažnih pozitivnih rezultata [20].

Osim veštačke inteligencije, drugi inovativni pristup koji bismo želeli da razmotrimo jeste upotreba genomike. Zahvaljujući naprednim tehnikama za profilisanje genoma, kao što je sekvenciranje sledeće generacije (engl. *next generation sequencing* - NGS), analize genoma obolelih tkiva su danas skoro neizbežni deo profilisanja tumora, što omogućava propisivanje najefikasnijih personalizovanih terapija koje ciljaju biomolekule odgovorne za razvoj raka [21]. Međutim, dostupnost sekvenciranja sledeće generacije (NGS) i inovativnih terapija zavisi od finansijskih sredstava zdravstvenog sistema, i identifikovani su različiti modeli za finansiranje ovih pristupa [22,23].

Pomenuti inovativni pristupi nisu nepoznati u Srbiji. Na nacionalnom nivou mapirano je trinaest organizacija opremljenih za NGS. Sve ove organizacije su u javnom vlasništvu, a njihovi sistemi sekvenciranja su različitih proizvođača (*Illumina*, *BGI*, *Oxford Nanopore Technologies*, *Thermo Fisher Scientific*, *PacBio*) [24]. Dostupnost inovativnih terapija se takođe povećava. Prema poslednjim podacima, Fond za zdravstveno osiguranje Republike Srbije finansira 17 inovativnih terapija za onkološke bolesti, a ukupni izdaci za njih su u 2024.

artificial intelligence (AI), and genome profiling are making a revolutionary difference in all aspects of health care. Therefore, there is a valid and justified question: can these innovative approaches improve the early detection and treatment of oncological diseases? While we leave the aspect of oncological diseases related to innovative diagnostic methods and therapies to the consideration of clinicians, pathologists, and molecular biology specialists, let us consider the first part, i.e., the early detection of oncological diseases. There are ongoing efforts and projects related to training AI models to be used in radiology for the valid detection of suspicious changes/lesions, particularly for reading mammography reports [14-17]. Several studies have proven that using AI in the first reading of radiology reports can be efficient and cost-effective. It can overcome an important barrier, such as the lack of highly qualified radiologists, known as one of the biggest bottlenecks in the healthcare systems worldwide. This is especially the case in developing countries, due to brain drain and because of the extensive training that doctors have to undergo before becoming specialists [18]. However, although AI has shown promise in mammography-based screening in retrospective evaluations, few prospective studies exist, which is why the scope of its application is still limited [19]. It is expected that in the future, AI might contribute to the early detection of clinically relevant cancers thus reducing the screen-reading workload without increasing false positives [20].

Apart from AI, the other innovative approach we would like to consider is the use of genomics. Thanks to the advanced techniques for genome profiling, one of which is known as Next Generation Sequencing (NGS), genomic analyses of diseased tissues are nowadays an almost inevitable part of tumor profiling, which leads to prescribing the most effective personalized treatments that target biomolecules responsible for cancer development [21]. However, the availability of NGS and innovative therapies depends on the financial resources of the healthcare system, and there are different models for securing funding for these approaches [22,23].

The aforementioned innovative approaches are not unknown in Serbia. At the national level, thirteen organizations equipped to perform NGS have been mapped. Their sequencing systems are from different manufacturers (*Illumina*, *BGI*, *Oxford Nanopore Technologies*, *Thermo Fisher Scientific*, *PacBio*). All of these organizations are publicly owned [24]. The availability of innovative therapies is also increasing. According to recent announcements, the National Health Insurance Fund of the Republic of Serbia is financing 17 innovative therapies for oncological diseases, and the overall

godini iznosili 18,5 milijardi dinara, što je skoro 157 miliona evra [25].

PRECIZNA MEDICINA I PRECIZNO JAVNO ZDRAVLJE

U proteklih 20 godina, zbog dostupnosti sekvenciranja sledeće generacije, koje omogućava znatno brže i jeftinije analize ljudskog genoma, pojam precizne medicine (koji se načelno smatra analognim sa pojmom personalizovane medicine) evoluirao je tako da u donošenje kliničkih odluka uključuje i profilisanje genoma. Iako ne postoji univerzalno prihvaćena definicija personalizovane medicine, savetodavna grupa programa Horizont 2020 je definiše kao „medicinski model u kojem se koristi karakterizacija fenotipova i genotipova pojedinaca (npr. molekularno profilisanje, medicinsko snimanje, podaci o životnom stilu) u cilju pravovremenog prilagođavanja terapijske strategije osobi i/ili utvrđivanja predispozicija za bolest i/ili pravovremene i ciljane prevencije“. Pristup lečenju raka po „univerzalnom“ principu postepeno je zamenjen prilagođavanjem terapije svakom pojedinačnom pacijentu, što je postavilo nove izazove pred kliničare i zdravstvene sisteme. Međutim, uspešna precizna medicina zahteva populacionu perspektivu, čime se otvara put ka uspostavljanju koncepta preciznog javnog zdravlja (engl. *precision public health* – PPH) [21]. Precizno javno zdravlje može se definisati kao „sredstvo za poboljšanje zdravlja stanovništva primenom novih tehnologija, posebno genomike i digitalnih tehnologija, koje bi usmeravale praksu javnog zdravlja generisanjem više individualno prilagođenih oblika delovanja i politika“ [26]. Drugim rečima, PPH se odnosi na obezbeđivanje „pravog oblika delovanja, pravoj populaciji, u pravo vreme“ [27], odnosno na korišćenje najboljih dostupnih podataka za efikasnije i delotvornije ciljno delovanje ka onima kojima je to potrebno [28]. Dva najveća pokretača u PPH su istraživanje genoma i zdravstvene informacione tehnologije koje prikupljaju podatke u vezi sa zdravljem u mašinski čitljivom obliku, zahvaljujući interoperabilnosti zdravstvenih informacionih sistema. Stručnjaci za zdravstvene sisteme, profesionalci u oblasti javnog zdravlja i donosioci odluka treba da razumeju inovativne, digitalne i „omika“ tehnologije (poslednje se odnosi na sufiks koji se javlja u rečima genomika, epigenomika, proteomika, metabolomika i metagenomika). Ove tehnologije nisu cilj same po sebi, već alati za promovisanje zdravlja i prevenciju bolesti, ukoliko se primenjuju razumno i odgovorno, odnosno ako ih prate odgovarajuće strategije upravljanja rizicima, kao što su savetovanje i nadzor. Ipak, da bi se opravdala njihova upotreba u širim razmerama potrebno je pozabaviti se i mnogim drugim metodološkim pitanjima i nedoumicama, što je posebno relevantno kod

expenditure for them was 18.5 billion dinars in 2024, which is almost 157 million euros [25].

PRECISION MEDICINE AND PRECISION PUBLIC HEALTH

In the past 20 years, due to the availability of NGS, which enables significantly faster and cheaper analyses of the human genome, the concept of precision medicine (generally considered analogous to personalized medicine) evolved to include genetic profiling in clinical decision-making. Although there is no universally accepted definition of personalized medicine, the Horizon 2020 Advisory Group defines it as “a medical model using characterization of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention”. The “one size fits all” approach to cancer treatment was gradually replaced by tailoring treatments to each individual, which has placed new challenges before clinicians and healthcare systems. However, successful precision medicine requires a population perspective, paving the way to establishing the precision public health (PPH) concept [21]. Precision public health can be defined as “a means of improving population health through the use of new technologies, particularly genomics and digital, which would guide public health practice by generating more individually tailored interventions and policies” [26]. In other words, PPH is about delivering “the right intervention, at the right time, to the right population” [27], or using the best available data to more effectively and efficiently target those in need [28]. The two biggest drivers in PPH are genomic research and health information technologies that collect health-related data in a machine-readable form, owing to the interoperability of health information systems. However, specialists in health systems, decision-makers, and public health professionals need to understand innovative, digital, and “omics” technologies (the latter is the suffix that applies to genomics, epigenomics, proteomics, metabolomics, and metagenomics). They are not the goal in themselves, but tools for health promotion and disease prevention, if applied reasonably and responsibly, i.e., if followed by appropriate risk management strategies such as counseling and surveillance. Still, many methodological considerations and concerns remain to be addressed in order to justify their use on a large scale, which is particularly relevant in their use for population genomic screening to identify risk factors for malignant diseases [26,29].

njihove upotrebe u populacionom skriningu genoma za identifikaciju faktora rizika za maligne bolesti [26,29].

GENOMIKA U SVETU I SRBIJI

Profilisanje genoma pojedinačnih pacijenata i opšte populacije danas je predmet istraživanja koja se sprovode širom sveta, uglavnom u razvijenim, ali i u zemljama u razvoju [21,30]. Na primer, kompanija *Genomics England* je pokrenula inicijativu pod nazivom „Projekat 100.000 genoma“ (engl. *100,000 Genomes Project*) sa ciljem da se sekvencira 100.000 genoma za oko 85.000 pacijenata registrovanih u njihovoj Nacionalnoj zdravstvenoj službi (engl. *National Health Service – NHS*), koji boluju od raka ili retkih bolesti, dok je Evropska unija pokrenula inicijativu „1+ milion genoma“ (engl. *1+ Million Genomes – 1+MG*), koja ima za cilj da obezbedi identifikovanje genomskog profila i pristup pratećim kliničkim podacima širom Evrope [31,32]. Projekat „Genom Evrope“ (engl. *Genome of Europe*) ima za cilj da izgradi evropsku mrežu nacionalnih genomskih referentnih kohorti za prikupljanje podataka o genetskom sastavu i zdravih i bolesnih osoba (sekvencirani genomi) [33].

U Srbiji su uloženi različiti naporu kako bi se potencijal genetičkih podataka iskoristio na dobrobit pacijenata i građana, ali su oni uglavnom fragmentirani i predstavljaju pojedinačne institucionalne aktivnosti [34]. Međutim, od novembra 2023. godine, u cilju fokusiranijeg delovanja na nacionalnom nivou, Srbija je postala i deo inicijative/konzorcijuma „Genom Evrope“, zajedno sa 29 zemalja Evropske unije (EU), i svega tri zemlje izvan EU (pored Srbije, još i Turska i Norveška) [33,35]. Očekuje se da će dobijeni nalazi dovesti do revolucionarnog uvida u genetsku strukturu, omogućavajući „personalizovane zdravstvene tretmane sa potencijalom da se unapredi prevencija bolesti“ [32].

U Srbiji su mapirani kapaciteti za sprovođenje analiza genoma i čini se da naša zemlja ima realan potencijal i volju da prati svetske trendove u ovoj oblasti [24,35]. Međutim, ostaju određeni izazovi, koji se, između ostalog, odnose i na nedostatak kvalifikovanog istraživačkog i medicinskog osoblja za analizu i tumačenje rezultata sekvenciranja. Da bi se rešilo ovo pitanje, Ministarstvo prosvete je 2025. godine pokrenulo prvi master program bioinformatike (*Master 4.0 Bioinformatika*) za obuku sledeće generacije studenata za bioinformatiku, genomiku, molekularnu biologiju, analizu kliničkih podataka, farmakogenetiku, primenu veštačke inteligencije u biologiji i medicini, kao i za analizu velikih podataka [36]. Takođe, u Srbiji je, na nacionalnom nivou, koncipirana studija za dobrovoljno profilisanje genoma među 1.000 osoba starosti 18-40 godina, iz opšte (zdrave) populacije [37]. Studija treba da bude praćena uspostavljanjem Registra genetičkih i biomedicinskih

GENOMICS IN THE WORLD AND SERBIA

Numerous projects and ongoing initiatives related to genomic profiling in patients and the general population are nowadays being applied worldwide, mostly in developed but also in developing countries [21,30]. For example, Genomics England launched an initiative called “100,000 Genomes Project” aiming to sequence 100,000 genomes from around 85,000 patients registered with their National Health Service (NHS), who are suffering from either cancer or a rare disease, while the European Union announced “1+ Million Genomes” (1+MG), an initiative aiming to secure access to genomics and the corresponding clinical data across Europe [31,32]. The “Genome of Europe” project aims to build a European network of national genomic reference cohorts to collect data on the genetic composition of both healthy and diseased individuals (sequenced genomes) [33].

In Serbia, various efforts have been implemented to use the power of genetic data for improvements in the well-being of citizens, but they are mostly fragmented and represent unrelated institutional activities [34]. Since November 2023, as a more focused national effort, Serbia has also become a part of the “Genome of Europe” initiative/consortium, together with 29 European Union (EU) countries and only three countries outside the EU (besides Serbia, also Turkey and Norway) [33,35]. These findings are expected to lead to groundbreaking insights into genetic structure, enabling “personalized healthcare treatments with the potential to improve disease prevention” [32].

Capacities for genomic analyses have been mapped in Serbia, and it seems that the country has reasonable potential and willingness to keep up with the global trends in this domain [24,35]. However, certain challenges remain, particularly the lack of qualified research and medical staff for analyzing and interpreting sequencing results. To address this issue, in 2025, the Ministry of Education launched the first Bioinformatics Master’s Program to train the next generation of students in bioinformatics, genomics, molecular biology, clinical data analysis, pharmacogenetics, the application of artificial intelligence in biology and medicine, as well as in big data analysis [36]. At the national level, a study on voluntary genomic profiling among 1,000 individuals 18-40 years old, from the general (healthy) population, is being conceptualized [37]. This needs to be followed by the project of establishing a Genetic and Biomedical Data Registry, i.e., an information system for storing and exchanging genetic data under the highest technical and security standards, for research and development purposes in biotechnology, healthcare, and genetics

podataka, odnosno informacionog sistema za čuvanje i razmenu genetičkih podataka po najvišim tehničkim i bezbednosnim standardima, za potrebe istraživanja i razvoja u biotehnologiji, zdravstvu i genetici [37]. Ove aktivnosti predstavljaju veliki podsticaj i priliku za dalji razvoj u korak sa svetom, ali i veliku odgovornost za obezbeđivanje najdelotvornijih intervencija za osobe sa identifikovanim genomskim rizicima.

MOGUĆNOSTI GENOMIKE U POPULACIONIM SKRININZIMA NA MALIGNA OBOLJENJA

Prema smernicama Američkog koledža za medicinsku genetiku i genomiku (engl. *American College of Medical Genetics and Genomics - ACMG*) i uslovima iz prve kategorije koje je definisao Centar za kontrolu bolesti i prevenciju (engl. *Centers for Disease Control and Prevention - CDC*) Sjedinjenih Američkih Država, najčešća i preporučena primena populacionog skrininga genoma jeste u cilju identifikovanja genskih mutacija koje predisponiraju pojedinca na jedno od sledećih stanja: nasledni sindrom dojke i jajnika (engl. *hereditary breast and ovarian cancer syndrome - HBOC*), koji predstavlja rizik za oboljevanje od karcinoma dojke, jajnika, jajovoda, peritoneuma i drugih karcinoma usled mutacija gena raka dojke 1 (engl. *breast cancer gene 1 - BRCA1*) ili gena raka dojke 2 (engl. *breast cancer gene 2 - BRCA2*), i Linčov sindrom (engl. *Lynch syndrome - LS*), koji predstavlja povećani rizik za oboljevanje od kolorektalnog, endometrijalnog, raka jajnika i drugih karcinoma [30,38].

Poznato je da mutacije gena *BRCA1* i *BRCA2* imaju relativno visoku penetrantnost: u meta-analizi koju su sprovedi Čen i Parmidani utvrđen je kumulativni rizik od raka dojke među nosiocima mutacija pri starosti od 70 godina od 57% za *BRCA1* (95% interval poverenja (CI) 47%-66%) i 49% za *BRCA2* (95% CI, 40%-57%), a bio je još niži za rak jajnika (40% i 18% za *BRCA1* i *BRCA2*, 95% CI 35%-46% i 95% CI 13%-23%) [39]. Sa druge strane, prevalencija *BRCA* mutacija među pacijentkinjama sa rakom dojke kreće se u rasponu od 1,8% u Španiji do 36,9% u Sjedinjenim Državama, prema sistematskom pregledu 70 studija širom sveta koji su sprovedi Armstrong i saradnici [40]. U nordijskim zemljama utvrđeno je da je naslednost raka dojke kod žena 31%, dok je kod kolorektalnog karcinoma 15% [41]. U Srbiji se na nacionalnom nivou, na Institutu za onkologiju i radiologiju Srbije, izvodi testiranje na prisustvo germinativnih mutacija u genima koji ukazuju na predispoziciju za nasledni rak dojke i jajnika i Linčov sindrom. Utvrđeno je da su najčešće mutacije kod raka dojke i jajnika na *BRCA1* (7,6%), *BRCA2* (4,8%), genu partneru i lokalizatoru *BRCA2* (engl. *partner and localizer of BRCA2 gene - PALB2*) (4,1%) i genu kinaza 2 kontrolne tačke (engl. *checkpoint kinase 2 gene - CHEK2*) (3,8%) [42]. Identi-

[37]. These activities represent a great incentive and opportunity, but also a great responsibility to deliver the most cost-effective interventions to persons with identified genomic risks.

THE POTENTIAL OF GENOMICS IN POPULATION SCREENING ASSOCIATED WITH MALIGNANT DISEASES

According to the American College of Medical Genetics and Genomics (ACMG) and the United States Centers for Disease Control and Prevention (CDC) Tier 1 conditions, the most common and recommended application of population genetic screening is for the identification of genetic mutations that predispose an individual to one of the following conditions: hereditary breast and ovarian cancer syndrome (HBOC), which presents a risk for breast, ovarian, tubal, peritoneal and other cancers due to mutations in breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2), and Lynch syndrome (LS), which represents an increased risk for colorectal, endometrial, ovarian and other cancers [30,38].

Mutations of the *BRCA1* and *BRCA2* genes are known for having relatively high penetrance: the cumulative risk for breast cancer among mutation carriers at the age of 70 was 57% for *BRCA1* (95% confidence interval (CI) 47%-66%) and 49% for *BRCA2* (95% CI 40%-57%), and even lower for ovarian cancer (40% and 18% for *BRCA1* and *BRCA2* respectively, 95% CI 35%-46% and 95% CI 13%-23%), as found in a meta-analysis conducted by Chen and Parmigiani [39]. On the other hand, the prevalence of *BRCA* mutations among patients with breast cancers is in the range of 1.8% in Spain to 36.9% in the United States, according to the systematic review of 70 studies worldwide conducted by Armstrong et al. [40]. In Nordic countries, the heritability of female breast cancer was found to be 31%, while for colorectal cancer it was found to be 15% [41]. In Serbia, testing for germline mutations in cancer susceptibility genes for hereditary breast and ovarian cancer and Lynch syndrome is performed at the national level, at the Institute for Oncology and Radiology of Serbia. The most frequent mutations in breast and ovarian cancer were found to be in *BRCA1* (7.6%), *BRCA2* (4.8%), the partner and localizer of *BRCA2* gene (*PALB2*) (4.1%), and the checkpoint kinase 2 gene (*CHEK2*) (3.8%) [42]. Identifying pathogenic and likely pathogenic variants in genes that carry a high predisposition for hereditary cancers allows for the stratification of families by risk and has become a widely accepted global practice.

It is important to note that if an individual is a carrier of the aforementioned genetic mutations, this does not necessarily mean that this person is unhealthy or will be unhealthy. This is, obviously, a matter of prob-

fikovanje patogenih i verovatnih patogenih varijanti u genima koji daju visoku predispoziciju za nasledne karcinome omogućava stratifikaciju porodica prema riziku i preraslo je u široko prihvaćenu globalnu praksu.

Važno je napomenuti da ako je osoba nosilac pomenutih genskih mutacija, to ne mora da znači da je ona automatski bolesna ili da će se razboleti. Ovo je, očigledno, pitanje verovatnoće koja se može modifikovati. Dobro je poznato da se bolest javlja kao interakcija između genetskih i ekoloških faktora rizika, kao što su izloženost stresu, nepovoljni uslovi životne sredine, zagađenje vazduha, nezdrav stil života (npr. pušenje, nedostatak fizičke aktivnosti, nezdrava ishrana), ali kako se tačno bolest razvija i šta i kada pokreće ispoljavanje genskih mutacija, odnosno pojavu novih mutacija i ispoljavanje bolesti, ostaje nerazjašnjeno. Osim genetike, potrebno je više informacija iz longitudinalnih studija o izloženosti faktorima rizika tokom života da bi se izgradilo znanje o prirodnom toku bolesti. Digitalne zdravstvene informacije mogu pomoći u individualnom prikupljanju podataka, dok je veštačka inteligencija korisna u analizi velikih baza podataka (engl. *big data*) i identifikovanju obrazaca i povezanosti između individualnih životnih iskustava, izloženosti i zdravstvenih ishoda. Međutim, kada se onkološka bolest na kraju desi, svaki tumor ima svoju genetiku, što se može dokazati pomoću sekvenciranja sledeće generacije (NGS) i genomskih analiza, a dostupne su i inovativne terapije za prevazilaženje genskih mutacija kao osnovnog uzroka maligne bolesti, što je predstavlja osnovu precizne medicine.

SOCIJALNI, PRAVNI I ETIČKI ASPEKTI

Imajući u vidu sve prethodno opisane činjenice, ne možemo a da se ne zapitamo: koja je korist ili dodatna vrednost poznavanja našeg genetskog statusa kada smo zdravi? Kako to utiče na naše izgleda da dobijemo određenu onkološku bolest, verovatnoću preživljavanja ukoliko se razbolimo ili kvalitet života povezan sa zdravljem? Trenutno, odgovor nedostaje, kao i saznanja o prirodnom toku bolesti [43]. Da li bi informacije o genetskom statusu povećale odziv pojedinca na redovne preglede i poboljšale izbore zdravog načina života? Ova i mnoga druga pitanja treba pažljivo razmotriti, a odgovor sigurno nije uniforman [44]. Iako nema sumnje da upotreba genomskih podataka ima značajan potencijal za preciznu medicinu, neophodna su posebna razmatranja kako bi se ove informacije koristile etički, odgovorno, svrsishodno i bezbedno, bez potencijalne zloupotrebe ili štete [45].

Potencijalno, informacija da je zdrava osoba nosilac genske mutacije može da ima neke prednosti, kao što je povećana motivacija za redovno praćenje svog zdravstvenog stanja i uzdržavanje od izlaganja faktorima rizika

ability which can be modified. It is well known that disease appears as an interaction between genetic and environmental risk factors. These risk factors include exposure to stress, unfavorable environmental conditions, such as air pollution, and unhealthy lifestyles (e.g., smoking, lack of physical activity, and unhealthy nutrition), but how exactly the disease develops and what and when triggers the penetrance of gene mutations, or the appearance of new ones and the expression of disease, remains unclear. More information is needed from longitudinal studies on lifetime exposure to risk factors, in addition to genetics, to build knowledge on the natural course of disease. Digital health information might help in individual data collection, while AI is useful in the analysis of big data and identification of patterns and associations between individual lifetime experiences, exposures, and health outcomes. However, when oncological disease eventually happens, each tumor has its own genetics, which can be proven by NGS and genomic analyses, and innovative therapies are available to address the genetic mutations as the root cause of malignant disease, which is the foundation of precision medicine.

SOCIAL, LEGAL, AND ETHICAL CONSIDERATIONS

Bearing all the previously described facts in mind, we cannot but ask ourselves: what are the benefits or the added value of knowing our genetic status when we are healthy? How does it affect our chances of getting a particular oncological disease, our survival, or our health-related quality of life? Currently, the answer is lacking, as is the knowledge related to the natural course of disease [43]. Would the information on genetic status increase an individual's compliance with regular checkups and improve healthy lifestyle choices? These and many other questions need to be carefully considered, and the answers to these questions are by no means uniform [44]. Although there is no doubt that the use of genomic data holds significant potential for precision medicine, special considerations are necessary in order to use this information ethically, responsibly, safely, and beneficially, without potential harm or misuse [45].

Potentially, the information that a person is a carrier of a gene mutation might have some advantages, such as increased motivation for regular monitoring of their health status and refraining from being exposed to behavioral risk factors that are under individual control. At the same time, this information could cause fear and anxiety. Furthermore, risk factors originating from the environment are public responsibility, and

u kontekstu određenih ponašanja koja su pod individualnom kontrolom. Istovremeno, ove informacije mogu da izazovu strah i anksioznost. Štaviše, faktori rizika koji potiču iz životne sredine su javna odgovornost, a države i vlade moraju da obezbede kako donošenje, tako i primenu odgovarajućih i preporučenih politika koje se odnose na stvaranje zdrave životne sredine. Najbolji negativan primer za to u Republici Srbiji je Strategija kontrole duvana koja je potpisana i ratifikovana pre skoro 20 godina i praćena donošenjem niza zakonskih i podzakonskih akata koji su, između ostalog, predviđali kreiranje javnih prostora bez duvanskog dima. Međutim, pušenje u zatvorenim prostorima mnogih ugostiteljskih objekata (a samim tim i pasivno izlaganje duvanskom dimu) u Srbiji danas još uvek nije zabranjeno, što znači da su ljudi u velikoj meri izloženi pasivnom pušenju. Pušenje je direktni faktor rizika za sva onkološka oboljenja, prevashodno za rak pluća, čiji je ASIR 2022. godine iznosio 40,4 na 100.000 stanovnika, što je Srbiju svrstalo na četvrto mesto u svetu (ispred Srbije su Mađarska, Kina i Nova Kaledonija) [46].

Informacija o tome da je neko nosilac genske mutacije sa relativno visokim potencijalom da se razvije u onkološku bolest može imati značajan negativan uticaj na nečije psihičko blagostanje, posebno ako se ne saopšti pravilno. Efekat koji ova informacija može da ima na članove porodice nosilaca patogenih mutacija je takođe aspekt koji treba uzeti u obzir. Dobra praksa predlaže savetovanje pre i posle genomskog testiranja i adekvatno upravljanje rizikom od bolesti [47]. Bez ovih resursa, bilo bi neodgovorno ostaviti pojedince da samoinicijativno i bez profesionalne podrške realizuju genomsko testiranje, u bilo kom okruženju. U razvijenijim sredinama postoje neke ideje i projekti koji se odnose na promovisanje testiranja genoma u primarnoj zdravstvenoj zaštiti [48,49]. Da bi bili uspešni i da ne bi naneli štetu, ovi projekti moraju da budu udruženi sa složenom infrastrukturom koja omogućava preventivne intervencije i kvalitetnu komunikaciju između pružaoca usluga i pojedinaca/pacijenata, obezbeđujući da se prednosti dobro razumeju i da strategije za upravljanje rizikom budu postavljene nakon dobijanja rezultata testiranja.

Kriterijumi za sprovođenje bilo koje vrste populacionog skrininga ustanovljeni su još 1968. godine, i testiranje genoma radi otkrivanja gena povezanih sa rizikom za malignim oboljenjima kod zdrave populacije nisu u tom smislu izuzetak [50,51]. Kriterijumi se odnose na dostupnost odgovarajućeg skrining testa, koji mora biti dovoljno osetljiv i specifičan, dostupan po niskoj ceni, lak za primenu, prihvatljiv, neinvazivan, bezbedan, udoban i isplativ. Većinu ovih kriterijuma moglo bi da ispuni sekvenciranje sledeće generacije kao alat za skrining, pri čemu je još uvek upitna njegova isplativost,

governments and societies have to ensure that appropriate and recommended policies related to building a healthy environment are launched and applied. The best negative example of this in the Republic of Serbia is the tobacco control strategy that was signed and ratified almost 20 years ago, followed by a set of national legislation that envisaged creating smoking-free public spaces, among other initiatives. However, nowadays, indoor smoking (and therefore passive exposure) in Serbia is still not banned in many restaurants and cafes, which means that people are greatly exposed to second-hand smoke. This is a direct risk factor for all oncological diseases, primarily lung cancer, whose ASIR was 40.4 per 100,000 population in 2022, which put Serbia in fourth place globally, preceded by Hungary, China, and New Caledonia [46].

Being aware of the fact that one is a carrier of a gene mutation with a relatively high penetrance potential to develop oncological disease may have a considerable negative impact on one's psychological well-being, especially if not communicated properly. The effect it has on family members of pathogenic mutation carriers is also an aspect to be considered. Good practice proposes counseling before and after genomic testing and adequate disease risk management [47]. Without these resources in place, it would be irresponsible to leave individuals to deal with genomic testing themselves, in any setting. In more developed environments, there are some ideas and projects related to promoting genomic testing in primary healthcare services [48,49]. To be successful and do no harm, these projects have to be followed by complex infrastructure that enables preventive interventions and high-quality communication between providers and individuals/patients, assuring that advantages are well understood and strategies for risk management are in place after receiving test results.

Criteria for any kind of population screening were established in 1968, and genomic testing for detecting genes associated with malignant diseases in healthy populations is no exception [50,51]. Criteria are related to the availability of an appropriate screening test, which has to be sufficiently sensitive and specific, available at a low cost, easy to apply, acceptable, non-invasive, safe, comfortable, and cost-effective. The majority of these criteria could be met by NGS as a screening tool, with cost-effectiveness still being debated, even in simulated cohorts with modeled expected outcomes, such as incidence and quality-adjusted life years (QALY) after survival [52-54].

The other criterion for population screening is the availability of effective interventions that make a difference in survival and QALY. Basically, in the case

čak i u istraživanjima na simuliranim kohortama i modelovanim očekivanim ishodima kao što su incidencija i godine života prilagođene za kvalitet (engl. *quality-adjusted life years* - QALY) nakon preživljavanja [52-54].

Drugi kriterijum za populacioni skrining je dostupnost delotvornih intervencija koje utiču na preživljavanje i QALY, a nakon identifikovanog prisustva rizika. U principu, kada su u pitanju „omika“ markeri rizika za onkološke bolesti, te delotvorne intervencije nisu ništa drugo do tradicionalne intervencije promocije javnog zdravlja i prevencije, koje su se pokazale kao strategije koje obezbeđuju najbolji rezultat naspram ulaganja. To su mere kontrole duvana, delovanje u smislu smanjenja zagađenja vazduha i promocije zdravih stilova života, ali i programi za rano otkrivanje kliničkih bolesti tradicionalnim skrining instrumentima sa dovoljnim nivoom osetljivosti (sposobnost da se pravilno identifikuju slučajevi bolesti tj. tačno pozitivni slučajevi) i specifičnosti (sposobnost da se pravilno identifikuju pojedinci koji su bez bolesti, odnosno tačno negativni slučajevi). Ovo nas vraća na početak pristupa kontroli onkoloških bolesti, odnosno na potrebu da se pošalje poruka da bez „staremodnih“ individualnih i populacionih mera koje su optimizovane i uspostavljene na nivou društva, ne možemo očekivati da rano otkrivanje genomskih faktora rizika može poboljšati preživljavanje i QALY u slučajevima poznatih genetskih stanja kao što su HBOC i Linčov sindrom. Čak i kada se skrining genskog panela za ova stanja obavlja kao lični izbor, obično od strane onih koji mogu to da priušte ili su visoko motivisani da preduzmu testiranje genoma, iste mere za promociju zdravlja i prevenciju bolesti treba da budu dostupne i pristupačne, i na individualnom i na populacionom nivou. Javnozdravstvene mere utiču na sve i trebalo bi da svakako postoje (kao što je stvaranje okruženja bez duvana, na primer), dok individualne mere promocije zdravlja (zdravi stilovi života, na primer) zavise od prihoda i socioekonomskog statusa pojedinca, te bi ukupni odgovor na rezultate genetičkog testiranja mogao da poveća zdravstvene nejednakosti [55].

IMPLIKACIJE U DOMENU ZDRAVSTVENE POLITIKE

Javnozdravstvene mere, promocija zdravlja i prevencija usmerena na dobro poznate faktore rizika za onkološke bolesti nisu izgubile na značaju, niti su ih umanjile mogućnosti koje pružaju genomika i veštačka inteligencija [56]. Nadležne zdravstvene institucije i donosioci odluka u oblasti zdravstvene politike trebalo bi da se fokusiraju na izgradnju zdravog okruženja isto koliko i na rad na tehničkoj i tehnološkoj zdravstvenoj informacionoj infrastrukturi neophodnoj za dalji razvoj genomike i preciznog javnog zdravlja [57,58]. Potreb-

of “omics” markers of risks for oncological disease, these interventions are just traditional public health promotion and prevention interventions, which have proven to be “best-buy” strategies. These are tobacco control measures, efforts related to the decrease of air pollution, and promotion of healthy lifestyles, but also programs for early detection of clinical diseases by traditional screening instruments with sufficient levels of sensitivity (ability to correctly identify cases of disease) and specificity (ability to correctly identify individuals who are disease free, i.e. true negative cases). This brings us back to the beginning, i.e., sending the message that without “old fashioned” individual and population measures, optimized and in place, we cannot expect robust evidence that early detection of genomic risk factors can improve survival and QALY in cases of known actionable genetic conditions such as HBOC, and Lynch syndrome. Even when gene panel screenings for these conditions are performed as a personal choice, typically by those who can afford or are highly motivated to pursue genomic testing, the same individual and public health promotion and prevention measures should be available and accessible. Public health measures affect everyone and should already be in place (such as creating tobacco-free environments, for example), while individual health promotion measures (healthy lifestyles, for example) depend on the income and socio-economic status of an individual. Therefore, the overall response to the results of genetic testing might increase health inequalities [55].

POLICY IMPLICATIONS

Public health measures, health promotion, and prevention related to well-known risk factors for oncological diseases did not lose their importance, and innovations such as genomics and artificial intelligence did not decrease their significance either [56]. Health governance bodies and health policy decision-makers should focus on building a healthy environment as much as on working on the technical and technological health information infrastructure necessary for further development of genomics and precision public health [57,58]. An environment for big genetic and health data sets storage that is protected and interoperable according to FAIR (findability, accessibility, interoperability, and reusability) principles needs to be created [59]. Leveraging biomedical research and development in Serbia is associated with creating a national register of genomics and health data, as a great national step forward towards the health promotion of our citizens, through precision medicine and precision public health.

no je stvoriti okruženje za skladištenje velikih genetičkih i zdravstvenih skupova podataka koje je zaštićeno i interoperabilno, u skladu sa principima nesmetanog pronalaženja, pristupačnosti, interoperabilnosti i ponovne upotrebe (engl. *findability, accessibility, interoperability, and reusability* - FAIR). [59]. Puna primena i dalji razvoj biomedicinskih istraživanja u Srbiji su u velikoj meri povezani sa formiranjem nacionalnog registra genomike i zdravstvenih podataka, što bi bio veliki iskorak ka unapređenju zdravlja građana, a putem primene precizne medicine i preciznog javnog zdravlja.

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INTRACEREBRALNO KRVARENJE I PRIMENA RAZLIČITIH VRSTA ANTIKOAGULANASA – KLINIČKA PREZENTACIJA I ISHODI LEČENJA

ORIGINALNI RAD

ORIGINAL ARTICLE

INTRACEREBRAL HEMORRHAGE AND THE USE OF VARIOUS TYPES OF ANTICOAGULANTS – CLINICAL PRESENTATION AND TREATMENT OUTCOMES

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SAŽETAK

Uvod: Antikoagulantna terapija igra ključnu ulogu u prevenciji i tretmanu različitih vaskularnih oboljenja, ali istovremeno povećava rizik od hemoragijskih komplikacija, uključujući intracerebralnu hemoragiju (ICH). Cilj ovog rada bio je ispitati ishod pacijenata sa ICH u zavisnosti od prethodne antikoagulantne terapije.

Metode: U pitanju je retrospektivna kohortna studija u koju je od 277 pacijenata sa ICH iz bolničkog registra lečenih od januara do novembra 2024. godine u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava“, uključeno njih 37. Svi pacijenti podeljeni su u dve grupe, na pacijente lečene antagonistima vitamina K (VKA) ili direktnim oralnim antikoagulantima (NOAK). Ishod lečenja pacijenata na otpustu i 90 dana nakon otpusta određivan je na osnovu modifikovane Rankin skale (mRS).

Rezultati: U grupi pacijenata prethodno lečenih VKA srednja vrednost mRS skora na otpustu bila je 4,6, dok je u grupi prethodno lečenih NOAK terapijom ona iznosila 5,1, što je bez statističke značajnosti između grupa ($p = 0,442$). Takođe statistička značajnost nije pronađena ni među mRS 90 dana nakon otpusta ($p = 0,341$). U grupi VKA-ICH srednja vrednost je iznosila 4,3, dok je u drugoj grupi ona iznosila 4,9. U prvoj grupi procenat letalnih ishoda bio je 58%, dok je u drugoj grupi 76%.

Zaključak: Pacijenti sa ICH i prethodnom terapijom VKA u odnosu na pacijente sa prethodnom NOAK terapijom su bez značajnih razlika u ishodu lečenja.

Ključne reči: intracerebralna hemoragija, antagonisti vitamina K, direktni oralni antikoagulansi

ABSTRACT

Introduction: Anticoagulant therapy plays a key role in the prevention and treatment of various vascular diseases, but it simultaneously increases the risk of hemorrhagic complications, including intracerebral hemorrhage (ICH). This study aimed to examine the outcomes of patients with ICH based on prior anticoagulant therapy.

Methods: This was a retrospective cohort study involving 37 out of 277 patients with ICH from the hospital registry treated between January and November 2024 at the Special Hospital for Cerebrovascular Diseases “Sveti Sava”. All patients were divided into two groups: those treated with vitamin K antagonists (VKA) or direct oral anticoagulants (NOAC). The treatment outcome of patients at discharge and 90 days after discharge was determined using the modified Rankin Scale (mRS).

Results: In the group of patients previously treated with VKA, the mean mRS score at discharge was 4.6, while in the group previously treated with NOAC therapy, it was 5.1, with no statistically significant difference between the groups ($p = 0.442$). Additionally, no statistical significance was found in the mRS 90 days after discharge ($p = 0.341$). In the VKA-ICH group, the mean value was 4.3, while in the other group, it was 4.9. In the first group, the mortality rate was 58%, while in the second group, it was 76%.

Conclusion: Patients with ICH and prior VKA therapy showed no significant differences in treatment outcomes compared to patients with prior NOAC therapy.

Keywords: intracerebral hemorrhage, vitamin K antagonists, direct oral anticoagulants

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UVOD

Prema poslednjim statističkim podacima, moždani udar je drugi vodeći uzrok smrti i treći vodeći uzrok smrti i invaliditeta zajedno [1]. Hemoragični moždani udar čini oko 20% svih moždanih udara, pri čemu je intracerebralna hemoragija (ICH) najčešći tip [2].

Primena oralne antikoagulantne terapije (OAK) je jedan od faktora rizika za ICH. Stopa propisivanja OAK se povećava, uglavnom zbog sve veće upotrebe u primarnoj i sekundarnoj prevenciji ishemijskog moždanog udara kod pacijenta sa nevalvularnom atrijskom fibrilacijom (AF) [2].

Stopa smrtnosti pacijenata nakon ICH iznosi oko 40% u roku od jednog meseca i 54% u roku od jedne godine, uprkos napretku u neurointenzivnoj nezi tokom poslednjih nekoliko decenija [2]. Upotreba antikoagulantnih lekova kod ovih pacijenata povezana je sa većom ekspanzijom hematoma, kao i posledičnim povećanim invaliditetom i stopom smrtnosti [3,4].

U prošlosti su se, zbog ograničene dostupnosti, široko koristili antagonisti vitamina K. Međutim, vremenom su se pojavile i alternativne opcije – direktni inhibitori trombina (dabigatran) i inhibitori faktora Xa (apiksaban, edoksaban i rivaroksaban), nazvani oralni antikoagulansi koji nisu antagonisti vitamina K (NOAK) [5].

Poznato je da upotreba VKA usled nevalvularne atrijske fibrilacije udvostručuje rizik od intrakranijskog krvarenja, čak i pod optimalnim uslovima lečenja. Pored povećane incidencije, ICH povezan sa VKA (VKA-ICH) povezan je sa većim volumenima hematoma, povećanim mortalitetom i lošim funkcionalnim ishodom. NOAK imaju sličnu efikasnost u prevenciji ishemijskog moždanog udara kod pacijenata sa nevalvularnom atrijskom fibrilacijom, sa upola manjom incidencijom ICH u poređenju sa warfarinom. Nalazi su kontradiktorni u pogledu ishoda pacijenata sa NOAK-povezanim ICH (NOAK-ICH) u poređenju sa VKA-ICH [6,7]. Iako NOAK nosi znatno manji rizik od ICH, NOAK-ICH postaje pitanje od značajne kliničke važnosti, s obzirom na široku i sve veću stopu propisivanja ovih lekova.

Modifikovana Rankinova skala je efikasna, pouzdana i jednostavna mera funkcionalnog ishoda koja se široko koristi u kliničkim ispitivanjima akutnog moždanog udara [8].

Cilj ovog rada bio je ispitati ishod pacijenata sa ICH u zavisnosti od prethodne antikoagulantne terapije.

METODE

Ovo je retrospektivna kohortna studija u koju je, iz bolničkog registra pacijenata sa ICH lečenih od januara do novembra 2024. godine u Specijalnoj bolnici za cerebrovaskularna oboljenja „Sveti Sava“, koji sadrži 277 pacijenata, uključeno njih 37.

INTRODUCTION

According to the latest statistical data, stroke is the second leading cause of death and the third leading cause of death and disability combined [1]. Hemorrhagic stroke accounts for approximately 20% of all strokes, with intracerebral hemorrhage (ICH) being the most common type [2].

The use of oral anticoagulant therapy (OAC) is one of the risk factors for ICH. The prescription rate of OAC is increasing, mainly due to its growing use in the primary and secondary prevention of ischemic stroke in patients with non-valvular atrial fibrillation (AF) [2].

The mortality rate after ICH is around 40% within one month and 54% within one year, despite advances in neurocritical care over the past few decades [2]. The use of anticoagulant medications in these patients is associated with greater hematoma expansion, and consequently with increased disability and mortality rates [3,4]. Due to limited availability, vitamin K antagonists (VKAs) were widely used in the past. However, over time, alternative options emerged - direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), collectively known as non-vitamin K oral anticoagulants (NOACs) [5]. It is well known that VKA use in the context of non-valvular atrial fibrillation doubles the risk of intracranial hemorrhage, even under optimal treatment conditions. In addition to the increased incidence, VKA-associated ICH (VKA-ICH) is linked to larger hematoma volumes, higher mortality, and poorer functional outcomes. NOACs offer similar efficacy in preventing ischemic stroke in patients with non-valvular atrial fibrillation, with approximately half the incidence of ICH compared to warfarin. However, findings remain contradictory regarding outcomes in patients with NOAC-related ICH (NOAC-ICH) compared to those with VKA-ICH [6,7]. Although NOACs carry a significantly lower risk of ICH, NOAC-ICH is becoming a matter of notable clinical importance due to the widespread and growing prescription of these drugs.

The modified Rankin Scale is an effective, reliable, and simple measure of functional outcome that is widely used in clinical trials of acute stroke [8].

This study aimed to evaluate the outcomes of patients with ICH depending on their prior anticoagulant therapy.

METHODS

This is a retrospective cohort study that included 37 patients from the hospital registry of patients with intracerebral hemorrhage (ICH) treated between January and November 2024 at the Special Hospital for Cerebrovascular Diseases "Sveti Sava," which contains a total of 277 patients.

Unapred definisani kriterijumi za isključenje bili su: ICH koji nije povezan sa antikoagulantnom terapijom, subduralno i subarahnoidalno krvarenje, kao i ICH povezan sa vaskularnim malformacijama, primarnim tumorima mozga, metastazama, septičkim embolijama i hemoragijskom transformacijom ishemijskog moždanog udara.

Prikupljeni su podaci o godinama starosti, polu, anamnestički podaci o prethodno lečenoj hipertenziji i dijabetesu, lekovima pre hospitalizacije (uključujući vrstu antikoagulantne terapije) i laboratorijskim podacima pri prijemu.

Svim pacijentima po dolasku u prijemnu ambulanu učinjen je CT endokranijuma, sa CT angiografijom glave i vrata.

Svi pacijenti podeljeni su u dve grupe na osnovu vrste antikoagulantne terapije - na pacijente lečene antagonistima vitamina K (VKA) i pacijente lečene direktnim oralnim antikoagulansima (NOAK).

Članovi tima za moždani udar ocenjivali su ishod lečenja pacijenata na otpustu i nakon 90 dana od otpusta na osnovu modifikovane Rankin skale (mRS), kao i bolnički mortalitet.

U zavisnosti od tipa varijabli i normalnosti raspodele, deskripcija podataka je prikazana kao n (%), aritmetička sredina $\pm$ standardna devijacija ($as \pm sd$) ili medijana (min-max). Za poređenje razlika između grupa sa podacima koji su imali normalnu raspodelu je korišćen Studentov t-test, dok je za podatke koji nisu imali normalnu raspodelu primenjen Mann-Whitney U test. Kategorijske varijable analizirane su pomoću hi-kvadrat testa ili Fisher-ovog egzaktnog testa, u zavisnosti od očekivanih frekvencija u tabelama kontingencije. Nivo statističke značajnosti je postavljen na $p < 0,05$. Za ispitivanje zavisnosti između promenljivih korišćen je Spearmanov test korelacije rangova. Sve statističke analize su sprovedene korišćenjem softvera GraphPad Prism 8.

REZULTATI

Od 277 pacijenata sa netraumatskom ICH lečenih u Specijalnoj bolnici za cerebrovaskularne bolesti „Sveti Sava“ od januara do novembra 2024. godine, u istraživanje je uključeno njih 37, a nakon primene kriterijuma za isključenje iz istraživanja. Zatim su na osnovu vrste antikoagulantne terapije pacijenti podeljeni na one koji su prethodno lečeni antagonistima vitamina K (VKA-ICH) ili direktnim oralnim antikoagulansima (NOAK-ICH). U grupi pacijenata lečenih VKA bilo je 20 pacijenata (54%), a u grupi lečenih NOAK je bilo 17 (46%) (Slika 1).

U grupi VKA-ICH je 11 pacijenata muškog (55%) i 9 pacijentkinja ženskog pola (45%) prosečne starosti 76,3 godina, dok je u grupi NOAK-ICH 6 pacijenta muš-

Predefined exclusion criteria were: ICH not associated with anticoagulant therapy, subdural and subarachnoid hemorrhage, as well as ICH related to vascular malformations, primary brain tumors, metastases, septic embolisms, and hemorrhagic transformation of ischemic stroke.

Data were collected on age, sex, medical history of previously treated hypertension and diabetes, medications used before hospitalization (including type of anticoagulant therapy), and laboratory findings at admission.

Upon arrival at the emergency department, all patients underwent a non-contrast cranial CT scan, followed by head and neck CT angiography.

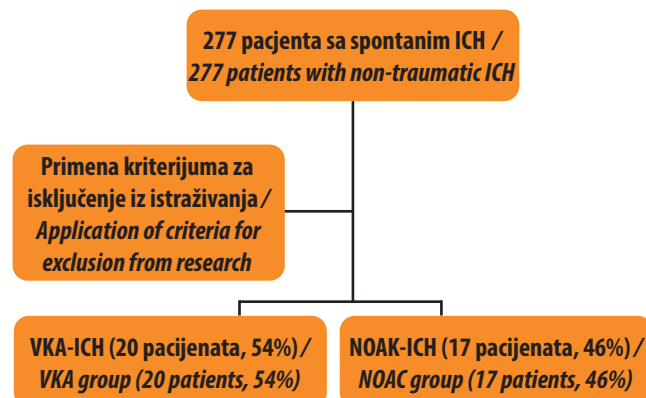
Patients were divided into two groups based on the type of anticoagulant therapy – those treated with vitamin K antagonists (VKAs) and those treated with direct oral anticoagulants (NOACs).

Stroke team members assessed patient outcomes at discharge and 90 days post-discharge using the modified Rankin Scale (mRS) and in-hospital mortality.

Data were described as n (%), mean $\pm$ standard deviation ($as \pm sd$), or median (min-max) depending on the type of variables and distribution normality. The student's t-test was used for normally distributed data to compare differences between groups, and the Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using the chi-square test or Fisher's exact test, depending on expected frequencies in contingency tables. A p-value < 0.05 was considered statistically significant. Spearman's rank correlation test was used to examine correlations between variables. All statistical analyses were performed using GraphPad Prism 8 software.

RESULTS

Out of 277 patients with non-traumatic intracerebral hemorrhage (ICH) treated at the Special Hospital for Cerebrovascular Diseases "Sveti Sava" from January to



Slika 1. Distribucija pacijenata sa ICH po grupama

Picture 1. Distribution of patients with ICH by group

kog pola (35%), odnosno 11 ženskog (65%), prosečne starosti 78,1 godina (Tabela 1).

Nisu pronađene statistički značajne razlike između grupa u anamnestičkim podacima vezanim za prethodno lečenu hipertenziju ($p = 1,000$) i dijabetes melitus ($p = 0,159$) (Tabela 1).

Među pristiglim rezultatima laboratorijskih analiza izdvojeni su markeri inflamacije kao mogući prediktori lošeg funkcionalnog ishoda pacijenata sa ICH. Nije bilo statistički značajnih razlika između grupa u vrednostima CRP ($p = 0,704$), limfocita ($p = 0,482$) i NLR ($p = 0,104$). Međutim, u NOAK-ICH grupi pacijenata srednje vrednosti leukocita ($p = 0,034$) i neutrofila ($p = 0,030$) bile su statistički veće (Tabela 2). U našem radu dokazana je statistički značajna pozitivna povezanost NLR i mRS na otpustu ($p = 0,002$), kao i 90 dana nakon otpusta ($p = 0,001$) (Tabela 3).

U VKA-ICH grupi pacijenata srednja vrednost mRS skora na otpustu iznosila je 4,6, dok je u NOAK-ICH grupi 5,1, što je bez statističke značajnosti između grupa ($p = 0,442$). U grupi VKA-ICH srednja vrednost mRS 90

November 2024, a total of 37 patients were included in the study after applying the exclusion criteria. Based on the type of anticoagulant therapy, patients were divided into those previously treated with vitamin K antagonists (VKA-ICH) and those treated with direct oral anticoagulants (NOAC-ICH). The VKA group included 20 patients (54%), while the NOAC group included 17 patients (46%) (Figure 1).

In the VKA-ICH group, there were 11 male patients (55%) and 9 female patients (45%) with an average age of 76.3 years. In the NOAC-ICH group, there were 6 male patients (35%) and 11 female patients (65%) with an average age of 78.1 years (Table 1).

No statistically significant differences were found between the groups in terms of medical history regarding previously treated hypertension ($p = 1.000$) and diabetes mellitus ($p = 0.159$) (Table 1).

Among the available laboratory results, inflammation markers were analyzed as potential predictors of poor functional outcome in patients with ICH. No statistically significant differences were found between

Tabela 1. Sociodemografski i anamnestički podaci pacijenata sa ICH u zavisnosti od grupe, bez statistički značajne razlike

Varijable / Variables	VKA-ICH	NOAK-ICH	p-vrednost / p-value
Starost, as $\pm$ sd / Age, as $\pm$ sd	76.3 $\pm$ 7.5	78.1 $\pm$ 8.3	0.490
Pol M/Ž / Gender M/F	11/9	6/11	0.231
Prethodno lečena hipertenzija, n (%) / Previously treated hypertension, n (%)	18 (90%)	16 (94%)	1.000
Prethodno lečen dijabetes mellitus, n (%) / Previously diabetes mellitus, n (%)	1 (5%)	4 (23.5%)	0.159

Tabela 2. Upporedni prikaz laboratorijskih markera inflamacije između grupa. Vrednosti leukocita i neutrofila bile su statistički značajno veće u grupi pacijenata NOAK-ICH

Varijable / Variables	VKA-ICH	NOAK-ICH	p-value
CRP (mg/L), median (range) / CRP (mg/L), median (range)	3.9 (0.6–54.2)	2.9 (1.1–186.0)	0.704
Leukociti ($10^9/L$), mean $\pm$ sd / Leukocytes ($10^9/L$), mean $\pm$ sd	10.2 $\pm$ 3.7	12.9 $\pm$ 3.6	0.034*
Neutrofilii ($10^9/L$), mean $\pm$ sd / Neutrophils ($10^9/L$), mean $\pm$ sd	8.2 $\pm$ 3.6	10.9 $\pm$ 3.7	0.030*
Limfociti ($10^9/L$), median (range) / Lymphocytes ($10^9/L$), median (range)	1.1 (0.2–3.3)	0.8 (0.4–2.7)	0.482
NLR, median (range) / NLR, median (range)	7.2 (1.9–44.5)	14.1 (1.6–32.3)	0.104

Tabela 3. Povezanost odnosa neutrofilii/limfociti (NLR) sa funkcionalnim ishodom pacijenta sa ICH na otpustu i 90 dana nakon otpusta

Table 3. Association between neutrophil-to-lymphocyte ratio (NLR) and functional outcome in patients with ICH at discharge and 90 days post-discharge

	mRS na otpustu / mRS on discharge	mRS nakon 90 dana / mRS after 90 days
NLR	$rs = 0.50$ $p = 0.002$	$rs = 0.56$ $p = 0.001$

Table 2. Comparative presentation of laboratory markers of inflammation between groups. The values of leukocytes and neutrophils were statistically significantly higher in the NOAK-ICH patient group

the groups in CRP levels ($p = 0.704$), lymphocyte count ($p = 0.482$), or neutrophil-to-lymphocyte ratio (NLR) ($p = 0.104$). However, the NOAC-ICH group had significantly higher mean leukocyte counts ($p = 0.034$) and neutrophil counts ($p = 0.030$) (Table 2).

Our study showed a statistically significant positive correlation between NLR and mRS at discharge ($p = 0.002$) as well as 90 days after discharge ($p = 0.001$) (Table 3).

Tabela 4. Ishod pacijenata sa ICH u zavisnosti od vrste prethodne antikoagulantne terapije, bez statističke značajnosti

Varijable / Variables	VKA-ICH	NOAK-ICH	p-vrednost / p-value
mRS, median (range) / mRS, median (range)	6 (1–6) mean (4.6)	6 (1–6) mean (5.1)	0.442
mRS nakon 90 dana, median (range) / mRS after 90 days, median (range)	6 (1–6) mean (4.3)	6 (1–6) mean (4.9)	0.341
Letalni ishod n (%) / Fatal outcome n (%)	11 (58%)	13 (76%)	0.238

Table 4. Patient outcomes with ICH based on the type of prior anticoagulant therapy, without statistical significance

dana nakon otpusta iznosila je 4,3, dok je u drugoj grupi ona iznosila 4,9, takođe bez statističke značajnosti između grupa ($p = 0,341$). U prvoj grupi bilo je 11 letalnih ishoda (58%), dok je u drugoj grupi bilo 13 letalnih ishoda (76%), bez statističke značajnosti ($p = 0,238$) (Tabela 4).

DISKUSIJA

Od uvođenja NOAC-a, više studija analiziralo je razlike između VKA-ICH i NOAC-ICH sa heterogenim rezultatima.

Koristeći se podacima iz Riksstroke i Švedskog registra, u studiji sa 2483 pacijenata nije pronađena značajna razlika u smrtnosti i funkcionalnom ishodu nakon 90 dana između NOAC-ICH i VKA-ICH, što je u korelaciji sa našom studijom [9].

Slični rezultati dobijeni su retrospektivnom opservacionom studijom u koju je uključeno 182 pacijenta; zaključeno je da je mortalitet podjednako visok kod pacijenata sa NOAC-ICH u odnosu na pacijente na drugim oralnim antikoagulantima [10].

Meta-analiza koja je uključivala sedam opservacionih studija pokazala je da je NOAC-ICH bio povezan sa manjim početnim volumenom hematoma i težinom moždanog udara (NIHSS) pri prijemu. VKA-ICH i NOAC-ICH imali su sličan funkcionalni ishod pri otpustu i nakon tromesečnog praćenja [11].

Naše istraživanje je u korelaciji sa meta-analizom Boulouis G. i saradnika, u koju je uključeno 12 studija i 3875 pacijenata. Nisu pronađene razlike između pacijenata sa NOAC-ICH i VKA-ICH u pogledu ukupnog mortaliteta pri otpustu, nepovoljnog funkcionalnog ishoda pri otpustu, kao i nakon tri meseca od otpusta [7].

Međunarodna multicentrična analiza upoređivala je mortalitet, funkcionalni ishod, ali i volumen intrakranijalnog krvarenja i ekspanziju hematoma između NOAC-ICH i VKA-ICH. Početni volumen ICH, ekspanzija hematoma, mortalitet nakon 90 dana i funkcionalni ishod bili su slični u obe grupe ispitanika [12].

Jedna retrospektivna studija bavila se sličnom temom. Naime, Malgorzata Miller i saradnici, analizira-

In the VKA-ICH group, the mean mRS score at discharge was 4.6, while in the NOAC-ICH group it was 5.1, with no statistically significant difference between the groups ($p = 0.442$). Ninety days after discharge, the mean mRS score was 4.3 in the VKA-ICH group and 4.9 in the NOAC-ICH group, also without statistical significance ($p = 0.341$). There were 11 deaths (58%) in the VKA-ICH group and 13 deaths (76%) in the NOAC-ICH group, again without statistical significance ($p = 0.238$) (Table 4).

DISCUSSION

Since the introduction of NOACs, several studies have analyzed the differences between VKA-ICH and NOAC-ICH with heterogeneous results.

A study involving 2,483 patients, using data from Riksstroke and the Swedish Stroke Register, found no significant difference in mortality or functional outcome after 90 days between NOAC-ICH and VKA-ICH, which correlates with our study findings [9].

Similar results were obtained in a retrospective observational study that included 182 patients; it concluded that mortality was equally high in patients with NOAC-ICH compared to those on other oral anticoagulants [10].

A meta-analysis including seven observational studies showed that NOAC-ICH was associated with a smaller initial hematoma volume and lower stroke severity (NIHSS) at admission. VKA-ICH and NOAC-ICH had similar functional outcomes at discharge and after a three-month follow-up [11].

Our research aligns with a meta-analysis by Boulouis G. and colleagues, which included 12 studies and 3,875 patients. The differences between NOAC-ICH and VKA-ICH patients were not found regarding overall mortality at discharge, poor functional outcomes at discharge, or three months post-discharge [7].

An international multicenter analysis compared mortality, functional outcome, ICH volume, and hematoma expansion between NOAC-ICH and VKA-ICH. Initial ICH volume, hematoma expansion, 90-day mor-

jući 102 pacijenta sa ICH koji su primali antikoagulantnu terapiju, pokazali su da upotreba NOAK nije bila povezana sa lošijim funkcionalnim ishodom nakon ICH [13].

U pojedinim kliničkim istraživanjima, praćenjem radioloških parametara, primećeno je da pacijenti sa ICH prethodno lečeni NOAK terapijom imaju manji volumen i ekspanziju hematoma, što je ranije viđeno i na životinjskim modelima, a što se delimično može objasniti različitim farmakološkim svojstvima između ovih klasa antikoagulanata [14]. Na taj način se mogu objasniti rezultati narednih istraživanja koji nisu u saglasnosti sa našom studijom.

Kineska multicentrična klinička studija pokazala je da je ICH kod pacijenata prethodno lečenih inhibitorima faktora Xa bio povezan sa većom smrtnošću u poređenju sa pacijentima bez oralne antikoagulantne terapije, dok su pacijenti na inhibitorima faktora Xa imali bolje ishode od onih sa ICH povezanim sa varfarinom [3].

Studijom koja je ispitala 161 pacijenta sa ICH, dobijena je medijana mRS skora tri meseca nakon hospitalizacije - u grupi pacijenata NOAK-ICH iznosila je 3, dok u grupi VKA-ICH ona iznosi 4, što predstavlja statistički značajnu razliku i nije u saglasnosti sa rezultatima naše studije [14].

Istom temom bavili su se i drugi autori. Istraživanjem, u koje je uvršćeno 196 pacijenata, zaključeno je da pacijenti sa NOAC-ICH imaju lakši neurološki deficit u poređenju sa VKA-ICH [15].

Upalni mehanizmi igraju važnu ulogu u intrakranijalnom krvarenju i povezani su sa razvojem pneumonije povezane sa moždanim udarom – *stroke-associated pneumonia* (SAP). Odnos neutrofila i limfocita (NLR) je pokazan kao najbolji prediktor za pojavu SAP i loš ishod pri otpustu pacijenata sa ICH, što je u korelaciji sa našim rezultatima. U ovom radu statistički značajno veće vrednosti leukocita i neutrofila bile su u grupi NOAK – ICH, to može objasniti nešto lošiji ishod pacijenata u toj grupi, bez statističke značajnosti [16,17].

S obzirom na heterogene rezultate ovih istraživanja, ukazuje se potreba za daljim prospektivnim, multicentričnim studijama kako bi se omogućila detaljnija analiza po tipovima antikoagulanasa, praćenje radioloških parametara i uticaj antidota na ishod ovih pacijenata.

ZAKLJUČAK

Pacijenti sa netraumatskom ICH i prethodnom terapijom VKA, u odnosu na pacijente sa prethodnom NOAK terapijom, su bez značajnih razlika u ishodu lečenja.

Sukob interesa: Nije prijavljen.

ality, and functional outcomes were similar in both groups [12].

A retrospective study conducted by Malgorzata Miller and colleagues, analyzing 102 patients with ICH on anticoagulant therapy, showed that NOAC use was not associated with worse functional outcomes after ICH [13].

In certain clinical studies, radiological parameters showed that patients with ICH previously treated with NOACs had smaller hematoma volume and expansion-this was also observed in animal models - which could be partly explained by the different pharmacological properties of these anticoagulant classes [14]. These findings might account for the results of subsequent studies that differ from ours.

A Chinese multicenter clinical study showed that ICH in patients previously treated with factor Xa inhibitors was associated with higher mortality compared to patients not on oral anticoagulants. However, patients on factor Xa inhibitors had better outcomes than those with warfarin-associated ICH [3].

A study involving 161 patients with ICH found that the median mRS score three months after hospitalization was 3 in the NOAC-ICH group, compared to 4 in the VKA-ICH group. This difference is statistically significant and conflicts with the results of our study [14].

Other authors have addressed this topic as well. A study of 196 patients concluded that patients with NOAC-ICH had milder neurological deficits than those with VKA-ICH [15].

Inflammatory mechanisms play an essential role in intracranial hemorrhage and are associated with the development of stroke-associated pneumonia (SAP). The neutrophil-to-lymphocyte ratio (NLR) best predicts SAP and poor discharge outcomes in ICH patients, which correlates with our findings. In this study, significantly higher leukocyte and neutrophil values were observed in the NOAC-ICH group, which may explain the slightly worse outcomes in that group, though without statistical significance [16,17].

Given the heterogeneous results of these studies, further prospective, multicenter studies are needed to allow for more detailed analysis by anticoagulant type, radiological parameter monitoring, and the impact of reversal agents on patient outcome.

CONCLUSION

Patients with non-traumatic ICH previously treated with VKAs, compared to those previously treated with NOACs, showed no significant differences in treatment outcomes.

Conflict of interest: None declared.

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UPRAVLJANJE LJUDSKIM RESURSIMA U NAMIBSKOJ POKRAJINSKOJ BOLNICI "N'GOLA KIMBANDA", ANGOLA

ORIGINALNI RAD

ORIGINAL ARTICLE

HUMAN RESOURCE MANAGEMENT AT NAMIBE PROVINCIAL HOSPITAL - N'GOLA KIMBANDA, ANGOLA

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SAŽETAK

U zdravstvenom sektoru, upravljanje ljudskim resursima uključuje planiranje, zapošljavanje, selekciju, obuku, razvoj karijere, evaluaciju učinka i promovisanje kvaliteta života radnika. Zdravstveni sektor se suočava sa problemima u upravljanju ljudskim resursima, kao što su nedostatak profesionalaca, loša raspodela funkcija, neadekvatni uslovi rada, ograničenost znanja i veština, kao i strategije upravljanja koje nisu usklađene sa potrebama stanovništva. Cilj istraživanja je da se opiše upravljanje ljudskim resursima u Namibskoj pokrajinskoj bolnici "N'Gola Kimbanda" i razvije akcioni plan za poboljšanje upravljanja.

Ključne reči: upravljanje, ljudski resursi, namibska pokrajinska bolnica, planiranje

ABSTRACT

Human resource management in the health sector encompasses planning, recruitment, selection, training, career development, performance evaluation, and efforts to enhance the quality of life for workers. However, the sector is facing a crisis due to challenges in human resource management, including workforce shortages, inefficient role distribution, inadequate working conditions, skill gaps, and management strategies that fail to align with the needs of the population. This research aims to analyze human resource management at the Namibe Provincial Hospital "N'Gola Kimbanda" and develop an action plan for its improvement.

Keywords: management, human resources, Namibe Provincial Hospital, planning

RESUMO

No sector da saúde, a gestão de recursos humanos envolve planeamento, recrutamento, seleção, treinamento, desenvolvimento de carreira, avaliação de desempenho e promoção da qualidade de vida dos trabalhadores. O sector da saúde enfrenta um colapso relacionado a problemas na gestão de recursos humanos, como a escassez de profissionais, má distribuição de funções, condições de trabalho inadequadas, limitações de conhecimento e competências, e estratégias de gestão desalinhadas com as necessidades da população. O objectivo da pesquisa é analisar a gestão de recursos humanos no Hospital Provincial do Namibe "N'Gola Kimbanda" e desenvolver um plano de acção para a melhoria dessa gestão.

Palavras-chave: gestão, recursos humanos, Hospital Provincial do Namibe, planeamento

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UVOD

U informatičkom dobu, od 1990-ih do danas, upravljanje zaposlenima sve više usvaja humanistički pristup, fokusirajući se na politike koje prepoznaju i vrednuju ljudski kapital unutar organizacija [1]. Dobar sistem upravljanja zahteva jasne ciljeve kako bi se osigurala efikasnost i efektivnost, kao i menadžere sposobne za strateško vođenje. U zdravstvenom sektoru, upravljanje ljudskim resursima uključuje planiranje, zapošljavanje, selekciju, obuku, razvoj karijere, evaluaciju učinaka i unapređenje kvaliteta života zaposlenih. Međutim, zdravstveni sektor suočava se s krizom u upravljanju ljudskim resursima, koju karakterišu nedostatak stručnog kadra, neefikasna raspodjela funkcija, neadekvatni radni uslovi, ograničenja u znanju i vještinama, kao i upravljačke strategije koje nisu usklađene s potrebama stanovništva. Ovi problemi rezultiraju stresom, nezadovoljstvom i niskim samopoštovanjem među zaposlenima, kao i nedovoljnom pomoći upitnog kvaliteta. Zbog toga je ključno da menadžeri prilagode tradicionalne prakse savremenim potrebama zaposlenih i organizacija.

Termin „ljudski resursi za zdravlje“ pojavio se 1950-ih u analizama medicinske obuke, koje je podsticala Panamerička zdravstvena organizacija [2]. Tokom 1970-ih, podržava se sistemski razvoj ljudskih resursa za zdravlje kroz program Strateške pripreme za zdravstveno osoblje [3]. Iako je Panamerička zdravstvena organizacija nastojala da definiše smernice za kontinuiranu edukaciju zdravstvenih kadrova, omogućavajući im da analiziraju svoj radni kontekst, identifikuju probleme, podstiču učešće i učestvuju u donošenju odluka, uloga ljudskih resursa u zdravstvenim sistemima dugo nije bila adekvatno vrednovana. Nedostatak stručnog kadra u mnogim zdravstvenim programima predstavljao je značajnu prepreku u postizanju zacrtanih ciljeva. Zadovoljstvo pacijenata danas je jedan od najvažnijih pokazatelja konkurentnosti medicinskih subjekata. Prepoznato je da, pored pozitivnih rezultata lečenja, element koji privlači pacijente u određeni zdravstveni centar jeste i visok kvalitet pruženih usluga. Zdravstveni menadžeri, stoga, usmeravaju svoje napore ka pravilnom upravljanju ljudskim resursima kako bi pacijentima obezbedili visokokvalitetne usluge, čime se, ujedno, povećava njihovo zadovoljstvo uslugom [4].

Ljudski resursi za zdravlje se trenutno smatraju ne samo strateškim kapitalom, već i glavnim resursom za rad svakog zdravstvenog sistema [5]. Međutim, kvalitet zdravstvenih usluga i pristup zdravstvenim uslugama zavise od ključnih faktora kao što su broj, geografska distribucija i vještine ljudskih resursa. Jedan od najvećih izazova, naročito za zemlje sa niskim prihodima, jeste organizacija radne snage, koja obuhvata obuku koja

INTRODUCTION

Since the 1990s, the information age has driven employee management toward a more humanistic approach, emphasizing policies that recognize and nurture human capital within organizations [1]. An effective management system relies on clear objectives to ensure efficiency and effectiveness, along with managers who demonstrate strong strategic leadership. In the health sector, human resource management encompasses planning, recruitment, selection, training, career development, performance evaluation, and initiatives to enhance employees' quality of life. However, the health sector is experiencing a crisis in human resource management, marked by a shortage of professional staff, inefficient role distribution, poor working conditions, skill and knowledge limitations, and management strategies misaligned with population needs. These issues lead to stress, dissatisfaction, and low self-esteem among employees, while also compromising the availability and quality of care. Therefore, it is crucial that managers adapt traditional practices to the modern needs of employees and organizations.

The term "human resources for health" emerged in the 1950s through analyses of medical training, driven by the Pan American Health Organization [2]. In the 1970s, the systemic development of human resources for health was supported through the Strategic Preparation for Health Personnel program [3]. Although the Pan American Health Organization has aimed to establish guidelines for the continuous education of health personnel, enabling them to analyze their work environment, identify challenges, foster engagement, and contribute to decision-making, the role of human resources in health systems has long been undervalued. The shortage of professional staff in many health programs has been a major obstacle to achieving established goals. Today, patient satisfaction is considered one of the key indicators of the competitiveness of healthcare organizations. It is acknowledged that, alongside positive treatment outcomes, the quality of services provided is a key factor in attracting patients to a particular health center. As a result, health managers focus their efforts on effectively managing human resources to deliver high-quality services, thereby enhancing patient satisfaction [4].

Human resources for health are now regarded not only as strategic capital but also as the primary resource driving the functioning of any health system [5]. However, the quality and accessibility of health services depend on key factors such as the number, geographical distribution, and skills of the healthcare workforce. One of the biggest challenges, particularly for low-income countries, is workforce organization.

nije usmerena na potrebe stanovništva, nizak kapacitet radnika da odgovore na zahteve korisnika, kao i poteškoće u privlačenju i zadržavanju stručnjaka. Štaviše, postoji hitna potreba da se obezbedi pravična i efikasna raspodela ljudskih resursa [5]. Imajući to u vidu, ključno je da se politike upravljanja zdravstvenim ljudskim resursima razvijaju strateški kako bi se poboljšala distribucija, obuka i kvalifikacije stručnjaka, posebno u zemljama sa nižim prihodima.

Situacija i problemi u vezi sa zdravstvenim kadrovima u Angoli

Prema Osnovnom zakonu o nacionalnom zdravstvenom sistemu Angole [6], država je obavezna da obezbedi univerzalni pristup zdravstvenoj zaštiti, u okviru raspoloživih ljudskih, tehničkih i finansijskih resursa. Štaviše, obuka i profesionalni razvoj, uključujući stalnu obuku u zdravstvenom sektoru, smatraju se osnovnim ciljevima za kontinuirani razvoj sistema.

Razvoj ljudskih resursa u zdravstvu u Angoli, pod kontrolom Ministarstva zdravlja, beleži značajan napredak u ukupnom broju kadrova na centralnom nivou u poslednjih pet godina, posebno u oblastima medicine, medicinskih sestara, dijagnostičkih tehničara i bolničara, što je omogućilo pravovremena rešenja. Prema trenutnim pokazateljima, na svakih 10 000 stanovnika dolaze dva lekara (2/10 000), devetnaest medicinskih sestara (19/10 000), četiri dijagnostička i terapijska tehničara (4/10 000), pet bolničkih pomoćnih radnika (5/10 000) i jedanaest radnika opšteg režima (11/10 000). Pored toga, postoji asimetrična geografska raspodela osoblja u sektoru, što predstavlja značajan izazov za Program planiranja, upravljanja i razvoja ljudskih resursa [7]. U Angoli postoje značajne varijacije u medicinskoj gustini među različitim provincijama i opštinama, sa većom koncentracijom profesionalaca u urbanim područjima, što se negativno odražava na ruralna i teško dostupna područja. Ovo doprinosi nejednakostima u kvalitetu pruženih usluga, što rezultira pretrpanošću bolnica, kašnjenjem u zbrinjavanju i dugim listama čekanja za hirurške intervencije. U mnogim slučajevima, ovi faktori su povezani s povećanom smrtnošću.

U 2020. godini, procena koju je sproveo Nacionalni program za kontrolu zanemarenih tropskih bolesti otkrila je nedostatak obuke i ograničene kapacitete među nekim pokrajinskim i opštinskim menadžerima u oblastima pogođenim zanemarenim tropskim bolestima [8]. Istraživanje je otkrilo da su intervjuisani zdravstveni radnici imali vrlo ograničeno znanje o patofiziologiji i metodama kontrole zanemarenih tropskih bolesti u Angoli. Ovi rezultati naglašavaju hitnu potrebu za ulaganjem u profesionalni razvoj kako bi se

This includes training that is not aligned with the population's needs, limited capacity among workers to meet user demands, and difficulties in attracting and retaining skilled professionals. Moreover, there is an urgent need to ensure a fair and efficient distribution of human resources. To address this, it is essential to develop health human resource management policies strategically, aimed at improving the distribution, training, and qualifications of professionals, particularly in lower-income countries.

The health workforce challenges and issues in Angola

According to the Basic Law on the National Health System of Angola [6], the state is responsible for ensuring universal access to healthcare, within the limits of available human, technical, and financial resources. Furthermore, training and professional development, including ongoing education in the health sector, are recognized as essential for the system's continuous advancement.

The development of human resources for health in Angola, overseen by the Ministry of Health, has made significant progress over the past five years, particularly in the fields of medicine, nursing, diagnostic technology, and paramedics. This growth has facilitated more timely and effective solutions to healthcare challenges. Current indicators show that for every 10,000 inhabitants, there are two doctors (2/10,000), nineteen nurses (19/10,000), four diagnostic and therapeutic technicians (4/10,000), five hospital auxiliary workers (5/10,000), and eleven general workers (11/10,000). Additionally, the unequal geographical distribution of personnel in the sector poses a significant challenge for the Human Resources Planning, Management, and Development Program [7]. In Angola, there are notable disparities in medical density across provinces and municipalities, with a higher concentration of professionals in urban areas. This imbalance negatively affects rural and remote regions, contributing to inequalities in the quality of services. As a result, there are issues such as hospital overcrowding, delays in care, and long waiting lists for surgical procedures. In many cases, these factors are linked to higher mortality rates.

In 2020, an assessment by the National Neglected Tropical Disease Control Program revealed a lack of training and limited capacity among provincial and municipal managers in areas affected by neglected tropical diseases [8]. The research found that the health workers interviewed had limited knowledge of the pathophysiology and control methods for neglected tropical diseases in Angola. These findings underscore the urgent need to invest in professional development

osigurala pravilna implementacija tehničkih smernica za programe kontrole zanemarenih tropskih bolesti na svim nivoima [8].

Nejednakosti u univerzalnom pristupu zdravstvenim uslugama, slab sistem upućivanja i kontrauputa na tri nivoa zaštite, nedostatak ljudskih resursa u količini i kvalitetu, nejednakost u njihovoj raspodeli između urbanih i ruralnih sredina, kao i neadekvatno upravljanje lekovima i medicinskim sredstvima, doveli su do nefikasnog upravljanja i regulisanja Nacionalnog zdravstvenog sistema Angole. Ovo je uzrokovalo pogoršanje zdravstvenog stanja stanovništva, koje je rezultat dvostrukog tereta zaraznih i hroničnih nezaraznih bolesti, što je dovelo do povećanja stope morbiditeta i mortaliteta, naročito u najugroženijim grupama [9].

Značaj upravljanja ljudskim resursima u zdravstvenim ustanovama

U dinamičnom okruženju u kojem se informacije brzo šire, zdravstvene ustanove sve više moraju da se suočavaju sa izazovom da budu kreativne, inovativne i efikasne u upravljanju troškovima. Stoga, neophodne su informacije koje pomažu u razumevanju složenosti procesa upravljanja ljudskim resursima, kao i u formiranju kompetentnih i vrhunskih timova u radnom okruženju koje pruža sigurnost, motivaciju i podršku, omogućavajući ljudima da daju svoj maksimum. Upravljanje ljudskim resursima u zdravstvenim organizacijama je važna komponenta kvalitetnog i efikasnog pružanja zdravstvenih usluga [10].

Među različitim elementima upravljanja, ljudi su najdinamičniji element i predstavljaju važnu imovinu u bolnicama i drugim ustanovama.

Iz perspektive Samboa [1] upravljanje ljudskim resursima je od velikog značaja jer vodi računa o osobi od njenog ulaska u ustanovu kroz formalne procedure do njenog izlaska usled penzionisanja ili napuštanja. Svetska zdravstvena organizacija [5] naglašava ključnu ulogu ljudskih resursa u zdravstvenim sistemima, koji obuhvataju različite dimenzije, poput sastava i raspodele radne snage, obuke, stručnih kvalifikacija, tržišta rada, organizacije rada, regulacije profesionalne prakse, radnih odnosa, kao i tradicionalnog upravljanja kadrovima. S druge strane, timovi ljudskih resursa u zdravstvu se bave složenim državnim propisima i sindikalnim ugovorima, kao i sve većim troškovima rada. Oni se takođe suočavaju sa jedinstvenim izazovima vezanim za bezbednost, nivo stresa i nedostatak stručnog kadra [11]. Tim za ljudske resurse odgovoran je za osiguravanje pravilne dokumentacije radnih propisa i redovno ažuriranje podataka o zaposlenima, kao i za saradnju sa pravnim odeljenjem kompanije na razvoju i implementaciji programa koji obučavaju zaposlene

to ensure the effective implementation of technical guidelines for NTD control programs at all levels [8].

Inequalities in universal access to healthcare, a weak referral and counter-referral system across all three levels of protection, shortages in both the quantity and quality of human resources, uneven distribution between urban and rural areas, and poor management of medications and medical resources have all contributed to ineffective management and regulation of Angola's National Health System. This has led to a decline in the population's health, driven by the dual burden of infectious and chronic non-communicable diseases, resulting in increased morbidity and mortality, particularly among the most vulnerable groups [9].

The importance of human resource management in healthcare institutions

In a fast-paced environment where information spreads quickly, healthcare institutions are increasingly tasked with being creative, innovative, and cost-effective. As such, access to accurate information is essential for understanding the complexities of human resource management and for building competent, high-performing teams. A supportive work environment that fosters security, motivation, and encouragement enables individuals to perform at their best. Human resource management in healthcare organizations is a critical component for ensuring the quality and efficiency of healthcare service delivery [10].

Among the various management elements, people are the most dynamic and valuable asset in hospitals and other healthcare institutions.

From Sambo's perspective [1], human resource management is crucial as it oversees an individual's journey within the institution, from their entry through formal procedures to their departure, whether through retirement or resignation. The World Health Organization [5] highlights the critical role of human resources in health systems, encompassing various dimensions such as workforce composition and distribution, training, professional qualifications, the labor market, work organization, regulation of professional practice, labor relations, and traditional personnel management. In addition, healthcare HR teams navigate complex government regulations, union contracts, and rising labor costs. They also encounter unique challenges related to security, stress levels, and staff shortages [11]. The Human Resources team is responsible for ensuring proper documentation of work regulations, regularly updating employee data, and collaborating with the legal department to develop and implement training programs that ensure compliance with the law and minimize the risk of illegal actions. Therefore, it is es-

kako da poštuju zakone i rizik od nezakonitih postupaka svedu na minimum. Stoga je ključno da organizacije imaju sveobuhvatnu viziju uloge ove oblasti, koja se fokusira na najvažniji resurs – ljude.

Cilj istraživanja je da se analizira upravljanje ljudskim resursima u Namibskoj pokrajinskoj bolnici „N’Gola Kimbanda” i razvije akcioni plan za njegovo poboljšanje. Ovaj istraživački rad temelji se na jednostavnoj deskriptivnoj studiji, koja koristi kvantitativni i kvalitativni pristup, s ciljem da opiše fenomen u odnosu na populaciju i identifikuje karakteristike ove populacije ili reprezentativnog uzorka.

METOD RADA

Istraživanje o upravljanju ljudskim resursima u Namibskoj pokrajinskoj bolnici „N’Gola Kimbanda”, sprovedeno je u periodu od 5. do 15. februara 2025. godine u vidu ankete, u kojoj je učestvovalo 20 zaposlenih koji obuhvataju načelnike i zamenike upravnika odeljenja ortopedije, eksternih konsultacija, laboratorije, urgentne službe (između ostalih), kao i odgovorne za ljudske resurse i odeljenje kontinuiranog usavršavanja. Među ispitanicima bilo je 14 stručnjaka ženskog pola i šest stručnjaka muškog pola. Što se tiče starosti anketiranih stručnjaka, šest stručnjaka pripada starosnom rasponu od 41 do 50 godina, devet stručnjaka starosnom rasponu od 31 do 40 godina, i pet stručnjaka rasponu od 21 do 30 godina. Što se tiče radnog staža, 12 ispitanika ima više od 10 godina radnog staža, dok 6 ispitanika stručnjaka ima manje od 10 godina radnog staža.

Kada je reč o našem istraživanju, važno je napomenuti da su ispitanici stručnjaci pokazali visok nivo volje i spremnosti da odvoje vreme za učešće, s obzirom na to da su, kao načelnici i zamenici direktora, imali ključnu ulogu u upravljanju i svakodnevnom funkcionisanju bolnice. Njihova iskustva i uvidi pružaju dragocenu perspektivu na efikasnost politike ljudskih resursa, omogućavajući dublju analizu procesa upravljanja. Anketu je sprovedena tako što je ispitanicima prvo opisana svrha istraživanja, a pitanja sa ponuđenim odgovorima na skali od 1 do 4 su prevedena na njihov maternji jezik i poslata putem imejla. Ispitanicima je ponuđen intervju za eventualne nedoumice u vezi sa pitanjima i odgovorima. Ispitanici su popunili upitnik svojeručno, a dobijeni odgovori su skenirani za kasniju analizu. Važno je naglasiti da su dobijeni odgovori anonimni.

Instrument istraživanja bio je upitnik za brzu procenu upravljanja ljudskim resursima, koji je originalno razvila Svetska zdravstvena organizacija 2004. godine, s ciljem procene aspekata upravljanja ljudskim resursima u zdravstvenom sektoru. U našem istraživanju je korišćeno treće izdanje upitnika, koje je kreirano uz pomoć Američke organizacije za međunarodni razvoj

sential for organizations to adopt a comprehensive view of this field, focusing on the most valuable resource – people.

The aim of this research is to analyze the management of human resources at the Namibe Provincial Hospital “N’Gola Kimbanda” and develop an action plan for its improvement. This study employs a descriptive design, utilizing both quantitative and qualitative approaches to describe the phenomenon within the population and identify the characteristics of the population or a representative sample.

METHOD

Research on human resource management at Namibe Provincial Hospital “N’Gola Kimbanda” was conducted from February 5 to 15, 2025, through a survey. The survey included 20 participants, comprising department heads and deputy heads from orthopedics, external consultations, laboratories, emergency services, and other departments, as well as those responsible for human resources and the department of continuous education. Among the respondents, there were 14 female professional and six male professionals. In terms of age, six respondents were between 41 and 50 years old, nine were between 31 and 40 years old, and five were between 21 and 30 years old. Regarding seniority, 12 respondents had more than 10 years of experience, while six had less than 10 years of experience. It is important to note that the professionals involved in our research demonstrated a strong willingness to participate, especially given their key roles as heads and deputy directors, which were crucial to the management and daily operations of the hospital. Their experiences and insights offer a valuable perspective on the effectiveness of HR policies, allowing for a more in-depth analysis of the management process. The survey began by explaining the research purpose to the respondents. The questions, with answers on a scale of 1 to 4, were translated into their native language and sent via email. Respondents were offered the option of an interview to clarify any questions or answers. The questionnaires were completed by hand, and the responses were scanned for subsequent analysis. It is important to note that all responses were kept anonymous.

The research instrument used was a questionnaire for the rapid assessment of human resource management, originally developed by the World Health Organization in 2004 to evaluate various aspects of human resource management in the health sector. Our study utilized the third edition of the questionnaire, which was updated in 2012 with the support of the American Organization for International Development [12]. The

2012. godine [12]. Prvi deo upitnika obuhvatao je socio-demografske podatke, dok je drugi deo sadržao pitanja koja su direktno povezana sa temom istraživanja: upravljanjem ljudskim resursima u Namibskoj pokrajinskoj bolnici "N'gola Kimbanda", Angola. Ponuđeni odgovori na skali od 1 do 4 ukazuju na stepen slaganja sa izjavama koje se odnose na postojanje, potpunost/razvoj i korišćenje u operativne i strateške svrhe. Na primer: 1 (delimično ili potpuno postoji), 2 (sadržaj je kompletan ili se razvija u tom smeru), 3 (sadržaj je kompletan i koristi se u svrhe za koje je razvijen), i 4 (koristi se i za strateško funkcionisanje).

Statistička analiza

Za deskripciju podataka korišćen je grafički prikaz koji prikazuje apsolutne učestalosti i relativne odnose. Povezanost između kategorija starosti i skorova po domenu procenjena je primenom Spearmanovog koeficijenta korelacije rangova. Statističke hipoteze testirane su na nivou statističke značajnosti (alfa nivo) od 0,05. Svi podaci obrađeni su u IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA) softverskom paketu.

REZULTATI

Karakteristike, organizacija i distribucija profesionalaca u Namibskoj provincijskoj bolnici „N'Gola Kimbanda"

Namibska pokrajinska bolnica „N'Gola Kimbanda", koja se nalazi u ulici Amilcar Cabral, u blizini Politehničke škole Namibe, glavna je referentna jedinica u provinciji Namibe, koja se ističe po kvalitetu svojih usluga i smeštajnom kapacitetu. Bolnica nudi širok spektar medicinskih usluga, uključujući opštu medicinu, hirurgiju, ortopediju, oftalmologiju, stomatologiju, otorinolaringologiju, hitne slučajeve, intenzivnu negu, dermatologiju, kardiologiju, neurologiju, ambulantne konsultacije, farmaciju, snimanje, kliničku analizu, hemioterapiju, i dobrovoljno testiranje na HIV [13].

Kada je reč o broju stručnjaka, važno je istaći da Namibska pokrajinska bolnica „N'Gola Kimbanda" trenutno ima 150 medicinskih sestara, 105 terapijskih i dijagnostičkih tehničara i 147 stručnjaka za podršku. Tim profesionalaca je raspoređen na način koji garantuje efikasnu uslugu, sa sledećom raspodelom: 2 lekara, 24 medicinske sestre i 7 specijalista u hirurškom bloku; 27 lekara, 28 medicinskih sestara i 11 specijalista hitne pomoći; te 2 lekara, 15 medicinskih sestara i 5 specijalista za podršku u Jedinici intenzivne nege. Pored toga, bolnica nudi usluge kao što su ambulantne konsultacije sa 3 lekara, 5 medicinskih sestara i 6 drugih stručnjaka, te radiografija sa 4 lekara, 19 tehničara i još jednim specijalistom. U sektoru ortopedije, bolnica ima 7 lekara,

first part of the questionnaire collected socio-demographic data, while the second part included questions directly related to the research topic: human resource management at Namibe Provincial Hospital "N'gola Kimbanda," Angola. Respondents were asked to rate their agreement with statements about the existence, completeness, development, and use of various HR management practices for both operational and strategic purposes. Responses were provided on a scale of 1 to 4: 1 (partially or completely exists), 2 (content is complete or being developed in that direction), 3 (content is complete and used for its intended purpose), and 4 (it is also used for strategic functioning).

Statistical analysis

Data were described using graphical displays, showing both absolute frequencies and relative proportions. The association between age categories and domain scores was assessed using Spearman's rank correlation coefficient. Statistical hypotheses were tested at a significance level (alpha) of 0.05. All data were analyzed using the IBM SPSS Statistics 22 software package (IBM Corporation, Armonk, NY, USA).

RESULTS

Characteristics, Organization, and Distribution of Professionals at Hopital Provincial do Namibe „N'Gola Kimbanda"

The Namibe Provincial Hospital "N'Gola Kimbanda," located on Amilcar Cabral Street, near the Namibe Polytechnic School, serves as the primary reference hospital in Namibe Province, renowned for the quality of its services and capacity to accommodate patients. The hospital offers a comprehensive range of medical services, including general medicine, surgery, orthopedics, ophthalmology, dentistry, otolaryngology, emergency care, intensive care, dermatology, cardiology, neurology, outpatient consultations, pharmacy, imaging, clinical analysis, chemotherapy, and voluntary HIV testing [13].

Namibe Provincial Hospital "N'Gola Kimbanda" currently employs 150 nurses, 105 therapeutic and diagnostic technicians, and 147 support specialists. The professional team is strategically distributed to ensure efficient service delivery, with the following allocation: 2 doctors, 24 nurses, and 7 specialists in the surgical block; 27 doctors, 28 nurses, and 11 emergency specialists; and 2 doctors, 15 nurses, and 5 support specialists in the Intensive Care Unit. In addition, the hospital provides outpatient consultations with 3 doctors, 5 nurses, and 6 other specialists, as well as radiography services with 4 doctors, 19 technicians, and an additional specialist. In the orthopedics department, the team in-

18 medicinskih sestara i 7 drugih stručnjaka; u oblasti opšte medicine radi 5 lekara, 18 medicinskih sestara i 4 druga stručna lica, a na hirurgiji tim čini 6 lekara, 16 medicinskih sestara i stručnjaka drugih profila. Nedostatak specijalista i dalje predstavlja ozbiljan problem. Zbog ovog problema, mnogi pacijenti, naročito oni sa povredama glave ili zastojem u radu bubrega, moraju biti prebačeni u Centralnu bolnicu Lubango, u provinciji Huila. Ovi transferi podrazumevaju visoke troškove prevoza, hrane i smeštaja za članove porodice, pored toga što dodatno otežavaju bolničku logistiku.

Ukratko, uprkos ovim izazovima, bolnička služba za kontinuiranu edukaciju nastavlja da igra osnovnu ulogu, promovišući obrazovanje i profesionalne kvalifikacije tehničkog i administrativnog osoblja. Vođena vrednostima kao što su etika, humanizam, inovativnost, kompetentnost i institucionalna posvećenost, bolnica kontinuirano radi na unapređenju nastavnih aktivnosti, obuka i istraživačkih aktivnosti. Ona sarađuje sa odgovornim osobama u oblastima ljudskih resursa, kliničkog menadžmenta i sestrinstva, s ciljem poboljšanja stručnosti i efikasnosti zaposlenih tehničara u svim inicijativama za unapređenje [13].

cludes 7 doctors, 18 nurses, and 7 other specialists. For general medicine, there are 5 doctors, 18 nurses, and 4 other professionals, while the surgery team consists of 6 doctors, 16 nurses, and specialists from various fields. The shortage of specialists remains a significant challenge. As a result, many patients, particularly those with head injuries or kidney failure, must be transferred to Lubango Central Hospital in Huila Province. These transfers incur high costs for transportation, food, and accommodation for family members, while also adding to the logistical challenges faced by the hospital.

In summary, despite these challenges, the hospital's continuing education service remains essential, playing a key role in the education and professional development of both technical and administrative staff. Guided by values such as ethics, humanism, innovation, competence, and institutional commitment, the hospital consistently strives to enhance teaching, training, and research activities. It collaborates closely with human resources, clinical management, and nursing teams to improve the expertise and efficiency of employed technicians across all improvement initiatives [13].

Grafikon 1. Karakterizacija ispitanika prema polu

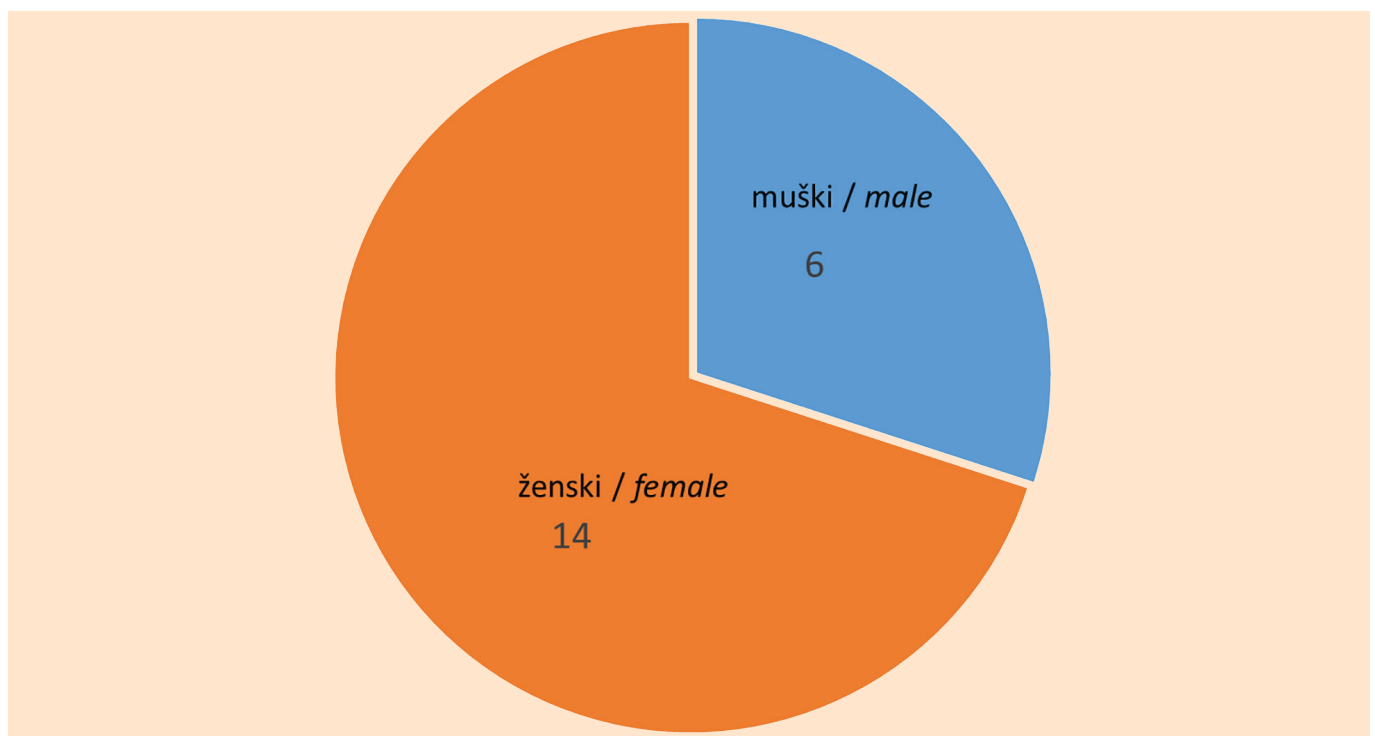


Chart 1. Respondents characterization by gender

Iz **Grafikona 2**, može se zaključiti da je od anketiranih stručnjaka njih 9 u starosnoj dobi od 31 do 40 godina, 6 u starosnoj dobi od 41 do 50 godina, a 5 u starosnoj dobi od 21 do 30 godina.

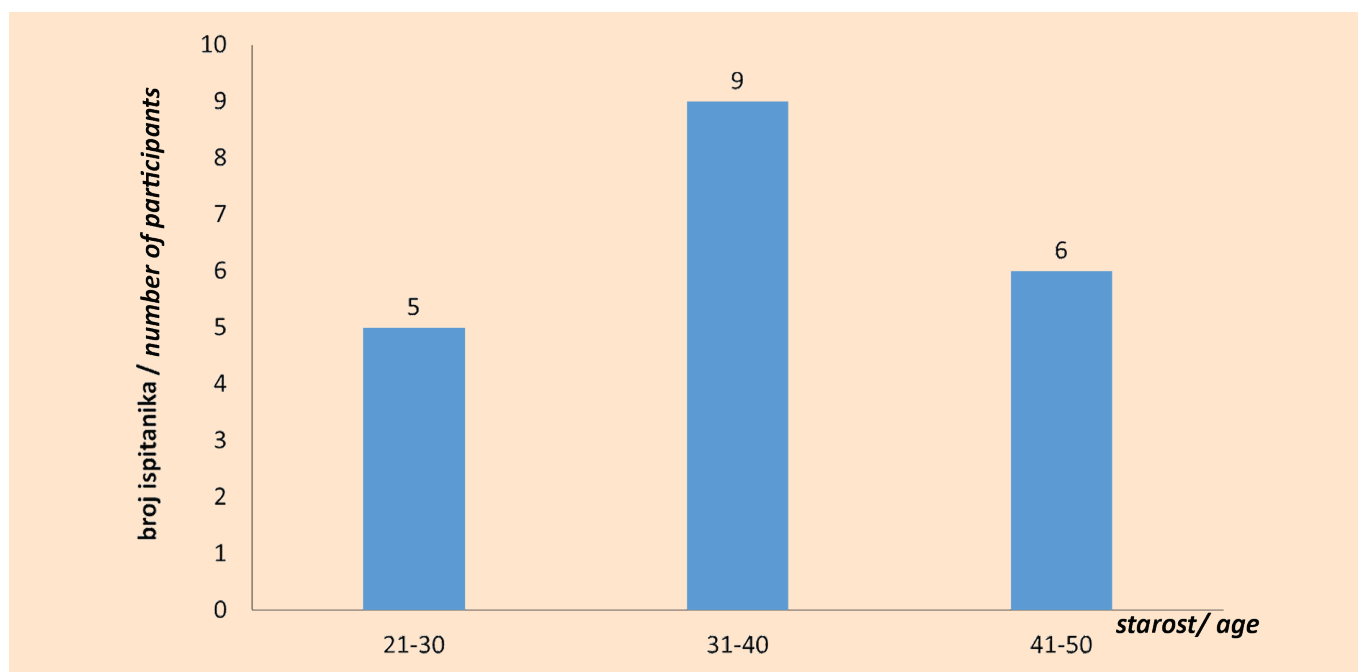
Nivo razvoja kapaciteta za upravljanje ljudskim resursima u Namibskoj pokrajinskoj bolnici „N'Gola

Based on **Chart 2**, it can be concluded that 9 of the surveyed professionals are between the ages of 31 and 40, 6 are between 41 and 50, and 5 are between 21 and 30.

The development level of human resource management capacity at Namibe Provincial Hospital "N'Go-

Grafikon 2. Karakterizacija ispitanika prema starosnoj grupi

Chart 2. Respondents characterization by age group



Kimbanda" razmatran je kroz pitanja vezana za budžet i osoblje odgovorno za funkcije upravljanja ljudskim resursima. Što se tiče osoblja zaduženog za kadrovske funkcije, 15 stručnjaka je navelo stepen 2, što ukazuje na to da postoji tim za upravljanje ljudskim resursima, ali sa ograničenim iskustvom u ovoj oblasti. Pet stručnjaka je navelo stepen 3, što ukazuje na to da postoji osoblje za ljudske resurse, ali samo za sprovođenje najosnovnijih procedura.

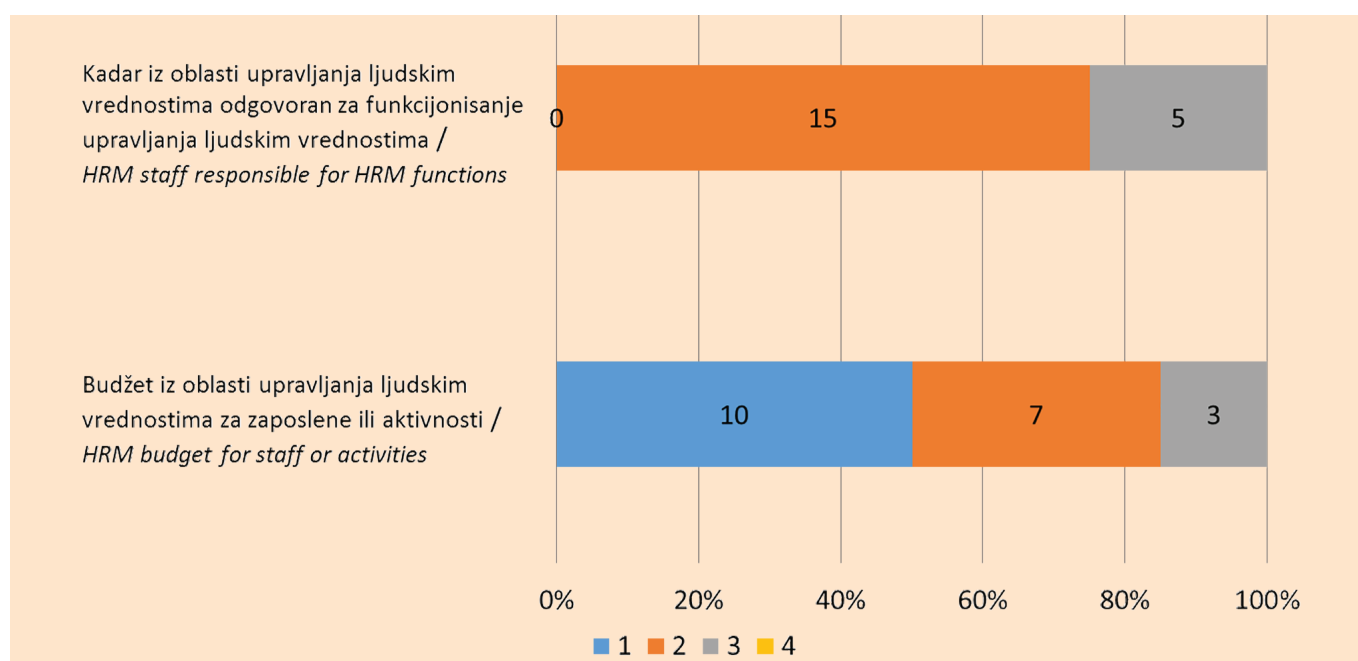
Što se tiče budžeta za upravljanje ljudskim resursima osoblja ili aktivnosti, 10 zaposlenih je odabralo

la Kimbanda" was evaluated based on factors such as the budget and the personnel responsible for human resource management functions. Regarding the staff in charge of human resource management, 15 experts rated the level as 2, indicating the presence of a human resource team, albeit with limited experience in the field. Five experts rated it at level 3, suggesting that there are human resources staff, but their responsibilities are confined to handling only the most basic procedures.

Regarding the human resource management budget for personnel or activities, 10 employees selected

Grafikon 3. Razvoj kapaciteta za upravljanje ljudskim resursima

Chart 3. Development of human resource management capacity



stepen 1, što znači da nema budžeta, dok je 7 stručnjaka odabralo stepen 2, sugerišući da postoji ograničen budžet, a troje zaposlenih stepen 3, što znači da je budžet dodeljen, ali je neredovan, i ne može se dugoročno na njega računati. Važno je istaći da, prema prikazanim podacima, nivo razvijenosti kapaciteta za upravljanje ljudskim resursima navedene bolnice predstavlja značajne izazove, iako kadrovski tim postoji, njegove funkcije su ograničene, što direktno utiče na efikasnost upravljanja ljudskim kapitalom ustanove.

Što se tiče planiranja ljudskih resursa, 3 ispitanika su odabrala stepen 2, navodeći da godišnji plan kadro-

grade 1, indicating the absence of a budget. Seven experts chose grade 2, suggesting a limited budget, while three employees selected grade 3, implying that a budget is allocated, but it is irregular and unreliable in the long term. It is important to note that, based on the data presented, the development level of human resource management capacity at the hospital reflects significant challenges. While a personnel team exists, its functions are limited, which directly impacts the efficiency of human capital management within the institution.

Regarding human resource planning, 3 respondents selected level 2, indicating that an annual per-

Grafikon 4. Razvoj sistema planiranja ljudskih resursa

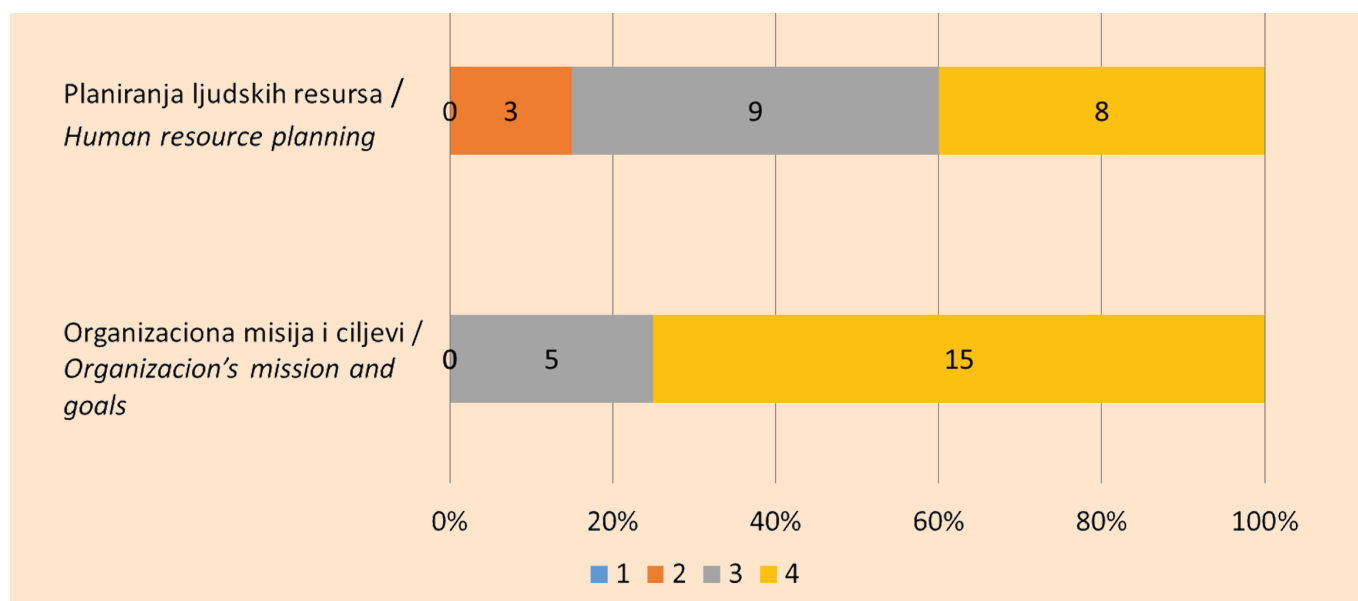


Chart 4. Development of the human resource planning system

va postoji, ali nije integrisan sa planom ustanove, njih 9 (stepen 3) smatra da plan jeste integrisan sa planom ustanove, ali nije delotvoran, dok je 8 ispitanika navelo stepen 4, što ukazuje na to da je godišnji plan kadrova integrisan sa planom ustanove i ima razvojno - stratešku svrhu. Pet ispitanika je navelo stepen 3, što znači da misija i ciljevi postoje i povezani su sa godišnjim planiranjem kadrova, dok je 15 ispitanika označilo stepen 4, što sugerise da misija i ciljevi postoje i da su povezani sa godišnjim i dugoročnim planiranjem i razvojem kadrova.

U vezi sa dosijeima zaposlenih, 7 ispitanih stručnjaka je navelo stepen 2, što ukazuje da postoje pojedinačni dosije zaposlenih ali se ne ažuriraju redovno, a dvoje je navelo stepen 3, što ukazuje na to da dosije postoje i redovno se ažuriraju, ali nema propisa o njihovom korišćenju. Čak 11 ispitanika navelo je stepen 4, što znači da su dosije o svim zaposlenima i propisi o njihovom korišćenju ažurirani.

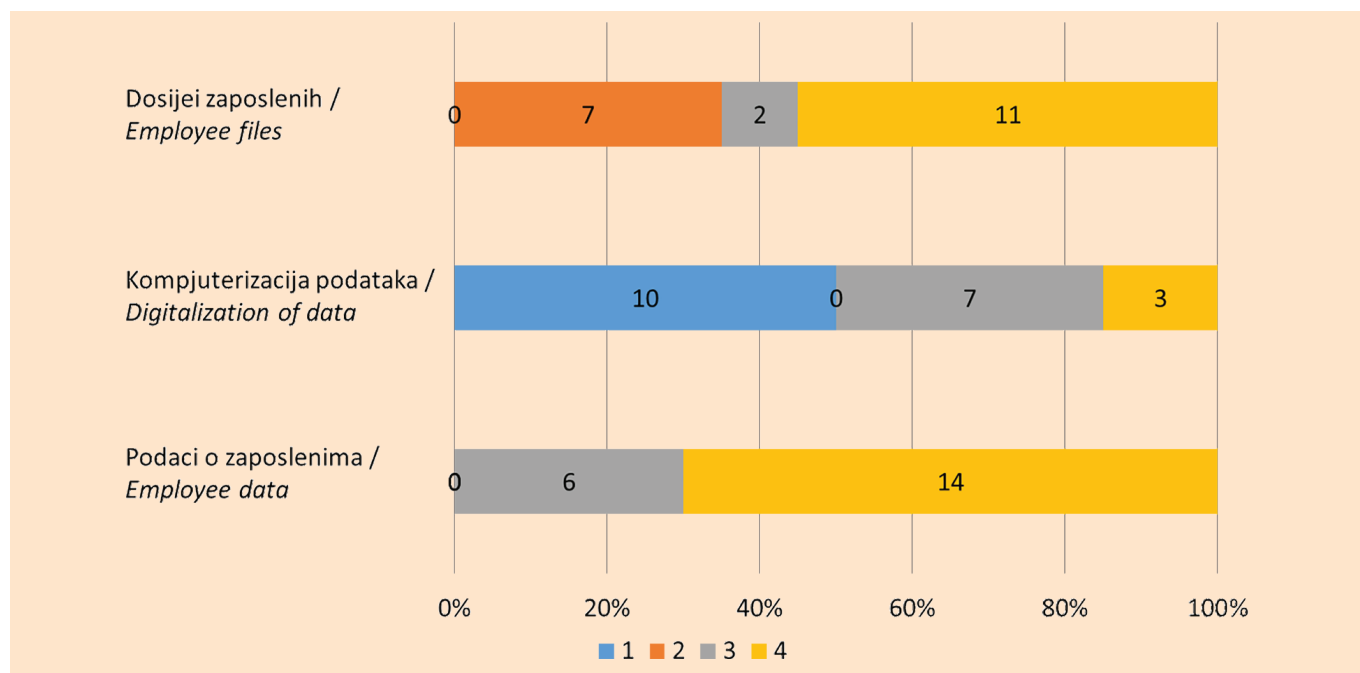
Što se tiče digitalizacije podataka, 10 ispitanika je navelo stepen 1, sugerišući da digitalizacija podataka

sonnel plan exists but is not integrated with the institution's overall plan. Nine respondents (level 3) believe the plan is integrated with the institution's plan, but lacks effectiveness. Eight respondents chose level 4, signifying that the annual personnel plan is both integrated with the institution's plan and serves a development-strategic purpose. Five respondents selected level 3, suggesting that the mission and goals are aligned with annual personnel planning, while 15 respondents chose level 4, indicating that the mission and goals are aligned with both annual and long-term personnel planning and development.

Regarding employee files, 7 of the interviewed professionals selected level 2, indicating that individual employee files exist but are not regularly updated. Two respondents chose level 3, suggesting that the files are both present and regularly updated, but there are no regulations governing their use. Notably, 11 respondents indicated level 4, meaning that the files for all employees are regularly updated, and regulations on their use are in place.

Grafikon 5. Razvoj sistema kadrovskih podataka

Chart 5. Development of the employee data system



ne postoji. Međutim, 7 ispitanika je navelo stepen 3, izjavljujući da su fajlovi nepotpuno digitalizovani, dok su 3 ispitanika izjavila da su identifikovali stepen 4, sugerišući da su fajlovi kompletno digitalizovani, redovno se ažuriraju i zaposleni su obučeni za njihovo održavanje. U pogledu podataka zaposlenih, 6 ispitanika je odabralo stepen 3, što znači da su svi podaci dostupni i ažurirani, ali se formalno ne koriste, dok je 14 ispitanika odabralo stepen 4, što sugeriše da su svi podaci dostupni i ažurirani i koriste se za razvoj kadrova.

Jedanaest ispitanika je navelo stepen 2, sugerišući da postoje izvesni naponi ali su neredovni, dvoje je navelo stepen 3, ističući da je usaglašavanje sa Zakonom o radu redovno ali ne i da ga se pridržavaju, dok je 7 ispitanika navelo stepen 4, što znači da je usaglašavanje sa zakonom o radu redovno kao i njegovo pridržavanje. Međutim, kada su u pitanju veze sa sindikatima i primenjivanje Zakona o radu, 13 ispitanika je navelo stepen 3, sugerišući da veze ne postoje, dok je 7 ispitanika odabralo stepen 4, ističući da sindikat učestvuje u rešavanju ili sprečavanju problema.

Što se tiče disciplinskih postupaka, i postupaka u vezi sa žalbama i otkazima, treba istaći da je troje ispitanika označilo stepen 3, navodeći da postoje jasna formalna uputstva, ali se ne sprovode dosledno, dok je 17 navelo stepen 4, što znači da su formalne procedure jasne, poznate svim zaposlenima i dosledno se sprovode. Kada je reč o podacima koji se odnose na priručnik o politici, 12 ispitanika je odabralo stepen 1, ukazujući na to priručnik da ne postoji, 3 ispitanika su navela stepen 3, sugerišući da postoji važeći priručnik ali nije dostupan svim zaposlenima i ne koristi se dosledno pri

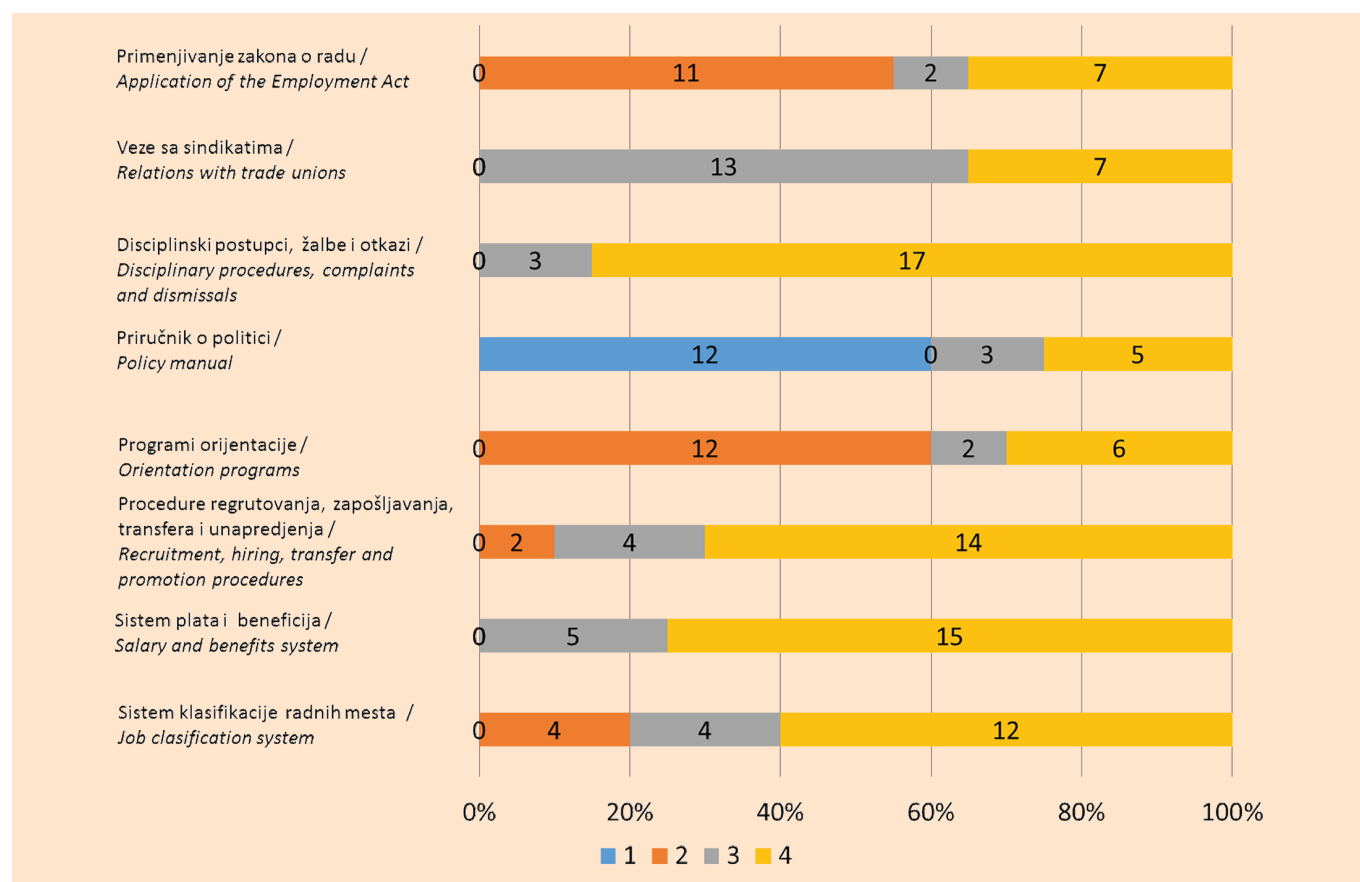
Regarding data digitization, 10 respondents selected level 1, indicating that data digitization is not implemented. However, 7 respondents chose level 3, stating that the files are partially digitized, while 3 respondents selected level 4, suggesting that the files are fully digitized, regularly updated, and employees are trained to maintain them. Regarding employee data, 6 respondents chose level 3, meaning that all data is available and up-to-date but not formally utilized, while 14 respondents selected level 4, indicating that all data is available, up-to-date, and used for staff development purposes.

Eleven respondents selected level 2, indicating that there are some efforts, but they are irregular. Two respondents chose level 3, highlighting that compliance with the Labor Law is regular but not consistently adhered to. Meanwhile, 7 respondents selected level 4, meaning that compliance with the Labor Law is both regular and fully adhered to. Regarding relations with trade unions and the application of the Labor Law, 13 respondents indicated level 3, suggesting that there are no established relations, while 7 respondents chose level 4, emphasizing that the union plays an active role in addressing or preventing issues.

Regarding disciplinary procedures, as well as procedures for appeals and dismissals, three respondents selected level 3, indicating that there are clear formal instructions, but they are not consistently implemented. In contrast, 17 respondents selected level 4, suggesting that the formal procedures are clear, well-known to all employees, and consistently enforced. When it comes to the policy manual, 12 respondents

Grafikon 6. Razvoj kadrovske prakse

Chart 6. Development of personnel practice



odlučivanju, dok je 5 navelo stepen 4, što ukazuje da postoji važeći priručnik, dostupan svim zaposlenima i koristi se dosledno za odlučivanje. Važno je istaći da je 12 anketiranih stručnjaka navelo stepen 2, otkrivajući da postoje formalni programi orijentacije ali se neredovno primenjuju; dva su navela stepen 3, ukazujući na to da se orijentacija rutinski pruža, ali nije potpuna, dok je 6 ispitanika navelo stepen 4, što znači da se orijentacija pruža rutinski i u potpunosti.

Što se tiče sistema regrutovanja, zapošljavanja, transfera i unapredjenja, dvoje anketiranih ispitanika je istaklo stepen 2, ukazujući da se postupci ne sprovode; četiri se odlučilo za stepen 3, što sugerise da se ne primenjuju dosledno; dok je 14 odabralo stepen 4, što ukazuje da se formalni sistemi koriste pri odlučivanju, kao i za praćenje.

U pogledu sistema plata i beneficija, 5 anketiranih stručnjaka je odabralo stepen 3, sugerisući da se svi zaposleni rutinski obaveštavaju, dok je 15 ispitanika odabralo stepen 4, naglašavajući da postoji formalan platni sistem koji rutinski primenjuje beneficije u svrhu razvoja. U pogledu Sistema klasifikacije radnih mesta, 4 stručnjaka su navela stepen 2, što ukazuje da postoje pokušaji, neizvesni i nekompletni, 4 su navela stepen 3, ukazujući na to da postoji sistem ali se ne koristi za druge funkcije upravljanja ljudskim resursima, dok je

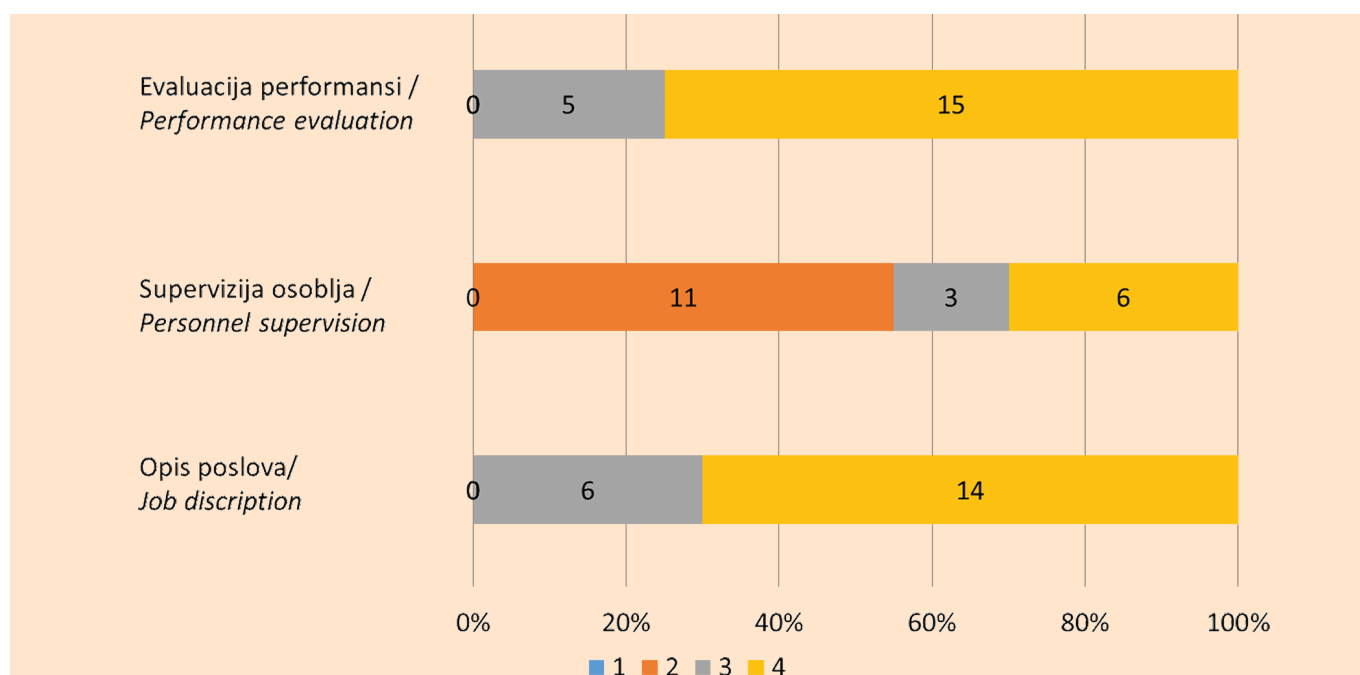
choso level 1, indicating that the manual does not exist. Three respondents selected level 3, suggesting that a valid manual exists but is not available to all employees and is not consistently used in decision-making. Meanwhile, five respondents selected level 4, indicating that the manual is valid, accessible to all employees, and consistently used for decision-making. It is also noteworthy that 12 respondents indicated level 2, revealing that there are formal orientation programs, but they are not regularly implemented. Two respondents selected level 3, indicating that orientation is routinely provided but not comprehensive, while six respondents indicated level 4, suggesting that orientation is routinely provided and thorough.

Regarding the system of recruitment, employment, transfer, and promotion, two of the surveyed respondents selected level 2, indicating that the procedures are not implemented. Four respondents chose level 3, suggesting that the procedures are not consistently applied. Meanwhile, 14 respondents selected level 4, indicating that formal systems are used both for decision-making and for ongoing monitoring.

Regarding the pay and benefits system, 5 of the surveyed experts selected level 3, indicating that all employees are routinely informed. Meanwhile, 15 respondents chose level 4, emphasizing that there is a

Grafikon 7. Razvoj upravljanja performansama

Chart 7. Development of performance management



12 profesionalaca odgovorilo odabравši stepen 4, što ukazuje da sistem postoji i zvanično se koristi za druge funkcije upravljanja ljudskim resursima.

Što se tiče evaluacija performansi, 5 ispitanika je navelo stepen 3, što znači da postoji sistem za svakog zaposlenog, ali se ne radi redovno, dok je 15 profesionalaca odgovorilo na stepen 4, što ukazuje da je evaluacija redovna i pomaže poboljšanju performansi i u procesu donošenja odluka. Jedanaest profesionalaca je navelo stepen 2, ukazujući na to da nadgledanje postoji, ali svrha i ishodi nadgledanja nisu adekvatno shvaćeni i korišćeni. Za troje profesionalaca, koji su se odlučili za stepen 3, nadgledanje je redovno i korisno za zaposlene, dok je šestoro profesionalaca navelo stepen 4, što znači da nadgledanje pomaže poboljšanju performansi i podstiče profesionalni razvoj zaposlenih.

U vezi sa opisom poslova, 6 stručnjaka je navelo stepen 3, što ukazuje da postoji specifičan opis za sve poslove, redovno se ažurira i primenjuje u proceni, dok je 14 stručnjaka navelo stepen 4, što znači da za sva radna mesta postoji konkretan opis i redovno ocenjivanje.

Kada je u pitanju razvoj kapaciteta za rukovođenje, važno je istaći da prezentovani podaci pokazuju da je od anketiranih stručnjaka njih troje navelo stepen 3, što ukazuje da postoje prilike i programi, ali samo za seniore, dok je 17 stručnjaka navelo stepen 4, što znači da su prilike i programi dostupni svima i ustanova ih koristi za razvoj kapaciteta za rukovođenje.

Što se tiče obuka kadrova, 13 ispitanika je istaklo stepen 2, ističući da se edukacija i obuka povremeno

formal pay system in place that regularly applies benefits for development purposes. In terms of the Job Classification System, 4 experts indicated level 2, suggesting that there are attempts, though uncertain and incomplete. Four others chose level 3, indicating that the system exists but is not used for other HRM functions, while 12 professionals selected level 4, indicating that the system exists and is officially used for other HRM functions.

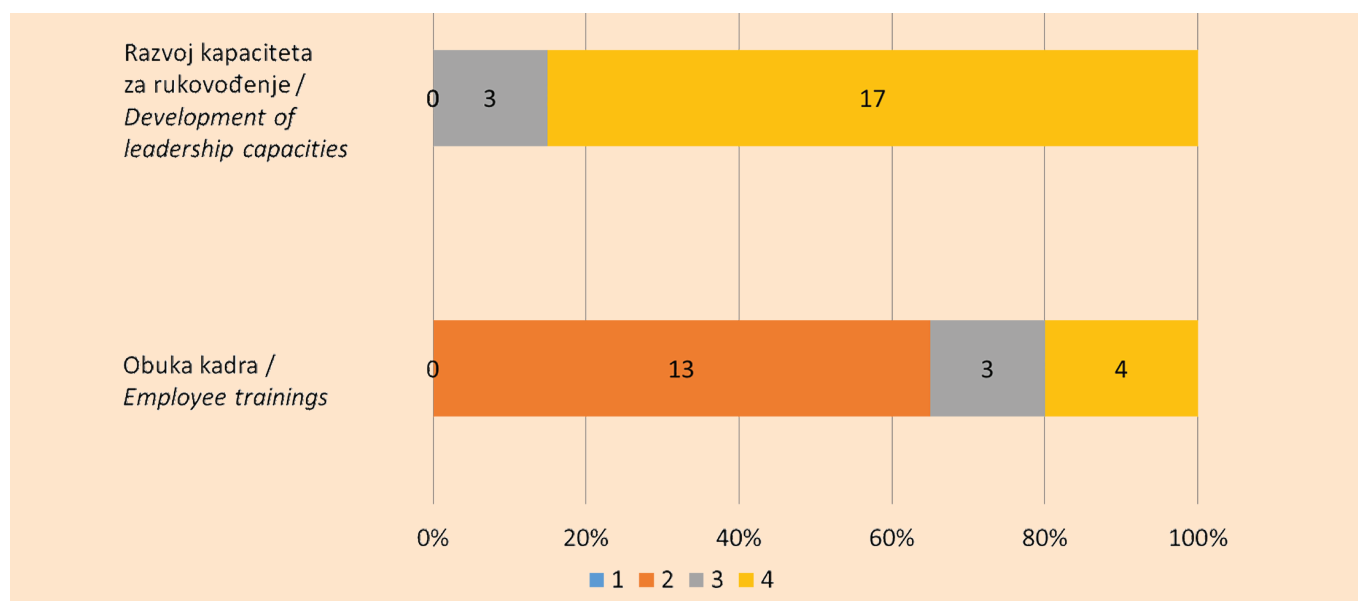
Regarding performance evaluations, five respondents selected level 3, indicating that while a system exists for each employee, it is not conducted regularly. Fifteen professionals chose level 4, signifying that evaluations are conducted consistently and contribute to both performance improvement and decision-making. Additionally, eleven professionals selected level 2, suggesting that supervision is present but its purpose and outcomes are not well understood or effectively utilized. Among those who chose level 3 (three respondents), supervision is perceived as regular and beneficial for employees. Meanwhile, six professionals selected level 4, indicating that supervision not only enhances performance but also supports professional development.

Regarding the job description, six experts selected level 3, indicating that specific descriptions exist for all positions, are regularly updated, and are used in assessments. Fourteen experts chose level 4, meaning that all jobs have clear descriptions and are subject to regular evaluation.

Regarding the development of leadership capacities, the data indicate that three surveyed professionals

Grafikon 8. Razvoj obuka

Chart 8. Training development



pružaju ali nisu prioritet; troje je odgovorilo stepenom 3, ukazujući da se obuka zasniva na stvarnim potrebama, ali nema podržavajućih mehanizama, dok su 4 ispitanika navela stepen 4, što znači da je obuka sastavni deo posla, da je zasnovana na stvarnim potrebama, i da je za njeno održavanje ustanova razvila mehanizam.

Postoji statistički značajna osrednja pozitivna povezanost kategorija starosti i upravljanja ljudskim vrednostima skora ($\rho = 0,54$; $p = 0,013$). Starije kategorije starosti povezane su sa višim skorovima za upravljanje ljudskim vrednostima.

selected level 3, meaning that opportunities and programs exist but are limited to senior staff. In contrast, 17 respondents chose level 4, signifying that such programs are available to all employees and actively used by the institution to foster leadership development.

Regarding employee training, 13 respondents selected level 2, noting that education and training are offered occasionally but are not a priority. Three respondents chose level 3, indicating that training is aligned with actual needs, though there are no supporting mechanisms in place. Meanwhile, four respondents selected level 4, meaning that training is an integral part of the job, tailored to real needs, and support-

Tabela 1. Korelaciona matrica povezanosti kategorija starosti i skorova po domenima

Table 1. Correlation matrix showing the association between age categories and scores across domains

Correlations / Correlations		Starost (kategorije) / Age (categories)	g1. Upravljanje ljudskim resursima / g1. HRM	g2. Planiranje / g2. Planning	g3. Podaci o kadrovima / g3. Staff Data	g4. Kadrovska politika i praksa / g4. Staff Policy and Practice	g5. Upravljanje performansama / g5. Performance Management
g1. Upravljanje ljudskim resursima / HRM	ρ	0,54					
	p	0,013					
g2. Planiranje / Planning	ρ	-0,14	-0,20				
	p	0,568	0,401				
g3. Podaci o kadrovima / Employee Data	ρ	-0,12	-0,01	-0,04			
	p	0,601	0,984	0,864			
g4. Kadrovska politika i praksa / Staff Policy and Practice	ρ	0,05	-0,31	0,22	-0,17		
	p	0,823	0,180	0,354	0,487		
g5. Upravljanje performansama / Performance management	ρ	0,30	0,08	-0,29	0,40	0,08	
	p	0,198	0,748	0,221	0,080	0,747	
g6. Obuka / Training	ρ	-0,32	-0,26	0,04	0,20	0,12	0,12
	p	0,170	0,269	0,861	0,394	0,610	0,627

DISKUSIJA

Uprkos činjenici da se ljudski resursi u zdravstvu Angole progresivno povećavaju kako bi se zadovoljila ogromna potražnja, analiza ljudskih resursa u Namibskoj pokrajinskoj bolnici „N'Gola Kimbanda" otkriva i napredak i izazove koji direktno utiču na kvalitet i efikasnost pruženih usluga. Sistem upravljanja ljudskim resursima ima nedostatke koji ograničavaju njegov potencijal da adekvatno zadovolji rastuću potražnju za zdravstvenom zaštitom.

Rezultati istraživanja ukazuju da, iako institucija ima tim zadužen za upravljanje ljudskim resursima, njegovo delovanje je ograničeno, jer stručnjaci za upravljanje ljudskim resursima imaju ograničeno iskustvo u toj oblasti i to samo za sprovođenje osnovnih procedura. Ovo pokazuje da, iako formalna struktura postoji, njena funkcionalnost je ograničena. Štaviše, nedostatak posebnog budžeta za upravljanje ljudskim resursima je takođe izazov sa kojim se suočava. Osim toga, budžet se dodeljuje neredovno. Ovo pojačava potrebu za boljom raspodelom resursa za jačanje ove oblasti. Još jedan kritičan aspekt jeste planiranje ljudskih resursa, koje, iako postoji, nije efikasno i nije integrisano u plan institucije. Ovaj nedostatak usklađenosti može otežati precizno predviđanje potreba za osobljem i efikasno prilagođavanje radne snage promenljivim zahtevima bolnica [14]. Štaviše, u mnogim afričkim zemljama nedostaju pouzdani podaci o zdravstvenim radnicima, uključujući njihov broj, kategorije, obrasce raspodele, nivo prakse i stope fluktuacije. Stoga mere koje se preduzimaju za poboljšanje stanja ljudskih resursa u zdravstvenom sektoru ne mogu uvek adekvatno odgovoriti na realnost [15]. Na primer, umesto obučavanja ključnih zaposlenih za određene usluge, efikasniji pristup može biti preraspoređivanje postojećih stručnjaka uz fokus na unapređenje učinka, povećanje plata te jačanje motivacije i zadržavanja tima [16]. Nedostatak kompjuterizovanih podataka jedan je od glavnih identifikovanih izazova za mnoge bolnice u Africi, ne samo u Angoli [17]. Nepotpuni ili neažurirani dosijei, kao i izostanak automatizovanog sistema, mogu otežati održavanje i korišćenje pouzdanih informacija, što negativno utiče na stručno upravljanje učinkom zaposlenih i otežava strateško donošenje odluka.

Rezultati istraživanja o opisu posla pokazuju da procesi nadzora nisu dobro shvaćeni niti korišćeni efikasno. Iako nadzor postoji, njegova primena i dalje nije jasna i delotvorna. Prema Sambo [1], da bi organizacije prevazišle izazove, neophodno je razvijanje organizacione veštine i veštine upravljanja ljudskim resursima. Međutim, iako u bolnici N'Gola Kimbanda postoje programi orijentacije za novozaposlene, njihova primena je neredovna. Ova nedoslednost može da ugrozi prilagođavanje i učinak novih zaposlenih, direktno utičući na kvalitet pru-

ed by developed mechanisms within the institution to ensure its continuity.

There is a statistically significant positive correlation between age categories and HRM scores ($\rho = 0.54$; $p = 0.013$), indicating that older age categories are associated with higher HRM scores.

DISCUSSION

Despite the progressive increase in human resources within Angolan healthcare to address the growing demand, an analysis of human resources at the Namibe Provincial Hospital "N'Gola Kimbanda", reveals both advancements and challenges that directly impact the quality and efficiency of services provided. The human resource management system has notable shortcomings that hinder its ability to effectively meet the expanding healthcare needs.

The research findings indicate that while the institution has a team responsible for human resource management, its effectiveness is limited. Human resource management experts have limited experience in the field, primarily focused on implementing basic procedures. This highlights that, although a formal structure exists, its functionality remains constrained. Moreover, the lack of a dedicated budget for human resource management poses a significant challenge, compounded by irregular budget allocations. These issues underscore the need for better resource allocation to strengthen this critical area. Another critical issue is human resource planning, which, although in place, lacks effectiveness and is not integrated into the institution's overall plan. This misalignment hampers the ability to accurately forecast staffing needs and adapt the workforce to the evolving demands of the hospital [14]. Furthermore, many African countries lack reliable data on healthcare workers, including information on their numbers, categories, distribution, levels of practice, and turnover rates. As a result, the measures implemented to improve human resources in the health sector often fail to align with the actual needs and realities on the ground [15]. For instance, rather than solely focusing on training key employees for specific services, a more effective approach could involve redeploying existing experts, with an emphasis on enhancing performance, increasing salaries, and strengthening team motivation and retention [16]. The lack of computerized data is a major challenge faced by many hospitals in Africa, including Angola [17]. Incomplete or outdated records, coupled with the absence of an automated system, hinder the ability to maintain and utilize reliable information. This not only negatively impacts the management of employee performance but also complicates the process of making informed strategic decisions.

ženih usluga. Stoga, iako strukturirani procesi postoje, postoji potreba da se poboljša razumevanje i primena praksi kao što je nadzor kako bi se osiguralo da se svi alati za upravljanje ljudima koriste optimalno i efikasno.

Pored toga, rezultati ukazuju na izazove u sprovođenju programa obuke i izgradnje kapaciteta za upravljanje kadrovima, posebno u integrisanju obuke u institucionalnu strategiju i obezbeđivanju odgovarajućih mehanizama podrške. Koliko je obuka za upravljanje kadrovima danas važna, potvrđuju drugi istraživači prema kojima menadžeri nisu samo administratori već postaju glavni pokretači kulture, razvoja talenata i uspeha organizacije [18]. Rezultati istraživanja su podložni ograničenjima ankete, kao što su davanje poželjnih odgovora, neznanje, neobaveštenost, ili nerazumevanje. Shodno tome, ovo istraživanje je podstaklo ispitanike da strateški razmotre određena pitanja o kojima možda ranije nisu razmišljali, zahvaljujući strukturisanom pristupu upitnika [12]. Da bi se izgradio željeni sistemi upravljanja kadrovima u bolnici, važno je naglasiti da „informacije ne treba prikupljati povremeno, kada se za tim ukaže potreba, već rutinski, kroz konsolidovane mehanizme, koji odgovaraju na zahteve menadžera u donošenju odluka” [5]. Aktuelnost ovog istraživanja, potvrđuje vest da je u aprilu 2024. godine Ministarstvo zdravlja Angole započelo programe edukacije za univerzalnu zdravstvenu pokrivenost u okviru koje je planirana i obuka za upravljanje ljudskim resursima, uz podršku Svetske banke [19].

Implikacije za praksu

Uzimajući u obzir navedeno, važno je naglasiti da je upravljanje ljudskim resursima u zdravstvenom sektoru u mnogim zemljama izrazito slabo, pri čemu nedostatak kapaciteta predstavlja ključnu prepreku za uspešnu primenu intervencija u oblasti zdravstvenih ljudskih resursa. Za bolnički kadar, pokazano je da profesionalno upravljanje zdravstvenim kadrovima ima efekta na obuku, timski rad, unapređenje, autonomiju, finansijske podsticaje, ocenjivanje učinka, zadržavanje zaposlenih, motivaciju i kvalitet usluga [20,21]. Zbog toga bolnica u kojoj je urađeno istraživanje mora da ulaže u strateška rešenja, uključujući integraciju planiranja ljudskih resursa sa strateškim planiranjem ustanove, implementaciju kompjuterizovanog sistema podataka, kao i unapređenje nadzora i jačanje obuke i stručnog usavršavanja.

Prema SZO [5], većina zemalja će morati da investira u programe profesionalnog razvoja, uključujući obuku, podučavanje, mentorstvo i profesionalnu podršku za ojačani okvir upravljanja ljudskim resursima i kapacitete na svim nivoima. Mnoge zemlje će morati da pokrenu ili ojačaju programe razvoja liderstva kako bi poboljšale nadzorne kapacitete u ruralnim područ-

The results of the job description survey indicate that supervisory processes are neither well understood nor effectively utilized. While supervision is in place, its implementation remains unclear and inefficient. According to Sambo [1], overcoming organizational challenges requires the development of both organizational and human resource management skills. However, despite the existence of orientation programs for new employees at "N'Gola Kimbanda" Hospital, their implementation remains inconsistent. This inconsistency can hinder the integration and performance of new employees, directly impacting the quality of services provided. Therefore, while structured processes are in place, it is crucial to enhance the understanding and application of practices such as supervision. This will ensure that all people management tools are utilized optimally and effectively.

Additionally, the results highlight challenges in implementing training programs and capacity-building initiatives for HR management, particularly in integrating training into the institutional strategy and providing adequate support mechanisms. The growing importance of personnel management training is reinforced by other researchers, who assert that managers are not merely administrators but key drivers of organizational culture, talent development, and overall success [18]. However, the research results are subject to limitations, such as biased responses, lack of knowledge, insufficient information, or misinterpretation. As a result, this research prompted respondents to strategically consider issues they may not have previously addressed, owing to the structured approach of the questionnaire [12]. To build effective personnel management systems within the hospital, it is crucial to emphasize that “information should not be collected sporadically, as needs arise, but routinely, through established mechanisms that meet the requirements of managers in decision-making” [5]. The relevance of this research is further validated by the recent announcement that in April 2024, the Ministry of Health of Angola launched education programs for universal health coverage, which will include human resource management training, supported by the World Bank [19].

Practice implications

Given the above, it is crucial to emphasize that human resource management in the healthcare sector remains weak in many countries, with a lack of capacity being a significant barrier to the successful implementation of health human resource interventions. For hospital staff, effective management of healthcare professionals has a direct impact on training, teamwork, promotion opportunities, autonomy, financial incentives, performance appraisal, employee retention, mo-

jima i stvorile povoljno radno okruženje za privlačenje i zadržavanje zdravstvenih radnika. Na centralnom nivou, menadžeri ljudskih resursa i kreatori politika koji mogu efikasno komunicirati sa zainteresovanim stranama, analizirati i razumeti njihovu moć i interese te pregovarati o kompromisima, ključni su za razvoj dugoročno održivih kadrovskih strategija. To uključuje i strategije za poboljšanje zadržavanja zdravstvenih radnika u udaljenim i ruralnim oblastima.

U skladu s navedenim, ovo istraživanje je ukazalo na potrebu za strateškim razvojem kapaciteta za upravljanje ljudskim resursima u ovoj bolnici. To podrazumeva uspostavljanje posebnog godišnjeg budžeta i angažovanje ili obuku stručnjaka za ulogu menadžera ljudskih resursa. Jedna od prioritarnih aktivnosti bolnice jeste integracija planiranja ljudskih resursa u strateško planiranje institucije, kako bi se osigurao neophodan kadar na godišnjem i dugoročnom nivou. Implementacija kompjuterizovanog sistema za upravljanje podacima o ljudskim resursima, uz digitalizaciju svih evidencija i procesa, omogućila bi redovnu sistemsku evaluaciju učinka i ažuriranje podataka o zaposlenima. Time bi se podstaklo efikasnije i agilnije upravljanje kadrovima, kontinuirano poboljšanje učinka i profesionalni razvoj zaposlenih. Ukoliko bi se u bolnici uspostavilo nadgledanje učinka i struktuirao program obuke za upravljanje i razvoj osnovnih i liderskih veština, evaluacija bi se mogla koristiti za promovisanje i razvoj zaposlenih.

ZAKLJUČAK

Namibska pokrajinska bolnica „N'Gola Kimbanda" implementirala je pojedine strukturirane prakse u upravljanju ljudskim resursima, ali se suočava sa nizom izazova koje treba prevazići. Izazovi uključuju nedostatak adekvatnog budžeta za sektor, slabu integraciju planiranja ljudskih resursa sa širim institucionalnim planiranjem, nedostatak ažuriranih podataka o zaposlenima, neefikasan nadzor i odsustvo funkcionalnog kompjuterizovanog sistema, što sve predstavlja značajne prepreke za efikasno upravljanje.

Vredi istaći da efikasna primena strategija za unapređenje upravljanja ljudskim resursima i institucionalnih performansi predstavlja ključ za održiv uspeh institucije. Zbog toga je od presudne važnosti ulaganje u kontinuirano unapređenje, transparentnost i valorizaciju ljudskog kapitala, kako bi institucija bila spremna da se suoči sa budućim izazovima i ostvari svoje strateške ciljeve.

Zahvalnica: Laboratorija za jačanje kapaciteta i performansi zdravstvenog sistema i kadrova za zdravstvenu pravičnost, Medicinski fakultet Univerziteta u Beogradu, Srbija.

Sukob interesa: Nije prijavljen.

tivation, and service quality [20,21]. Therefore, the hospital where the research was conducted must invest in strategic solutions, including integrating human resource planning with the institution's overall strategic planning, implementing a computerized data system, enhancing supervision, and strengthening training and professional development.

According to the WHO [5], most countries will need to invest in professional development programs, such as training, coaching, mentoring, and professional support, to strengthen human resource management frameworks and capacity at all levels. Many countries will also need to initiate or enhance leadership development programs to improve supervisory capacity in rural areas and create an environment conducive to attracting and retaining healthcare workers. At the central level, HR managers and policymakers who can effectively communicate with stakeholders, analyze their power and interests, and negotiate trade-offs are essential for developing long-term, sustainable HR strategies. These strategies should include measures to improve the retention of healthcare workers in remote and rural areas.

In line with the above, this research highlights the need for strategic development of human resource management capacities within the hospital. This includes establishing a dedicated annual budget and either hiring or training experts for the role of human resources managers. One of the hospital's key priorities is integrating human resource planning into the institution's overall strategic planning to ensure the availability of necessary staff both annually and long-term. The implementation of a computerized system for managing human resource data, along with the digitization of all records and processes, would enable systematic, regular performance evaluations and timely updates of employee data. This would foster more efficient and agile personnel management, continuous performance improvement, and the professional development of staff. Additionally, if the hospital were to establish a performance monitoring system, structure a management training program, and develop both basic and leadership skills, evaluations could be used to support employee promotion and development.

CONCLUSION

Namibe Provincial Hospital "N'Gola Kimbanda" has implemented some structured practices in human resource management, but it faces several challenges that must be addressed. These include insufficient budgeting for the sector, poor integration of human resource planning with broader institutional planning, outdated employee data, ineffective supervision, and the absence of a functional computerized system.

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- These issues present significant barriers to effective management.
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KORELACIJA CITOGENETIKE I STEPENA FIBROZE KOSTNE SRŽI U PRIMARNOJ MIJELOFIBROZI

ORIGINALNI RAD

ORIGINAL ARTICLE

CORRELATION OF CYTOGENETICS AND GRADE OF BONE MARROW FIBROSIS IN PRIMARY MYELOFIBROSIS

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SAŽETAK

Uvod/Cilj: Primarna mijelofibroza je klonska mijeloproliferativna neoplazma koju karakterišu fibroza kostne srži i ekstramedularna hematopoeza. Fibroza često otežava aspiraciju i biopsiju kostne srži, što takođe otežava i dijagnozu bolesti. Uprkos tome, citogenetska analiza je moguća iz aspirata kostne srži ili iz periferne krvi. Kariotip je nezavisan prognostički parametar u primarnoj mijelofibrozi. Prognostički značaj stepena fibroze kostne srži u primarnoj mijelofibrozi je još uvek diskutabilan. Cilj studije bio je ispitati značaj fibroze kostne srži na ukupno preživljavanje pacijenata sa primarnom mijelofibrozo, kao i korelaciju kariotipa i stepena fibroze kostne srži ovih pacijenata.

Materijal i metode: Ispitivanje korelacije kariotipa i stepena fibroze kostne srži obuhvatilo je 120 od ukupno 136 pacijenata sa primarnom mijelofibrozo. Koristili smo stratifikaciju hromozomskih abnormalnosti prema preporukama prognostičkih scoring sistema: Lille, Mayo, Internacionalnog i Dinamičkog internacionalnog. Analiza kariotipa vršena je konvencionalnom citogenetskom metodom. Biopsije koštne srži pacijenata obojene su metodom Gordon Sweet.

Rezultati: Kod 136 pacijenata sa primarnom mijelofibrozo nije registrovana statistički značajna razlika ($p = 0,084$) u preživljavanju, bez obzira na stepen fibroze kostne srži. Takođe, nije registrovana korelacija između kariotipa ili hromozomskih aberacija različitog stepena rizika sa stepenom fibroze kostne srži (Lille $p = 0,293$; Mayo $p = 0,108$); Internacionalni prognostički scoring sistem $p = 0,086$; Dinamički internacionalni prognostni scoring sistem ($p = 0,613$) kod 120 pacijenata sa primarnom mijelofibrozo.

Zaključak: Iako nismo konstatovali korelaciju kariotipa i stepena fibroze kostne srži, smatramo da oba parametra treba da budu zastupljena u nekim od novih Prognostnih Scoring Sistema za primarnu mijelofibrozu.

Glavne reči: primarna mijelofibroza, kariotip, biopsija kostne srži

ABSTRACT

Introduction/Aim: Primary myelofibrosis is a clonal myeloproliferative neoplasm characterized by bone marrow fibrosis and extramedullary hematopoiesis. Fibrosis often complicates bone marrow aspiration and biopsy, further hindering disease diagnosis. Despite this, cytogenetic analysis is possible from bone marrow aspirate or peripheral blood. Karyotype is an independent prognostic parameter in primary myelofibrosis. The prognostic significance of bone marrow fibrosis grade in primary myelofibrosis remains debatable. This study aimed to investigate the impact of bone marrow fibrosis on overall survival in patients with primary myelofibrosis, as well as to examine the correlation between karyotype and bone marrow fibrosis grade in these patients.

Materials and Methods: The study of the correlation between karyotype and bone marrow fibrosis grade included 120 out of 136 patients with primary myelofibrosis. We used the stratification of chromosomal abnormalities according to the recommendations of prognostic scoring systems: Lille, Mayo, International, and Dynamic International. Karyotype analysis was performed using the conventional cytogenetic method. Bone marrow biopsies of patients were stained using the Gordon-Sweet method.

Results: In 136 patients with primary myelofibrosis, no statistically significant difference in survival was observed ($p = 0.084$) regardless of the bone marrow fibrosis grade. Additionally, no correlation was found between karyotype or chromosomal aberrations of varying risk levels and bone marrow fibrosis grade (Lille $p = 0.293$; Mayo $p = 0.108$; International Prognostic Scoring System $p = 0.086$; Dynamic International Prognostic Scoring System $p = 0.613$) in 120 patients with primary myelofibrosis.

Conclusion: Although we did not establish a correlation between karyotype and bone marrow fibrosis grade, we believe that both parameters should be incorporated into new prognostic scoring systems for primary myelofibrosis.

Keywords: primary myelofibrosis, karyotype, bone marrow biopsy

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UVOD

Primarna mijelofibroza (PMF) je klonska mijeloproliferativna neoplazma (MPN) koju karakterišu fibroza kostne srži (KS) i ekstramedularna hematopoeza [1,2]. Pacijenti sa PMF-om su heterogeni na prezentaciji. Poznato je da nepovoljni prognostički faktori uključuju stariju dob, prisustvo konstitucionih simptoma, anemiju, smanjen ili povišen broj leukocita, trombocitopeniju, cirkulišuće mijeloblaste i prisustvo klonskih hromozomskih aberacija [3,4].

Citogenetski podaci u PMF-i su često oskudni i neuvjerljivi. Njihov prognostički značaj ograničen je teškoćama u dobijanju metafaza dobrog kvaliteta iz aspirata KS [5]. Međutim, studije koje su izveštavale o uspešnoj citogenetici pokazale su da se rekurentne citogenetske abnormalnosti viđaju kod otprilike jedne trećine pacijenata pri postavljanju dijagnoze, i da se njihova učestalost povećava tokom bolesti. Najčešće aberacije u PMF-i (+1q, 13q-, 20q-, +9, +8) javljaju se kod dve trećine pacijenata sa patološkim kariotipom [6]. Druge abnormalnosti, kao što su balansirane translokacije, kompleksno aberantni kariotipovi i koegzistencija dva ili više nepovezana patološka klona, su retke. Ipak, citogenetika je jedan od osnovnih prognostičkih parametara u aktuelnim Prognoznim Skoring sistemima (PSS) u PMF-i.

Za razliku od citogenetike, fibroza je ključni histopatološki nalaz u biopsiji KS pacijenata sa PMF-om i predstavlja glavni dijagnostički kriterijum za PMF prema klasifikaciji Svetske zdravstvene organizacije (SZO) [7]. Fibroza je reaktivni fenomen koji nastaje zbog abnormalnosti sazrevanja megakariocita, koji oslobađaju povećane količine upalnih i fibrogenih citokina, a oni podstiču taloženje retikulina i kolagenih vlakana, stvaranje novih sudova i osteoskleroze [8].

Prema evropskom konsenzusu, fibroza KS procenjuje se u oblastima hematopoeze semikvantitativno, skalom od 4 nivoa: stepen 0 – odsutan; stepen 1 – slaba mreža retikulina sa mnogo ukrštanja, posebno u perivaskularnim područjima; stepen 2 – difuzno i gusto povećanje retikulina sa ekstenzivnim presecima, povremeno sa fokalnim snopovima kolagena i/ili fokalnom osteosklerozom; stepen 3 – difuzno i gusto povećanje retikulina sa ekstenzivnim presecima i grubim snopovima kolagena, često udruženim sa osteosklerozom [9]. Ovi kriterijumi su pojačani i revidirani novim kriterijumima SZO za dijagnozu PMF-a iz 2016. [10]. Još uvek ne postoji jasan stav o fibrozi KS kao prognostičkom parametru u PMF-u.

Cilj našeg istraživanja, čiji su rezultati predstavljeni u ovom radu, bio je ispitati postoji li korelacija između citogenetskih podataka i stepena fibroze KS u biopsiranim uzorcima pacijenata sa potvrđenom dijagnozom

INTRODUCTION

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm (MPN) characterized by bone marrow (BM) fibrosis and extramedullary hematopoiesis [1,2]. Patients with PMF present with heterogeneous clinical features. It is known that unfavorable prognostic factors include older age, the presence of constitutional symptoms, anemia, decreased or increased leukocyte count, thrombocytopenia, circulating myeloblasts, and the presence of clonal chromosomal aberrations [3,4].

Cytogenetic data in PMF are often scarce and inconclusive. Their prognostic significance is limited by the difficulty in obtaining high-quality metaphases from bone marrow aspirates [5]. However, studies reporting successful cytogenetic analysis have shown that recurrent cytogenetic abnormalities are observed in approximately one-third of patients at diagnosis, and their frequency increases throughout the disease. The most common aberrations in PMF (+1q, 13q-, 20q-, +9, +8) occur in two-thirds of patients with an abnormal karyotype [6]. Other abnormalities, such as balanced translocations, complex aberrant karyotypes, and the coexistence of two or more unrelated pathological clones, are rare. Nevertheless, cytogenetics remains one of the key prognostic parameters in current Prognostic Scoring Systems (PSS) for PMF.

Unlike cytogenetics, fibrosis is a crucial histopathological finding in BM biopsies of PMF patients and represents a primary diagnostic criterion for PMF according to the World Health Organization (WHO) classification [7]. Fibrosis is a reactive phenomenon caused by abnormal megakaryocyte maturation, leading to the release of increased amounts of inflammatory and fibrogenic cytokines. These cytokines stimulate the deposition of reticulin and collagen fibers, the formation of new blood vessels, and osteosclerosis [8].

According to the European consensus, BM fibrosis is assessed in hematopoietic areas using a semi-quantitative scale with four levels: grade 0 – absent; grade 1 – a loose network of reticulin with many intersections, especially in perivascular areas; grade 2 – diffuse and dense increase reticulin with extensive intersections, occasionally with focal bundles of collagen and/or focal osteosclerosis; grade 3 – diffuse and dense increase reticulin with extensive intersections and coarse collagen bundles, often associated with osteosclerosis [9]. These criteria were reinforced and revised by the new WHO diagnostic criteria for PMF introduced in 2016 [10]. There is still no clear consensus on BM fibrosis as a prognostic parameter in PMF.

The aim of our study, whose results are presented in this paper, was to investigate whether there is a correlation between cytogenetic data and the degree of bone marrow (BM) fibrosis in biopsied samples of pa-

PMF-a. Korelaciju smo testirali korišćenjem PSS-a (Lille, Mayo, IPSS i DIPS), koji imaju najčešću i najdužu primenu u kliničkoj praksi za prognozu PMF-a. Osim toga, ovi PSS-i jasno definišu hromozomske aberacije kao nezavisan prognostični parametar za bolesnike sa PMF-om. Svaki od primenjenih PSS-a daje stratifikaciju kariotipa, bilo da je normalan ili aberantan, kao i hromozomske aberacije u prognostične grupe različitog stepena rizika (povoljan, nepovoljan, srednje povoljan-1, srednje povoljan-2), što je olakšalo ispitivanje korelacije kariotipa, odnosno hromozomskih aberacija različitog stepena rizika, sa stepenom fibroze KS na skali od 0-3 prema evropskom konsenzusu (MF-0, MF-1, MF-2, MF-3) [9].

PACIJENTI I METODE

Pacijenti

U periodu od januara 2004. do decembra 2010. godine, na Klinici za hematologiju Univerzitetskog kliničkog centra Srbije u Beogradu, dijagnostikovana su 144 pacijenta sa PMF-om. Svi pacijenti ispunjavali su dijagnostičke kriterijume SZO za PMF [11,12]. Klinički, laboratorijski i patohistološki podaci, zajedno sa citogenetskim rezultatima, prikupljeni su retrospektivno do 2013. godine. Pacijenti sa post-politemijskom i post-esencijalnom trombocitemijskom mijelofibrozo (post-PV-MF i post-ET-MF) isključeni su iz studije.

Od 144 novodijagnostikovana pacijenata sa PMF-om, izvještaj o patohistološkim nalazima bio je dostupan za 136 pacijenata (136/144). Citogenetska analiza nije bila moguća kod 16 od 136 pacijenata (16/136). Centralni deo ispitivanja ove studije predstavljaju klinički i dijagnostički parametri 120 pacijenata kod kojih je bilo moguće ispitati korelaciju kariotipa sa stepenom fibroze KS. Njihovi podaci su bili dostupni u kliničkoj arhivi. Kod 24 pacijenta, od ukupno 144 (24/144) sa dijagnozom PMF-a, koji su lečeni na klinici u navedenom periodu, nisu mogli biti uključeni u studiju jer nisu imali jedan od dva nalaza: patohistološki ili citogenetski. U vreme prikupljanja podataka za ovu studiju, 78 pacijenata (65%) bilo je živo, dok 42 pacijenta (35%) nije preživelo.

Podaci o aspiratima i biopsijama KS korišćeni za istraživanje uzeti su iz arhive uz saglasnost pacijenata ili njihovih porodica. Studiju je odobrio Etički komitet Univerzitetskog kliničkog centra Srbije u Beogradu.

METODE

Citogenetska analiza

Konvencionalna citogenetska analiza vršena je na metafazama dobijenim iz nestimuliranih ćelija iz aspirata KS ili iz kultura periferne krvi, korišćenjem prethodno objavljene tehnike [13]. Kariotipovi su interpretirani

tients with a confirmed diagnosis of primary myelofibrosis (PMF). We tested this correlation using PSS (Lille, Mayo, IPSS, and DIPS), which are the most commonly and extensively used scoring systems in clinical practice for PMF prognosis. Additionally, these PSS clearly define chromosomal aberrations as an independent prognostic parameter for PMF patients. Each applied PSS stratifies the karyotype, whether regular or aberrant, as well as chromosomal aberrations, into prognostic groups of varying risk levels (favorable, unfavorable, intermediate-1, intermediate-2), which facilitated the examination of the correlation between karyotype, or chromosomal aberrations of different risk levels, with the degree of BM fibrosis on a scale of 0-3 according to the European consensus (MF-0, MF-1, MF-2, MF-3) [9].

PATIENTS AND METHODS

Patients

From January 2004 to December 2010, a total of 144 patients with PMF were diagnosed at the Clinic for Hematology of the University Clinical Center of Serbia in Belgrade. All patients met the WHO diagnostic criteria for PMF [11,12]. Clinical, laboratory, and pathohistological data, along with cytogenetic results, were collected retrospectively until 2013. Patients with post-polycythemia vera myelofibrosis (post-PV-MF) and post-essential thrombocythemia myelofibrosis (post-ET-MF) were excluded from the study.

Out of the 144 newly diagnosed PMF patients, pathohistological reports were available for 136 patients (136/144). Cytogenetic analysis was not possible in 16 of the 136 patients (16/136). The core focus of this study was the clinical and diagnostic parameters of 120 patients in whom the correlation between karyotype and BM fibrosis grade could be assessed. Their data were available in the clinical archives.

A total of 24 out of 144 PMF patients (24/144) diagnosed and treated at the clinic during the study period were excluded from the study because they lacked either a pathohistological or cytogenetic report. At the time of data collection for this study, 78 patients (65%) were alive, while 42 patients (35%) had not survived.

Data on BM aspirates and biopsies used for the research were obtained from the archive with the consent of the patients or their families. The Ethics Committee of the University Clinical Center of Serbia in Belgrade approved the study.

METHODS

Cytogenetic analysis

Conventional cytogenetic analysis was performed on metaphases obtained from unstimulated cells in bone

prema Međunarodnom sistemu za humanu citogenetiku nomenklaturu [14].

Patohistološka analiza

Biopsije KS obojene su metodom Gordon Sweet. Fibroza je ocenjena korišćenjem Bauermeister sistema iz 1971. godine [15] (skala 0–4) i konsenzusom revidiranog evropskog sistema (skala 0–3).

Statistika

Statistička analiza korelacije citogenetike i fibroze KS izvršena je korišćenjem nekoliko PSS-a. Preživljavanje se merilo od dijagnoze do poslednjeg kontakta ili smrti. Podaci su predstavljeni kao medijana (min-max) ili n (%). Razlika između Lille, IPSS, Mayo i DIPSS kategorija po BMF analizirana je Mann-Whitney U testom (dve grupe) i Kruskal-Wallis testom (tri ili četiri grupe). Preživljavanje je procenjeno korišćenjem Kaplan-Meier krive i Log-rank testa za grupna poređenja. Sve analize obavljene su korišćenjem SPSS 20.0 (IBM Corp.). Vrednosti verovatnoće ($p \leq 0,05$ smatrane su statistički značajnim.

REZULTATI

S obzirom na činjenicu da je fibroza KS jedan od vodećih parametara za dijagnozu PMF-a i jedan od dva parametra ispitivanja u našoj studiji, testirali smo i ukupno preživljavanje kod 136 pacijenata sa PMF-om u zavisnosti od stepena fibroze KS. Statističko ispitivanje ukupnog preživljavanja pokazalo je da se vreme preživljavanja ne razlikuje statistički značajno u odnosu na stepen fibroze KS ($p = 0,084$). Međutim, u grupi ispitanika bio je mali broj pacijenata sa fibrozom stepena 0 (MF-0), svega tri. Iz tog razloga smo iz statistike isključili grupu pacijenata sa MF-0, nakon čega smo utvrdili da postoji statistički značajna razlika ($p = 0,043$) u preživljavanju pacijenata sa fibrozom stepena MF-1, MF-2 i MF-3.

Iz ove grupe pacijenata sa PMF-om odabrali smo 120 pacijenata koji su imali kompletne kliničke, patohistološke i citogenetske podatke. U tabeli 1 prikazane su njihove karakteristike u vreme postavljanja dijagnoze. Srednja starost je bila 65,5 godina (raspon 28–80); 45 pacijenata (37,5%) bilo je mlađe od 60 godina. Odnos žena i muškaraca bio je 47/72. Medijana završetka praćenja u 2013. godini iznosila je 83 meseca, pri čemu je zabeleženo 42 (35,0%) smrtnih slučajeva. Prisustvo konstitucionih simptoma bilo je primećeno kod 23 pacijenta (19,3%), hemoglobin $< 100 \text{ g/L}$ kod 16 (13,3%), broj leukocita $< 4 \text{ ili } > 30 \times 10^9/\text{L}$ kod 15 (12,5%), broj trombocita $< 100 \times 10^9/\text{L}$ kod 9 (7,5%), cirkulišućih blasta $\geq 1\%$ kod 21 (17,5%) i splenomegalija kod 68 (56,7%) pacijenata. Normalan kariotip je bio zastupljen

marrow aspirates or peripheral blood cultures using a previously published technique [13]. Karyotypes were interpreted according to the International System for Human Cytogenetic Nomenclature [14].

Pathohistological analysis

BM biopsies were stained using the Gordon-Sweet method. Fibrosis was assessed using the Bauermeister system from 1971 [15] (scale 0–4) and the consensus of the revised European system (scale 0–3).

Statistics

Statistical analysis of the correlation between cytogenetics and BM fibrosis was performed using several PSS. Survival was measured from diagnosis to the last contact or death. Data were presented as median (min-max) or n (%). Differences between Lille, IPSS, Mayo, and DIPSS categories by BMF were analyzed using the Mann-Whitney U test (for two groups) and the Kruskal-Wallis's test (for three or four groups). Survival was estimated using the Kaplan-Meier curve and the Log-rank test for group comparisons. All analyses were conducted using SPSS 20.0 (IBM Corp.). Probability values ($p \leq 0.05$) were considered statistically significant.

RESULTS

Given that BM fibrosis is one of the key parameters for diagnosing PMF and one of the two main parameters examined in our study, we also analyzed overall survival in 136 PMF patients based on the degree of BM fibrosis. The statistical analysis of overall survival revealed that survival time did not differ significantly according to BM fibrosis grade ($p = 0.084$). However, there were only three patients with grade 0 fibrosis (MF-0) in the study group. For this reason, we excluded the MF-0 group from the statistical analysis, after which we found a statistically significant difference ($p = 0.043$) in survival among patients with fibrosis grades MF-1, MF-2, and MF-3.

From this PMF patient group, we selected 120 patients with complete clinical, pathohistological, and cytogenetic data. Table 1 presents their characteristics at the time of diagnosis. The median age was 65.5 years (range 28–80), with 45 patients (37.5%) being younger than 60 years. The female-to-male ratio was 47/72. The median follow-up duration in 2013 was 83 months, with 42 deaths (35.0%) recorded. Constitutional symptoms were observed in 23 patients (19.3%), hemoglobin $< 100 \text{ g/L}$ in 16 (13.3%), leukocyte count < 4 or $> 30 \times 10^9/\text{L}$ in 15 (12.5%), platelet count $< 100 \times 10^9/\text{L}$ in 9 (7.5%), circulating blasts $\geq 1\%$ in 21 (17.5%), and splenomegaly in 68 (56.7%) patients. A normal karyotype was present in 88 patients (88/120 or 73.3%), while 32

Tabela 1. Osnovne karakteristike 120 upisanih pacijenata

Karakteristike / Characteristics	Medijana (raspon) / Median (range)	Broj pacijenata / Number of patients	%
Godine > 60 g / Age > 60 years	65.5 (28–80)	75	62.5
Godine ≤ 60 g / Age ≤ 60 years		45	37.5
Žene/Muškarci / Female/Male		47/72	39/61
Konstituzioni simptomi / Constitutional symptoms		23	19.3
Hb < 100g/L / Hemoglobin < 100g/L	129.5 (45–169)	16	13.3
Le < 4 ili >30x10 ⁹ /L / Leukocyte count < 4 or >30x 10 ⁹ /L	11.1 (1.6–83.2)	15	12.5
Tr < 100 x 10 ⁹ /L / Platelets count < 100 x 10 ⁹ /L	687.5 (28–684)	9	7.5
Blasti u perifernoj krvi ≥1% / Circulating blasts ≥ 1%	(0–9)	21	17.5
Palpabilna splenomegalija (cm) / Palpable splenomegaly (cm)	(0–24)	68	56.7
Kariotip / Karyotype		120	
Normalan / Normal		88	73.3
Aberantan / Aberrant		32	26.7
Smrtnost / Deaths		42	35.0

Table 1. Baseline characteristics of the 120 enrolled patients

kod 88 pacijenata (88/120 ili 73,3%), a aberantan kod preostalih 32 bolesnika (32/120 ili 26,7%) (Tabela 1).

Svi pacijenti klasifikovani su prema Evropskom konsenzusu o stepenu fibroze KS [9]. Primeri morfoloških karakteristika PMF-a i stepena fibroze KS prikazani su na Slici 1. Stratifikacija pacijenata prema stepenu fibroze i citogenetskim podacima prikazani su u Tabeli 2. U redovima Tabele 2. dati su PSS-i i stratifikacija hromozomskih aberacija po prognoznim grupama različitog stepena rizika, dok su u kolonama tabele dati stratifikovani stepeni fibroze KS bolesnika sa skalom od 0-3. Distribucija broja pacijenata koji su imali adekvatan kariotip (normalan ili aberantan) ili hromozomske aberacije, određenog stepena rizika sa adekvatnim stepenom fibroze u KS prikazana je u tabeli. Pokazatelj da je distribucija pacijenata po broju i procentu tačna nalazi se u pretposlednjoj koloni, u kojoj je prikazan zbir ukupnog broja ispitanih bolesnika. Za svaki PSS ukupan broj bolesnika mora biti 120 ($n = 120$), što znači da i zbir procentualne zastupljenosti bolesnika sa odgovarajućim kariotipom ili hromozomskim aberacijama i sa određenim stepenom fibroze KS mora biti 100%.

Distribucija fibroze KS naših pacijenata ($n = 120$) bila je takva da je najveći broj ($n = 55$ ili 45,8%) imao stepen fibroze MF-2, slede pacijenti sa stepenom fibroze MF-3 ($n = 42$ ili 35%), manje je pacijenata bilo sa fibrozom MF-1 ($n = 20$ ili 16,7%), i kao što smo pomenuli, najmanje je bilo pacijenata sa fibrozom MF-0 ($n = 3$ ili 2,5%) (Tabela 2).

Statistička analiza korelacije fibroze KS i kariotipa, korišćenjem Lille PSS-a [3] za citogenetiku, nije pokazala značajnu statističku razliku ($p = 0,293$) (Tabela 2). Ne

patients (32/120 or 26.7%) had an aberrant karyotype (Table 1).

All patients were classified according to the European consensus on BM fibrosis grading [9]. Examples of the morphological characteristics of PMF and BM fibrosis grades are shown in Figure 1. The stratification of patients based on fibrosis grade and cytogenetic data is presented in Table 2. The rows of Table 2 display the PSS classifications and the stratification of chromosomal aberrations into prognostic risk groups of different levels, while the columns present the stratified BM fibrosis grades of patients on a scale from 0 to 3. The distribution of patients with an adequate karyotype (normal or aberrant) or chromosomal aberrations of

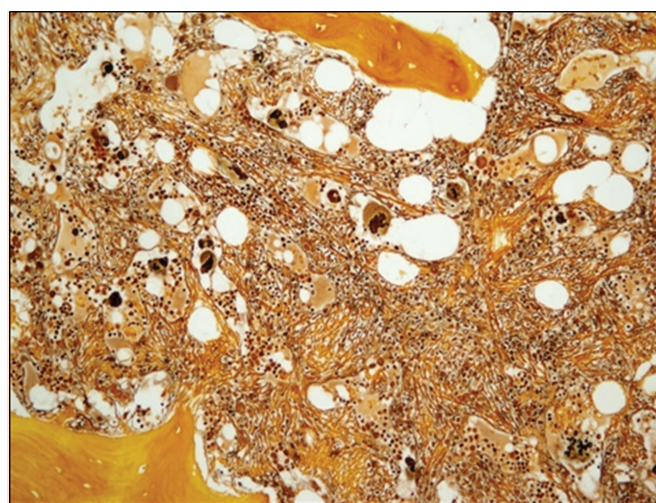
**Slika 1.** MF-3, Gordon Sweet x200, Gusta retikulinska vlakna i snopovi kolagena**Picture 1.** MF-3, Gordon Sweet x200, Dense reticulin fibers, and bundles of collagen

Tabela 2. Stratifikacija 120 pacijenata sa primarnom mijelofibrozoj prema citogenetskim podacima iz aktuelnih prognostičkih sistema bodovanja i evropskog konsenzusa o stepenovanju fibroze koštane srži**Table 2.** Stratification of 120 patients with primary myelofibrosis according to the cytogenetic data from current prognostic scoring systems and the European consensus on grading of bone marrow fibrosis

Fibroza koštane srži (FKS) (n = 136)/ Bone marrow fibrosis (BMF) (n = 136) Korelacija kariotipa i FKS (n = 120) / Correlation of karyotype and BMF (n = 120)								
PSS	Kariotip / Karyotype	Kategorija rizika / Risk category	Grade 0 (n = 3); n (%)	Grade 1 (n = 20); n (%)	Grade 2 (n = 55); n (%)	Grade 3 (n = 42); n (%)	Ukupno (n = 120) n (%)	p
Lille [3]	1. normalan / <i>normal</i>	povoljan / <i>favorable</i>	0 (0)	17 (19.3)	44 (50.0)	27 (30.7)	88 (73.3)	0.293 ^a
	2. aberantan / <i>aberrant</i>	nepovoljan / <i>unfavorable</i>	3 (9.4)	3 (9.4)	11 (34.4)	15 (46.9)	32 (26.7)	
Mayo [16]	1. normalan / <i>normal</i>	povoljan / <i>favorable</i>	0 (0)	17 (19.3)	44 (50.0)	27 (30.7)	88 (73.3)	0.108 ^b
	2. 13q- or 20q-	srednji / <i>intermediate</i>	0 (0)	0 (0)	1 (20.0)	4 (80.0)	5 (4.2)	
	3. ostale aberacije / <i>other aberrations</i>	nepovoljan / <i>unfavorable</i>	3 (9.4)	3 (9.4)	10 (37.0)	11 (40.7)	27 (22.5)	
IPSS [17]	1. +9 or 13q- or 20q-	povoljan / <i>favorable</i>	1 (12.5)	0 (0)	2 (25.0)	5 (62.5)	8 (6.7)	0.086 ^b
	2. normalan / <i>normal</i>	srednji-1 / <i>intermediate-1</i>	0 (0)	17 (19.3)	44 (50.0)	27 (30.7)	88 (73.3)	
	3. ostale aberacije / <i>other aberrations</i>	srednji-2 / <i>intermediate-2</i>	2 (9.5)	3 (14.3)	9 (42.9)	7 (33.3)	21 (17.5)	
	4. +8 ili kompleks kariotip (≥ 3 aberacija) / <i>+8 or complex karyotype (≥ 3 aberrations)</i>	nepovoljan / <i>unfavorable</i>	0 (0)	0 (0)	0 (0)	3 (100.0)	3 (2.5)	
DIPSS [18]	1. sole 13q- t/dup(1q) sole 20q- sole +9 Ostale pojedinačne aberacije / <i>other sole aberrations</i> dve aberacije isključujući nepovoljne / <i>two aberrations excluding unfavorable</i> Normalni kariotip / <i>normal karyotype</i>	povoljan / <i>favorable</i>	2 (1.9)	19 (17.4)	51 (46.8)	37 (33.9)	109 (90.8)	0.613 ^a
	2. kompleksni kariotip / <i>complex karyotype</i> (≥ 3 aberrations) sole +8 sole -5/5q- sole -7/7q- i(17q) inv(3) 12p- 11q23 Dve aberacije uključujući bar jednu nepovoljnu / <i>two aberrations including at least one unfavorable</i>	nepovoljan / <i>unfavorable</i>	1 (9.1)	1 (9.1)	4 (36.4)	5 (45.4)	11 (9.2)	

^aMann-Whitney U test ^bKruskal-Wallis test

postoji korelacija između normalnog ili aberantnog kariotipa sa određenim stepenom fibroze u KS pacijenata. U grupi pacijenata sa normalnim kariotipom (povoljan) najviše je bilo pacijenata sa fibrozom MF-2 (50,0%), zatim MF-3 (30,7%) i MF-1 (19,3%). U grupi pacijenata sa aberantnim kariotipom (nepovoljan) najviše ih je bilo sa stepenom fibroze MF-3 (46,9%), zatim MF-2 (34,4%) i pacijenata sa fibrozom MF-1 i MF-0 (9,4%) (Tabela 2).

Korišćenjem citogenetske stratifikacije Mayo PSS-a [16] za ispitivanje povezanosti kariotipa i stepena fibroze KS nije potvrđena statistički značajna razlika u učestalosti stepena fibroze KS između posmatranih grupa pacijenata sa različitim kariotipom ($p = 0,108$) (Tabela 2). Najviše pacijenata sa stepenom fibroze MF-2 (50,0%) bilo je kod pacijenata sa normalnim kariotipom (povoljan). U grupi pacijenata sa aberacijama 13q- ili 20q- (srednji) najviše je bilo pacijenata sa MF-3 (80,0%) i jedan pacijent (20,0%) sa MF-2. Nije bilo pacijenata sa stepenom fibroze KS MF-1 i MF-0.

Kod pacijenata sa drugim hromozomskim aberacijama u kariotipu, najviše je bilo pacijenata sa stepenom fibroze KS MF-3 (40,7%), slede pacijenti sa MF-2 fibrozom (37,0%), pa pacijenti sa stepenom fibroze MF-1 i MF-0 sa istom učestalošću (9,4%).

Ispitivanjem povezanosti fibroze KS i kariotipa korišćenjem IPSS-a [17], takođe je utvrđeno da nema značajne statističke razlike u učestalosti stepena fibroze KS ($p = 0,086$) (Tabela 2). Ne postoji povezanost između kariotipa i hromozomskih aberacija različitog stepena značaja (povoljan, srednji-1, srednji-2, nepovoljan) sa stepenom fibroze KS. U grupi pacijenata sa povoljnim hromozomskim aberacijama (+9 ili 13q- ili 20q-) najviše je bilo pacijenata sa fibrozom MF-3 (62,5%), zatim pacijenata sa MF-2 (25,0%), jedan pacijent je bio sa MF-0 (12,5%). Nije bilo pacijenata sa fibrozom MF-1. Distribucija stepena fibroze KS kod pacijenata sa normalnim kariotipom (srednji-1) bila je ista kao kod primene Lille i Mayo PSS-a. U grupi pacijenata sa drugim hromozomskim abnormalnostima (srednji-2) najviše je bilo pacijenata sa MF-2 (42,9%), zatim sa fibrozom MF-3 (33,3%) i pacijenti sa fibrozom MF-1 (14,3%). Najmanje je bilo pacijenata sa fibrozom MF-0 (9,5%). U grupi pacijenata sa trizomijom hromozoma 8 i kompleksnim kariotipom (nepovoljan) bili su samo pacijenti sa fibrozom MF-3 (100,0%).

Primenom DIPSS-a [18] takođe nije registrovana statistički značajna povezanost ($p = 0,613$) između citogenetskih rezultata i dokumentovanog stepena fibroze KS. Prema preporukama DIPSS-a, pacijenti su svrstani u samo dve prognozne kategorije na osnovu nalaza kariotipa. Povoljnu kategoriju čine hromozomske aberacije koje predstavljaju dobar prognozni parametar, kao i u prethodno pomenutim PSS-ima, neke druge aber-

a specific risk level, along with the corresponding BM fibrosis grade, is illustrated in the table.

An indicator of the accuracy of the distribution of patients by number and percentage is provided in the penultimate column, which displays the total number of patients examined. For each PSS, the total number of patients must be 120 ($n = 120$), meaning that the sum of the percentage representation of patients with a corresponding karyotype or chromosomal aberrations and a specific bone marrow (BM) fibrosis grade must equal 100%.

The distribution of BM fibrosis among our patients ($n = 120$) revealed that the highest number ($n = 55$, 45.8%) had fibrosis grade MF-2, followed by patients with fibrosis grade MF-3 ($n = 42$, 35%). Fewer patients had fibrosis grade MF-1 ($n = 20$ or 16.7%), and as mentioned, the lowest number had fibrosis grade MF-0 ($n = 3$ or 2.5%) (Table 2).

Statistical analysis of the correlation between BM fibrosis and karyotype, using the Lille PSS [3] for cytogenetics, did not reveal a statistically significant difference ($p = 0.293$) (Table 2). There was no correlation between a regular or aberrant karyotype and the degree of bone marrow (BM) fibrosis in patients. Among patients with a normal karyotype (favorable), the majority had fibrosis MF-2 (50.0%), followed by MF-3 (30.7%) and MF-1 (19.3%). Among patients with an aberrant karyotype (unfavorable), the highest proportion had a fibrosis grade of MF-3 (46.9%), followed by MF-2 (34.4%), and those with fibrosis grades of MF-1 and MF-0 (9.4%) (Table 2).

Using the cytogenetic stratification of the Mayo PSS [16] to examine the association between karyotype and BM fibrosis grade, no statistically significant difference was confirmed in the frequency of BM fibrosis grades among the observed patient groups with different karyotypes ($p = 0.108$) (Table 2). The highest number of patients with fibrosis grade MF-2 (50.0%) was found in those with a normal karyotype (favorable). In the group of patients with 13q- or 20q- aberrations (intermediate), most had MF-3 (80.0%), while one patient (20.0%) had MF-2. There were no patients with BM fibrosis grades MF-1 or MF-0.

Among patients with other chromosomal aberrations in their karyotype, the majority had BM fibrosis grade MF-3 (40.7%), followed by MF-2 (37.0%), while MF-1 and MF-0 were present at the same frequency (9.4%).

Examining the association between BM fibrosis and karyotype using IPSS [17] also showed no significant statistical difference in the frequency of BM fibrosis grades ($p = 0.086$) (Table 2). There was no correlation between karyotype and chromosomal aberrations of different

racije (t/dup(1q), druge solo i dvostruke povoljne aberacije)), kao i normalan kariotip. Nepovoljnu kategoriju predstavljaju nepovoljne hromozomske aberacije kao i u IPSS-u (+8, kompleksan kariotip), kao i druge (-5/5q-, -7/7q-, i(17q), inv(3), 12p-, 11q23). U grupi pacijenata sa povoljnim kariotipskim karakteristikama najviše ih je bilo sa stepenom fibroze MF-2 (46,8%), zatim slede pacijenti sa MF-3 stepenom fibroze (33,9%), zatim pacijenti sa MF-1 (17,4%), a najmanje je bilo pacijenata sa MF-0 stepenom fibroze KS (1,9%). Kod pacijenata sa nepovoljnim kariotipskim izmenama, stepen fibroze KS MF-3 bio je registrovan kod najvećeg broja pacijenata (45,4%), zatim slede pacijenti sa fibrozom gradusa MF-2 (36,4%). Pacijenti sa MF-1 i MF-0 stepenom fibroze bili su zastupljeni sa istom učestalošću (9,1%).

DISKUSIJA

Ukupno preživljavanje u PMF-i zavisi od kliničkih, laboratorijskih, citogenetskih i molekularnih karakteristika bolesti. Na njega utiču starost pacijenta, fizičko stanje i komorbiditeti. U to svrhu su kreirani mnogi PSS-i, koji kombinacijom svih ovih podataka omogućavaju svrstavanje pacijenata sa PMF-om u kategorije sa različitim nivoom rizika. Imperativ stratifikacije pacijenata sa PMF-om na osnovu stepena rizika je odabir što povoljnije, personalizovane terapije, koja će omogućiti pacijentu kvalitetniji život i duže preživljavanje.

U istoriji primene PSS-a u PMF-i, citogenetika je zauzela poziciju nezavisnog parametra u prognozi bolesti. U prvim ispitivanjima preživljavanja pacijenata u odnosu na citogenetiku, procenjeno je da je normalan kariotip povoljan, a aberantan kariotip nepovoljan prognozni parametar [3]. Kasnije je ustanovljeno da su neke hromozomske aberacije (+9, 13q-, 20q-) bile povezane sa dužim preživljavanjem u odnosu na normalan kariotip. Ove aberacije definisane su kao dobar prognozni parametar [16]. Neki drugi kariotipski rearanžmani (+8 ili kompleksani kariotip, -5/5q-, -7/7q-, 11q23, i(17q), inv(3), 12p-) dovođeni su u vezu sa kratkim preživljavanjem pacijenata, i po drugim PSS-a definisani su kao loš prognozni parametar [17,18]. Sve u svemu, citogenetska analiza i kariotip imaju značajno mesto u dijagnostici PMF-a, ali još značajnije mesto u prognozi PMF-a.

Suprotna je situacija sa stepenom fibroze KS kod PMF-a i uopšte kod MPN-i. Fibroza KS značajno različitog stepena može biti povezana sa tri glavna entiteta MPN-i (policitemijom verom – PV, esencijalnom trombocitemijom – ET i primarnom mijelofibrozaom – PMF), bilo pri prezentaciji, kao kod PMF-e, ili nakon progresije bolesti PV-e i ET-e. Ažurirana klasifikacija SZO iz 2008. usvojila je Evropski konsenzus o ocenjivanju fibroze KS [9], četvorostepeni sistem sa ocenama 0–3 [7]. Razvoj

prognostic significance (favorable, intermediate-1, intermediate-2, unfavorable) with BM fibrosis grade.

Among patients with favorable chromosomal aberrations (+9 or 13q- or 20q-), the majority had a fibrosis grade of MF-3 (62.5%), followed by MF-2 (25.0%), while one patient had a grade of MF-0 (12.5%). There were no patients with MF-1 fibrosis. The distribution of BM fibrosis grades in patients with a normal karyotype (intermediate-1) was the same as in the Lille and Mayo PSS classifications.

In the group of patients with other chromosomal abnormalities (intermediate-2), most had MF-2 (42.9%), followed by MF-3 (33.3%), while MF-1 fibrosis was present in 14.3% of cases. The lowest number of patients had MF-0 fibrosis (9.5%). In the group of patients with on chromosome 8 and a complex karyotype (unfavorable), all patients had MF-3 fibrosis (100.0%).

The application of DIPSS [18] also did not reveal a statistically significant association ($p = 0.613$) between cytogenetic results and the documented degree of bone marrow fibrosis (KS). According to DIPSS recommendations, patients were classified into only two prognostic categories based on karyotype findings. The favorable category includes chromosomal aberrations that are considered suitable prognostic parameters, as in the previously mentioned PSSs, along with some other aberrations (t/dup(1q), other solo and double favorable aberrations), as well as a normal karyotype. The unfavorable category comprises poor prognostic chromosomal aberrations, such as those found in IPSS (+8, complex karyotype), along with others, including (-5/5q-, -7/7q-, i(17q), inv(3), 12p-, and 11q23).

Among patients with favorable karyotypic characteristics, the majority had fibrosis grade MF-2 (46.8%), followed by those with fibrosis grade MF-3 (33.9%), then those with MF-1 (17.4%), while the smallest number of patients had MF-0 fibrosis (1.9%). Among patients with unfavorable karyotypic alterations, fibrosis grade MF-3 was the most common (45.4%), followed by patients with MF-2 fibrosis (36.4%). Patients with MF-1 and MF-0 fibrosis grades were represented with the same frequency (9.1%).

DISCUSSION

Overall survival in PMF depends on the disease's clinical, laboratory, cytogenetic, and molecular characteristics. It is influenced by patient age, physical condition, and comorbidities. To address this, numerous PSSs have been developed, integrating these factors to categorize PMF patients into different risk levels. The imperative of risk stratification in PMF is to select the most favorable, personalized therapy that ensures a better quality of life and prolonged survival.

fibroze KS predstavlja postepenu evoluciju odsutne ili minimalne retikulinske fibroze, do izražene retikulinske i/ili kolagenske fibroze često povezane sa osteosklero-
zom, a precizno određivanje stepena fibroze je od su-
štinskog značaja, kako za početnu klasifikaciju MPN-i,
tako i za identifikaciju progresije bolesti [19]. Iako je fi-
broza KS glavni dijagnostički kriterijum za PMF, stepen
fibroze nije uključen u konvencionalne PSS-e. Nedav-
no je naglašeno da je tačna procena stepena fibroze KS
ključna tačka za predviđanje prognoze PMF-e [8].

Analizom ukupnog preživljavanja svih 136 pacije-
nata sa PMF-om, u zavisnosti od stepena fibroze KS,
dobili smo rezultat da ne postoji ($p = 0,084$) statistič-
ka značajnost u preživljavanju. U tom slučaju može-
mo doneti kontraverzni zaključak da stepen fibroze
nije značajan činilac za preživljavanje kod pacijenata
sa PMF-om, iako je jedan od osnovnih dijagnostičkih
kriterijuma. Međutim, kada smo analizu ponovili bez
3 pacijenta sa stepenom fibroze MF-0, dobijena je sta-
tistička značajnost u preživljavanju ($p = 0,043$). Isključi-
vanjem samo tri pacijenta sa stepenom fibroze MF-0 iz
grupe od 136 pacijenata sa PMF-om, potvrđeno je da
fibroza ipak utiče na ukupno preživljavanje kod PMF-e.
To takođe sugerise da bi trebalo dobro razmotriti sve
dijagnostičke parametre pre donošenja definitivne
dijagnoze da se radi o bolesti PMF-i, ili o eventualnoj
transformaciji primarne bolesti PV-e i ET-e u sekundar-
nu bolest mijelofibrozu.

Većina naših pacijenata imala je fibrozu KS stepe-
na MF-2 i MF-3 (46% i 35%). Skoro trećina pacijenata
je imala MF-3, što je veoma interesantno s obzirom na
činjenicu da se naša retrospektivna studija odnosi na
podatke pacijenta prikupljenim tokom primarnih spe-
cijalističkih pregleda i prilikom postavljanja inicijalne
dijagnoze.

Prema nekim literaturnim podacima [20] u pre fi-
brotičnoj fazi PMF-e (stepen fibroze MF-0), aberantan
kariotip zastupljen je kod 18% pacijenata, a nepovolj-
no aberantan kariotip (≥ 3 aberacije, +8, -5/5q-, -7/7q-,
i(17q), inv(3), 12p-, 11q23, kompleksan kariotip) kod
4–8% slučajeva. Iz tih podataka možemo zaključiti da
niži stepen fibroze KS (MF-0 i MF-1) korelira sa povolj-
nim hromozomskim aberacijama i normalnim kario-
tipom i obrnuto, viši stepeni fibroze (MF-2 i MF-3) KS
je u korelaciji sa nepovoljnom citogenetikom. Sličnu
analizu smo uradili u našoj grupi bolesnika. Koristili
smo jednostavne kategorizacije kariotipa (normalan,
aberantan), po preporukama Lille PSS-a [3]. Primenili
smo i naprednije kategorizacije kariotipa koje sadrže
određene hromozomske aberacije (+9, 13q-, 20q-, +8,
kompleksan kariotip) sa različitim stepenom nepovolj-
nosti, kao što su Mayo PSS-em [16] i IPSS-em [17]. Ta-
kođe, primenjen je DIPSS-em [18] koji predlaže samo

In the history of PSS application in PMF, cytogenet-
ics has been recognized as an independent prognostic
parameter. Early survival studies based on cytogenet-
ics indicated that a normal karyotype was a favorable
prognostic factor, while an aberrant karyotype was
considered unfavorable [3]. Later, it was found that
certain chromosomal aberrations (+9, 13q-, 20q-) were
associated with more prolonged survival compared to
a normal karyotype. These aberrations were defined
as good prognostic markers [16]. Conversely, other
karyotypic rearrangements (+8 or complex karyotype,
-5/5q-, -7/7q-, 11q23, i(17q), inv(3), 12p-) were linked to
shorter survival and were classified as poor prognos-
tic markers in other PSSs [17,18]. Overall, cytogenetic
analysis and karyotyping play a significant role in the
diagnosis of PMF but an even greater role in its prog-
nosis.

The situation is different when it comes to BM fibro-
sis in PMF and MPN in general. BM fibrosis of varying
degrees can be associated with the three main MPN en-
tities-polycythemia vera (PV), essential thrombocythe-
mia (ET), and primary myelofibrosis (PMF)-either at pre-
sentation, as in PMF, or following disease progression
in PV and ET. The updated 2008 WHO classification ad-
opted the European consensus on BM fibrosis grading
[9], which introduced a four-tiered system ranging from
grade 0 to 3 [7]. The progression of BM fibrosis follows
a gradual evolution from absent or minimal reticulin fi-
brosis to extensive reticulin and/or collagen fibrosis, of-
ten accompanied by osteosclerosis. Precise assessment
of fibrosis grade is crucial for the initial classification
of MPNs as well as for identifying disease progression
[19]. Although BM fibrosis is a key diagnostic criterion
for PMF, its grading has not been incorporated into con-
ventional PSSs. Recently, it has been emphasized that
an accurate assessment of BM fibrosis grade is a critical
factor in predicting PMF prognosis [8].

By analyzing the overall survival of all 136 PMF pa-
tients based on the degree of BM fibrosis, we found no
statistically significant difference in survival ($p = 0.084$).
This could lead to the controversial conclusion that the
degree of fibrosis is not an important factor in survival
for PMF patients, despite being one of the key diagnos-
tic criteria. However, when we repeated the analysis ex-
cluding the three patients with MF-0 fibrosis, statistical
significance in survival emerged ($p = 0.043$). By remov-
ing only three MF-0 patients from the cohort of 136, it
was confirmed that fibrosis indeed influences overall
survival in PMF. This also suggests that all diagnostic
parameters should be carefully considered before de-
finitively diagnosing PMF or determining whether the
disease represents a secondary transformation of PV or
ET into myelofibrosis.

dve kategorije kariotipa sa definisanim povoljnim i nepovoljnim hromozomskim aberacijama. Ni u jednom od primenjenih PSS-a nije registrovana statistička značajnost u korelaciji kariotipa i stepena fibroze KS (Lille $p = 0,293$; Mayo $p = 0,108$; IPSS $p = 0,086$; DIPSS $p = 0,613$) (Tabela 2).

Naš osnovni cilj u radu je bio da testiramo povezanost, odnosno korelaciju citogenetskih rezultata i patohistoloških rezultata pacijenata sa dijagnozom PMF-e, sa pretpostavkom da postoji povezanost ova dva dijagnostička, prognostička parametra. Činjenica je da smo koristili PSS-e po kojima su normalan ili aberantan kariotip, odnosno hromozomske aberacije stratifikovane u prognostne kategorije na osnovu njihovog uticaja na ukupno preživljavanje pacijenata sa PMF-om. S druge strane, fibroza KS je nepovoljan dijagnostički nalaz za pacijente sa PMF-om i što je gradus fibroze veći, bolest je u višem stadijumu. Na osnovu ovih činjenica očekivali smo da će postojati pozitivna povezanost ili direktna korelacija citogenetskih i patohistoloških nalaza, odnosno da će aberantan kariotip ili „nepovoljne“ hromozomske aberacije biti češće registrovane kod pacijenata sa stepenom fibroze MF-2 i MF-3, što bi se verifikovalo rezultatima statističkih analiza. Međutim, naši rezultati su suprotni, nije dokazana direktna korelacija prognostno „nepovoljnih“ hromozomskih aberacija sa višim stepenima fibroze KS (MF-2 i MF-3), niti korelacija normalnog kariotipa i „povoljnih“ hromozomskih aberacija sa stepenom fibroze KS MF-0 i MF-1 u PMF-i.

ZAKLJUČAK

Koliko nam je poznato, naša studija je prvi pokušaj ispitivanja korelacije citogenetike i patohistologije, ova dva važna dijagnostička i prognostička parametra za PMF-u. Studija obuhvata 136 pacijenata sa PMF-om, što je relativno veliki broj pacijenata na dijagnozi za jedan kliničko, dijagnostički centar na Zapadnom Balkanu. Kod 120 pacijenata testirana je korelacija citogenetskih rezultata i patohistoloških podataka o stepenu fibroze KS, primenom korisnih PSS-a. Iako smo očekivali pozitivnu korelaciju između kariotipa (normalan, aberantan) i hromozomskih aberacija različitog stepena prognoze (povoljan, nepovoljan) sa stepenom fibroze KS po preporukama Evropskog konsenzusa, dobili smo suprotan rezultat. Ne postoji korelacija tipa kariotipa, odnosno hromozomskih aberacija različitog stepena prognoze sa stepenom fibroze KS kod bolesnika sa PMF-om. Ipak, naša je namera da se nastavi sa ispitivanjem korelacije stepena fibroze KS sa citogenetikom kao i „driver“ mutacijama u PMF-u, kroz neku buduću, prospektivnu studiju.

The majority of our patients had BM fibrosis grades MF-2 and MF-3 (46% and 35%). Nearly one-third had MF-3, which is particularly interesting given that our retrospective study is based on patient data collected during initial specialist examinations and at the time of primary diagnosis.

According to some literature data [20], in the profibrotic phase of PMF (MF-0 fibrosis), an aberrant karyotype is present in 18% of patients, while an unfavorable aberrant karyotype (≥ 3 aberrations, +8, -5/5q-, -7/7q-, i(17q), inv(3), 12p-, 11q23, complex karyotype) is found in 4–8% of cases. Based on these data, we can conclude that lower degrees of BM fibrosis (MF-0 and MF-1) correlate with favorable chromosomal aberrations and a normal karyotype, whereas higher fibrosis grades (MF-2 and MF-3) are associated with unfavorable cytogenetics.

We conducted a similar analysis in our patient group. We employed simple karyotype categorizations (normal and aberrant) based on the Lille PSS recommendations [3]. Additionally, we applied advanced karyotype categorizations that included specific chromosomal aberrations (+9, 13q-, 20q-, +8, complex karyotype) with different levels of unfavorable prognosis, as classified by Mayo PSS [16] and IPSS [17]. The DIPSS model [18], which proposes only two karyotype categories (favorable and unfavorable chromosomal aberrations), was also applied. In none of these PSS models did we find a statistically significant correlation between karyotype and BM fibrosis grade (Lille $p = 0.293$; Mayo $p = 0.108$; IPSS $p = 0.086$; DIPSS $p = 0.613$) (Table 2).

Our primary aim was to test the association between cytogenetic and histopathological findings in PMF patients, assuming that a correlation exists between these two diagnostic and prognostic parameters. The fact is that we used PSS models in which normal or aberrant karyotypes and chromosomal aberrations were stratified into prognostic categories based on their impact on overall survival in PMF patients. On the other hand, BM fibrosis is considered an unfavorable diagnostic finding for PMF patients, with higher fibrosis grades indicating a more advanced disease stage. Based on these facts, we expected a positive association or direct correlation between cytogenetic and histopathological findings—that is, that aberrant karyotypes or “unfavorable” chromosomal aberrations would be more frequently observed in patients with MF-2 and MF-3 fibrosis, as confirmed by statistical analysis. However, our results were contrary to this expectation, as we found no direct correlation between prognostically “unfavorable” chromosomal aberrations and higher degrees of BM fibrosis (MF-2 and MF-3) or

SKRAĆENICE

PMF – primarna mijelofibroza
MPN – mijeloproliferativna neoplazma
KS – kosna srž
PSS – prognostički scoring sistem
SZO – svetska zdravstvena organizacija
PV – policitemija vera
ET – esencijalna trombocitemija

Dodatak: Ovaj rad predstavlja prikaz nekih od rezultata naučno istraživačkog ispitivanja dr sc. Vesne Đorđević radi izrade doktorske teze pod nazivom „Tip i učestalost hromozomskih aberacija i značaj molekularnog markera JAK2V617F u primarnoj mijelofibrozi“.

Sukob interesa: Nije prijavljen.

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between a normal karyotype and “favorable” chromosomal aberrations with lower fibrosis grades (MF-0 and MF-1) in PMF.

CONCLUSION

To the best of our knowledge, our study is the first attempt to investigate the correlation between cytogenetics and histopathology-two crucial diagnostic and prognostic parameters for PMF. The study includes 136 PMF patients, which represents a relatively large number of cases at the time of diagnosis for a single clinical and diagnostic center in the Western Balkans. In 120 patients, we analyzed the correlation between cytogenetic findings and histopathological data on BM fibrosis grade using relevant PSS models.

Although we expected a positive correlation between karyotype (normal, aberrant) and chromosomal aberrations of different prognostic significance (favorable, unfavorable) with BM fibrosis grade, following the recommendations of the European consensus, our results showed the opposite. There was no correlation between karyotype type or chromosomal aberrations of different prognostic significance and BM fibrosis grade in patients with PMF.

However, we intend to continue investigating the correlation between BM fibrosis grade, cytogenetics, and “driver” mutations in PMF through a future prospective study.

ABBREVIATIONS AND ACRONYMS

PMF – primary myelofibrosis
MPN – myeloproliferative neoplasm
BM – bone marrow
PSS – prognostic Scoring System
WHO – world health organization
PV – polycythemia vera
ET – essential thrombocythemia

Appendix: This paper presents some of the results from the scientific research study conducted by Dr. Vesna Đorđević as part of her doctoral thesis entitled “Type and Frequency of Chromosomal Aberrations and the Significance of the JAK2V617F Molecular Marker in Primary Myelofibrosis.”

Conflict of interest: None declared

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DA LI DA OSTANEM ILI DA ODEM? PERCEPCIJA SRPSKIH MEDICINSKIH RADNIKA, ISELJENIKA U NEMAČKOJ

ORIGINALNI RAD

ORIGINAL ARTICLE

SHOULD I STAY OR SHOULD I GO? PERCEPTIONS OF SERBIAN EMIGRANT MEDICAL WORKERS IN GERMANY

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SAŽETAK

Uvod: Različite pokretačke sile su kroz istoriju dovodile do prinudne ili dobrovoljne migracije zdravstvenih radnika.

Cilj: Cilj ove studije je da se steknu novi uvidi u rad stranih lekara sa Zapadnog Balkana zaposlenih u Nemačkoj.

Materijal i metode: Godine 2023, sprovedena je kvalitativna studija preseka kojom su analizirani: motivacija lekara za emigriranje iz matičnih zemalja, njihovo profesionalno napredovanje u Nemačkoj, nemački pravni sistem, i ukupno zadovoljstvo lekara.

Rezultati: Najvažniji rezultati studije ističu bolje plate lekara u inostranstvu i nedostatak mogućnosti za usavršavanje u njihovim matičnim zemljama kao glavne razloge za emigraciju. Lekari imigranti su pretežno bili zadovoljni profesionalnim napredovanjem u Nemačkoj, ali su bili manje zadovoljni nemačkim pravnim sistemom.

Zaključak: Zapošljavanje lekara sa Zapadnog Balkana može smanjiti preopterećenost nemačkog zdravstvenog sistema, nastalog usled značajnog nedostatka kvalifikovanog kadra. Sprovedenje istraživanja na većim uzorcima biće od ključnog značaja za razumevanje faktora zadovoljstva lekara migranata, što na kraju može omogućiti uspešnije zadržavanje medicinskog kadra.

Ključne reči: sistem zdravstvene zaštite, emigracija, lekari, Zapadni Balkan, Nemačka

ABSTRACT

Background: Throughout history, various driving forces have influenced both forced and voluntary migrations of healthcare workers.

Objective: This study aims to obtain new insights into the work activities of foreign doctors from the Western Balkans practicing medicine in Germany.

Materials and Methods: In 2023, a qualitative cross-sectional study was conducted to analyze physicians' motivation for emigration from their home countries, their professional status development in Germany, the German legal system, and overall satisfaction of the physicians.

Results: The main findings highlight better salaries for doctors abroad and no development opportunities in their home countries as the main reasons for emigration. Immigrant physicians were mainly satisfied with their professional status development in Germany, but less satisfied with the German legal system.

Conclusion: Employing doctors from the Western Balkans can alleviate the burden on the German healthcare system caused by the significant shortage of skilled labor force.

Keywords: healthcare system, emigration, physicians, Western Balkans, Germany

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UVOD

Migracije su složena i dugotrajna pojava koja je značajno uticala na razvoj nacija širom sveta. Stanovništvo mnogih zemalja, kao što su Sjedinjene Američke Države, Kanada i Australija, uglavnom čine migranti ili potomci migranata koji su se doselili u potrazi za boljim prilikama, sigurnošću ili novim početkom. Kroz istoriju su različite pokretačke sile uticale i na prinudne i na dobrovoljne migracije, kao što su ekonomske teškoće, politička nestabilnost, promene u životnoj sredini i želja za istraživanjem i sticanjem novih iskustava. Pored političkog i društvenog konstrukta ka liberalizaciji trgovine i tržišta rada u sektoru zdravstva i nege, demografske promene u smeru starenja stanovništva, zajedno sa epidemiološkim pomeranjem ka dvostrukom opterećenju i zaraznih i nezaraznih bolesti u nekim zemljama, povećavaju potrebu za zdravstvenom zaštitom i doprinose planiranju politika usmerenih na regulisanje nedostatka zdravstvenog kadra i uslova rada [1-5].

Ljudski kapital u zdravstvu u mnogim bogatim zemljama čine medicinski radnici koji su svoje obrazovanje stekli u inostranstvu. Na primer, on se kreće od 57,8% svih lekara u Izraelu, 42,1% u Norveškoj i 40,5% u Irskoj do 0,6% u Litvaniji [6]. U Nemačkoj i Sloveniji, popularnim destinacijama za zapošljavanje mnogih srpskih lekara i medicinskih sestara, ima 13,8% i 15,8% inostranih lekara i 9,6% i 5,5% stranih medicinskih sestara [6]. Bilateralni sporazumi o mobilnosti i migraciji zdravstvenih radnika privukli su pažnju brojnih aktera poslednjih decenija [7]. Međunarodno zapošljavanje medicinskih radnika je složeno pitanje sa mnogo uglova posmatranja. To može biti aspekt pružaoca usluga orijentisan na poboljšanje pružanja zdravstvenih usluga, te vladina strategija koja pomaže u smanjenju nezaposlenosti na lokalnom nivou, ali se takođe može posmatrati kao neuspeh rukovodstva da zadrži stručni kadar potreban za efikasan rad. Napravljeni su različiti bilateralni sporazumi kako bi se zadovoljili interesi svih strana, uz posebni akcenat na prava i dobrobit mobilnih imigrantskih zdravstvenih radnika. Takođe je važno prepoznati, istražiti i poboljšati prednosti kružnih migracija [8,9].

Dok obrasci migracije radne snage utiču na zdravstvenu zaštitu u mnogim zemljama, oni takođe predstavljaju i potpuno nove aspekte za zdravstvene radnike koji odlučuju da li da ostanu ili odu. Razumevanje konteksta i trenutnih okolnosti zdravstvenih radnika migranata je od suštinskog značaja, jer pruža vredan uvid u promovisanje zapošljavanja i kulturnog, ekonomskog i socijalnog razvoja koji ispunjava njihova očekivanja [10]. Uzimanje u obzir iskustava radnika migranata može da pomogne u pronalaženju rešenja za negativne uticaje prekomerne migracije. Regrutovanje

INTRODUCTION

Migration is a complex and longstanding phenomenon that has significantly influenced the development of nations worldwide. Many countries, such as the United States, Canada, and Australia, have populations largely comprised of migrants or descendants of migrants seeking better opportunities, safety, or a new beginning. Throughout history, various driving forces have influenced both forced and voluntary migrations, such as economic challenges, political instability, environmental changes, and the desire to explore and gain new experience. In addition to the political and social construct towards trade and labor market liberalization in health and care sectors, the demographic transition towards population aging, together with the epidemiological shift towards the double burden of communicable and non-communicable diseases in some countries, are increasing the need for health care and contributing to policy planning to regulate health worker shortages and workplace conditions [1-5].

The human health capital in many wealthy countries consists of foreign-trained medical workers. For example, it ranges from 57.8 % of all medical doctors in Israel, 42.1% in Norway, and 40.5% in Ireland, to 0.6% in Lithuania [6]. In Germany and Slovenia, popular job destinations for many Serbian medical doctors and nurses, there are 13.8% and 15.8% foreign-trained medical doctors and 9.6% and 5.5% foreign-trained nurses [6]. Bilateral agreements on health workers' mobility and migration have drawn the attention of numerous stakeholders in recent decades [7]. International recruitment of medical workers is a complex issue with many aspects of the truth. It may be a provider approach to enhance healthcare service delivery, a governmental strategy to help reduce local unemployment, but it can also be seen as a management failure to keep the expertise needed for efficient operation. A variety of bilateral agreements have been created to accommodate the interests of all parties while emphasizing the rights and benefits of mobile and migrant healthcare workers. It is also important to recognize, explore, and enhance the benefits of circular migrations [8,9].

As workforce migration patterns influence healthcare in many countries, they also present unprecedented considerations for health workers deciding whether to stay or leave. Understanding the context and current circumstances of migrant health workers is essential, as it provides valuable insights into promoting employment and cultural, economic, and social development that meet their expectations [10]. Listening to the migrant workers' experiences can help find solutions to addressing the negative impacts of excessive migration. Recruiting healthcare professionals is chal-

zdravstvenih radnika predstavlja izazov za mnoge pružaoce usluga koji nastoje da održe nivo usluga i da drže pod kontrolom tendencije u fluktuaciji zaposlenih [11]. Takođe je važno uzeti u obzir percepcije i iskustva zdravstvenih radnika migranata kako bi kreatori politike postali svesni stepena u kojem aktivne mere mogu doprineti suzbijanju negativnih efekata migracije i mobilnosti u Evropskoj uniji ublažavanjem njihovih posledica i unošenjem promena [12].

Studija je sprovedena u cilju sticanja novih uvida u radne aktivnosti stranih lekara sa Zapadnog Balkana zaposlenih u Nemačkoj. Ciljevi studije su bili da se ispituju motivi lekara za emigriranje iz svojih matičnih zemalja, njihov status profesionalnog razvoja u Nemačkoj, nemački pravni sistem i opšte zadovoljstvo lekara.

MATERIJALI I METODE

Ova kvalitativna studija preseka sprovedena je 2023. godine kako bi se analizirali motivi lekara za emigraciju iz svojih matičnih zemalja, njihovo profesionalno napredovanje u Nemačkoj, nemački pravni sistem i opšte zadovoljstvo lekara.

Ciljnu populaciju su činili lekari iz trećih zemalja Zapadnog Balkana, uključujući Srbiju, Bosnu i Hercegovinu, Crnu Goru i Severnu Makedoniju. Takođe, ciljnu grupu su morali da čine lekari koji su imali licencu za rad zaposleni u Nemačkoj. Ukupno, 41 od 150 licenciranih lekara kontaktiranih iz regiona Berlina i Saksonije je odgovorilo i popunilo anketu.

Instrumenti istraživanja su bili posebno osmišljen upitnik i detaljni intervjui. Upitnik se sastojao od 38 pitanja kreiranih na osnovu relevantne literature i postavljenih preko onlajn platforme *Survio*. Ovakvo istraživanje je bilo moguće zahvaljujući saradnji sa Berlinskom lekarskom komorom i Saksonskom lekarskom komorom. Druge savezne države, međutim, nisu pristale da učestvuju. Komore su pisale odgovarajućim lekarima i prosledila anketu. Istraživanje je sprovedeno anonimno i u skladu sa *BDSG* (nem. Bundesdatenschutzgesetz), odnosno Saveznim zakonom o zaštiti podataka.

Nakon obavljene ankete urađena su dva intervjua, jedan sa muškim lekarom a jedan sa doktorkom – oni su prihvatili poziv da daju detaljni intervju. Intervjui su pokazali i sličnosti i razlike. Oba intervjua su se bavila emigracijom iz Srbije u Nemačku, s tim što se prvi intervju bavio emigracijom i napuštanjem prethodnog posla dok se drugi fokusirao na emigraciju nakon medicinskog fakulteta. Oba intervjua su korišćena isključivo radi boljeg povezivanja sa rezultatima upitnika i kako bi se stekao uvid u probleme pojedinaca, izazove sa kojima se susreću i dobrobitima koje uživaju.

Podaci i informacije prikupljeni tokom studije su pažljivo analizirani primenom deskriptivnih statističkih

lenging for many providers who struggle to maintain service performance and manage personnel turnover intentions [11]. It is also important to acknowledge perceptions and experiences of migrant health workers in order to alert policymakers to the extent that active measures can contribute to counteracting the negative effects of migration and mobility in the European Union by mitigating and making changes [12].

The study was conducted to gain new insights into the work activities of foreign doctors from the Western Balkans working in Germany. The study's objectives were to explore physicians' motives for emigrating from their home countries, their professional development status in Germany, the German legal system, and the general satisfaction of physicians.

MATERIALS AND METHODS

This qualitative cross-sectional study was conducted in 2023 to analyze physicians' motives for emigration from their home countries, their professional status development in Germany, the German legal system, and the general satisfaction of physicians.

The population of interest comprised doctors from the Western Balkans' third countries, including Serbia, Bosnia and Herzegovina, Montenegro, and North Macedonia. In addition, the target group had to be licensed and working in Germany. In total, 41 out of 150 licensed physicians contacted from the regions of Berlin and Saxony responded and were surveyed.

The study instruments were a specific questionnaire and in-depth interviews. The questionnaire comprised 38 questions created based on the relevant literature and uploaded via the online platform *Survio*. Such a survey was possible in cooperation with the Berlin Medical Association and the Saxony Medical Association. Other federal states, however, did not agree to participate. The associations wrote to the respective doctors and forwarded the survey. The survey was conducted anonymously and in keeping with the *BDSG* (Ger. *Bundesdatenschutzgesetz*), i.e., the Federal Data Protection Act.

Two interviews were conducted after the survey was completed, one with a male and one with a female doctor, who accepted the invitation for an in-depth interview. The interviews have shown both similarities and differences. Both interviews dealt with emigration from Serbia to Germany, the difference being that the first interview dealt with emigration and leaving a job. In contrast, the second interview focused on emigration after medical school. Both interviews were exclusively used to establish a better connection with the questionnaire results and to ensure a view of the individual persons' problems, the challenges they have encountered, and the benefits they have enjoyed.

metoda. Ove metode su omogućile detaljnu analizu obrazaca i karakteristika skupova podataka, razjašnjavajući fundamentalne trendove i složenosti povezane sa lekarima migrantima.

Rezultati su predstavljeni kao učestalost (procenti). Metod korišćen za testiranje statističkih hipoteza bio je Fišerov egzaktni test. Statističke hipoteze su analizirane na nivou značajnosti od 0,05. Statistička analiza podataka izvršena je putem softvera *IBM SPSS Statistics 24* (IBM Corporation, Armonk, NI, USA).

REZULTATI

Sociodemografske karakteristike ispitanika

Tabela 1 pokazuje da je udeo ispitanika ženskog pola bio 56,1% ($n = 23$), dok su 43,9% ispitanika ($n = 18$) bili muškarci. Većina ispitanika su bili starosti 20-35 godina. Ispitanici su većinom bili ili u braku, $n = 18$ (43,9%), ili su bili samci, $n = 19$ (46,3%). Ispitanici su bili poreklom iz Srbije, $n = 19$ (46,3%), Bosne i Hercegovine, $n = 9$ (22%), Crne Gore, $n = 7$ (17,1%), i Severne Makedonije, $n = 6$ (16,4%). Rezultati pokazuju da su neki lekari sa Zapadnog Balkana živeli u Nemačkoj 1–5 godina, $n = 20$ (48,8%), dok su drugi živeli u Nemačkoj 5–10 godina, $n = 12$ (29,3%), ili preko 10 godina, $n = 7$ (17,7%), jedan ispitanik, $n = 1$

The data and information gathered throughout the study were meticulously analyzed using descriptive statistical methods. These methods allowed a thorough analysis of the dataset patterns and characteristics, shedding light on the fundamental trends and intricacies associated with migrant physicians.

The results are presented as frequency (percentages). The method used for testing statistical hypotheses was Fisher's exact test. Statistical hypotheses were analyzed at the level of significance of 0.05. Statistical data analysis was performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Sociodemographic characteristics of the respondents

Table 1 shows that the proportion of female respondents was 56.1% ($n = 23$), while 43.9% of respondents ($n = 18$) were male. The majority of respondents were 20-35-year-olds. Most were either married, $n = 18$ (43.9%), or single, $n = 19$ (46.3%). The respondents were originally from Serbia, $n = 19$ (46.3%), Bosnia and Herzegovina, $n = 9$ (22%), Montenegro, $n = 7$ (17.1%), and North Macedonia, $n = 6$ (16.4%). The results show that some doctors

Tabela 1. Sociodemografske karakteristike ispitanika

Karakteristika / Characteristic	Female (number) / Ženski pol (broj)	Female (%) / Female (%)	Muški pol (broj) / Male (number)	Muški pol (%) / Male (%)	p-vrednost / p-value
Ukupno / Total	23	56.10%	18	43.9%	
Starost / Age					0.600
25-35	15	65.22%	10	55.6%	
35-45	6	26.09%	4	22.2%	
45-65	2	8.70%	4	22.2%	
Bračno stanje / Marital status					0.363
Neudata/neoženjen / Single	9	39.13%	10	55.6%	
Udata/oženjen / Married	10	43.48%	8	44.4%	
Razvedena/Razveden / Divorced	3	13.04%	0	0.0%	
Udovica/Udovac / Widowed	1	4.35%	0	0.0%	
Zemlja porekla / Country of origin					0.168
Srbija / Serbia	9	59.10%	10	40.9%	
Bosna i Hercegovina / Bosnia and Herzegovina	8	55.60%	1	44.4%	
Crna Gora / Montenegro	3	57.10%	4	42.9%	
Severna Makedonija / North Macedonia	3	50.00%	3	50.0%	
Dužina boravka u Nemačkoj / Duration of stay in Germany					1.000
0-1 godine / 0-1 years	1	4.35%	0	0.0%	
1-5 godina / 1-5 years	11	47.83%	9	50.0%	
5-10 godina / 5-10 years	6	26.09%	6	33.3%	
Više od 10 godina / More than 10 years	4	17.39%	3	16.7%	
Rođen-a u Nemačkoj / Born in Germany	1	4.35%	0	0.0%	

Table 1. Sociodemographic characteristics of the respondents

(2,4%), rođen je u Nemačkoj, a drugi, $n = 1$ (2,4%), je živio u Nemačkoj manje od godinu dana. Žene i muškarci u studiji se nisu značajno razlikovali ($p > 0,05$) prema starosnoj kategoriji, bračnom stanju, zemlji porekla ili trajanju boravka u Nemačkoj (Tabela 1).

Motivi za emigriranje

U Tabeli 2 su prikazani motivi za emigriranje iz matične zemlje. Analiza pokazuje da je od 41 anketiranog lekara, 38 (92,7%) emigriralo iz svojih matičnih zemalja, a troje (7,3%) su ili rođeni u inostranstvu ili su bili na školovanju. Prema učestalosti najčešći razlozi za imigraciju u Nemačku uključivali su bolje plate za lekare u inostranstvu, $n = 19$ (19,6%), nedostatak mogućnosti za razvoj u matičnoj zemlji, $n = 19$ (19,6%), bolje mogućnosti za dalje usavršavanje i razvoj karijere u inostranstvu, $n = 18$ (18,6%), više socijalnih beneficija u Nemačkoj, $n = 17$ (19,6%), nedostatak perspektive u karijeri u matičnoj zemlji, $n = 13$ (13,4%). Po sopstvenom svedočenju, određeni broj, $n = 5$ (5,2%), nije mogao da navede poseban razlog. Deo ispitanika, $n = 16$ (34,8%), odlučio je da emigrira u Nemačku samostalno neposredno nakon završenih studija medicine, nešto manje anketiranih, $n = 9$ (19,6%), došlo je u Nemačku sa mužem/ženom i decom, neki, $n = 7$ (15,2%), su emigrirali sa roditeljima ili rođacima, neki, $n = 6$ (13%), su emigrirali uz pomoć agencije za zapošljavanje, dok je bilo onih, $n = 5$ (10,9%), koji su sami došli u Nemačku nakon završene srednje škole.

U vreme anketiranja, jedan broj ispitanika, $n = 21$ (51,2%), radio je u bolnicama, neki su, $n = 10$ (24,4%), radili u ambulantama, izvestan broj ispitanika, $n = 4$ (9,8%), bio je zaposlen u drugim tipovima stacionarnih ustanova, neki su, $n = 2$ (4,9%), radili u ustanovama za rehabilitaciju, dok je preostali ispitanik $n = 1$ (2,4%), bio zaposlen u domu za negu starih lica. Polovina ispitanika, $n = 21$ (51,2%), radila je na poziciji lekara 1–5 godina, određeni broj lekara, $n = 11$ (26,8%), radio je na datom radnom mestu već 5–10 godina, drugi su, $n = 8$ (19,5%), radili kao lekari duže od 10 godina, a preostali ispitanik, $n = 1$ (2,4%) radio je kao lekar između jednog meseca i godinu dana.

Uvid u prihode je pokazao da je određeni broj anketiranih lekara, $n = 19$ (46,3%), zarađivao više od 4.500 € mesečno, nešto manje od trećine njih, $n = 13$ (31,7%), zarađivalo je 3.500€–4.500€, dok je preostali broj, $n = 9$ (22%) zarađivao €2.500–€3.500 mesečno. Takođe, većina ispitanika, $n = 26$ (63,4%), odmah je našla posao lekara u Nemačkoj, dok ostali, $n = 15$ (36,6%), nisu odmah našli posao.

Tadašnje zadovoljstvo poslom ispitanika pokazalo je da je određeni broj ispitanika, $n = 11$ (26,8%), bio vrlo zadovoljan, izvestan broj ispitanika $n = 26$

from the Western Balkans had lived in Germany for 1–5 years $n = 20$ (48.8%), while others had lived in Germany for 5–10 years $n = 12$ (29.3%), or over 10 years, $n = 7$ (17.7%), while one respondent was born in Germany, $n = 1$ (2.4%), and another, $n = 1$ (2.4%), had lived in Germany for under a year. Women and men in the study did not differ significantly ($p > 0.05$) by age category, marital status, country of origin, or duration of stay in Germany (Table 1).

Motives for emigration

Table 2 shows the motives for emigration from the home country. The analysis shows that of the 41 doctors surveyed, 38 (92.7%) had emigrated from their home countries, and 3 (7.3%) were either foreign-born or in training. Regarding the frequency, most common reasons for immigrating into Germany included better salaries for doctors abroad, $n = 19$ (19.6%), no development opportunities in the home country, $n = 19$ (19.6%), better further training and career opportunities abroad, $n = 18$ (18.6%), more social benefits in Germany, $n = 17$ (17.5%), no career prospects in the home country, $n = 13$ (13.4%). By their own testimony, for no particular reason $n = 5$ (5.2%). A proportion of respondents, $n = 16$ (34.8%), decided to emigrate to Germany alone directly after their medical studies, slightly fewer of those surveyed, $n = 9$ (19.6%), came to Germany with their husband/wife and children, some, $n = 7$ (15.2%) emigrated with parents or relatives, some, $n = 6$ (13%) emigrated with the help of an employment agency, while there were those, $n = 5$ (10.9%), who came to Germany on their own after graduating from high school.

At the time of the survey, a number of respondents, $n = 21$ (51.2%), worked in hospitals, some, $n = 10$ (24.4%), worked in outpatient facilities, some, $n = 4$ (9.8%), were employed in other inpatient facilities, others, $n = 2$ (4.9%), worked in rehabilitation clinics, while the remaining respondent, $n = 1$ (2.4%), was employed in a nursing home. Half of the respondents, $n = 21$ (51.2%), had been working as doctors for 1–5 years, some, $n = 11$ (26.8%), had held the position for 5–10 years, others, $n = 8$ (19.5%), had been working as physicians for more than 10 years, and the remaining respondent, $n = 1$ (2.4%), had been working as a doctor for between one month and one year.

The financial background showed that a number of the surveyed doctors, $n = 19$ (46.3%), earned more than €4,500 per month, a little less than a third, $n = 13$ (31.7%), earned €3,500–€4,500, while the remaining number, $n = 9$ (22%), earned €2,500–€3,500. Also, most of the responders, $n = 26$ (63.4%), immediately found jobs as doctors in Germany, whereas others, $n = 15$ (36.6%), did not find a job immediately.

Tabela 2. Razlozi za preseljenje lekara u Nemačku

Table 2. Reasons for the migration of physicians to Germany

Aspekti / Aspects	Broj / Number	Procentat % / Percentage %
Da li ste emigrirali? / Have you emigrated?		
Da / Yes	38	92.68%
Ne / No	3	7.32%
Koji su bili vaši razlozi za preseljenje u Nemačku? */ What were your reasons for moving to Germany? *		
Bolje plate za lekare u inostranstvu / Better salaries for doctors abroad	38	92.7%
Nepostojanje prilika za profesionalno napredovanje u matičnoj zemlji / No development opportunities in the home country	38	92.7%
Bolje prilike za usavršavanje i napredovanje u karijeri u inostranstvu / Better training and careers abroad	38	92.7%
Bolja socijalna zaštita u inostranstvu / More social benefits abroad	32	78.0%
Nije bilo prilike za zaposlenje u matičnoj zemlji / No job prospects in home country	27	65.9%
Ako ste emigrirali, kada ste odlučili da emigrirate u Nemačku? / If you emigrated, when did you decide to emigrate to Germany?		
Doputovao-la sam ovde sam-a nakon završetka studija / I travelled here on my own after medical school	16	34.8%
Došao-la sam sa porodicom (mužem/ženom/decom) / I came with my family (husband/wife/children)	9	19.6%
Došao-la sam sa roditeljima/rođacima / I arrived with my parents/relatives	7	15.2%
Došao-la sam preko agencije (za zapošljavanje stručnog kadra) / I arrived with the help of an agency (for employing professionals).	6	13.0%
Došao-la sam sam-a nakon završene srednje škole / I came alone after graduating from high school.	5	10.9%
Ostalo, npr. pridružio-la sam se porodici / Other, e.g. family reunion	3	6.5%
U kojoj instituciji trenutno radite? / In which institution do you currently work?		
Bolnica / Hospital	21	51.2%
Ambulantne ustanove (npr. lekarske ordinacije) / Outpatient facilities (e.g., doctors' offices)	10	24.4%
Klinike sa ležećim pacijentima / Inpatient facilities	4	9.8%
Domovi za negu starih i drugih lica / Nursing home	1	2.4%
Klinike za rehabilitaciju / Rehabilitation clinics	2	4.9%
Ostalo, npr. instituti / Other, e.g., institutes	3	7.3%
Kolika vam je plata? / What is your salary?		
€4.500 i više / €4,500 and more	19	46.3%
€3.500–€4.500	13	31.7%
€2.500–€3.500	9	22.0%
Koliko ste dugo na sadašnjem poslu? / How long have you been in your job?		
1–5 godina / 1–5 years	21	51.2%
5–10 godina / 5–10 years	11	26.8%
Više od 10 godina / More than 10 years	8	19.5%
Kraće od jedne godine / Less than a year	1	2.4%
Da li ste dobili posao kao lekar odmah u Nemačkoj? / As a doctor, did you get a job in Germany right away?		
Da / Yes	26	63.4%
Ne / No	15	36.6%
Koliko ste zadovoljni sa sadašnjim zaposlenjem? / How satisfied are you with your current job?		
Prilično zadovoljan-na / Somewhat satisfied	26	63.4%
Vrlo zadovoljan-na / Very satisfied	11	26.8%
Prilično nezadovoljan-na / Somewhat dissatisfied	2	9.8%
Vrlo nezadovoljan-na / Very dissatisfied	0	0.0%
Gde ste stanovali kada ste prvo stigli u Nemačku? / Where did you live when you first emigrated to Germany?		
U svom stanu / In my flat	15	36.6%
Ostalo, npr. u bolničkom stanu / Other, e.g., hospital flats	9	22.0%
Kod rodbine/familije / With my relatives/extended family	8	19.5%
Sa suprugom (+/- deca) / With my spouse (+/- children)	4	9.8%
U hotelu / At a hotel	3	7.3%
Kod roditelja / With my parents	2	4.9%

* višestruki odgovori (n, %) / multiple answers (n, %)

(63,4%) izjavio je da je prilično zadovoljan, dok su ostali, $n = 4$ (9,8%), izjavili da su zadovoljni. Glavni razlozi za veliko zadovoljstvo bili su sledeći: posedovanje sopstvene lekarske prakse, dobra radna atmosfera i rukovodioci, kao i dobra struktura u bolnici. S druge strane, razlozi za nisko zadovoljstvo bili su sledeći: veća želja za radom na istraživačkom institutu, nedostatak specijalista i nedostatak ravnoteže između posla i privatnog života.

Kada su se prvobitno doselili u Nemačku, više od trećine ispitanika, $n = 15$ (36,3%), živelo je u sopstvenom stanu, neki, $n = 8$ (19,5%), živeli su sa rođacima odnosno familijom, drugi, $n = 4$ (9,8%), živeli su sa supružnikom i decom, dok su ostali ispitanici $n = 2$ (4,95%) živeli sa roditeljima.

Profesionalni status

Podaci u **Tabeli 3** pokazuju da većina ispitanika, $n = 34$ (82,9%), nije imala privremeni posao tokom prvog boravka u Nemačkoj, dok su ostali, $n = 7$ (17,1%), imali privremeni posao. Takođe, većina lekara, $n = 33$ (80,5%), nije bila zaposlena na istom radnom mestu u vreme istraživanja kao kada su stigli u Nemačku, dok neki lekari, $n = 8$ (19,5%), nisu promenili posao. Nadalje, rezultati pokazuju da je više od polovine lekara, $n = 23$ (56,1%), menjalo posao dva ili tri puta, nešto više od trećine, $n = 14$ (34,1%), promenilo je posao jednom ili dva puta, a preostali ispitanici, $n = 4$ (9,8%), menjali su posao više od tri puta.

Za potvrdu statusa lekara u Nemačkoj i dobijanje dozvole za rad, uslov je često bila nostrifikacija diplome sa studija medicine (odnosno dobijanje tzv. Aprobacije – licence za obavljanje lekarske delatnosti), $n = 36$ (23,5%), završen kurs nemačkog jezika, $n = 33$ (21,6%), podnošenje zahteva za vizu, $n = 32$ (20,9%), položen test znanja, $n = 27$ (17,6%), završena dodatna obuka, $n = 20$ (13,1%). Kod nekih ispitanika, $n = 13$ (31,7%), proces je trajao do šest meseci, kod drugih, $n = 17$ (41,5%), trajao je do 12 meseci, neki ispitanici, $n = 10$ (24,4%), prošli su kroz proces koji je trajao 1–3 godine, dok je kod preostalog ispitanika, $n = 1$ (2,4%), bilo potrebno više od tri godine. Prema rezultatima, više od polovine ispitanika, $n = 22$ (53,7%), prošlo je kroz proces bez pomoći, ostali su, $n = 14$ (34,1%), imali pomoć rođaka, prijatelja i porodice, a neki su, $n = 5$ (12,2%), imali pomoć agencija za zapošljavanje u Nemačkoj.

Nemački pravni sistem

Studija se takođe bavi pitanjem da li se nemački pravni sistem dobro brine o ljudima ili se oni suočavaju sa poteškoćama. **Tabela 4** pokazuje da je deo ispitanika, $n = 9$ (22%), bio zadovoljan nemačkim pravnim sistemom, da je većina, $n = 29$ (70,7%), bila prilično zado-

The job satisfaction of the doctors, at the time, showed that a certain number of the respondents, $n = 11$ (26.8%) were very satisfied, a number of the respondents, $n = 26$ (63.4%), stated that they were rather satisfied, while the remaining doctors, $n = 4$ (9.8%), were satisfied. The main reasons for high satisfaction were the following: having their own outpatient medical practice, having a good working atmosphere and superiors, and having a good structure in the hospital. On the other hand, the reasons for low satisfaction were the following: having a greater desire to work at a research institute, the shortage of specialists, and a lack of work-life balance.

When they first immigrated to Germany, more than a third of the respondents, $n = 15$ (36.3%), lived in their own flat, some, $n = 8$ (19.5%), lived with relatives and family, others, $n = 4$ (9.8%), lived with their spouse and children, while the remaining respondents, $n = 2$ (4.95%), lived with their parents.

Professional status

The data in **Table 3** show that a majority of the respondents, $n = 34$ (82.9%), did not have a temporary job during their first stay in Germany, whereas others, $n = 7$ (17.1%), did have temporary employment. Also, a majority of the doctors, $n = 33$ (80.5%), were not employed at the same job at the time of the survey as when they arrived in Germany, whereas some doctors, $n = 8$ (19.5%), had not changed their job. Furthermore, the results show that more than a half of the doctors, $n = 23$ (56.1%), had changed their jobs two or three times, a little over a third, $n = 14$ (34.1%), had changed their jobs once or twice, and the remaining respondents, $n = 4$ (9.8%), had changed their jobs more than three times.

For physicians to establish themselves as doctors in Germany and get a work permit, the conditions often included medical degree recognition (Approbation – license to practice medicine), $n = 36$ (23.5%), completing a course in the German language, $n = 33$ (21.6%), visa application, $n = 32$ (20.9%), passing a knowledge test, $n = 27$ (17.6%), and completing additional training, $n = 20$ (13.1%). For some respondents, $n = 13$ (31.7%), the process took up to six months, for others, $n = 17$ (41.5%), it took up to 12 months, some respondents, $n = 10$ (24.4%), went through a process lasting 1–3 years, while for the remaining respondent, $n = 1$ (2.4%), it took more than three years. According to the results, more than half of the respondents, $n = 22$ (53.7%), went through the process without help, others, $n = 14$ (34.1%), had help from relatives, friends and family, and some, $n = 5$ (12.2%), had help from employment agencies in Germany.

Tabela 3. Status zaposlenja i profesionalnog napredovanja u Nemačkoj

Table 3. Occupational status and career development in Germany

Aspekti / Aspects	Broj /Number	Procenat/ Percentage %
Da li ste u početku imali privremeni posao? Did you have a temporary job at the beginning?		
Ne / No	34	82.1%
Da / Yes	7	17.1%
Da li ste na istom poslu od kada ste došli u Nemačku? / Have you been at the same workplace since you arrived in Germany?		
Ne / No	33	80.5%
Da / Yes	8	19.5%
Koliko ste često menjali posao? / How often have you changed jobs?		
2-3 puta / 2-3 times	23	56.1%
1-2 puta / 1-2 times	14	34.1%
>3 puta / >3 times	4	9.8%
Šta ste morali da uradite da biste se zaposlili u Nemačkoj?*/ What did you have to do to be able to work in Germany? *		
Nostrifikacija diplome (licenca za rad) / Recognition of my medical degree (Approbation – licence to practice medicine)	36	23.5%
Kurs nemačkog jezika (specijalizovani test) / Take a course in the German language (specialized language test)	33	21.6%
Dobijanje vize / Apply for a visa	32	20.9%
Polaganje testa znanja / Pass a knowledge test	27	17.6%
Dodatna obuka / Complete additional supplementary training	20	13.1%
Ostalo, boravišna dozvola / Other e.g., residence permit	5	3.3%
Koliko je dugo trajao proces pre nego što ste mogli da počnete da radite u Nemačkoj? / How long did the process take for you to begin working in Germany?		
Do 12 meseci / Up to 12 months	17	41.5%
Do 6 meseci / Up to 6 months	13	31.7%
1-3 godine / 1-3 years	10	24.4%
Više od 3 godine / More than 3 years	1	2.4%
Ko vam je pomogao sa prijavljivanjem i celim procesom? /Who helped you with the application and the whole process?		
Sam-a / Myself	22	53.7%
Rodbina/prijatelji/porodica / Relatives/friends/family	14	34.1%
Agencija (za zapošljavanje stručnog kadra) / Agency (for employing professionals)	5	12.1%

*višestruki odgovori (n, %) / multiple answers (n, %)

voljna, dok su neki, $n = 3$ (7,3%), bili samo zadovoljni. Razlozi za poteškoće bili su prevelika birokratija ili nedostatak pomoći u pravnim pitanjima. Većina ispitanika, $n = 28$ (68,3%), izjavila je da nije naišla na pozitivnu diskriminaciju, a neki ispitanici, $n = 13$ (31,7%), su izjavili da su se susreli sa ovom vrstom diskriminacije, uključujući tu i brže dobijanje termina za operacije i termina u opštini, kao i dobijanje odobrenja od strane Nacionalnog udruženja lekara obaveznog zdravstvenog osiguranja. Pored toga, analiza je pokazala da se pozitivna diskriminacija (npr. afirmativne akcije prema imigrantima koje stimulišu njihovu integraciju uprkos razlikama koje mogu postojati) povremeno javljala u više slučajeva, $n = 32$ (78%), nego što se javljala često, $n = 9$ (22%). Rezultati takođe pokazuju da se određeni broj ispitanika, $n = 19$ (46,3%), suočio

The German legal system

The study also deals with the question of whether individuals are well looked after by the German legal system or face difficulties. Table 4 shows that some of the respondents, $n = 9$ (22%), were satisfied with the German legal system, while the majority, $n = 29$ (70.7%), were rather satisfied, while some, $n = 3$ (7.3%), were merely satisfied. The reasons for the difficulties were too much bureaucracy or the absence of assistance with legal matters. A majority of the respondents, $n = 28$ (68.3%), stated that they did not encounter any positive discrimination, with some respondents, $n = 13$ (31.7%), reported encountering this type of discrimination, including getting appointments for operations and at the town hall more quickly, and also receiving

Tabela 4. Rezultati o nemačkom pravnom sistemu

Table 4. Results on the German legal system

Aspekti / Aspects	Broj /Number	Procenat/ Percentage %
Da li smatrate da ste dobili adekvatan tretman od strane nemačkog pravnog sistema? / Do you feel well served by the German legal system?		
Prilično zadovoljan-na / Rather satisfied	29	70.7%
Vrlo zadovoljan-na / Very satisfied	9	22.0%
Prilično nezadovoljan-na / Rather dissatisfied	3	7.3%
Vrlo nezadovoljan-na / Very dissatisfied	0	0.0%
Da li ste doživeli pozitivnu diskriminaciju u Nemačkoj? / Have you encountered positive discrimination in Germany?		
Ne / No	28	68.3%
Da / Yes	13	31.7%
Da li mislite da se afirmativno delovanje dešava često ili sporadično? / Do you think affirmative action is frequent or more isolated?		
Sporadično / Occasional	32	78.0%
Često / Happens often	9	22.0%
Da li ste doživeli negativnu diskriminaciju u Nemačkoj? / Have you encountered negative discrimination in Germany?		
Ne / No	22	53.7%
Da / Yes	19	46.3%
Da li mislite da se negativna diskriminacija dešava često ili sporadično? / Do you think negative discrimination is frequent or more isolated?		
Sporadično / Occasional	23	56.1%
Često / Happens often	18	43.9%
Da li mislite da imate bolje prilike u karijeri u Nemačkoj? / Do you think you have better career opportunities in Germany?		
Da / Yes	24	58.8%
Ne znam / I do not know	14	34.1%
Ne / No	3	7.3%

sa negativnom diskriminacijom (npr. diskriminacija usmerena na omalovažavanje i nanošenje štete pojedincu), za razliku od onih, $n = 22$ (53,7%), koji nisu doživeli negativnu diskriminaciju. Pored toga, oblici negativne diskriminacije uključivali su i favorizaciju nemačkih (domaćih) lekara za dalje usavršavanje, ili namerno ignorisanje od strane kolege u bolnici. Rezultati ciljne grupe takođe pokazuju da se negativna diskriminacija dešavala povremeno u više od polovine slučajeva, $n = 23$ (56,1% %), dok su drugi, $n = 18$ (43,9% %), smatrali da se dešavala često.

Rezultati studije predstavljeni u Tabeli 4 takođe pokazuju prilike u karijeri dostupne lekarima u Nemačkoj. Rezultati pokazuju da je jedan broj ispitanika, $n = 24$ (58,5%), smatrao da imaju dobre prilike za karijeru u Nemačkoj, određeni broj ispitanika, $n = 14$ (34,1%), izjavio je da ne zna, dok su drugi, $n = 3$ (7,3%), smatrali da nemaju perspektivu za karijeru (Tabela 4).

Stepen zadovoljstva

Skoro četvrtina ispitanika, $n = 10$ (24,4%), izjavila je da je veoma zadovoljna, dok je većina, $n = 31$ (75,6%), izrazila prilično zadovoljstvo svojim životom u Nemačkoj (Tabela 5). Glavni razlozi za ovo zadovoljstvo bili su sledeći: socijalna sigurnost u Nemačkoj, dobra

authorization from the Association of Statutory Health Insurance Physicians. In addition, analysis showed that positive discrimination (e.g., affirmative actions towards immigrants stimulating their integration despite the differences that may exist) occurred occasionally in more cases, $n = 32$ (78%), than often, $n = 9$ (22%). The results also show that a certain number of respondents, $n = 19$ (46.3%), had faced negative discrimination (e.g., discrimination aimed at belittling and harming an individual) in contrast to those, $n = 22$ (53.7%), who had not experienced negative discrimination. In addition, forms of negative discrimination included German (native) doctors being favored for further training, or colleagues in the hospital deliberately ignoring immigrant doctors. The results of the target group also show that negative discrimination occurred occasionally in more than half of the cases, $n = 23$ (56.1% %), whereas others, $n = 18$ (43.9% %), believed that it occurred frequently.

The study results presented in Table 4 also demonstrate the career opportunities available to doctors in Germany. The results show that a number of the respondents, $n = 24$ (58.5%), felt they had promising career opportunities in Germany, some, $n = 14$ (34.1%), said that they did not know, while others, $n = 3$ (7.3%), felt that they had no promising career opportunities (Table 4).

perspektiva za karijeru, kao i visok nivo bezbednosti u Nemačkoj. S druge strane, neke stvari su se pokazale kao smetnja potpunom zadovoljstvu, kao što su visoki troškovi života, odvojenost od porodice i prijatelja u matičnoj zemlji, preterana birokratija.

Interesantni su bili i rezultati koji su se odnosili na pitanje da li ispitanici mogu da zamisle da trajno žive u Nemačkoj. Jedan broj ispitanika, $n = 18$ (43,9%), izjavio je da ne zna, skoro trećina, $n = 13$ (31,7%), potvrdila je da želi da ostane u Nemačkoj za stalno, dok su drugi, $n = 10$ (24,4%), izjavili da ne žele da žive u Nemačkoj zauvek. Motivi za odluku o životu u Nemačkoj bili su: socijalna sigurnost, bolja perspektiva za karijeru i uređen život. Međutim, ovo se nije odnosilo na sve ispitanike, jer se takođe moglo desiti da dođe do odluke o potpunom povratku u slučaju da se ispitanici nisu osećali prijatno na poslu. Pored toga, naša analiza pokazuje da jedan broj ispitanika, $n = 21$ (51,2%), nije razmišljao o povratku u matičnu zemlju, dok su drugi, $n = 20$ (48,8%), razmišljali o tome. Razlozi za povratak u domovinu koje su ispitanici naveli su: društveni milje, različite navike, razdvojenost od porodice i prijatelja (privatni razlozi), kao i manje birokratije u sopstvenoj zemlji. Analize dalje pokazuju da većina ispitanika, $n = 25$ (61%), nije razmišljala o emigriranju iz Nemačke u druge zemlje, dok je više od trećine, $n = 16$ (39%), razmišljalo o preseljenju u zemlje poput SAD, Austrije, Švajcarske i skandinavskih zemalja. Navedeni razlozi su: više beneficija za lekare, npr. kraća udaljenost od matične zemlje (Austrija), bo-

Satisfaction

Almost a quarter of the respondents, $n = 10$ (24.4%), stated that they were very satisfied, while a majority, $n = 31$ (75.6%), felt rather satisfied with their life in Germany (Table 5). The main reasons for this satisfaction were as follows: the social security in Germany, the promising career opportunities, and that Germany is a safe country. On the other hand, some matters proved to be a hindrance to complete satisfaction, such as the high cost of living, separation from family and friends in the home country, and excessive bureaucracy.

The results concerning the question of whether respondents could imagine living in Germany permanently were also interesting. A number of respondents, $n = 18$ (43.9%), stated that they did not know, almost a third, $n = 13$ (31.7%), confirmed that they wanted to stay in Germany permanently, while others, $n = 10$ (24.4%), stated that they did not want to live in Germany forever. The motivation for the decision to live in Germany permanently was: social security, better career opportunities, and an organized way of life. However, this did not apply to all respondents, as they could also decide to return completely if they did not feel comfortable at work. In addition, our analysis shows that a number of respondents, $n = 21$ (51.2%), had not considered moving back to their home country, while others, $n = 20$ (48.8%), had considered it. The reasons for moving back to their home country stated by the respondents were: the social milieu, different habits,

Tabela 5. Stepen zadovoljstva ispitanika u Nemačkoj

Table 5. Satisfaction of respondents in Germany

Aspekti / Aspects	Broj / Number	Procentat / Percentage %
U kojoj meri ste zadovoljni svojim životom u Nemačkoj? / How satisfied are you with your life in Germany?		
Prilično zadovoljan-na / Rather satisfied	31	75.6%
Vrlo zadovoljan-na / Very satisfied	10	24.4%
Prilično nezadovoljan-na / Rather dissatisfied	0	0.0%
Vrlo nezadovoljan-na / Very dissatisfied	0	0.0%
Možete li da zamislite da zauvek živite u Nemačkoj? / Can you imagine living in Germany permanently?		
Ne znam / I do not know	18	43.9%
Da / Yes	13	31.7%
Ne / No	10	24.4%
Da li ste ikada razmišljali da se vratite su svoju zemlju? / Have you ever thought about returning to your home country?		
Ne / No	21	51.2%
Da / Yes	20	48.8%
Da li ste ikada razmišljali da se preselite u drugu zemlju radi napretka u karijeri? / Have you ever thought about moving to another country to further your career?		
Ne / No	25	61.0%
Da / Yes	16	39.0%

lje centrirane strukture zaštite i, u nekim slučajevima, bolje plate. Rezultati pokazuju da je, generalno gledano, većina lekara bila zadovoljna životom u Nemačkoj, navodeći postojanje dobre perspektive za karijeru, kao i dostupnost kvalitetne obuke.

Intervjui

Osim upitnika, obavljena su i dva intervjua koja su pokazala dve različite karakteristike. Prvi intervju je bio sa osobom koja je napustila posao u matičnoj zemlji da bi emigrirala u Nemačku i tamo radila, dok je drugi intervju bio sa zdravstvenim radnikom koji je u Nemačku došao nakon završenih studija medicine.

Oba intervjua su otkrila poteškoće koje su se javile i duge vremenske periode koji su protekli pre nego što su ispitanici uspeali da okončaju proces dobijanja boravišne dozvole i proceduru priznavanja diplome. Prvi intervju je jasno pokazao da je ispitanica odluku o emigriranju u Nemačku smatrala pozitivnom. Sagovornica je napustila svoju domovinu, Srbiju, zbog nepovoljne društvene, političke i ekonomske situacije, u potrazi za boljim uslovima za sebe i svoju porodicu. Nasuprot tome, Nemačka je pružala široku perspektivu za karijeru, finansijski prosperitet i stabilnu političku situaciju. Međutim, ovaj intervju je takođe otkrio veće poteškoće u Nemačkoj u pogledu ravnoteže između posla i privatnog života i birokratije. Drugi intervju je takođe bio o pozitivnom iskustvu emigracije iz Srbije u Nemačku. Sagovornik je došao direktno u Nemačku nakon što je završio studije medicine uz pomoć agencije koja dovodi kvalifikovano osoblje u Nemačku. Agencija je mogla da mu garantuje posao, mesto za boravak i pomoć u prevođenju i overi dokumenata. Razlozi za emigraciju su bili loša obuka lekara nakon diplomiranja u Srbiji, kao i nemogućnost slobodnog izbora specijalizacije. Ovaj sagovornik se, međutim, susreo i sa negativnom diskriminacijom, iako je to dobro podneo i doživeo je više kao motivaciju da se još više potruži. Istakao je i stabilnost Nemačke, kao i dobru perspektivu za karijeru, ali je preteranu birokratiju shvatio kao nedostatak. Sagovornik je naveo da mu je cilj bio da završi specijalizaciju u Berlinu i otvori sopstvenu dermatološku praksu.

DISKUSIJA

Analiza anketa pokazuje jasne motive za iseljavanje iz Srbije, Bosne i Hercegovine, Crne Gore i Severne Makedonije, uključujući finansijske aspekte, nedostatak mogućnosti za profesionalni razvoj u zemlji porekla, te bolju perspektivu za dalje usavršavanje i karijeru u inostranstvu. Ovi nalazi potvrđuju savremena saznanja o razlozima migracija [13-15]. Sveobuhvatan pregled faktora koji utiču na migraciju u i iz Ujedinjenog Kra-

missing family and friends (private reasons), as well as less red tape in their own country. The analyses further show that a majority of respondents, $n = 25$ (61%), had not contemplated emigrating from Germany to other countries, whereas, more than a third, $n = 16$ (39%), had considered moving to countries such as the USA, Austria, Switzerland, and the Scandinavian countries. The reasons stated were: more benefits for the doctors, for example, a shorter distance from the home country (Austria), better-centered care structures, and, in some cases, better salaries. The results show that, in general, the majority of the doctors were satisfied with life in Germany, stating that good career opportunities and good training were available.

Interviews

In addition to the questionnaire, two interviews were conducted with two different characteristics. The first interview was with a person who gave up their job in their home country to emigrate to Germany and work there, while the second interview was with a health-care professional who came to Germany after completing their medical studies.

Both interviews revealed difficulties and lengthy periods that elapsed before the interviewees managed to complete the residence permit process and the degree recognition procedure. The first interview made it clear that the decision to emigrate to Germany was considered a positive one. The interviewee left her home country, Serbia, due to the unfavorable social, political, and economic situation, in search of better conditions for herself and her family. In contrast, Germany could offer a wide range of career opportunities, financial prosperity, and a stable political situation. However, this interview also revealed more difficulties in Germany regarding work-life balance and bureaucracy. The second interview was also about a positive experience of emigration from Serbia to Germany. The interviewee came directly to Germany after completing his medical studies with the help of an agency that brings qualified personnel to Germany. The agency was able to guarantee him a job, a place to stay, and assistance with translating and verifying documents. The reason for emigration was the poor training of doctors in Serbia after graduation, as well as not having a free choice of specialty. This interviewee, however, also encountered negative discrimination, although he took it well and saw it more as motivation to do more. The stability of Germany was also emphasized, as well as the good aspect of career opportunities, but the excessive bureaucracy was also perceived as a shortcoming. The interviewee stated that his goal was to complete his specialization in Berlin and open his own dermatology practice.

ljevstva otkriva da je odluka lekara da migriraju složena i da zahteva pažljivo razmatranje različitih faktora pritiska i privlačenja koji deluju na makro, mezo i mikro nivoima [13].

U našem istraživanju, većina ispitanika je u Nemačku došla sa svojim partnerom, odnosno sa suprugom i decom, ili su došli kod porodice/rodbine. Ponovno okupljanje porodice ili porodične vrednosti i okolnosti često su od značaja za migracionu politiku [14], bilo kao prepreka [15] ili kao podsticajni faktor za emigraciju [14]. Na naše ispitanike uticale su i bolje mogućnosti obrazovanja za decu i bolja perspektiva u karijeri životnih partnera. Sve veći broj dokaza sugerise da su obrazovne mogućnosti bile i ostale značajni aspekt kod migracije zdravstvenih radnika širom sveta [16-18]. Većina naših ispitanika nije imala privremeni posao na početku svog boravka u Nemačkoj i menjala je radna mesta 2-3 puta od svog dolaska, što možda nije neuobičajeno za medicinsko osoblje u ranim fazama karijere.

Polovina ispitanika je veći deo procesa prijavljivanja završila bez ičije pomoći, dok je jedna trećina dobila pomoć rođaka, a samo mali broj je tražio pomoć agencije. Ovo ukazuje na to da je poverenje ključni element u regulisanju migracionih tokova. Prijavljivanje je obuhvatalo niz koraka, kao što su priznavanje kvalifikacija, pohađanje kurseva jezika, regulisanje statusa vize, dodatna obuka ili dobijanje boravišne dozvole. Da bi osoba mogla da obavlja praksu kao strani lekar u Nemačkoj, mora da bude ispunjen niz kriterijuma, uključujući licencu za bavljenje medicinom (odnosno priznavanje diplome sa studija medicinske), specijalistički test jezika, kao i vizu, poznatu kao plava karta. U nekim slučajevima morala je i da se završi dodatna obuka. Zbog birokratije i drugih faktora, proces traje i do 12 meseci, što možda i nije predugo u poređenju sa kašnjenjem u procesu dobijanja radne dozvole u Sjedinjenim Državama.

Naši podaci su takođe pokazali da je većina ispitanika lekara radila u ustanovama stacionarnog tipa, kao što su bolnice, na šta je možda uticala potražnja za uslugama, bolje plate, kao i pravni instrumenti koji podržavaju kliničke specijalnosti [19-21]. Finansijski aspekt je pokazao da se radilo o ljudima sa visokim zaradama na putu ka vrhuncu karijere.

Ispitanici su izrazili da ih je nemački pravni sistem dobro uslužio i nisu iskusili nikakvu značajnu negativnu diskriminaciju, ali je takođe bilo malo pozitivne diskriminacije. Mogućnost da se angažuju strani lekari ili da se privuče interesovanje ogleda se u nekim pravnim aspektima. Od 1. januara 2016. godine, propis „*Vestbalkanordnung*“ § 26 stav 2 Pravilnika o zapošljavanju predviđa da državljani Albanije, Bosne i Hercegovine,

DISCUSSION

The analysis of the surveys shows clear motives for emigration from Serbia, Bosnia and Herzegovina, Montenegro, and North Macedonia. These include financial aspects, lack of professional development opportunities, and better opportunities for further training and careers abroad. These findings confirm the contemporary knowledge of the reasons for migration [13-15]. A comprehensive review of the factors influencing migration to and from the United Kingdom reveals that a physician's decision to migrate is nuanced and necessitates careful consideration of various push and pull factors operating at macro, meso, and micro levels [13].

In our study, most respondents came to Germany with their partner, i.e., with their wife/husband and children, or they came to stay with family/relatives. The family reunion or family values and circumstances are often of migration policy relevance [14], either as a barrier [15] or as a push factor for emigration [14]. Our respondents were also influenced by better educational opportunities for their children and better career opportunities for their partners. Growing evidence suggests that educational opportunities have been and will continue to be a significant issue for the migration of health workers worldwide [16-18]. The majority of our respondents did not have a temporary job at the beginning of their stay in Germany and have changed workplaces 2-3 times since arriving, which might not be uncommon for medical personnel in early career stages.

Half of the respondents completed most of the application process without anyone's help, while one-third received assistance from relatives, and only a small number received help from an agency. This indicates that trust is a key element in regulating migration flows. The application included a variety of tasks, such as the recognition of qualifications, taking language courses, regulating the visa status, additional training, or obtaining residence permits. For a person to be able to practice as a foreign doctor in Germany, a number of criteria must be met, including a license to practice medicine (recognition of medical degree), a specialist language test, and a visa, also known as a blue card. In some cases, additional training must also be completed. Due to the bureaucracy and other factors, the process takes up to 12 months, which may not be too long compared to the delays in the work permit process in the United States.

Our data also showed that most physician respondents worked in inpatient facilities, such as hospitals, which might have been influenced by the demand for services, better salaries, as well as the legal instruments supporting clinical specialties [19-21]. The financial aspect showed that these were high earners on their way to the peak of their careers.

Kosova, Crne Gore, Severne Makedonije i Srbije mogu dobiti odobrenje uz proveru prioriteta za bilo koju vrstu zaposlenja [22]. To znači da i nekvalifikovani kadar može da podnese zahtev za radnu vizu i da živi u Nemačkoj. Kvalifikovani radnici lakše dolaze u Nemačku, jer su oni najtraženiji.

Opšta slika ukazuje na zadovoljstvo preseljenjem u Nemačku. Takođe je jasno da su potrebna značajna poboljšanja u domenu birokratije. Kada su u pitanju sagovornici u intervjuima, zanimljivo je napomenuti da su oboje morali da prevaziđu brojne birokratske prepreke da bi se bavili medicinom u Nemačkoj. Oboje su takođe emigrirali u Nemačku iz sličnih razloga: u matičnoj zemlji nije bilo mogućnosti za profesionalni razvoj, ali su u inostranstvu videli bolje prilike za dalje usavršavanje i bolju perspektivu u karijeri, kao i veće plate nego u matičnoj zemlji. Oboje intervjuisanih ispitanika su bili u Nemačkoj 5–10 godina i stvorili su za sebe stabilno okruženje. Oboje su imali identične probleme sa imigracionim vlastima [23], uključujući vreme čekanja, odsustvo podrške i nedostatak odgovarajuće strukture. Ipak, ispitanici su bili zadovoljni trenutnim životom i izjavili da ne planiraju da napuštaju Nemačku, ali da se nadaju i promeni i poboljšanju životnih prilika.

Fluktuacija u zdravstvenim strukama u Nemačkoj je sve veća, a zapošljavaju se strani asistenti, lekari i medicinsko osoblje. Treba, dakle, naglasiti da je stranim državljanima sve primamljivije da grade karijeru u Nemačkoj. Raznovrsnost mogućnosti se takođe povećava iz godine u godinu, a samim tim raste i interesovanje u inostranstvu. Konačno, može se reći da se očekuje da će imigracija lekara iz inostranstva rasti svake godine. Tada će se javiti potreba da se obezbedi bolja ravnoteža između posla i privatnog života, poboljšana birokratska podrška i usmeravan proces.

Zapošljavanje lekara sa Zapadnog Balkana može da ublaži teret nemačkog zdravstvenog sistema izazvanog velikim nedostatkom kvalifikovane radne snage. Istraživanja su pokazala da više od 60% lekara razmatra da u potpunosti napusti rad u zdravstvenoj zaštiti pacijenata [24]. Nemačka ima ukupno 84,6 miliona stanovnika, od čega 42,8 miliona žena i 41,7 miliona muškaraca (podaci iz 2023. godine) [25]. Od 84,6 miliona stanovnika, oko 73,6 miliona ljudi je pokriveno obaveznom zdravstvenim osiguranjem, oko 8,7 miliona je privatno osigurano, a preostala dva miliona ljudi su ili primaoci socijalne pomoći, pripadnici policije i oružanih snaga ili neosigurani [26]. Demografska promena koja postepeno postaje karakteristična za Nemačku je od velikog značaja. Podaci nemačkog Saveznog zavoda za statistiku pokazuju da je značajno povećan udeo stanovništva starijeg od 55 godina,

The interviewees felt well looked after by the German legal system and had not experienced any major negative discrimination, but there had also been little positive discrimination. An opportunity to recruit foreign doctors or to arouse interest is reflected in some legal aspects. Since January 1, 2016, the regulation "Westbalkanordnung" § 26 paragraph 2 of the Employment Ordinance stipulates that nationals of Albania, Bosnia and Herzegovina, Kosovo, Montenegro, North Macedonia, and Serbia can obtain approval with a priority check for any type of employment [22]. This means that non-qualified personnel can also apply for a work visa and live in Germany. People who are qualified workers have an easier time coming to Germany, as skilled workers are the most sought-after.

The overall picture is one of satisfaction with having emigrated to Germany. It is also clear that there is a need for significant improvements in bureaucracy. In connection with the interviewees, it was interesting to note that they both had to overcome numerous bureaucratic hurdles in order to practice medicine. Both also emigrated to Germany for similar reasons: there were no development opportunities in their home country, however, they saw better training and career opportunities abroad, as well as higher salaries than in their home country. The interviewees had both been in Germany 5–10 years and had created a stable environment. They both experienced identical problems with immigration authorities [23], including the waiting time, absence of support, and lack of appropriate structure. Nevertheless, the interviewees were satisfied with their current life and stated that they had no plans of leaving Germany, but that they also hoped for a change and improvement in their living circumstances.

Fluctuation in the healthcare professions in Germany is increasing, and foreign assistants, doctors, and nursing staff are being recruited. It should, therefore, also be emphasized that it is becoming all the more enticing for foreign citizens to build a career in Germany. The variety of opportunities is also increasing from year to year and thus the interest abroad is growing. Finally, it can be said that the immigration of doctors from abroad is expected to increase each year. Then, there will be a need to ensure better work-life balance, improved bureaucratic support, and a guided process.

The recruitment of doctors from the Western Balkans can ease the burden on the German healthcare system caused by the high shortage of skilled labor. Studies have shown that more than 60% of doctors are considering leaving patient care completely [24]. Germany has a total population of 84.6 million, of which 42.8 million are women and 41.7 million are men (as of 2023) [25]. Of the 84.6 million inhabitants, around 73.6 million peo-

dok se broj radno sposobnih osoba starijih od 18 godina smanjuje [27]. Podaci ukazuju i na nizak natalitet koji je doveo i nastaviće da dovodi do demografskih promena. U poređenju sa 1950. godinom, očekivano trajanje života je danas znatno duže: za žene je 83,9 godina, a za muškarce 79,2 godine. U Nemačkoj se očekuje konstantno produžavanje očekivanog trajanja života, a prema prognozi Saveznog zavoda za statistiku, ono će se do 2070. godine produžiti za oko 5 godina [27].

Uprkos dostupnosti postojećih podataka, neophodna su buduća istraživanja, koja uključuju veće uzorke i imigrante iz šireg spektra zemalja. Ovo će nam pomoći da bolje razumemo razloge migracije lekara, izazove sa kojima se migranti susreću i faktore koji utiču na njihovu odluku da ostanu u Nemačkoj ili se vrate u svoje matične zemlje. Sprovedenje ovog istraživanja će biti od ključnog značaja za povećanje zadovoljstva lekara migranata, što će na kraju doprineti boljoj stopi zadržavanja u medicinskog kadra.

ZAKLJUČAK

Većina ljudi koji su se doselili u Nemačku su zadovoljni svojom odlukom. Međutim, postoji jasna potreba za značajnim poboljšanjima, kao što je uklanjanje birokratskih prepreka. Angažovanje lekara sa Zapadnog Balkana može pomoći u smanjenju opterećenja nemačkog zdravstvenog sistema, koji se suočava sa velikim nedostatkom kvalifikovanog kadra. S obzirom na tekući nedostatak kvalifikovanih zdravstvenih radnika u Nemačkoj i demografski razvoj zemlje, ciljano zapošljavanje stranih medicinskih stručnjaka putem bilateralnih sporazuma postaje sve relevantnije. Budući sporazumi bi mogli da pomognu da se smanje administrativne prepreke, da olakšaju priznavanje stručnih kvalifikacija, i da poboljšaju integraciju stranih stručnjaka. Ojačana međunarodna saradnja, posebno sa zemljama Zapadnog Balkana i drugim regionima sa viškom medicinskog kadra, predstavlja stratešku meru za osiguranje dugoročne stabilnosti pružanja zdravstvene zaštite u Njemačkoj uz uspostavljanje održivih mehanizama migracije.

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ple are covered by statutory health insurance, around 8.7 million are privately insured, and the remaining two million people are either welfare recipients, members of the police and armed forces, or uninsured [26]. The demographic change that is gradually becoming characteristic of Germany is of considerable importance. Data from the Federal Statistical Office shows that the proportion of the population over the age of 55 has significantly increased, while the number of people of working age over 18 is decreasing [27]. The data also points to a low birth rate, which has led and will continue to lead to demographic change. Compared to 1950, life expectancy today is significantly higher: it is 83.9 years for women and 79.2 years for men. A constant increase in life expectancy is expected in Germany, and according to the forecast of the Federal Statistical Office, it will increase by around 5 years by 2070 [27].

Despite the availability of existing data, future research is necessary, involving larger sample sizes and immigrants from a broader range of countries. This will help us better understand the reasons behind physician migration, the challenges that migrants encounter, and the factors influencing their decision to stay in Germany or return to their home countries. Conducting this research will be instrumental in enhancing the satisfaction of migrant physicians, ultimately contributing to better retention rates in the medical workforce.

CONCLUSION

Most people who have moved to Germany are satisfied with their decision. However, there is a clear need for significant improvements, such as removing bureaucratic hurdles. Hiring doctors from the Western Balkans can help reduce the strain on the German healthcare system, which is facing a severe shortage of skilled workers. Given the ongoing shortage of skilled healthcare professionals in Germany and the country's demographic development, the targeted recruitment of foreign medical professionals through bilateral agreements is becoming increasingly relevant. Future agreements could help reduce administrative barriers, facilitate professional recognition, and improve the integration of foreign professionals. Strengthened international cooperation, particularly with Western Balkan countries and other regions with a surplus of medical personnel, represents a strategic measure to ensure the long-term stability of healthcare provision in Germany while establishing sustainable migration mechanisms.

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SAŽETAK

Plazmocitna leukemija je veoma retka i agresivna forma plazmocitne diskrazije koju odlikuje loša prognoza, kratko preživljavanje i loš odgovor na primenjenu terapiju. Kliničke manifestacije su različite, ali se najčešće sreće ekstramedularna forma bolesti, hiperkalcemija, anemija, trombocitopenija, oštećenje bubrežne funkcije i povećanje koncentracije laktat dehidrogenaze. Postoje brojne citogenetske abnormalnosti koje dovode do veće proliferacije, inhibicije apoptoze, promene u ekspresiji adhezivnih molekula i hemokinskih receptora. I pored uvođenja novih terapijskih modaliteta zasnovanih na primeni bortezomiba i imunomodulatornih lekova, kao i primeni biološke terapije, terapijski ishod je još uvek nezadovoljavajući.

Ključne reči: plazmocitna leukemija, citogenetske abnormalnosti, imunomodulatorni lekovi

ABSTRACT

Plasma cell leukemia (i.e., plasmacytic leukemia) is a very rare and aggressive form of plasma cell dyscrasia characterized by a poor prognosis, short survival time, and a poor response to the administered therapy. Clinical manifestations vary, however, the extramedullary form of the disease is the most common, as are hypercalcemia, anemia, thrombocytopenia, impaired renal function, and increased lactate dehydrogenase concentration. Numerous cytogenetic abnormalities lead to greater proliferation, inhibition of apoptosis, and changes in the expression of adhesion molecules and chemokine receptors. Despite the introduction of new therapeutic modalities based on bortezomib, immunomodulatory drugs, and biological therapy, the therapeutic outcome is still unsatisfactory.

Keywords: plasma cell leukemia, cytogenetic abnormalities, immunomodulatory drugs

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UVOD

Plazmocitna leukemija predstavlja retku i veoma agresivnu formu plazma ćelijske diskrazije. U većini plazma ćelijskih diskrazija maligni plazmociti naseljavaju koštanu srž gde stupaju u brojne ćelijske i humoralne interakcije za mikro sredinom koštane srži [1]. Povremeno, plazmociti mogu da napuste koštanu srž i da se nađu u perifernoj krvi, odakle potencijalno mogu da nasele i parenhimatozne organe. Nalaz plazmocita u perifernoj krvi nije ujedno i dovoljan kriterijum za postavljanje dijagnoze plazmocitne leukemije. Naime, ranije definisani dijagnostički kriterijumi za plazmocitnu leukemiju, kao što je postojanje najmanje 20% plazmocita među leukocitima periferne krvi ili više od $2 \times 10^9/L$ plazmocita u perifernoj krvi, redefinisani su nedavno, pa je tako, od 2013. godine, Međunarodna radna grupa za mijelom (engl. *International Myeloma Working Group – IMWG*) potvrdila da je za dijagnozu neophodno najmanje 5% plazmocita u perifernoj krvi [2,3]. Incidencija plazmocitne leukemije u Evropi je oko 0,04 pacijenta na 100.000 stanovnika, a takođe se sreće kod 2%–4% obolelih od multiplog mijeloma [1,4]. Bolest se karakteriše kratkim periodima remisije i ranim relapsima. Stoga je i očekivano kratko preživljavanje – petogodišnje preživljavanje je oko 10%, uz napomenu da je nešto bolje kod pacijenata sa primarnom plazmocitnom leukemijom [5].

Plazmocitna leukemija može biti primarna – javlja se kao „de novo” bolest (1%–2% bolesnika sa multiplim mijelomom) i sekundarna – predstavlja leukemijsku transformaciju refraktornog multiplog mijeloma ili se javlja kod relapsa multiplog mijeloma (incidencija 2%–9%) [6]. Bez obzira da li se radi o primarnoj ili sekundarnoj plazmocitnoj leukemiji, prognoza je veoma loša. Biologija i kliničke manifestacije primarne i sekundarne plazmocitne leukemije se razlikuju (Tabela 1). Naime, pacijenti sa primarnom plazmocitnom leukemijom pokazuju bolji terapijski odgovor ako se leče agresivnom hemioterapijom i autologom transplantacijom matičnih ćelija hematopoeze ali se, na žalost, vrlo brzo registruju i recidivi bolesti koji su najčešće refraktorni na terapiju [4]. Sa druge strane, sekundarna plazmocitna leukemija pokazuje znatno lošiji terapijski odgovor (manje od 50% pacijenata) sa vrlo brzim fatalnim ishodom [1]. Kao posledica uvođenja novih terapijskih modaliteta i povećanja prosečne dužine života pacijenata obolelih od multiplog mijeloma, učestalost sekundarne plazmocitne leukemije je u porastu [4]. Ovaj porast učestalosti sekundarne plazmocitne leukemije se može objasniti i povećanom prevalencijom obolelih od multiplog mijeloma, što je posledica produžetka dužine života, kao i primenom više terapijskih linija u toku lečenja multiplog mijeloma, što može doprineti

INTRODUCTION

Plasma cell leukemia (i.e., plasmacytic leukemia) is a rare and exceptionally aggressive form of plasma cell dyscrasia. In most plasma cell dyscrasias, malignant plasma cells infiltrate the bone marrow, engaging in numerous cellular and humoral interactions with the bone marrow microenvironment [1]. Occasionally, plasma cells can leave the bone marrow and enter the peripheral blood, where they can potentially colonize parenchymal organs. The finding of plasma cells in the peripheral blood is not a sufficient criterion for establishing a diagnosis of plasma cell leukemia. Namely, previously defined diagnostic criteria for plasma cell leukemia, such as the existence of at least 20% of plasma cells among peripheral blood leukocytes or more than $2 \times 10^9/L$ plasma cells in peripheral blood, have been redefined recently, consequently, as of 2013, the International Myeloma Working Group (IMWG) has confirmed that the presence of at least 5% of plasma cells in peripheral blood is necessary for diagnosis [2,3]. The incidence of plasma cell leukemia in Europe is about 0.04 patients per 100,000 inhabitants, and it is also found in 2%–4% of patients with multiple myeloma [1,4]. The disease is characterized by short periods of remission and early relapses. Therefore, a short survival time is expected - the five-year survival is around 10%, however, it should be noted that it is slightly better in patients with primary plasma cell leukemia [5].

Plasma cell leukemia can be primary, occurring as a *de novo* disease (1%-2% of patients with multiple myeloma) and secondary, representing the leukemic transformation of refractory multiple myeloma or occurring in relapsed multiple myeloma (incidence 2%-9%) [6]. Regardless of whether it is primary or secondary plasma cell leukemia, the prognosis is poor. The biology and clinical manifestations of primary and secondary plasma cell leukemia differ (Table 1). Namely, patients with primary plasma cell leukemia show a better therapeutic response if they are treated with aggressive chemotherapy and autologous hematopoietic stem cell transplantation. However, unfortunately, relapses of the disease, which are most often refractory to therapy, are also registered within a short space of time [4]. On the other hand, secondary plasma cell leukemia shows a significantly worse therapeutic response (less than 50% of patients) with a swift fatal outcome [1]. Due to the introduction of new therapeutic modalities and the increase in the average life expectancy of patients suffering from multiple myeloma, the frequency of secondary plasma cell leukemia is increasing [4]. This increase in the frequency of secondary plasma cell leukemia can be explained by the higher prevalence of patients with multiple myeloma, which is a conse-

Tabela 1. Revised Cardiac Risk Index-Lee kriterijumi

	Primarna plazmocitna leukemija	Sekundarna plazmocitna leukemija
Epidemiologija	Javlja se u mlađem životnom dobu	Javlja se u starijem životnom dobu
Kliničke i laboratorijske karakteristike	- Česta ekstrapredularna bolest - Visoka koncentracija kreatinina - Visoka koncentracija beta-2-mikroglobulina	- Česta koštana bolest
Molekularne karakteristike	- Uglavnom hipodiploidna - Česta translokacija 11;14	- Uglavnom hiperdiploidna - Česte translokacije 11;14, 4;14, 14;16
Preživljavanje	Duže	Kraće

Table 1. Revised Cardiac Risk Index-Lee Criteria

	Primary plasma cell leukemia	Secondary plasma cell leukemia
Epidemiology	Occurs at a younger age	Occurs in old age
Clinical and laboratory characteristics	- Frequent extramedullary disease - High creatinine concentration - High concentration of beta-2-microglobulin	- Frequent bone disease
Molecular characteristics	- Mostly hypodiploid - Frequent translocation 11;14	- Mostly hyperdiploid - Frequent translocations 11;14, 4;14, 14;16
Survival	Longer	Shorter

klonskoj selekciji i novim genetskim promenama [7]. Ipak, i pored toga, primarna plazmocitna leukemija je češća forma bolesti i čini oko 60%–70% pacijenata [2].

Biologija plazmocitne leukemije

Jedna od osnovnih karakteristika većine plazma ćelijskih diskrazija je proliferacija malignih plazmocita uglavnom u koštanoj srži. Zahvaljujući adhezivnim molekulima eksprimiranim na plazmocitima i ćelijskim interakcijama sa mikrosredinom koštane srži, ovi maligni plazmociti ostaju najčešće locirani u koštanoj srži. Kod plazmocitne leukemije, zbog promenjene ekspresije pojedinih adhezivnih molekula, maligni plazmociti lako napuštaju koštanu srž, ulaze u perifernu krv i naseljavaju parenhimatozne organe [8]. Čelije plazmocitne leukemije pokazuju smanjenu ekspresiju *NCAM* (neural cell adhesion molecule *CD56*) molekula, kao i *LFA* (leukocyte function associated antigen-1), *VLA-5* (very late antigen 5), *CD9*, *CD82* i drugih adhezivnih molekula, čime se smanjuje vezivanje ćelija plazmocitne leukemije za stromalne ćelije koštane srži i tako olakšava migracija u perifernu krv [9,10].

Postojanje brojnih citogenetskih aberacija je tipično za ćelije plazmocitne leukemije. Naime, ćelije plazmocitne leukemije su najčešće diploidne ili hipodiploidne (oko 80%) dok su plazmociti u multiplom mijelomu najčešće hiperdiploidni [3,5]. Najčešće citogenetske aberacije koje se javljaju u ćelijama plazmocitne leukemije su delecija hromozoma 13 i monozomija i sreću se kod više od 85% obolelih [5,10]. Abnormalnost hromozoma 1 (delecija ili amplifikacija) su takođe če-

quence of the extension of life expectancy, as well as the use of more therapeutic lines during the treatment of multiple myeloma, which can contribute to clonal selection and new genetic changes [7]. Nevertheless, primary plasma cell leukemia is the more common form of the disease and accounts for about 60%–70% of patients [2].

Biology of plasma cell leukemia

One of the main characteristics of most plasma cell dyscrasias is the proliferation of malignant plasma cells mainly into the bone marrow. Due to adhesion molecules expressed in plasma cells and cellular interactions with the bone marrow microenvironment, these malignant plasma cells most often remain in the bone marrow. In plasma cell leukemia, due to the altered expression of certain adhesion molecules, malignant plasma cells easily migrate from the bone marrow, enter the peripheral blood, and inhabit parenchymatous organs [8]. Plasmacytic leukemia cells show a reduced expression of *NCAM* molecules (neural cell adhesion molecule *CD56*), as well as of *LFA* (leukocyte function associated antigen-1), *VLA-5* (very late antigen 5), *CD9*, *CD82*, and other adhesion molecules, thereby reducing the binding of plasmacytic leukemia cells to bone marrow stromal cells and consequently facilitating migration into the peripheral blood [9,10].

The presence of numerous cytogenetic aberrations is typical for plasmacytic leukemia cells. Namely, plasmacytic leukemia cells are most often diploid or hypoploid (about 80%), while plasmacytes in multiple

ste kod obolelih od plazmocitne leukemije, naročito kod primarne forme bolesti [5,11,12]. Kod većine ćelija plazmocitne leukemije se sreće translokacija t(14;16) i delecija 17p, čime se objašnjava i česta translokacija IgH kao i ekspresija ciklina D1 [4]. Translokacije t(11;14) i t(4;14) se javljaju sa približno istom učestalošću kao kod obolelih od multiplog mijeloma [4]. Primenom naj-savremenijih metoda molekularnog ispitivanja utvrđena je visoka učestalost mutacija TP53 i K/NRAS gena [5]. Značaj svake od ovih detektovanih citogenetskih abnormalnosti je još uvek nedovoljno poznat, mada se smatra da su povezane sa agresivnijim kliničkim tokom bolesti i lošijom prognozom.

Kliničke manifestacije

Klinička slika obolelih od plazmocitne leukemije se u izvesnoj meri razlikuje od multiplog mijeloma. Prosečna starost obolelih od plazmocitne leukemije je 61 godina, što je oko 10 godina manje nego prosečna starost obolelih od multiplog mijeloma [4]. Većina obolelih od plazmocitne leukemije ima veliku tumorsku masu koja uzrokuje gubitak u telesnoj težini, povremeno noćno preznojavaње, simptome bubrežne insuficijencije, anemije, te hemoragijski sindrom. Naime, zbog velike tumorske mase i najčešće masivne infiltracije koštane srži pacijenti imaju izraženu anemiju i trombocitopeniju. Pored toga, veoma često postoji infiltracija perifernih organa pa se javljaju hepatosplenomegalija i limfadenopatija, kao i infiltracija pluća, pleure, testisa, centralnog nervnog sistema i mišića uz postojanje simptoma i kliničkih znakova tipičnih za infiltrovana tkiva [3-6,8-10]. Bol u kostima i osteolizne lezije se javljaju nešto ređe nego kod obolelih od multiplog mijeloma [3-6,8-10].

Laboratorijski nalaz

Zbog infiltracije koštane srži, najveći broj obolelih od plazmocitne leukemije pokazuje postojanje normocitne anemije (oko 80%) i trombocitopenije (oko 60%), a često postoji i leukocitoza uz apsolutnu plazmocitozu (iznad $2 \times 10^9/L$) [4,6]. Kod većine obolelih javlja se *rouleaux* fenomen u perifernom razmazu [4,6].

U biohemijskim analizama, najčešće se registruju povećana serumska aktivnost laktat dehidrogenaze i beta-2-mikroglobulina, hiperkalcemija i povećanje serumske koncentracije kreatinina i uree [6,7]. Kod većine bolesnika se registruje postojanje M-komponente u serumu i to najčešće u klasi IgG (oko 50%), kao i IgA (oko 15%), dok su IgD i IgE veoma retki [6]. Kod oko 80% obolelih od plazmocitne leukemije sreće se Bens Džonsova proteinurija [6].

Biopsija koštane srži obično pokazuje masivnu infiltraciju ćelijama plazmocitne leukemije uz potiski-

myeloma are most often hyperdiploid [3,5]. The most common cytogenetic aberrations that occur in plasmacytic leukemia cells are deletion of chromosome 13 and monosomy which are found in more than 85% of patients [5,10]. Chromosome 1 abnormalities (deletion or amplification) are also common in patients with plasma cell leukemia, especially in those with the primary form of the disease [5,11,12]. Translocation t(14;16) and deletion 17p are found in the majority of plasmacytic leukemia cells, which explains the frequent translocation of IgH as well as the expression of cyclin D1 [4]. Translocations t(11;14) and t(4;14) occur with approximately the same frequency as in patients with multiple myeloma [4]. Using the most modern molecular testing methods, a high frequency of TP53 and K/NRAS gene mutations has been determined [5]. The significance of each of these detected cytogenetic abnormalities is still insufficiently known, although they are believed to be associated with a more aggressive clinical course of the disease and a poorer prognosis.

Clinical manifestations

The clinical presentation of patients with plasma cell leukemia differs to some extent from the one found in multiple myeloma. The average age of patients with plasma cell leukemia is 61 years, which is about 10 years less than the average age of patients with multiple myeloma [4]. Most patients with plasma cell leukemia have a large tumor mass that causes weight loss, occasional night sweats, symptoms of kidney failure, anemia, and hemorrhagic syndrome. Namely, due to the large tumor mass and most often massive infiltration of the bone marrow, patients have severe anemia and thrombocytopenia. In addition, there is very often infiltration of peripheral organs, resulting in hepatosplenomegaly and lymphadenopathy, as well as infiltration of the lungs, pleura, testicles, central nervous system, and muscles with the presence of symptoms and clinical signs typical of infiltrated tissues [3-6,8-10]. Bone pain and osteolytic lesions occur somewhat less often than in patients with multiple myeloma [3-6,8-10].

Laboratory findings

Due to bone marrow infiltration, the largest number of patients with plasmacytic leukemia show the existence of normocytic anemia (about 80%) and thrombocytopenia (about 60%), and there is often leukocytosis with absolute plasmacytosis (above $2 \times 10^9/L$) [4,6]. In the majority of patients, the *rouleaux* phenomenon is present in the peripheral blood smear [4,6].

Biochemical analyses most often register increased serum activity of lactate dehydrogenase, and beta-2-mikroglobulin, as well as hypercalcemia, and an

vanje ostalih loza hematopoeze. Kod pojedinih bolesnika, morfologija plazmocita nije promenjena, ali kod drugih dominiraju nezrele forme sa izrazito bazofilnom citoplazmom, dva jedra, velikim jedarčetom i perinuklearnim haloom [1,6,8].

Dijagnoza

Dijagnoza bolesti postavlja se primenom protočne citometrije periferne krvi. Naime, imunofenotipski, ćelije plazmocitne leukemije su CD38 i CD138 pozitivne kao i u multiplom mijelomu, ali u odnosu na plazmocyte u multiplom mijelomu, pokazuju veću ekspresiju molekula CD20, CD23, CD28, CD44, CD43, uz sniženu ekspresiju molekula CD9, CD56, CD71, CD117 i HLA-DR (Tabela 2) [5,8]. Detekcijom najmanje 5% plazmocita sa gore navedenim imunofenotipom među leukocitima periferne krvi, postavlja se dijagnoza plazmocitne leukemije. Po postavljenoj dijagnozi, neophodno je učiniti radiografiju skeleta ili primeniti druge radiološke metode, poput kompjuterizovane tomografije - skenera (CT), nuklearne magnetne rezonance (NMR) ili pozitronske emisije tomografije (PET skener) čitavog tela, radi detekcije ekstramedularne bolesti. Takođe je neophodno, primenom fluorescentne *in situ* hibridizacije (engl. *fluorescence in situ hybridization* - *FISH*), utvrditi postojanje citogenetskih aberacija sa naročitim osvrtnom na postojanje delecije hromozoma 17p, delecije hromozoma 13q, delecije hromozoma 1p, translokacije hromozoma 14 (t(11;14), t(4;14), t(14;16)) [8].

Prognostički faktori

Loši prognostički faktori obolelih od plazmocitne leukemije su starost preko 60 godina, trombocitopenija ispod $100 \times 10^9/L$, broj plazmocita u perifernoj krvi veći od $20 \times 10^9/L$, niska serumska koncentracija albumina, hiperkalcemija, povećana koncentracija laktat dehidrogenaze i beta-2-mikroglobulina, lošiji *performance* status, kao i izostanak terapijskog odgovora na indukcionu terapiju [10,12-15]. Pored toga, postojanje hipodiploidije, kompleksnog kariotipa, delecije 13q, delecije 17p, delecije 1p i amplifikacije 1q udruženo je sa lošijim ukupnim preživljavanjem [11,12]. Do uvođenja novih agenasa i autologe transplantacije prosečno preživljavanje obolelih od plazmocitne leukemije iznosilo je od 4–11 meseci [9]. Uvođenje novih terapijskih modaliteta, kao i transplantacije matičnih ćelija hematopoeze, produžilo je prosečno preživljavanje obolelih i ono sada iznosi 2–3 godine [16].

Terapija

Uzimajući u obzir agresivnost bolesti, terapiju je neophodno započeti odmah po postavljenoj dijagnozi. Postoje izvesne razlike u lečenju primarne i sekundar-

increase in serum creatinine and urea concentrations [6,7]. In most patients, the presence of the M-component in the serum is registered, most often of the IgG class (about 50%), as well as IgA (about 15%), while IgD and IgE are very rare [6]. About 80% of patients with plasma cell leukemia have Bence-Jones proteinuria [6].

Bone marrow biopsy usually shows massive infiltration by plasmacytic leukemia cells with suppression of other hematopoietic lineages. In some patients, the morphology of plasmocytes is not changed, but in others, immature forms dominate, with a distinctly basophilic cytoplasm, two nuclei, a large nucleolus, and a perinuclear halo [1,6,8].

Diagnosis

The diagnosis of the disease is established using flow cytometry of peripheral blood. Namely, immunophenotypically, plasmacytic leukemia cells are CD38 and CD138 positive as is the case in multiple myeloma, but compared to plasma cells in multiple myeloma, they show a higher expression of CD20, CD23, CD28, CD44, and CD43 molecules, with reduced expression of CD9, CD56, CD71, CD117 and HLA-DR molecules (Table 2) [5,8]. By detecting at least 5% of plasma cells with the above-mentioned immunophenotype among peripheral blood leukocytes, the diagnosis of plasma cell leukemia is established. After the diagnosis is made, it is necessary to take radiography of the skeleton or apply other radiological methods, such as computerized tomography (CT), nuclear magnetic resonance imaging (NMRI), or positron emission tomography (PET) of the whole body, to detect extramedullary disease. It is also necessary to determine, using fluorescence in situ hy-

Tabela 2. Tumačenje risk skora

Table 2. Interpretation of risk score

Plazmocitna leukemija / Plasma cell leukemia	
CD38	Slična / Similar
CD138	Slična / Similar
CD20	Povećana / Elevated
CD23	Povećana / Elevated
CD28	Povećana / Elevated
CD44	Povećana / Elevated
CD43	Povećana / Elevated
CD9	Snižena / Decreased
CD56	Snižena / Decreased
CD71	Snižena / Decreased
CD117	Snižena / Decreased
HLA-DR	Snižena / Decreased

ne plazmocitne leukemije. Odabir terapijskog režima uglavnom zavisi od činjenice da li je pacijent kandidat za autologu transplantaciju ili ne.

Primena konvencionalne hemioterapije u lečenju primarne plazmocitne leukemije nije dala zadovoljavajuće rezultate, pa je indukciona terapija plazmocitne leukemije, bez obzira da li je pacijent kandidat za autologu transplantaciju ili ne, zasnovana na primeni proteazomnih inhibitora i/ili imunomodulatornih lekova [15,17]. Terapijski režimi zasnovani na primeni bortezomiba u lečenju primarne plazmocitne leukemije rezultiraju ukupnim terapijskim odgovorom (engl. *overall response rate* – ORR) od 76%–80% [2,17]. Primena lenalidomida u kombinaciji sa deksametazonom takođe daje ohrabrujuće rezultate u lečenju [16]. Još bolje rezultate beleži lečenje primenom kombinacije bortezomiba, lenalidomida i deksamezotona uz dodatak elotuzumaba [7]. Uvođenje karfilzomiba (druga generacija proteazomnih inhibitora), u kombinaciji sa lenalidomidom i deksametazonom, dovodi do ukupnog terapijskog odgovora kod 93% bolesnika uz postizanje kompletnih remisija kod 33% obolelih [18].

Ako je pacijent kandidat za autologu transplantaciju matičnih ćelija, posle indukciono visokodozne hemioterapije primenjuje se melfalan u visokim dozama kao režim kondicioniranja i sprovodi autologa transplantacija. Primenom ove terapije postiže se kompletna remisija kod do 40% obolelih [19]. Za mlađe pacijente koji imaju podudarnog donora postoji mogućnost da se lečenje nastavi primenom i alogene transplantacije matičnih ćelija hematopoeze [20,21]. Posle završene indukciono terapije i/ili transplantacije matičnih ćelija hematopoeze, preporuka je primeniti terapiju održavanja primenom lenalidomida, bortezomiba ili deksamezotona do progresije bolesti [8].

Prilikom primene indukciono terapije postoji rizik od nastanka sindroma lize tumora. Velika tumorska masa i visok proliferativni potencijal malignih plazmocita su faktori rizika za ovu komplikaciju lečenja. Stoga je preporučeno da se u ovoj fazi lečenja primenjuje adekvatna rehidracija uz urikosupresore uz neprekidni monitoring pacijenta [9]. Osim toga, usled primene proteazomnih inhibitora i imunomodulatornih lekova, savetuje se primena i profilaktičke antivirusne i antikoagulantne terapije [9].

Terapija relapsa primarne plazmocitne leukemije zavisi od starosti pacijenta, *performance* statusa, terapijskog odgovora na prethodnu terapiju, primenjenih prethodnih terapija, komorbiditeta i bubrežne insuficijencije. Svakako se savetuje primena kombinacije novih terapijskih agenasa ali je terapijski uspeh veoma mali [8,18,21]. Literaturni podaci o terapijskom uspehu terapijskih modaliteta zasnovanih na primeni bortezo-

bridization (FISH), the existence of cytogenetic aberrations with particular reference to the presence of the deletion of chromosome 17p, deletion of chromosome 13q, deletion of chromosome 1p, and translocation of chromosome 14 (t(11;14), t(4;14), t(14;16)) [8].

Prognostic factors

Poor prognostic factors for patients with plasma cell leukemia are as follows: age over 60 years, thrombocytopenia below $100 \times 10^9/L$, plasma cell count in peripheral blood greater than $20 \times 10^9/L$, low serum albumin concentration, hypercalcemia, increased concentration of lactate dehydrogenase and beta-2-microglobulin, poorer performance status, as well as lack of therapeutic response to induction therapy [10,12–15]. In addition, the presence of hypodiploidy, complex karyotype, 13q deletion, 17p deletion, 1p deletion, and 1q amplification is associated with worse overall survival [11,12]. Before the introduction of new agents and autologous transplantation, the average survival of patients with plasma cell leukemia was 4–11 months [9]. The introduction of new therapeutic modalities, as well as hematopoietic stem cell transplantation, has extended the average survival of patients and it is now 2–3 years [16].

Treatment

Bearing in mind the aggressiveness of the disease, it is necessary to start treatment immediately after diagnosis. There are certain differences in the treatment of primary and secondary plasma cell leukemia. The choice of therapeutic regimen mainly depends on whether the patient is a candidate for autologous transplantation or not.

The application of conventional chemotherapy in the treatment of primary plasma cell leukemia did not give satisfactory results, therefore, the induction therapy for plasma cell leukemia, regardless of whether the patient is a candidate for autologous transplantation or not, is based on the use of proteasome inhibitors and/or immunomodulatory drugs [15,17]. Therapeutic regimens based on bortezomib in the treatment of primary plasma cell leukemia result in an overall response rate (ORR) of 76%–80% [2,17]. The application of lenalidomide in combination with dexamethasone has also given encouraging results in treatment [16]. Even better results have been recorded with a combination of bortezomib, lenalidomide, and dexamethasone with the addition of elotuzumab [7]. The introduction of carfilzomib (second-generation proteasome inhibitors), in combination with lenalidomide and dexamethasone, leads to an overall therapeutic response in 93% of patients, with complete remission registered in 33% of patients [18].

miba i karfilzomiba, kao i monoklonskih antitela su vrlo oskudni. Terapija sekundarne plazmocitne leukemije zavisi od starosti bolesnika, komorbiditeta, prethodnog terapijskog odgovora i dužine trajanja terapijskog odgovora postignutog primenom prethodne terapije, pa još uvek ne postoji zlatni standard lečenja. Bez obzira na primenjeni terapijski režim, uspeh je veoma mali i preživljavanje je obično svega nekoliko meseci [4].

Uzimajući u obzir vrlo skromne rezultate u lečenju primarne i sekundarne plazmocitne leukemije, očekuje se da bi primena novih agenasa poput venetoklaksa, pomalidomida, iksazomiba, selineksora, karfilzomiba, daratumumaba, anti-CD38 monoklonskih antitela, BRAF/MEK inhibitora, CAR-T terapije i drugih, mogla dovesti do poboljšanja terapijskog odgovora [4,9]. Rezultati do sada publikovanih studija su vrlo oskudni, ali ipak obećavaju.

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If the patient is a candidate for autologous stem cell transplantation, after the application of induction high-dose chemotherapy, high-dose melphalan is administered as a conditioning regimen, and autologous transplantation is performed. With this therapy, complete remission is achieved in up to 40% of patients [19]. For younger patients with a matched donor, it is possible to continue treatment with allogeneic hematopoietic stem cell transplantation [20,21]. After the completion of induction therapy and/or transplantation of hematopoietic stem cells, it is recommended to apply maintenance therapy using lenalidomide, bortezomib, or dexamethasone until disease progression [8].

The application of induction therapy carries the risk of tumor lysis syndrome. A large tumor mass and high proliferative potential of malignant plasma cells are risk factors for this treatment complication. Therefore, it is recommended that in this treatment phase, appropriate rehydration and uricosuppressors should be administered with continuous monitoring of the patient [9]. In addition, due to the use of proteasome inhibitors and immunomodulatory drugs, the use of prophylactic antiviral and anticoagulant therapy is advised [9].

Primary plasma cell leukemia relapse treatment depends on the patient's age, performance status, therapeutic response to previous treatment, previously administered treatments, comorbidities, and renal insufficiency. Application of a combination of new therapeutic agents is definitely advised, but the therapeutic success is very low [8,18,21]. Literature data on the therapeutic success of modalities based on the use of bortezomib, carfilzomib, and monoclonal antibodies are very scarce. The treatment of secondary plasma cell leukemia depends on the patient's age, comorbidities, previous therapeutic response, and the duration of the therapeutic response achieved with the previous therapy, therefore, there is still no gold-standard of treatment. Regardless of the applied therapeutic regimen, success is very low, and survival is usually only a few months [4].

Bearing in mind the very limited results in the treatment of primary and secondary plasma cell leukemia, it is expected that the application of new agents such as venetoclax, pomalidomide, ixazomib, selinexor, carfilzomib, daratumumab, anti-CD38 monoclonal antibodies, BRAF/MEK inhibitors, CAR-T therapy and other agents, could lead to an improvement in therapeutic response [4,9]. The results from the studies published so far are very limited, but promising.

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DIROFILARIOZA DONJEG OČNOG KAPKA: REDAK SLUČAJ OČNE PARAZITSKE INFEKCIJE SA MOGUĆOM ENDEMSKOM EKSPOZICIJOM

PRIKAZ SLUČAJA

CASE REPORT

LOWER EYELID DIROFILARIOSIS: A RARE CASE OF OCULAR PARASITIC INFECTION WITH POSSIBLE ENDEMIC EXPOSURE

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SAŽETAK

Uvod: Dirofilarioza, uzrokovana parazitskom nematodom *Dirofilaria repens*, predstavlja zoonozu sa retkim očnim manifestacijama koje se sve češće prijavljuju u regionima sa povećanom rasprostranjenošću parazita. Infekcija se kod ljudi manifestuje lokalizovanom inflamatornom reakcijom a zahvaćenost oka može dovesti do značajne nelagodnosti i dijagnostičkih izazova. Iako se često povezuje sa putovanjem u endemska područja, kao što je Mediteran, dirofilarioza je takođe endemska u Srbiji, što ukazuje na mogućnost lokalne transmisije.

Prikaz slučaja: Pacijentkinja, stara 38 godina, javila se sa senzacijom pokreta u donjem kapku desnog oka, nakon povratka sa odmora u Grčkoj. Pregledom je ustanovljeno postojanje lokalizovanog otoka i opipljive pokretne mase u donjem kapku desnog oka. Hirurškim putem izvršena je ekstirpacija nematode, a dalja parazitološka analiza je potvrdila prisustvo *Dirofilaria spp.* S obzirom na to da je Srbija endemsko područje za dirofilariozu, ne može se isključiti mogućnost da je infekcija nastala pre putovanja. Prethodno prisutni simptomi su se potpuno povukli nakon zahvata, bez daljih komplikacija tokom praćenja. Ovaj slučaj ističe važnost razmatranja parazitskih infekcija u diferencijalnoj dijagnozi novonastalih lokalizovanih masa na kapku, naročito kod pacijenata sa podatkom o skorijem putovanju u endemske oblasti, odnosno onima koji u njima žive.

Zaključak: Opisom ovog slučaja predstavljena je klinička prezentacija i uspešno lečenje dirofilarioze kapka, retke okularne manifestacije infekcije nematodom *Dirofilaria spp.* Podatak o putovanju u endemske regione može pobuditi sumnju na parazitske uzročnike inflamacije oka, ali treba uzeti u obzir i mogućnost lokalne transmisije u područjima poput Srbije. Pravovremena dijagnoza i hirurška intervencija često dovode do potpunog izlečenja. Potrebna su dodatna istraživanja kako bi se bolje razumela geografska rasprostranjenost dirofilarioze u endemskim područjima, njene okularne manifestacije, kao i komplikacije koje mogu nastati zbog neadekvatne dijagnostike i lečenja.

Ključne reči: dirofilarioza, okularna manifestacija, masa na kapku, parazitska infekcija

ABSTRACT

Introduction: Dirofilariosis, caused by the parasitic nematode *Dirofilaria repens*, is a zoonotic disease with rare ocular manifestations that are being increasingly reported in regions experiencing expanded parasite distribution. Infection in humans manifests as a localized inflammatory reaction and ocular involvement can lead to significant discomfort and diagnostic challenges. While often associated with travel to endemic areas, such as the Mediterranean region, dirofilariosis is also endemic in Serbia, which highlights the possibility of local transmission.

Case report: A 38-year-old female patient presented with unusual sensations of movement in her lower eyelid following a vacation in Greece. Clinical examination revealed localized swelling and a palpable moving mass in the lower eyelid. Surgical excision of the lesion was performed, and parasitological analysis confirmed the presence of *Dirofilaria spp.* Given that dirofilariosis is also endemic in Serbia, the possibility of pre-existing local infection before the patient's trip cannot be excluded. The patient's symptoms resolved completely after surgery, with no recurrence or complications noted during follow-up. This case underscores the need for considering parasitic infections in the differential diagnosis of eyelid masses, especially in patients who have recently traveled to or live in endemic areas.

Conclusion: This case highlights the clinical presentation and successful management of lower eyelid dirofilariosis, a rare ocular manifestation of *Dirofilaria spp.* infection. While a travel history to endemic regions can raise suspicion, endemicity in regions like Serbia necessitates factoring in the possibility of local transmission. Early detection and prompt surgical intervention are often curative. Further research is needed to understand local transmission dynamics and the ocular involvement of dirofilariosis in endemic areas, as well as complications that may arise due to inadequate diagnosis and treatment.

Keywords: dirofilariosis, ocular manifestation, eyelid mass, parasitic infection

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UVOD

Dirofilarioza je zoonotska parazitska infekcija uzrokovana nematodama iz roda *Dirofilaria*, koje prvenstveno inficiraju pse i druge mesoždere. Infekcije kod ljudi nastaju slučajno kada zaraženi komarci prenesu larve na ljude putem ujeda. Dve vrste koje su najčešće uključene u dirofilariozu kod ljudi su *Dirofilaria immitis* i *Dirofilaria repens* [1]. *Dirofilaria immitis* obično izaziva plućnu dirofilariozu, koja pogađa pluća i plućne arterije, dok je *Dirofilaria repens* češće povezana sa potkožnim i okularnim infekcijama [2].

U regionima kao što je mediteranski basen, posebno u zemljama kao što je Grčka, infekcije nematodom *Dirofilaria repens* pospešuje velika prevalencija komaraca, te prisustvo zaraženih životinja, odnosno rezervoara [3]. Srbija je takođe prepoznata kao endemsko područje za nematodu *Dirofilaria repens* a brojne studije govore o značajnom stepenu prisustva infekcije i kod pasa i kod ljudi. Sistematska istraživanja od 2008. godine na ovamo su potvrdila da klima u Srbiji, populacije komaraca, kao i pasa kao rezervoara infekcije, stvaraju povoljne uslove za endemsko prenošenje. Tasić i saradnici su dokumentovali dirofilariozu pasa na severu Srbije [4], dok su Tasić-Otašević i saradnici, kao i Momčilović i saradnici prijavili više slučajeva autohtonih ljudskih infekcija, uključujući potkožne i subkonjunktivne oblike [5,6].

Iako je očna dirofilarioza neuobičajena, ona predstavlja jedinstveni dijagnostički izazov zbog svojih varijabilnih kliničkih manifestacija, koje mogu uključivati otok, crvenilo, osećaj nelagodnosti ili senzacije slične stranom telu u zahvaćenom području [7]. U nekim slučajevima, pacijenti prijavljuju karakterističan osećaj „da se nešto pomera“ ispod kože ili oko oka, što se pripisuje pokretljivosti nematode unutar potkožnog tkiva [8].

Ovom prilikom, opisujemo slučaj 38-godišnje žene koja je imala senzacije pokretanja u donjem kapku nakon odmora provedenog na jednom grčkom ostrvu. Iako je njena istorija putovanja u početku izazvala sumnju na uvezenu slučaj, infekcija je mogla da dobije i u Srbiji, gde je *Dirofilaria repens* endemična. S obzirom na životni ciklus i brzinu rasta nematode *Dirofilaria repens*, ne može se isključiti mogućnost autohtone infekcije u Srbiji, što naglašava dijagnostičku složenost ovakvih slučajeva.

Uprkos tome što su simptomi po svojoj prirodi zabrinjavajući, očna dirofilarioza generalno ima povoljnu prognozu nakon hirurškog uklanjanja parazita. Retko dolazi do recidiva, a pacijenti se obično u potpunosti oporave. Međutim, usled faktora kao što su povećani broj putovanja na globalnom nivou, klimatske promene i širenje populacije komaraca, učestalost dirofilarioze kod ljudi raste [8]. Rano prepoznavanje kliničkih

INTRODUCTION

Dirofilariosis is a zoonotic parasitic infection caused by nematodes belonging to the *Dirofilaria* genus, which primarily infect dogs and other carnivores. Human infections occur incidentally when infected mosquitoes transfer larvae to humans through bites. The two species most frequently implicated in human dirofilariosis are *Dirofilaria immitis* and *Dirofilaria repens* [1]. *Dirofilaria immitis* commonly causes pulmonary dirofilariosis, affecting the lungs and pulmonary arteries, whereas *Dirofilaria repens* is more frequently associated with subcutaneous and ocular infections [2].

In regions such as the Mediterranean basin, particularly in countries like Greece, *Dirofilaria repens* infections are facilitated by high mosquito prevalence and the presence of infected animals, i.e., reservoirs [3]. Serbia is also recognized as an endemic area for *Dirofilaria repens*, with numerous studies highlighting significant infections in both dogs and humans. Since 2008, systematic research has confirmed that the climate in Serbia, mosquito populations, and canine reservoirs create favorable conditions for endemic transmission. Tasić et al. documented canine dirofilariosis in northern Serbia [4], while Tasić-Otašević et al. and Momčilović et al. reported multiple cases of autochthonous human infections, including subcutaneous and subconjunctival forms [5,6].

Though ocular dirofilariosis is uncommon, it presents a unique diagnostic challenge due to its variable clinical manifestations, which can include swelling, redness, discomfort, or sensations akin to a foreign body in the affected area [7]. In some instances, patients report a distinctive sensation of “something moving” beneath the skin or around the eye, attributed to the nematode’s motility within subcutaneous tissue [8].

In this instance, we report the case of a 38-year-old woman who presented with sensations of movement in her lower eyelid following her vacation on a Greek island. While her travel history initially raised suspicion of an imported case, the infection could also have been acquired in Serbia, where *Dirofilaria repens* is endemic. Considering the life cycle and growth rate of *Dirofilaria repens*, the possibility of autochthonous infection in Serbia cannot be excluded, which underscores the diagnostic complexity of such cases.

Despite the concerning nature of the symptoms, ocular dirofilariosis generally has a favorable prognosis following surgical removal of the parasite. Recurrence is rare, and patients typically achieve full recovery. However, with factors such as increased global travel, climate change, and expanding mosquito populations, the incidence of human dirofilariosis has been on the rise [8]. Early recognition of the clinical signs is crucial

znakova je ključno jer se tako izbegava uspostavljanje pogrešne dijagnoze i sprovođenje nepotrebnih procedura a omogućava brzo uklanjanje parazita i prestanak simptoma.

Ovaj slučaj stavlja u prvi plan važnost razmatranja parazitskih infekcija u diferencijalnoj dijagnozi masa nepoznatog porekla ili senzacija pokreta u očnim kapcima. Kliničari moraju da budu na oprezu, ne samo kod pacijenata sa nedavnom istorijom putovanja u endemska područja, već i kod pacijenata koji borave u oblastima u kojima je ustanovljena lokalna vektorska populacija, kao što je Srbija, gde se sve češće prijavljuju slučajevi infekcije kod ljudi. Sama činjenica da nije izvesno da li je infekcija ove pacijentkinje uvezena ili autohtona dodatno naglašava potrebu za povećanom svešću prilikom uspostavljanja dijagnoze, i u endemskim i u neendemskim područjima.

PRIKAZ SLUČAJA

Tridesetosmogodišnja pacijentkinja se javila našoj oftalmološkoj klinici žaleći se na neobičnu senzaciju u spoljašnjem delu donjeg kapka. Prijavila je da je senzacija počela sedam dana nakon povratka sa odmora na grčkom ostrvu. Boravila je na ostrvu Tasos od prvog do 18. jula, a prvi put je registrovala senzaciju u kapku 31. jula. Opisala je da joj se ova senzacija naizmenično javlja i nestaje a ogleda se u osećanju kao da joj se „nešto pomera“ unutar kapka. Pacijentkinja je negirala bol, svrab ili crvenilo i nije bilo povezanih sistemskih simptoma kao što su povišena temperatura, umor ili limfadenopatija. Nije bilo značajnih pojava zabeleženih u njenoj prethodnoj medicinskoj dokumentaciji – odsustvo prethodne istorije alergija, sistemskih bolesti ili operacija na očima. Nije uzimala nikakve lekove, a nije se sećala ni ujeda komaraca tokom odmora. U periodu od osam meseci pre odmora u Grčkoj, pacijentkinja nije putovala van Beograda i nije prethodno boravila na selu, bila blizu reka ili u kontaktu sa životinjama. Takođe se nije sećala ujeda komaraca pre ovog događaja.

Oftalmološki pregled je pokazao da pacijentkinja ima normalnu oštrinu vida (20/20) na oba oka. Prednji i zadnji segmenti očiju bili su potpuno normalni. Nije bilo znakova hiperemije konjunktive, pojave iscedka ili abnormalnosti rožnjače. Prvi spoljni pregled kapaka nije otkrio nikakav vidljiv otok, eritem ili abnormalnu masu. Međutim, kako je pacijentkinja nastavila da opisuje senzaciju pokretanja u kapku, malo, lokalizovano uzvišenje postalo je primetno u medijalnom delu donjeg kapka. Pri bližem posmatranju, uočena je struktura nalik crvu koja se kreće ispod kože. Nakon palpacije, struktura je nestala, ali se ponovo pojavila nekoliko minuta kasnije u temporalnom delu donjeg kapka (Slika 1).

to avoid misdiagnosis and unnecessary procedures, enabling prompt removal of the parasite and resolution of symptoms.

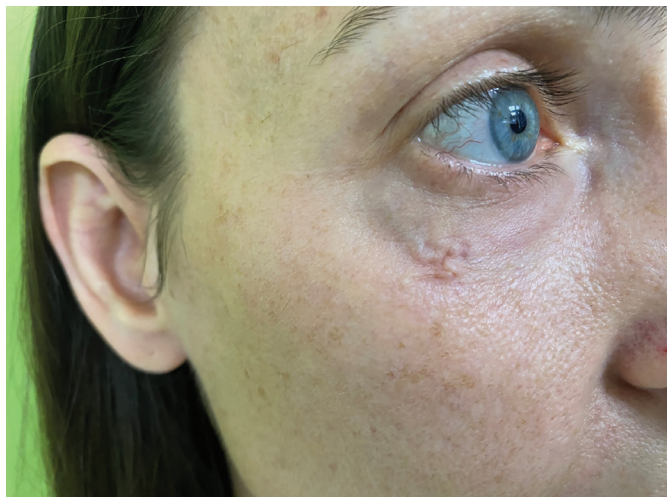
This case emphasizes the importance of considering parasitic infections in the differential diagnosis of unexplained eyelid masses or movement sensations. Clinicians must remain vigilant not only in patients with a recent history of traveling to endemic regions but also in patients residing in or traveling to areas with established local vector populations, such as Serbia, where incidental human infections are being increasingly reported. The uncertainty as to whether this patient's infection was imported or autochthonous further emphasizes the need for enhanced diagnostic awareness in both endemic and non-endemic settings.

CASE REPORT

A 38-year-old woman presented at our ophthalmology clinic complaining of an unusual sensation in the outer part of her lower eyelid. She reported that the sensation had started seven days after returning from a vacation spent on a Greek island. She had been on the island of Thasos from July 1 to July 18, and she first noticed the sensation in her eyelid on July 31. She described it as intermittent and stated that she felt as though "something was moving" inside the eyelid. The patient denied any pain, itching, or redness, and there were no associated systemic symptoms such as fever, fatigue, or lymphadenopathy. Her medical history was unremarkable, with no previous history of allergies, systemic diseases, or ocular surgeries. She had not been taking any medications, and she did not remember any mosquito bites during her holiday. The patient had not traveled outside Belgrade in the eight months before her holiday and reported no prior trips to the countryside, being near rivers, or being exposed to animals. She also did not recall any mosquito bites before this event.

On examination, the patient's visual acuity was 20/20 in both eyes. The anterior and posterior segments of the eyes were completely normal. There was no evidence of conjunctival hyperemia, discharge, or corneal abnormalities. Initial external inspection of the eyelid did not reveal any visible swelling, erythema, or abnormal masses. However, as the patient continued to describe the sensation of movement, a small, localized elevation became noticeable in the medial part of the lower eyelid. On closer observation, a worm-like structure was seen moving beneath the skin. Upon palpation, the structure disappeared but reappeared several minutes later in the temporal part of the lower eyelid (Figure 1).

Given the clinical presentation, we suspected a parasitic infection. An infectious diseases specialist

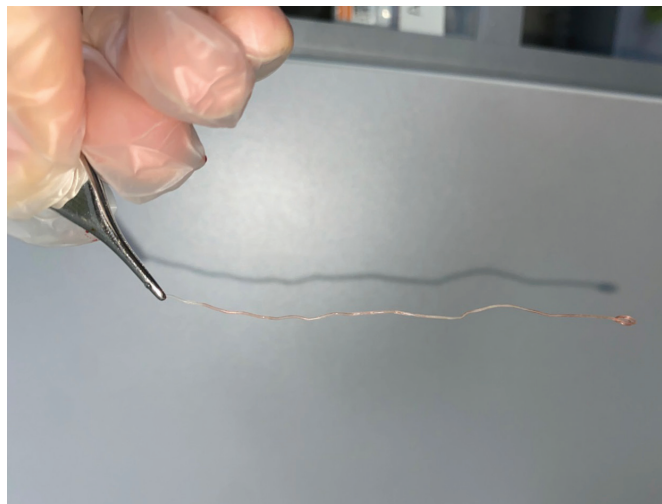


Slika 1. Preoperativna fotografija tridesetosmogodišnje pacijentkinje koja prikazuje desni donji kapak sa vidljivim blagim otokom koji ukazuje na potkožnog parazita (*Dirofilaria* spp.). Pacijentkinja je pre hirurškog uklanjanja imala senzaciju nelagodnosti i kretanja unutar kapka, što je u skladu sa prisustvom parazita

Picture 1. Preoperative image of a 38-year-old female patient showing the right lower eyelid with visible slight swelling indicative of a subcutaneous parasite (*Dirofilaria* spp.). The patient experienced discomfort and the sensation of movement within the eyelid, correlating with parasitic presence, before surgical removal

S obzirom na kliničku sliku, posumnjali smo na parazitsku infekciju. Infektolog je sproveo inicijalne analize krvi, koje nisu pokazale abnormalnosti, a test na eozinofiliju je bio negativan. Obavestili smo pacijentkinju o verovatnoj dijagnozi i preporučili hitno uklanjanje parazita. Pacijentkinja je pristala na proceduru. Nije bilo potrebe za lokalnom anestezijom. Čekali smo da se parazit ponovo pojavi ispod kože. Kada je pokret ponovo bio vidljiv, napravljen je mali rez na temporalnom delu donjeg kapka i finim pincetom je izvađen parazit sličan crvu. Izmerena je nematoda dužine preko 12 centimetara. Procedura je protekla bez komplikacija, a pacijentkinja nije osetila ni bol ni nelagodnost tokom ili nakon uklanjanja nematode (Slika 2). Ekstrahovani parazit je poslat na odeljenje parazitologije na identifikaciju. Dobijeni rezultat potvrdio je da je u pitanju *Dirofilaria* spp.

Nakon ekstrakcije, infektolog je izvršio dodatna ispitivanja, uključujući i rentgen srca i pluća, koja su pokazala normalne rezultate. Metoda koncentracije po Notu je takođe korišćena za testiranje mikrofilarije u krvi, a rezultati su bili negativni. Nivoi imunoglobulina E (IgE) su bili u normalnom opsegu (ispod 4,7 IU/ml; referentni opseg 0–100 IU/ml). Testovi krvi su ponovljeni sedam dana nakon inicijalnog testa, bez uočenih značajnih promena. S obzirom na odsustvo mikrofilarija i normalne laboratorijske nalaze, dodatna antiparazitska terapija nije bila indikovana i infekcija je klasifikovana



Slika 2. Prikazan je tanak, izduženi parazitski organizam (*Dirofilaria* spp.) uhvaćen pincetom nakon hirurške ekstrakcije. Crvolika struktura je duga 12 centimetara

Picture 2. A thin, elongated parasitic organism (*Dirofilaria* spp.) is shown being held with tweezers after surgical extraction. The worm-like structure is 12 centimeters long

conducted initial blood tests, which showed no abnormalities, and the patient's results were negative for eosinophilia. We informed the patient about the likely diagnosis and recommended immediate removal of the parasite. The patient consented to the procedure. Without the need for local anesthesia, we waited for the parasite to reappear under the skin. Once the movement was visible again, a small incision was made in the temporal part of the lower eyelid, and using fine forceps, the worm-like parasite was extracted. The nematode measured over 12 centimeters in length. The procedure was uncomplicated, and the patient did not experience any pain or discomfort during or after the removal (Figure 2). The extracted parasite was sent to the parasitology department for identification and the result confirmed *Dirofilaria* spp.

Following the extraction, the infectious diseases specialist conducted additional tests, including radiography of the heart and lungs, which showed normal results. Knott's concentration method was also used to test for microfilariae in the blood, and the results were negative. IgE levels were within the normal range (below 4.7 IU/ml; reference range 0–100 IU/ml). The blood tests were repeated seven days after the initial test, with no significant changes observed. Given the absence of microfilariae and normal lab findings, additional antiparasitic treatment was not indicated and the infection was classified as an amicrofilaremic case of *Dirofilaria* spp. infection successfully treated surgically.

Postoperatively, the patient did not require any additional treatment, and the small incision healed well,

kao amikrofilaremični slučaj infekcije nematodom *Dirofilaria spp.* koja je uspešno izlečena hirurškim putem.

Postoperativno, pacijentkinji nije bilo potrebno dodatno lečenje, a mali rez je dobro zarastao, ostavljajući jedva vidljiv ožiljak. Mesec dana kasnije, nalaz kliničkog pregleda pacijentkinje je i dalje bio normalan, bez znakova recidiva ili dodatnih simptoma.

DISKUSIJA

Inficiranje ljudi nematodom *Dirofilaria* nastaje kada komarac koji ujede domaćina unese infektivnu larvu trećeg stadijuma (L3) u njegov krvotok. Mada su ljudi slučajni domaćini pa se larva retko razvije u odraslog crva, u nekim slučajevima je ovo napredovanje moguće. Kod pacijentkinje čiji smo slučaj opisali, larva je sazrela u svoj odrasli oblik, ilustrujući jedan od neuobičajenih razvoja događaja koji može dovesti do ovakvog ishoda.

Okularna dirofilarioza, iako retka, mora se uzeti u obzir kao diferencijalna dijagnoza kod pacijenata koji imaju nerazjašnjeno oticanje očnih kapaka ili osećaj pokretanja u kopcima, posebno kod onih koji su putovali u područja gde je *Dirofilaria* endemična. U slučaju naše pacijentkinje, ona je prethodno boravila na grčkom ostrvu, koje je deo mediteranske regije poznate po endemskim infekcijama koje prenose komarci. Međutim, s obzirom na životni ciklus i brzinu rasta nematode *Dirofilaria repens*, ovu infekciju je pacijentkinja mogla dobiti i u Srbiji, gde je autohtona dirofilarioza dobro dokumentovana [9]. Pun životni ciklus nematode *Dirofilaria repens*, uključujući faze larve i prepatentni period pre izlučivanja mikrofilarija, obično traje 6-9 meseci. Kod ljudi, *Dirofilaria repens* često ne dostiže punu zrelost, ali dužina parazita od dvanaest centimetara ukazuje na to da se infekcija možda dogodila nekoliko meseci ranije, što nam govori da je malo verovatno da je ona nastala prilikom prethodnog putovanja pacijentkinje.

U Srbiji su dokumentovani slučajevi dirofilarioze i kod ljudi i kod životinja, posebno u oblastima duž rečnih tokova gde preovlađuju komarci prenosioci. Džamić i saradnici su prijavili slučajeve potkožne infekcije nematodom *Dirofilaria repens* u Srbiji i Crnoj Gori, uključujući periokularnu lokalizaciju, i istakli ulogu regionalnih vektora u prenošenju [10]. Naša pacijentkinja, koja nije prethodno boravila na selu i koja živi u urbanom okruženju, pokazuje da su gradski slučajevi mogući i da urbano okruženje ne bi trebalo da isključuje dirofilariozu kao diferencijalnu dijagnozu. Tasić i saradnici su takođe uočili značajno inficiranje pasa u Srbiji, naglašavajući značaj zoonotskih rezervoara u izloženosti ljudi nematodi *Dirofilaria repens* [11]. Imajući u vidu ove nalaze i ograničenu istoriju putovanja pacijentkinje van Beograda, endemsko poreklo infekcije u Srbiji se može smatrati verovatnim.

leaving a barely visible scar. One month later, the patient's clinical examination findings remained normal, with no signs of recurrence or additional symptoms.

DISCUSSION

Human infection with *Dirofilaria* occurs when a mosquito introduces an infective third-stage larva (L3) into the bloodstream when biting the host. While humans are accidental hosts and the larva rarely develops into an adult worm, in some cases, this progression is possible. In the patient we have described, the larva matured into its adult form, illustrating one of the uncommon scenarios in which this can happen.

Ocular dirofilariosis, though rare, must be taken into consideration as a differential diagnosis in patients presenting with unexplained eyelid swelling or sensations of movement, particularly in those who have traveled to regions endemic to *Dirofilaria*. In our case, the patient had recently visited a Greek island, which is part of the Mediterranean region known for endemic mosquito-borne infections. However, given the life cycle and growth rate of *Dirofilaria repens*, this infection could have been also acquired in Serbia, where autochthonous dirofilariosis is well documented [9]. The full life cycle of *Dirofilaria repens*, including larval stages and the prepatent period before microfilariae excretion, typically spans 6–9 months. In humans, *Dirofilaria repens* often fails to reach full maturity, yet the parasite's twelve-centimeter length suggests that infection may have occurred several months earlier, making recent travel an unlikely origin.

In Serbia, dirofilariosis cases have been documented in both humans and animals, particularly in areas along river courses where mosquito vectors are prevalent. Džamić et al. reported cases of subcutaneous *Dirofilaria repens* infection in Serbia and Montenegro, including periocular sites, and highlighted the role of regional vectors in transmission [10]. The case of our patient, who had no recent exposure to the countryside and lived in an urban setting, demonstrates that urban cases are possible and that the urban setting should not exclude dirofilariosis as a differential diagnosis. Tasić et al. also noted significant canine infections in Serbia, underscoring the importance of zoonotic reservoirs in human exposure to *Dirofilaria repens* [11]. Given these findings and the patient's limited travel history outside of Belgrade, endemic origin in Serbia remains plausible.

The pathogenesis of human dirofilariosis involves mosquito-borne transmission of infective larvae, which migrate through subcutaneous tissues and mature into adult worms, reaching 10 to 15 centimeters in length. Simon et al. reported that *Dirofilaria repens*

Patogeneza ljudske dirofilarioze uključuje prenos infektivnih larvi od strane komaraca. Larve migriraju kroz potkožno tkivo i sazrevaju u odrasle crve, dostižući dužinu od 10 do 15 centimetara. Simon i saradnici su naveli da *Dirofilaria repens* može da se nastani u različitim periokularnim strukturama, kao što su očni kapak, orbita i subkonjunktivalna tkiva, izazivajući simptome kretanja [12]. Džamić i saradnici su dokumentovali nekoliko slučajeva u kojima su pacijenti iskusili osećaj kretanja ispod kože, što sugerše da je ovo karakteristično za infekcije nematodom *Dirofilaria repens* [9].

Epidemiološki gledano, nedavne studije su dokumentovale porast u broju slučajeva očne dirofilarioze u području Mediterana, što je posledica klimatskih promena i mobilnosti ljudi. Na ovaj način se proširuju staništa komaraca vektora. Pupiće-Bakrač i saradnici su razmatrali slučajeve mikrofilaremije kod ljudi naglašavajući važnost kontrole vektora u prevenciji infekcija [13]. Značaj kontrole širenja infekcije je očigledan jer se svest o riziku od nematode *Dirofilaria* sada odnosi i na urbana, neendemska područja, što je u skladu sa našim slučajem u kojem se sumnjalo na autohtonu dirofilariozu.

Hirurško uklanjanje je osnova lečenja očne dirofilarioze i nudi siguran i delotvoran pristup uz minimalne komplikacije. Kalogeropoulos i saradnici su naglasili da ekscizija obično rešava simptome bez potrebe za dodatnom terapijom. U slučaju naše pacijentkinje, odsustvo mikrofilarije i normalan nivo IgE u krvi potvrdili su amikrofilaremičnu infekciju, što govori u prilog tome da je hirurško lečenje dovoljno [3]. I Tasić-Otašević i saradnici su dokumentovali slučajeve gde je samo ekscizija bila adekvatna metoda lečenja, bez potrebe za sistemskom terapijom, što se poklapa sa ishodom naše pacijentkinje, kod koje nakon uklanjanja nematode nije primećen recidiv [14]. Važno je napomenuti da se, na osnovu opšteg konsenzusa, antihelmintička terapija obično ne preporučuje za slučajeve površinske dirofilarioze.

Dijagnostikovanje očne dirofilarioze može predstavljati izazov zbog njene varijabilne i nespecifične prezentacije. Engelsberg i Blekberg su istakli potrebu da se parazitske infekcije uključe u diferencijalnu dijagnozu periokularnih masa, posebno kod pacijenata iz endemskih područja ili onih koji su nedavno putovali [7]. Pogrešne dijagnoze mogu dovesti do neodgovarajućeg lečenja, kao što su antibiotici ili steroidi, koji su neefikasni kod parazitskih infekcija. Nadalje, Radovanović Spurnić i saradnici su naglasili važnost blagovremenog otkrivanja i hirurškog uklanjanja, kako bi se sprečilo nepotrebno i potencijalno štetno lečenje [15]. Naš slučaj naglašava potrebu da se *Dirofilaria* uzme u obzir kao diferencijalna dijagnoza, ne samo u endemskim regionima, već i kod pacijenata sa periokularnim simptomima koji nisu prethodno putovali.

can lodge in various periocular structures, such as the eyelid, orbit, and subconjunctival tissues, causing symptoms of movement [12]. Džamić et al. documented several cases wherein patients experienced sensations of movement in subcutaneous sites, suggesting that this mobility is characteristic of *Dirofilaria repens* infections [9].

Epidemiologically, recent studies have documented a rise in the number of ocular dirofilariosis cases in Mediterranean regions, driven by climate change and the mobility of humans, both of which expand mosquito vector habitats. Pupiće-Bakrač et al. discussed human microfilaremia cases, underlining the importance of vector control in preventing infections [13]. The infection control implication is clear as awareness of *Dirofilaria* infection risk extends even to urban, non-endemic areas, which is in keeping with our case of suspected autochthonous dirofilariosis.

Surgical excision remains the cornerstone of ocular dirofilariosis treatment, offering a safe and effective approach with minimal complications. Kalogeropoulos et al. emphasized that excision typically resolves symptoms without the need for additional therapy. In our case, the absence of microfilariae in blood tests and a normal IgE level confirmed an amicrofilaremic infection, supporting the sufficiency of surgical management [3]. Similarly, Tasić-Otašević et al. documented cases where excision alone was appropriate, with no need for systemic therapy, which coincides with our patient's outcome, where no recurrence was observed post-removal [14]. It is important to note that, based on general consensus, antihelmintic therapy is not typically recommended for cases of superficial dirofilariosis.

Diagnosing ocular dirofilariosis can be challenging due to its variable and nonspecific presentation. Engelsberg and Bläckberg highlighted the need to include parasitic infections in the differential diagnosis of periocular masses, particularly in patients from endemic areas or those with recent travel history [7]. Misdiagnoses can lead to inappropriate treatments, such as antibiotics or steroids, which are ineffective for parasitic infections. Additionally, Radovanović Spurnić et al. emphasized the importance of timely detection and surgical removal, to prevent unnecessary and potentially harmful management [15]. Our case emphasizes the need to consider *Dirofilaria* as a differential diagnosis not only in endemic regions but also in non-traveling patients with periocular symptoms.

Finally, the case of our patient highlights the importance of public and professional awareness of dirofilariosis risks in both endemic and emerging regions. Diagnosing this condition requires more than clinical

Najzad, slučaj naše pacijentkinje ističe važnost javne i profesionalne svesti o rizicima dirofilarioze, kako u endemskim tako i u područjima u kojima se od nedavno beleži ova infekcija. Dijagnostikovanje ovog stanja zahteva više od kliničke sumnje; neophodna je stručna procena mikrobiologa specijalizovanog za parazitologiju kao i upotreba naprednih dijagnostičkih instrumenata, uključujući radiološko snimanje, imunodijagnostiku i molekularne tehnike. Savić i saradnici su sprovedi seroepidemiološku studiju u severnom delu Srbije, dokumentujući značajnu seroprevalenciju kod ljudi i pasa. Oni su istakli ulogu ekoloških i faktora životne sredine u prenošenju infekcije [16]. Edukacija putnika i stanovnika o preventivnim merama, kao što je izbegavanje izloženosti komarcima, i dalje je ključno. Kliničari u Srbiji i drugim područjima u kojima je zabeleženo širenje dirofilarioze moraju da održavaju visok nivo svesti i uzmu u obzir ovu parazitsku infekciju u slučajevima kod kojih postoje periokularni simptomi.

ZAKLJUČAK

Prikazani slučaj očne dirofilarioze ističe potrebu da kliničari održavaju visok stepen sumnje na parazitske infekcije kod pacijenata koji imaju atipične periokularne simptome, posebno onih koji su prethodno putovali u endemske regione ili su boravili u oblastima sa lokalnom populacijom vektora. U ovom slučaju, uspešno uklanjanje nematode *Dirofilaria spp.* dovelo je do potpunog razrešenja simptoma i minimalnog ožiljka. Sa povećanjem broja putovanja na globalnom nivou, klimatskim promenama i širenjem staništa komaraca, ključno je prepoznati potencijal dirofilarioze u endemskim i neendemskim područjima. Rana dijagnoza i pravovremena hirurška intervencija su od suštinskog značaja kako bi se izbegli nepotrebni tretmani i osigurali optimalni ishodi za pacijenta.

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suspicion; it necessitates the expertise of microbiologists specializing in parasitology and the use of advanced diagnostic tools, including radiological imaging, immunodiagnostics, and molecular techniques. Savić et al. conducted a seroepidemiological study in the northern part of Serbia, documenting significant seroprevalence in humans and canines and emphasizing the role of environmental and ecological factors in transmission [16]. Educating travelers and residents about preventive measures, such as avoiding mosquito exposure, remains critical. Clinicians in Serbia and other regions experiencing the spread of dirofilariasis must maintain a high level of awareness and consider this parasitic infection in cases presenting with periocular symptoms.

CONCLUSION

The presented case of ocular dirofilariasis highlights the need for clinicians to maintain a high index of suspicion for parasitic infections in patients presenting with atypical periocular symptoms, especially those with recent travel history to endemic regions or residing in areas with local vector populations. In the case of our patient, successful removal of the *Dirofilaria spp.* led to complete symptom resolution and minimal scarring. With the increase in global travel, climate change, and expanding mosquito habitats, it is crucial to recognize the potential for dirofilariasis in both endemic and non-endemic regions. Early diagnosis and timely surgical intervention are essential to avoid unnecessary treatments and to ensure optimal patient outcomes.

Conflict of interest: None declared.

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LEČENJE COVID-19 PRIMENOM LEKA CASIRIVIMAB/INDEVIMAB KOD PACIJENTA SA POVREDOM VRATNOG DELA KIČME: PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

TREATMENT OF COVID-19 WITH CASIRIVIMAB/INDEVIMAB IN A PATIENT WITH CERVICAL SPINE INJURY: A CASE REPORT

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SAŽETAK

Uvod/Cilj: Prikazujemo pacijenta obolelog od COVID-19 sa povredom vratne kičme koji je lečen primenom antivirusnog leka casirivimab/indevimab (Regen-CoV), monoklonskih antitela za COVID-19, u toku bolničkog lečenja u Kovid bolnici Batajnica Univerzitetskog kliničkog centra Srbije.

Prikaz slučaja: Primena leka casirivimab/indevimab (Regen-CoV) sprečila je razvoj teže slike Covida-19 i dovela je do brze negativizacije nazofaringealnog brisa na SARS-CoV-2 kod našeg pacijenta koji je imao povredu vratne kičme. Pacijentu je uspešno izvršena operacija vratne kičme u Institutu za ortopedsko-hirurške bolesti Banjica, koja je dovela do povlačenja neuroloških deficita koje je imao ranije.

Zaključak: Pokazali smo još jednu veoma važnu indikaciju za primenu leka casirivimab/indevimab (Regen-CoV) u bolničkim uslovima, koja je, po terapijskim Protokolima, bila *off-label*.

Ključne reči: COVID-19, casirivimab/indevimab, terapija monoklonskim antitelima, povreda vratne kičme

ABSTRACT

Introduction/Aim: We present a patient suffering from COVID-19 with a cervical spine injury who was treated with the antiviral drug casirivimab/indevimab (Regen-CoV), monoclonal antibodies for COVID-19, during hospital treatment at the Batajnica Hospital of the University Clinical Center of Serbia.

Case report: The administration of the drug casirivimab/indevimab (Regen-CoV) prevented the development of a more severe picture of Covid-19 and led to the rapid negativization of the nasopharyngeal swab for SARS-CoV-2 in our patient who had a cervical spine injury. The patient underwent successful cervical spine surgery at the Institute for Orthopedic-Surgical Diseases in Banjica, which led to the recovery of the neurological deficits he had previously.

Conclusion: We showed another significant indication for using casirivimab/indevimab (Regen-CoV) in hospital conditions, which was *off-label* according to therapeutic protocols.

Keywords: COVID-19, casirivimab/indevimab, monoclonal antibody therapy, cervical spine injury

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UVOD

Tokom pandemije COVID-19, svetska naučna zajednica intenzivno je radila na pronalaženju inovativnih terapijskih pristupa koji bi efikasno pomogli u borbi protiv SARS-CoV-2. Jedan od njih je i lek Regen-CoV®, mešavina monoklonskih antitela (casirivimab (REGN10933) / indevimab (REGN10987)), koji se pokazao efikasnim u smanjenju opterećenja organizma virusom (engl. *virus load*) što se posledično manifestuje blažom kliničkom slikom i smanjenom potrebom za lečenjem pacijenata u bolničkim uslovima i smrću [1].

Lek casirivimab/indevimab (Regen-CoV®), prema preporukama Američke agencije za hranu i lekove (FDA), primenjuje se samo kod pacijenata koji se leče u vanbolničkim uslovima [2], imaju blagu kliničku sliku COVID-19 i kojima nije potrebna hospitalizacija i bolničko lečenje. Primena ovog leka ne savetuje se kod hospitalizovanih pacijenata, kao i kod pacijenata koji imaju potrebu za primenom oksigenoterapije [2], s obzirom na to da primena ovog leka kod ovih pacijenata može dovesti do deterioracije kliničke slike i pogoršanja opšteg stanja sa mogućim posledičnim fatalnim ishodom.

Tokom lečenja pacijenata u prvom talasu COVID-19 pandemije 2020. godine, postavljena je hipoteza da kod pacijenata koji razviju hiperreaktivni imunski odgovor [3] dolazi do posledičnog razvoja hipoksemije, koja zahteva hospitalizaciju i primenu oksigenoterapije. Iz tog razloga započeta je primena imunomodulatorne terapije u lečenju SARS-CoV-2 infekcije, nakon čega je sprovedeno naučno istraživanje koje je navedenu hipotezu potvrdilo [4]. Dokazano je da SARS-CoV-2 ulazi u ćelije preko ACE2 receptora za koji se vezuje S (engl. *spike*) protein na površini virusa [5]. Lek casirivimab/indevimab predstavlja kombinaciju dva humana monoklonska antitela koja deluju tako što se vezuju za navedeni S protein, ispoljavajući snažan inhibitorski efekat na sposobnost vezivanja virusa za ćelije domaćina, samim tim neutrališući SARS-CoV-2 [6,7]. Zbog učestalih mutacija spike proteina i posledične rezistencije na terapiju pojedinačnim antitelima, započeta je primena kombinacija antitela u cilju prevencije nastanka novih mutacija i razvoja dalje rezistencije virusa [8,9].

U ovom radu prikazaćemo slučaj pacijenta kome je u bolničkim uslovima aplikovan lek casirivimab/indevimab radi sprečavanja dalje progresije COVID-19 i postizanja brze negativizacije RT-PCR testa nazofaringealnog brisa na SARS-CoV-2, s ciljem omogućavanja daljeg lečenja osnovne bolesti pacijenta. Ovaj slučaj je naročit ne samo zbog primene leka van dotadašnjih zvaničnih preporuka, prema kojima se on primenjivao isključivo u vanbolničkim uslovima, već i zbog kompleksnosti samog slučaja, koji je zahtevao multidisciplinarni pristup lečenju i omogućavanje što ranijeg

INTRODUCTION

During the COVID-19 pandemic, the global scientific community worked intensively to find innovative therapeutic approaches that would effectively aid in the fight against SARS-CoV-2. One of them is the drug Regen-CoV®, a combination of monoclonal antibodies (casirivimab (REGN10933) / indevimab (REGN10987)), which has proven effective in reducing the viral load in the body, consequently resulting in a milder clinical presentation, a decreased need for hospitalization, and lower mortality rates [1].

According to the recommendations of the U.S. Food and Drug Administration (FDA), casirivimab/indevimab (Regen-CoV®) is intended exclusively for use in outpatients with mild COVID-19 who do not require hospitalization or inpatient treatment [2]. The use of this drug is not advised for hospitalized patients or those requiring oxygen therapy [2], as its administration in these cases may lead to a deterioration in clinical status and a possible fatal outcome.

During the treatment of patients in the first wave of the COVID-19 pandemic in 2020, the hypothesis was proposed that patients who develop a hyperreactive immune response [3] consequently experience hypoxemia, necessitating hospitalization and oxygen therapy. This led to the initiation of immunomodulatory therapy in the treatment of SARS-CoV-2 infection, followed by scientific research that confirmed this hypothesis [4]. It has been proven that SARS-CoV-2 enters cells through the ACE2 receptor, to which the S protein on the viral surface binds [5]. Casirivimab/indevimab is a combination of two human monoclonal antibodies that bind to this S protein, exerting a strong inhibitory effect on the virus's ability to attach to host cells, thereby neutralizing SARS-CoV-2 [6,7]. Due to frequent mutations of the spike protein and the subsequent development of resistance to single-antibody therapy, combinations of antibodies have been introduced to prevent the emergence of new mutations and further viral resistance [8,9].

In this paper, we present a case of a patient who received casirivimab/indevimab in a hospital setting to prevent further progression of COVID-19 and achieve rapid RT-PCR test negativization of the nasopharyngeal swab for SARS-CoV-2, enabling further treatment of the patient's underlying condition. This case is noteworthy not only because the drug was used outside the existing official recommendations, which restricted its use to outpatient settings, but also due to the complexity of the case itself. It required a multidisciplinary treatment approach and the earliest possible hospital management, including surgical treatment outside the COVID-19 care system.

hospitalnog zbrinjavanja, odnosno hirurškog lečenja pacijenta van COVID-19 sistema.

PRIKAZ SLUČAJA

Naš pacijent, starosti 23 godine, zadobio je povrede dva vratna kičmena pršljena (C5 i C6) u saobraćajnoj nesreći pet dana pre prijema u Kovid bolnicu Batajnica Univerzitetskog kliničkog centra Srbije u Beogradu. Zbog ove povrede, shodno terapijskim protokolima, bilo je indikovano strogo mirovanje uz imobilizaciju vratnog dela kičme pomoću Šancovog okovratnika, kao i hitno operativno lečenje u specijalizovanoj tercijarnoj ustanovi. U objektivnom nalazu, neposredno po povređivanju, pacijent je imao potpunu slabost sva četiri ekstremiteta, da bi se nekoliko sati posle povređivanja povratila delimična funkcija desne strane tela, a kasnije i leve noge, dok je zaostajala slabost leve ruke. Sprovedena je radiološka dijagnostika, pri čemu je u nalazu Magnetne rezonancije vratnog dela kičme opisana spondilolisteza na nivou C5-C6, gradus II/III, zatim leva dorzolateralna ekstruzija intervertebralnog diska C5-C6, kao i stenoza spinalnog kanala uz kompresiju medule i znake mijelopatije, uz prisustvo fraktura leve lamine C5 i levog transversalnog nastavka C6 (Slika 1). Na radiografskom snimku glave opisana je fraktura medijalnog dela krova desne orbite. Na urađenom ultrazvučnom pregledu trbuha nisu viđeni znaci traume unutrašnjih organa, a radiografski snimci grudnog koša, karlice i levog ramena su bili urednog nalaza.

Pacijent je primarno zbrinut u regionalnom zdravstvenom centru. Tada je od tegoba imao bol u vratu, koji se širio duž leve ruke i kičmenog stuba, uz prisutnu slabost leve ruke. Petog dana hospitalizacije, zbog nemogućnosti operativnog lečenja u toj ustanovi, preveđen je u Institut za ortopedsko-hirurške bolesti Batajnica u Beogradu koji se specijalizovano bavi lečenjem bolesti i povreda koštano-zglobnog sistema. Prilikom hospitalizacije u ovu ustanovu, pacijentu je rutinski učinjen brzi antigenski test nazofaringealnog brisa na SARS-CoV-2 čiji je nalaz bio pozitivan. Tada je od strane spinalnog hirurga indikovano hiruško lečenje čim se za to steknu uslovi u smislu negativizacije testa na SARS-CoV-2, kao i strogo mirovanje u postelji, a pacijent je preveđen u Kovid bolnicu Batajnica Univerzitetskog kliničkog centra Srbije u Beogradu, najveću Kovid bolnicu u Srbiji, radi lečenja COVID-19.

U trenutku prvog pregleda u našoj ustanovi, pacijent je mogao da pokreće donje ekstremitete, uz prisutnu izraženu slabost leve ruke, kao i blagu slabost leve noge, i intenzivne bolove u vratu, koji su se propagirali duž kičmenog stuba i leve ruke. Ostali somatski nalaz je bio uredan, uz održavanje dobrih vitalnih parametara. Anamnestički, pacijent je negirao prisustvo hroničnih bolesti, prethodne operacije i primenu lične terapije.

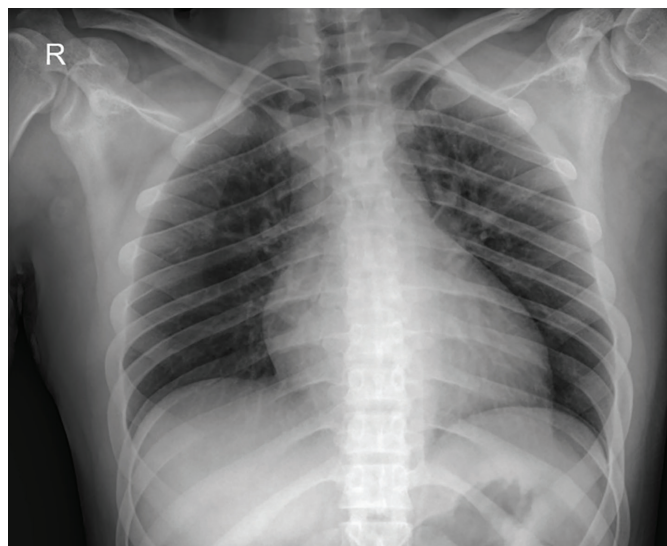
CASE REPORT

Our patient, a 23-year-old male, sustained injuries to two cervical vertebrae (C5 and C6) in a traffic accident five days before being admitted to the COVID Hospital Batajnica at the University Clinical Center of Serbia in Belgrade. Due to the nature of the injury, therapeutic protocols dictated strict immobilization of the cervical spine using a Schanz collar, as well as urgent surgical intervention at a specialized tertiary facility. Upon initial examination following the injury, the patient exhibited complete weakness in all four extremities. However, a few hours later, partial function returned to the right side of his body, followed by his left leg, while weakness in his left arm persisted. Radiological diagnostics, including MRI of the cervical spine, revealed spondylolisthesis at the C5-C6 level, grade II/III, left dorsolateral extrusion of the C5-C6 intervertebral disc, spinal canal stenosis with medullary compression and signs of myelopathy, as well as fractures of the left lamina of C5 and the left transverse process of C6 (Figure 1). A skull X-ray revealed a fracture of the medial roof of the right orbit. Abdominal ultrasound showed no signs of internal organ trauma, and radiographs of the chest, pelvis, and left shoulder were unremarkable.



Slika 1. NMR vratne kičme: spondilolisteza na nivou C5–C6, gradus II/III, leva dorzolateralna ekstruzija intervertebralnog diska C5–C6, kao i stenoza spinalnog kanala uz kompresiju medule i znake mijelopatije, i prisustvo fraktura leve lamine C5 i levog transversalnog nastavka C6

Picture 1. MRI of the cervical spine: spondylolisthesis at the C5–C6 level, grade II/III, left dorsolateral extrusion of the C5–C6 intervertebral disc, as well as spinal canal stenosis with medullary compression and signs of myelopathy, along with fractures of the left lamina of C5 and the left transverse process of C6



Slika 2. RTG snimak pluća na dan prijema u Kovid bolnicu Batajnica, uredan nalaz

Picture 2. Chest X-ray on the day of admission to the COVID hospital Batajnica, normal findings

Tokom hospitalizacije, pacijent je pregledan od strane ortopeda, neurohirurga i neurologa, kada je indikovana MDCT angiografija glave i vrata, koja je bila urednog nalaza, a zatim i CT glave i vrata, gde je na nivou pršljenova C5–C6 viđen nalaz identičan prethodnom, uz preostali uredan nalaz. U neurološkom nalazu je sve vreme bila prisutna monopareza leve ruke srednje teškog stepena.

Pri prijemu u Kovid Bolnicu Batajnica UKCS pacijent je imao blagu kliničku sliku COVID-19, uredan radiografski nalaz snimka pluća (Slika 2), i uredan nalaz laboratorijskih analiza krvi (Tabela 1 i 2). U objektivnom nalazu je bio respiratorno i hemodinamski stabilan, urednog auskultatornog nalaza nad plućima. Konzilijarno je odlučno da se pacijentu u bolničkim uslovima, u izolaciji od drugih bolesnika, jednokratno parenteralno (intravenski) primeni lek casirivimab/indevimab u jednoj preporučenoj dozi. Odluka o primeni ovog leka

Tabela 1. Vrednosti kompletne krvne slike, parametara koagulacije i parametara zapaljenja u toku lečenja pacijenta u Kovid bolnici Batajnica UKCS

Laboratorijske analize krvi/ Blood Laboratory Analyses	Le	Ly	Er	Hgb	Tr	CRP	PCT	INR	D-dimer
Referentne vrednosti/ Reference Values	3.4–9.7 x 10 ⁹ /L	1.2–3.4 x 10 ⁹ /L	4.34–5.72 x 10 ¹² /L	138–175 g/L	158–424 x 10 ⁹ /L	0.0–3.0 mg/L	> 0.5 ng/L		cut off 0.5 mg/L
Pri prijemu/ On Admission	7.7	2.17	5.45	164	252	2.0	0.05	1.0	0.43
Pri otpustu/ On Discharge	11.4	2.77	5.29	161	266	2.0	0.03	0.99	0.44

The patient was initially treated at a regional health-care center. At that time, his primary complaints included neck pain radiating down his left arm and spine, along with weakness in his left arm. On the fifth day of hospitalization, due to the facility's inability to provide surgical treatment, he was transferred to the Institute for Orthopedic-Surgical Diseases Banjica in Belgrade, a specialized center for musculoskeletal conditions and injuries. Upon admission to this facility, a routine rapid antigen test for SARS-CoV-2 was performed on a nasopharyngeal swab, yielding a positive result. The spinal surgeon then indicated surgical treatment as soon as conditions permitted, specifically upon achieving a negative SARS-CoV-2 test. Meanwhile, the patient was advised to remain on strict bed rest and was transferred to the COVID Hospital Batajnica at the University Clinical Center of Serbia, the largest COVID hospital in Serbia, for COVID-19 management.

Upon initial examination at our institution, the patient was able to move his lower extremities but had significant weakness in his left arm, mild weakness in his left leg, and intense neck pain radiating along the spine and left arm. The remaining somatic examination findings were unremarkable, and his vital parameters were stable. His medical history was negative for chronic diseases, previous surgeries, or any long-term medication use.

During hospitalization, the patient was assessed by an orthopedic surgeon, a neurosurgeon, and a neurologist. MDCT angiography of the head and neck was performed, yielding normal results. A subsequent CT scan of the head and neck confirmed findings consistent with the previous imaging at the C5–C6 level, with no additional abnormalities. Neurological examination consistently revealed moderate left-arm monoparesis.

Upon admission to the COVID Hospital Batajnica, the patient had a mild clinical presentation of COVID-19, a normal chest X-ray (Figure 2), and unremarkable blood test results (Tables 1 and 2). He was respiratory and hemodynamically stable, with normal pulmonary auscultation. A multidisciplinary team de-

Table 1. Values of complete blood count, coagulation parameters, and inflammation markers during the patient's treatment at the COVID hospital Batajnica UKCS.

Tabela 2. Vrednosti biohemijskih analiza krvi u toku lečenja pacijenta u Kovid bolnici Batajnica UKCS

Biohemijske analize / Blood Laboratory Analyses	Glucose	eGFR	Proteins	Albumin	Na ⁺	K ⁺	AST	ALT
Referentne vrednosti / Reference Values	3.9–6.1 mmol/L	> 60mL/min/1.73m ²	62/81 g/L	34–55 g/L	135–148 mmol /L	3.5–5.1 mmol /L	U/L	U/L
Pri prijemu / On Admission	5.1	> 60	69	41	137	3.6	18	20
Pri otpustu / On Discharge	4.2	> 60	67	41	135	3.6	18	19

Table 2. Blood Biochemistry Values During the Treatment of the Patient at the COVID Hospital Batajnica UKCSBatajnica UKCS.

je doneta u cilju sprečavanja razvoja teže kliničke slike koja bi mogla ugroziti opšte stanje pacijenta i dovesti do daljih komplikacija primarne bolesti. Takođe, primenom ove terapije omogućila bi se brža negativizacija testa na SARS-CoV-2, što bi ubrzalo neophodno i hitno hiruško lečenje u što kraćem roku.

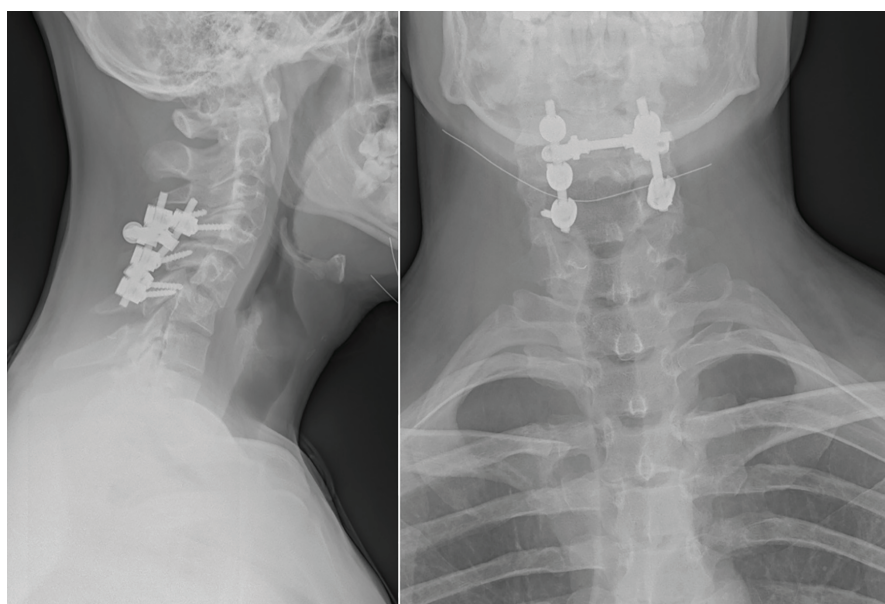
Sedam dana nakon primene leka casirivimab/imdevimab pacijent je testiran na SARS-CoV-2 pomoću Real Time PCR testa nazofaringealnog brisa, i rezultat testa je bio negativan. U tom trenutku pacijent je bio stabilnog, dobrog opšteg stanja, bez simptoma vezanih za COVID-19, uz uredan nalaz RTG snimka pluća (Slika 3) i urednih vrednosti laboratorijskih analiza krvi (Tabela 1 i 2). Preveden je na dalje lečenje u Institut za ortopedsko-hirurške bolesti Banjica u Beogradu radi neophodnog hirurškog lečenja.

Pacijent je po prevodu operisan, 18 dana nakon inicijalnog povređivanja, kada je urađena repozicija C5 vratnog pršljena uz unutrašnju spinalnu stabilizaciju C4–C6 (Slike 4 i 5). U postoperativnom toku došlo je do daljeg neurološkog oporavka. Na kontrolnom pregledu



Slika 3. Kontrolni RTG snimak pluća pred otpust iz Kovid bolnice Batajnica UKCS, uredan nalaz

Picture 3. Follow-up chest X-ray before discharge from the COVID hospital Batajnica UKCS, normal findings



Slika 4 i 5. RTG snimak vratne kičme posle uspešne operacije i stabilizacije vratnih pršljenova

Picture 4 i 5. X-ray of the cervical spine after successful surgery and stabilization of cervical vertebrae

četiri meseca kasnije, pacijent je imao uredan neurološki nalaz na svim ekstremitetima. Ponovljeno testiranje RT-PCR testom nazofaringealnog brisa na SARS-CoV-2 mesec dana nakon primene casirivimab/indevimab dalo je negativan rezultat, uz odsustvo uobičajenih tegoba vezanih za COVID-19 u kliničkom nalazu.

DISKUSIJA

Lečenje COVID-19 je od početka pandemije bio pravi izazov za zdravstvene sisteme svih država širom sveta. U pokušajima da na što bezbedniji i brži način pomognemo pacijentima, u praksi smo primenjivali različite oblike terapije. Primena imunomodulatorne antivirusne terapije činila se kao izuzetno dobra opcija za lečenje nekomplikovanog oblika COVID-19 kod pacijenata koji ne zahtevaju hospitalizaciju, a koji imaju rizik za razvoj teškog oblika ove bolesti. Međutim, usled izuzetno dobre efikasnosti leka casirivimab/indevimab, koji je inicijalno bio namenjen samo za primenu u vanbolničkim uslovima kod pacijenata sa blagom kliničkom slikom, počinje se sa prvim pokušajima lečenja ovim lekom u hospitalnim uslovima, uz pozitivne rezultate [10]. U skladu sa ovim rezultatima, u novembru 2021. godine objavljene su zvanične preporuke za primenu leka casirivimab/indevimab u hospitalnim uslovima [11].

Indikacije za primenu antivirusne terapije monoklonskim antitelima su ambulantni pacijenti sa blagom ili umereno teškim oblikom COVID-19 koji imaju visok rizik za progresiju i hospitalizaciju, ili za fatalan ishod.

Monoklonska antitela se primenjuju jednokratno, nakog čega je potrebna izolacija bolesnika kako ne bi došlo do ponovne zaraze. Ova terapija se može primeniti i kod hospitalizovanih bolesnika ukoliko postoje isti rizici i ukoliko se radi o asimptomatskim ili pacijentima sa blagom i umereno teškom formom bolesti, a koji su hospitalizovani iz nekog drugog razloga koji nije COVID-19 [2,12].

Tokom primene antitela u terapiji COVID-19 primećena je učestala pojava rezistencije virusa prilikom primene jednog antitela, zbog čega je pribegnuto primeni kombinacije dva antitela u vidu leka casirivimab/indevimab [13], uz odlične rezultate u lečenju, ali i u izbegavanju razvoja rezistencije. Kombinacija casirivimaba i indevimaba predstavlja kombinaciju visokoafinitetnih humanih monoklonskih IgG antitela, koja se vezuju direktno za S protein na površini SARS-CoV-2 i na taj način sprečavaju ulazak virusa u ćelije domaćina [2].

Lek casirivimab/indevimab, prema preporukama, primenjuje se u vanbolničkim uslovima kod pacijenata u ranoj fazi zaražavanja, kod kojih nije potrebna primena oksigenoterapije, ali sa prisutnim visokim rizikom za razvoj teškog oblika COVID-19. Cilj ove terapije je

cided to administer a single intravenous dose of casirivimab/indevimab in a hospital setting, in isolation from other patients. The rationale for this decision was to prevent disease progression, which could compromise the patient's overall condition and lead to complications related to his primary injury. Additionally, this therapy was expected to accelerate the negativization of the SARS-CoV-2 test, thereby facilitating the urgent surgical intervention required.

Seven days after receiving casirivimab/indevimab, the patient underwent RT-PCR testing for SARS-CoV-2 via a nasopharyngeal swab, which returned a negative result. At this point, he was in stable condition, free of COVID-19 symptoms, with a normal chest X-ray (Figure 3) and unremarkable blood test results (Tables 1 and 2). He was subsequently transferred back to the Institute for Orthopedic-Surgical Diseases Banjica in Belgrade for the necessary surgical treatment.

The patient underwent surgery 18 days after the initial injury, during which C5 vertebral repositioning and internal spinal stabilization of C4–C6 were performed (Figures 4 and 5). Postoperatively, he exhibited further neurological improvement. At a follow-up examination four months later, he had a normal neurological status in all extremities. Repeat RT-PCR testing for SARS-CoV-2 one month after casirivimab/indevimab administration remained negative, and he showed no clinical signs of COVID-19.

DISCUSSION

The treatment of COVID-19 has been a major challenge for healthcare systems worldwide since the beginning of the pandemic. In an effort to help patients as safely and quickly as possible, various therapeutic approaches have been implemented in practice. The use of immunomodulatory antiviral therapy appeared to be an extremely beneficial option for treating mild COVID-19 cases in outpatients at risk of developing severe disease. However, due to the exceptional efficacy of casirivimab/indevimab, initially intended for outpatient use in patients with mild disease, the first attempts at hospital treatment with this drug began, yielding positive results [10]. Based on these findings, official recommendations for the administration of casirivimab/indevimab in hospitalized patients were published in November 2021 [11].

The indications for monoclonal antibody antiviral therapy include ambulatory patients with +mild to moderate COVID-19 who are at high risk of progression, hospitalization, or fatal outcome.

Monoclonal antibodies are administered as a single dose, followed by patient isolation to prevent reinfection. This therapy can also be used in hospitalized

postizanje adekvatnog imunološkog odgovora na infekciju kod onih pacijenata koji nisu postigli adekvatan odgovor na infekciju, odnosno kod onih koji su imali visok titar virusa [8,14].

Naš pacijent je imao blagu kliničku sliku, uredan nalaz RTG pluća i tokom hospitalizacije nije zahtevao primenu oksigenoterapije. Pacijent nije imao rizik za tešku formu COVID-19, ali uzimajući u obzir njegovo stanje i povredu vratne kičme, kao i neophodnost strogog mirovanja, gde bi i kašalj mogao dodatno da iskomplikuje tok osnovne bolesti, spadao je u pacijente sa visokim rizikom. Tokom njegovog lečenja bilo je važno sprečiti razvoj težih simptoma ove bolesti, koji bi mogli da otežaju i dodatno prolongiraju njegovo operativno lečenje.

Ovaj mladi čovek imao je povredu vratnih pršljenova, sa posledičnom stenozom kičmenog kanala i znacima mijelopatije, kao i prisustvom spinalne nestabilnosti (engl. *spinal instability*), što se smatra indikacijom za urgentno hiruško lečenje [15-20]. Iz tog razloga, još jedan važan cilj koji smo imali tokom lečenja ovog pacijenta lekom casirivimab/indevimab bio je postizanje brze negativizacije nazofaringealnog brisa na SARS-CoV-2, koja je potvrđena u literaturi [10,11], a postignuta je i u ovom slučaju. Uz primenu svih dostupnih modaliteta lečenja i nege koji su nam bili dostupni, uspešno su izbegnute potencijalne komplikacije odlaganja hiruškog lečenja povreda kičme, za koje je zabeleženo učestalije javljanje tokom COVID-19 pandemije [21]. Kod povreda kičme sa prisutnom kompresijom savetuje se hiruško lečenje u vremenskom periodu od 8 do 24 sata od povređivanja kako bi se postigli najbolji rezultati u oporavku neurološke funkcije [22,23]. Iako je pacijent operisan nekoliko dana kasnije, njegov oporavak je protekao uredno, sa neurološkim nalazom koji ne ukazuje na zaostale neurološke ispade.

U literaturi postoji mali broj studija u kojima je lek casirivimab/indevimab primenjivan kod hospitalizovanih pacijenata sa prisutnom blagom kliničkom slikom [24], među kojima i jedna koja se bavi primenom leka casirivimab/indevimab kod pacijenata koji su bili na niskim dozama kiseonične potpore [14], uz ohrabrujuće rezultate, što se slaže sa ishodom lečenja koji je postignut kod našeg pacijenta.

ZAKLJUČAK

Kroz ovaj slučaj uspešno je prikazano da je uz multidisciplinarni pristup lečenju pacijenta, kao i primenu imunomodulatorne terapije, postignuto brzo izlečenje COVID-19 i negativizacija nazofaringealnog brisa na SARS-CoV-2, a zatim i urgentno hiruško lečenje akutne povrede vratnog dela kičme, koje je pretilo da permanentno ugrozi kvalitet života našeg mladog pacijenta.

patients who meet the same risk criteria and who are asymptomatic or have mild to moderate disease but are hospitalized for reasons unrelated to COVID-19 [2,12].

During the use of monoclonal antibodies in COVID-19 treatment, frequent viral resistance was observed when a single antibody was used, prompting the introduction of combination therapy with casirivimab/imdevimab [13]. This approach has demonstrated excellent treatment efficacy and prevented resistance development. Casirivimab and imdevimab are high-affinity human monoclonal IgG antibodies that bind directly to the SARS-CoV-2 spike (S) protein, preventing the virus from entering host cells [2].

According to recommendations, casirivimab/imdevimab is used in outpatient settings for patients in the early phase of infection who do not require oxygen therapy but are at high risk for severe COVID-19. The goal of this therapy is to achieve an adequate immune response in patients who have not mounted a sufficient response to the infection or who have a high viral load [8,14].

Our patient had a mild clinical presentation, normal chest X-ray findings, and did not require oxygen therapy during hospitalization. Although he was not at risk for severe COVID-19, considering his cervical spine injury and the necessity for strict immobilization-where even coughing could complicate his primary condition-he was classified as a high-risk patient. Preventing the progression of severe symptoms was crucial to avoid further delays in the necessary surgical treatment.

This young man sustained cervical spine injuries, resulting in spinal canal stenosis, myelopathy, and spinal instability, which are indications for urgent surgical intervention [15-20]. Therefore, another important goal of administering casirivimab/imdevimab was to achieve rapid SARS-CoV-2 clearance from the nasopharyngeal swab, as documented in the literature [10,11], and successfully achieved in this case. By utilizing all available treatment modalities and care strategies, we successfully avoided complications associated with delaying spinal surgery, which had been more frequently reported during the COVID-19 pandemic [21]. For spinal injuries with compression, surgery is recommended within 8 to 24 hours of injury to achieve the best neurological recovery outcomes [22,23]. Although our patient underwent surgery several days later, his recovery progressed favorably, with no residual neurological deficits.

The literature contains few studies on the use of casirivimab/imdevimab in hospitalized patients with mild clinical presentation [24], including one study in-

Pokazali smo i da je *off-label* primena imunomodulatorne antivirusne terapije monoklonskim antitelima kod obolelih od COVID-19 delotvorna i spasonosna, ali i indikovana kod pacijenata koji su hospitalizovani iz nekog drugog medicinskog razloga, a ne zbog COVID-19, kod kojih nije prošlo više od 5 dana od pojave prvih simptoma, kod pacijenata koji zahtevaju dalju hospitalizaciju i lečenje ili kod pacijenata koji mogu biti otpušteni na dalje kućno lečenje.

Ovi zaključci su veoma važni i za ubuduće, u cilju daljeg pristupa lečenja pacijenata sa različitim virusnim infekcijama, a za koje ne postoji specifična antivirusna ili preventivna terapija.

Sukob interesa: Nije prijavljen.

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CONCLUSION

This case successfully demonstrates that a multidisciplinary approach, combined with immunomodulatory therapy, enabled rapid COVID-19 recovery and SARS-CoV-2 clearance, followed by urgent surgical treatment of an acute cervical spine injury that threatened the young patient's quality of life.

We have also shown that the off-label use of monoclonal antibody-based immunomodulatory therapy for COVID-19 is both effective and life-saving. It is particularly indicated for patients hospitalized for reasons other than COVID-19, provided that no more than five days have elapsed since symptom onset, for those requiring ongoing hospitalization and treatment, or for patients who can be discharged for home care.

These findings are highly significant for future treatment strategies in patients with various viral infections for which no specific antiviral or preventive therapy exists.

Conflict of interest: None declared.

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PERIFERNA PARALIZA FACIJALNOG NERVA KAO MANIFESTACIJA NEUROENDOKRINOLOGIJSKOG TUMORA SREDNJEG UHA – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

PERIPHERAL PARALYSIS OF THE FACIAL NERVE AS A MANIFESTATION OF NEUROENDOCRINE TUMOR OF THE MIDDLE EAR – CASE REPORT

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SAŽETAK

Uvod: Periferna paraliza facijalnog nerva je akutna idiopatska paraliza često povezana sa virusnim infekcijama kao što je reaktivacija virusa *Herpes simplex* tipa 1. Neuroendokrini tumori (NET) srednjeg uva (MEANT) su retki i prisutni su sa nespecifičnim simptomima, uključujući gubitak sluha, otalgiju i neuropatiju, što otežava ranu dijagnozu.

Prikaz slučaja: Prikazan je slučaj 47-godišnje pacijentkinje lečene od hroničnog otitisa od 2020. Godine 2024., početak paralize perifernog facijalnog nerva podstakao je naprednu dijagnostiku, uključujući MRI, CT, biopsiju i imunohistohemijske analize, potvrđujući MEANT. Lečenje je uključivalo hiruršku eksciziju, terapiju gama nožem i redovno praćenje tumorskih markera. Odložena dijagnoza tumora istakla je potrebu za povećanom kliničkom sumnjom u slučajevima hronične patologije uha sa atipičnom progresijom.

Zaključak: Neuroendokrini tumori srednjeg uva predstavljaju dijagnostički i terapijski izazov zbog svoje retkosti i nespecifične prezentacije. Rano prepoznavanje perifernog paralize facijalnog nerva kao potencijalnog pokazatelja osnovnog maligniteta je ključno. Multidisciplinarno upravljanje, integrišući napredno snimanje, histopatološke potvrde, hirurške intervencije i pomoćne terapije, poboljšavaju ishode i minimiziraju rizik od recidiva. Lekari opšte medicine igraju ključnu ulogu u identifikaciji ranih simptoma kako bi se smanjila dijagnostička kašnjenja.

Ključne reči: paraliza perifernog facijalnog nerva, hronični otitis srednjeg uha, retki tumori, rano prepoznavanje bolesti, opšta medicina

ABSTRACT

Introduction: Acute idiopathic peripheral facial nerve paralysis is often linked to viral infections such as *Herpes simplex* virus type 1 reactivation. Neuroendocrine tumors (NETs) of the middle ear (MEANT) are rare and present with non-specific symptoms, including hearing loss, otalgia, and neuropathy, complicating early diagnosis.

Case report: Report the case of a 47-year-old patient treated for chronic otitis since 2020. In 2024, the onset of peripheral facial nerve paralysis prompted advanced diagnostics, including MRI, CT, biopsy, and immunohistochemical analyses, confirming MEANT. Treatment included surgical excision, gamma knife therapy, and regular tumor marker monitoring. A delayed diagnosis of the tumor highlighted the need for heightened clinical suspicion in cases of chronic ear pathology with atypical progression.

Conclusion: Neuroendocrine tumors of the middle ear are diagnostic and therapeutic challenges due to their rarity and non-specific presentation. Early recognition of peripheral facial nerve paralysis as a potential indicator of an underlying malignancy is critical. Multidisciplinary management, integrating advanced imaging, histopathological confirmation, surgical intervention, and adjuvant therapies, improves outcomes and minimizes relapse risks. General practitioners play a pivotal role in identifying early symptoms to reduce diagnostic delays.

Keywords: peripheral facial nerve paralysis, chronic otitis media, rare tumors, early recognition of the disease, general medicine

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UVOD

Periferna paraliza facijalnog nerva je često nepoznatog uzroka. Smatra se idiopatskim stanjem iako se sve više dokaza povezuje s virusnim infekcijama, poput reaktivacije *Herpes simplex* virusa tipa 1 [1]. Karakteristična klinička slika uključuje iznenadnu slabost ili paralizu mišića jedne strane lica, što može biti praćeno bolom iza uha, oslabljenim čulom ukusa i povećanom osjetljivošću na zvukove.

Postavljanje dijagnoze periferne paralize facijalnog nerva je kliničko ali podrazumeva da se izuzmu u obzir drugi mogući uzroci [2]. Diferencijalna dijagnoza može da ukaže na niz različitih bolesti i stanja. Moždani udar na primer za razliku od periferne paralize facijalnog nerva, često zahvata samo donji deo lica i povezan je s drugim neurološkim deficitima [3]. Lajmska bolest može imitirati perifernu paralizu facijalnog nerva, ali se obično javlja u endemskim područjima i prati je borelijski eritem [4]. Tumori baze lobanje su takođe uzrok, ali retko i mogu uzrokovati slične simptome, što naglašava važnost snimanja magnetnom rezonancom [5,6]. Infekcije poput otitis media i *Herpes zoster oticus* (Ramsay Hunt sindrom) mogu uzrokovati slične simptome, ali su obično praćeni bolom ili osipom pa nas tu drugi klinički simptomi navode na pravi uzrok. Autoimuna stanja poput Guillain-Barré sindroma i sarkoidoza takođe mogu biti razmatrane diferencijalno dijagnostički [5].

Neuroendokrini tumori (NET) predstavljaju raznoliku grupu tumora koje nastaju iz neuroendokrinih ćelija. Ove ćelije, koje dele karakteristike neurološkog i endokrinog sistema, mogu se pronaći u različitim organima i tkivima tela. NET su relativno retki ali mogu biti lokalizovani u plućima, digestivnom traktu, pankreasu pa čak i u srednjem uvu, što predstavlja posebnu i nedovoljno istraženu podgrupu. Neuroendokrini tumori srednjeg uva, poznati i kao neuroendokrini adenomatni tumori srednjeg uva (MEANT), izuzetno su retki i čine manje od 2% svih tumora srednjeg i unutrašnjeg uva. Do danas je u literaturi na engleskom jeziku prijavljeno manje od 150 slučajeva, pod različitim nazivima, uključujući karcinoidne tumore, adenome srednjeg uva, adenomatne tumore srednjeg uva, adenokarcinoidne tumore i amfikrine tumore. Prvi dokumentovani primarni adenomatni tumor ograničen na šupljinu srednjeg uva opisan je 1976. godine. NET se dele na dobro diferentovane (tipično benigni ili niskog malignog potencijala) i loše diferentovane (visokog malignog potencijala). Histološki, ovi tumori izlučuju specifične markere poput sinaptofizina i hromogranina, što olakšava dijagnostiku putem imunohistohemije [7-9]. Klinička slika zavisi od lokalizacije i sekretorne aktivnosti tumora [8]. Ovi tumori se često nazivaju *adenomatous neuroendocrine tumors* (NAME) ili timpanalni adenom. Oni se najčešće manife-

INTRODUCTION

Peripheral facial nerve paralysis is often of unknown origin. It is considered an idiopathic condition, although increasing evidence links it to viral infections, such as the reactivation of *Herpes simplex* virus type 1 [1]. The characteristic clinical presentation includes sudden weakness or paralysis of the muscles on one side of the face, which may be accompanied by pain behind the ear, diminished sense of taste, and increased sensitivity to sound.

Diagnosing peripheral facial nerve paralysis is clinical but requires ruling out other possible causes [2]. The differential diagnosis may suggest a range of different diseases and conditions. Stroke, for instance, unlike peripheral facial nerve paralysis, often affects only the lower part of the face and is associated with other neurological deficits [3]. Lyme disease can mimic peripheral facial nerve paralysis but usually occurs in endemic areas and is accompanied by a *Borrelia*-related erythema [4]. Skull base tumors are also a rare cause but can produce similar symptoms, highlighting the importance of magnetic resonance imaging [5,6]. Infections such as otitis media and *Herpes zoster oticus* (Ramsay Hunt syndrome) may cause similar symptoms but are usually accompanied by pain or rash, which helps guide us to the correct cause. The differential diagnosis should also consider autoimmune conditions like Guillain-Barré syndrome and sarcoidosis [5].

Neuroendocrine tumors (NETs) represent a diverse group of tumors arising from neuroendocrine cells. These cells, which share characteristics of the nervous and endocrine systems, can be found in various organs and tissues throughout the body. NETs are relatively rare but can be localized in the lungs, gastrointestinal tract, pancreas, and even the middle ear, representing a distinct and under-researched subgroup. Neuroendocrine tumors of the middle ear, also known as middle ear adenomatous neuroendocrine tumors (MEANTs), are sporadic and account for less than 2% of all middle and inner ear tumors. To date, fewer than 150 cases have been reported in the English literature, under various names, including carcinoid tumors, middle ear adenomas, middle ear adenomatous tumors, adenocarcinoid tumors, and amphicrine tumors. The first documented primary adenomatous tumor confined to the middle ear cavity was described in 1976. NETs are classified as well-differentiated (typically benign or of low malignant potential) and poorly differentiated (highly malignant). Histologically, these tumors secrete specific markers such as synaptophysin and chromogranin, which aid diagnosis via immunohistochemistry [7-9]. The clinical presentation depends on the tumor's location and secretory activity [8]. These tumors are often

stuju simptomima poput gubitka sluha, tinitusa ili osećaja punoće u uhu [9]. Histopatološki, NET srednjeg uha mogu pokazivati mešovitu neuroendokrinu i ne-neuroendokrinu komponentu [7]. Smatra se da MEANT tumori potiču iz epitela koji oblaže sluznicu srednjeg uha, što predstavlja produžetak i modifikaciju respiratornog epitela [8]. Dijagnostika uključuje dijagnostičke metode poput kompjuterizovana tomografija temporalne kosti (CT) i magnetna rezonanca (MRI), dok je konačna potvrda moguća samo putem biopsije i imunohistohemijskog pregleda. Iako su NET srednjeg uha izuzetno retki, prevalencija je nešto veća kod muškaraca srednje životne dobi [8,10]. Klinički simptomi zavise od veličine i lokalnog širenja tumora. Većina pacijenata prezentira se s jednostranim gubitkom sluha, dok manji deo može razviti otoreju ili bol [11].

PRIKAZ SLUČAJA

Pacijentkinja, stara 47 godina, lečena je konzervativno i paracentezom zbog hroničnog nesupurativnog otitisa i uočenog sadržaja u mastoidnoj šupljini na MRI pregledu. U avgustu 2024. javila se kao hitan slučaj zbog periferne paralize facijalnog nerva, što je iniciralo dodatna ispitivanja.

Izveden je operativni zahvat timpanoplastike sa mastoidektomijom i rekonstrukcijom slušnih koštica na levoj strani, a patohistološki nalaz ukazao je na adenoidno-cistični karcinom. Revizija nalaza kasnije je potvrdila neuroendokrini tumor srednjeg uha (MEANT), klasifikovan kao G1 neuroendokrini adenom sa niskim proliferativnim potencijalom ($Ki-67 < 1\%$). Imunohistohemijski profil uključuje pozitivne markere (INSM1, sinaptofizin, p63) i negativne markere (hromogranin A, CD117, CK7, SOX-10).

Radiološki nalazi, uključujući MR i CT pregled, ukazali su na postoperativne promene i prisustvo tumorskog resta sa infiltracijom u nivou baze kranijuma, sa ekstrakranijalnom i temporobazalnom ekstenzijom, ali bez znakova moždanog edema i intrakranijalnog krvarenja. CT vrata i gornjeg abdomena nije pokazao značajne limfadenopatske promene, dok je cistična lezija jetre (9 mm) klasifikovana kao benigna. Predložen je multidisciplinarni terapijski pristup koji obuhvata hiruršku eksciziju postoperativnu gama nož (*gamma knife*) terapiju i praćenje neuroendokrinih tumorskih markera (CgA i NSE). Preporučena je konsultacija sa ORL hirurgom, neurohirurgom i onkologom radi dalje procene i praćenja.

DISKUSIJA

Prikaz ovog slučaja neuroendokrinoelogičnog tumora srednjeg uha (MEANT) ističe ključnu ulogu ranog prepoznavanja simptoma od strane lekara opšte medicine, naro-

referred to as **adenomatous neuroendocrine tumors (NAME)** or tympanic adenomas. They commonly present with symptoms such as hearing loss, tinnitus, or a sensation of fullness in the ear [9]. Histopathologically, middle ear NETs may exhibit a mixed neuroendocrine and non-neuroendocrine component [7]. It is believed that MEANTs originate from the epithelium lining the middle ear mucosa, which is a continuation and modification of respiratory epithelium [8]. Diagnostic methods include imaging such as computed tomography (CT) of the temporal bone and magnetic resonance imaging (MRI), while definitive confirmation is only possible through biopsy and immunohistochemical examination. Although middle ear NETs are extremely rare, their prevalence is slightly higher in middle-aged men [8,10]. Clinical symptoms depend on the size and local spread of the tumor. Most patients present with unilateral hearing loss, while a smaller portion may develop otorrhea or pain [11].

CASE REPORT

A 47-year-old female patient was initially treated conservatively and with paracentesis for chronic nonsuppurative otitis and a noted mass in the mastoid cavity observed on MRI. In August 2024, she presented as an emergency case due to peripheral facial nerve paralysis, which prompted further investigation.

A surgical procedure was performed, including tympanoplasty with mastoidectomy and ossicular chain reconstruction on the left side. The initial histopathological finding suggested adenoid cystic carcinoma. However, a subsequent review of the pathology confirmed a middle ear neuroendocrine tumor (MEANT), classified as a G1 neuroendocrine adenoma with low proliferative potential ($Ki-67 < 1\%$). The immunohistochemical profile showed positive markers (INSM1, synaptophysin, p63) and negative markers (chromogranin A, CD117, CK7, SOX-10).

Radiological findings, including MRI and CT scans, indicated postoperative changes and the presence of residual tumor with infiltration at the skull base, exhibiting both extracranial and temporobasal extension, but without signs of cerebral edema or intracranial hemorrhage. CT scans of the neck and upper abdomen showed no significant lymphadenopathy, while a 9 mm cystic liver lesion was classified as benign.

A multidisciplinary therapeutic approach was proposed, including surgical excision, postoperative gamma knife therapy, and monitoring neuroendocrine tumor markers (CgA and NSE). Consultations with an ENT surgeon, neurosurgeon, and oncologist were recommended for further evaluation and follow-up.

čito kod pacijenata sa dugotrajnim ili ponavljajućim simptomima. Pacijentkinja je od 2020. godine lečena zbog hroničnog otitisa sa evidentnim zastoynim sadržajem u mastoidnom nastavku, što je već tada ukazivalo na potrebu za detaljnijim ispitivanjem i multidisciplinarnim pristupom. U ovom slučaju, tek razvoj periferne facijalnog nerva 2024. godine podstakao je dalje dijagnostičke korake, što ukazuje na potencijalni vremenski jaz između pojave simptoma i postavljanja tačne dijagnoze. Neuroendokrini tumori srednjeg uha su retki i često izazivaju nespecifične simptome poput hronične otalgije, otoreje ili gubitka sluha, što otežava njihovo rano prepoznavanje [1-3,5]. Klinička sumnja lekara opšte medicine može igrati ključnu ulogu u ubrzavanju dijagnostičkog procesa. Rano prepoznavanje simptoma poput trajne otalgije, gubitka sluha i periferne neuropatije od strane lekara opšte medicine moglo bi poboljšati ishod, jer omogućava ranije uvođenje dijagnostičkih procedura, poput MR i CT [12]. Dijagnostički izazovi uključuju i specifičnost patohistoloških nalaza, gde je imunohistohemijski profil tumora ključan za diferencijaciju MEANT od drugih karcinoma. Na primer, pozitivni markeri poput INSM1 i sinaptofizina, zajedno sa niskim Ki-67 indeksom (< 1%), ukazuju na nizak proliferativni potencijal ovog tumora [7,13,14]. Ki67 je antigen vezan za proliferaciju ćelija koji igra ključnu ulogu u deobi ćelija i proliferaciji tumorskih ćelija. Visok indeks Ki67 ukazuje na aktivnu proliferaciju ćelija, potencijalno signalizirajući rizik od malignog tumora [8,9].

Međutim, bez ranijeg prepoznavanja, ovi nalazi često dolaze kasno u kliničkom toku bolesti, kada su potrebne agresivne terapijske mere. Multidisciplinarni pristup lečenju, koji uključuje hiruršku eksciziju i postoperativnu gama nož terapiju, pokazao se kao efikasan u upravljanju ovakvim slučajevima [13]. Takođe, praćenje markera kao što su hromogranin A (CgA) i neuron-specifična enolaza (NSE) ključno je za procenu odgovora na terapiju i otkrivanje recidiva [10,13,14]. Ovaj slučaj naglašava potrebu za kontinuiranom edukacijom lekara opšte medicine o važnosti prepoznavanja ranih simptoma malignih bolesti srednjeg uha. Uvođenje dijagnostičkih algoritama i bliska saradnja sa specialistima mogu unaprediti kvalitet nege i značajno poboljšati prognozu kod pacijenata sa sličnim stanjima.

ZAKLJUČAK

Neuroendokrini tumori srednjeg uha iako retki, mogu izazvati značajne dijagnostičke i terapijske izazove. Manifestacija periferne paralize facijalnog nerva kao prvog simptoma kod ovih tumora zahteva brzu i preciznu dijagnozu kako bi se obezbedilo pravovremeno lečenje i smanjio rizik od trajnih posledica. Uloga leka-

DISCUSSION

This case report of a middle ear neuroendocrine tumor (MEANT) highlights the crucial role of early symptom recognition by general practitioners, particularly in patients with persistent or recurrent symptoms. Since 2020, the patient had been treated for chronic otitis with evident effusion in the mastoid process, which already indicated the need for more thorough evaluation and a multidisciplinary approach. In this case, it was not until the development of peripheral facial nerve palsy in 2024 that further diagnostic steps were initiated, pointing to a potential time gap between symptom onset and accurate diagnosis. Middle ear neuroendocrine tumors are rare and often present with non-specific symptoms such as chronic otalgia, otorrhea, or hearing loss, which complicates early recognition [1-3,5]. Clinical suspicion from the general practitioner can expedite the diagnostic process. Primary care physicians could improve outcomes by early recognition of symptoms such as persistent otalgia, hearing loss, and peripheral neuropathy by enabling earlier diagnostic procedures like MRI and CT scans [12].

Diagnostic challenges also include the specificity of histopathological findings, where the immunohistochemical profile of the tumor is essential for differentiating MEANT from other carcinomas. For instance, positive markers such as INSM1 and synaptophysin, combined with a low Ki-67 index (<1%), indicate a low proliferative potential of this tumor [7,13,14]. Ki-67 is a proliferation-associated antigen that plays a key role in cell division and tumor cell proliferation. A high Ki-67 index indicates active cell proliferation, potentially signaling the risk of malignancy [8,9]. However, without earlier recognition, these findings often appear late in the clinical course of the disease, when aggressive therapeutic interventions are already necessary. A multidisciplinary treatment approach, including surgical excision and postoperative gamma knife therapy, has proven effective in managing such cases [13]. Additionally, monitoring markers such as chromogranin A (CgA) and neuron-specific enolase (NSE) is essential for evaluating treatment response and detecting recurrence [10,13,14].

This case emphasizes the need for continuous education of general practitioners regarding the importance of recognizing early symptoms of malignant middle ear diseases. Implementing diagnostic algorithms and close collaboration with specialists can improve the quality of care and significantly enhance the prognosis for patients with similar conditions.

CONCLUSION

Although rare, middle ear neuroendocrine tumors can pose significant diagnostic and therapeutic challeng-

ra opšte medicine kao prvog koji se sreće sa pacijentom i multidisciplinarni pristup koji uključuje kliničku evaluaciju, radiološke metode i patohistološku analizu ključan je za postavljanje dijagnoze i određivanje optimalnog tretmana. Iako tumori sa niskim proliferativnim potencijalom imaju povoljniju prognozu, praćenje zbog mogućih recidiva i metastaza ostaje od kritične važnosti.

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es. The manifestation of peripheral facial nerve paralysis as an initial symptom in such tumors necessitates prompt and accurate diagnosis to ensure timely treatment and reduce the risk of permanent consequences. The role of the general practitioner as the first point of contact, along with a multidisciplinary approach involving clinical evaluation, radiological methods, and histopathological analysis, is essential for establishing a diagnosis and determining the optimal treatment. While tumors with low proliferative potential tend to have a more favorable prognosis, continuous monitoring for possible recurrences and metastases remains critically important.

Conflict of interest: None declared.

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Srpski medicinski časopis Lekarske komore objavljuje do sada neobjavljene originalne stručne i naučne radove, pregledne članke, kratka saopštenja, uvodnike, pisma uredniku, meta-analize, prikaze slučajeva, aktuelne teme, prikaze knjiga, radove iz istorije medicine i drugo, iz svih oblasti medicine, farmacije i stomatologije, čime doprinosi promociji i razvoju struke i nauke. Časopis se objavljuje u papirnom i elektronskom obliku četiri puta godišnje.

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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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