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EDITORIJAL



„Zdravlje je glavni uslov da čovek svoju metu postiže.”

Vasa Pelagić

Poštovane kolegice i kolege,

Približavajući se petogodišnjici izlaženja prvog broja Srpskog medicinskog časopisa Lekarske komore, Uredništvo sa zadovoljstvom ističe da je u tom periodu publikovano više od 200 stručno-naučnih radova i prikaza knjiga sa različitom tematikom iz praktično svih oblasti medicinskih nauka. Ostvarili smo strateško partnerstvo sa Institutom za medicinska istraživanja Univerziteta u Beogradu, koji je postao suizdavač našeg časopisa. Zalaganjem Uredništva da se održi visok kvalitet objavljenih rukopisa i da se izvrši njihova pravilna i potpuna recenzija, kao i da se poštuju svi drugi kriterijumi koji obezbeđuju vredan stručno-naučni doprinos, Časopis je, 2023. godine, upisan na Listu kategorisanih naučnih časopisa Ministarstva nauke, tehnološkog razvoja i inovacija.

Prvih pet godina postojanja Časopisa nisu bile ni lake ni jednostavne. Stoga, sa posebnim ponosom ističemo da smo i u vreme pandemije KOVID-19 oboljenja, i tokom suštinskih i organizacionih promena u cilju poboljšanja i osavremenjivanja strukture i kvaliteta samog Časopisa, kao i sada, u svetlu skorašnjih, veoma dinamičnih svetskih i lokalnih dešavanja, istrajali u svom primarnom cilju: stručnom i naučnom promovisanju zdravlja pojedinca i nacije kao jedne od najvažnijih društvenih kategorija.

U broju koja je pred vama, predstavljamo originalne radove naših uvaženih koleginica iz Angole, Tereze Vilunge Čituko Kandido i Franciske da Karidade Feliks Čitange, u kojima su prikazana iskustva iz oblasti javnog zdravlja i upravljanja kadrovskim i informacionim aspektima zdravstvenog sistema ove zemlje.

Kristina Jevremović i saradnici, u svom originalnom radu, prikazuju inicijalne rezultate svog istraživanja o inhibitornom dejstvu probiotičkih bakterija na rast i razvoj uzročnika lajmske borelioze.

Pregledni rad Biljane Đorđević i saradnika bavi se karakteristikama reproduktivnog bioekonomskog tržišta, dok se u preglednom radu Milene S. Pandrc i Vanje Kostovski razmatraju različiti aspekti antiishemijske terapije u lečenju hroničnog koronarnog sindroma.

Sanja Momčilović i saradnici donose nam veoma zanimljiv pregled značaja interakcije mezenhimalnih matičnih ćelija i makrofaga u inflamatornoj mikrosredini.

Dolika D. Vasović i saradnici saopštavaju prikaz slučaja melanocitoma glave optičkog nerva uz jukstapilarni nevus horioideje, upoređujući svoje iskustvo sa pregledom literature.

EDITORIAL

"The fundamental prerequisite for a person to reach their goal is health."

Vasa Pelagić

Dear colleagues,

As the fifth anniversary of the first issue of the Serbian Journal of the Medical Chamber approaches, the Editorial Board is pleased to highlight that over 200 professional and scientific papers, as well as book reviews, on various topics from virtually all fields of medical science, have been published during this period. We have established a strategic partnership with the Institute for Medical Research of the University of Belgrade, which has become a co-publisher of our journal. Thanks to the Editorial Board's commitment to maintaining the high quality of published manuscripts, ensuring proper and thorough peer review, and adhering to all other criteria necessary to provide valuable professional and scientific contributions, the Journal was included in the List of Categorized Scientific Journals by the Serbian Ministry of Science, Technological Development and Innovation, in 2023.

The first five years of the Journal were neither easy nor simple. Therefore, we take particular pride in emphasizing that—even during the COVID-19 pandemic, throughout essential and organizational changes aimed at improving and modernizing the structure and quality of the Journal itself, and now, in light of recent dynamic global and local events—we have remained steadfast in our primary goal: the professional and scientific promotion of individual and national health as one of the most important societal values.

In the current issue of the Journal, we present original articles by our esteemed colleagues from Angola, Teresa Vilunga Chituko Candido and Francisca da Caridade Felix Chitanga, which showcase the experiences in the areas of public health, as well as human resource and health system information management, within the country's healthcare system.

In their original article, Kristina Jevremović et al. present the initial results of their research on the inhibitory effect of probiotic bacteria on the growth and development of the causative agents of Lyme borreliosis.

The review article by Biljana Đorđević et al. explores the characteristics of the reproductive bioeconomy market, while the review article by Milena S. Pandrc and Vanja Kostovski discusses various aspects of anti-ischemic therapy in the treatment of chronic coronary syndrome.

Sanja Momčilović et al. present a compelling review of the significance of the interaction between mesenchymal stem cells and macrophages within the inflammatory microenvironment.

Dolika D. Vasović et al. report a case of melanocytoma of the optic nerve head coexisting with juxtapapillary choroidal nevus, comparing their findings with a review of the literature.

Aleksandra Petrović i saradnici prikazuju slučaj lečenja teške otvorene povrede stopala sadejstvom rekonstruktivnih hirurških tehnika, vakuum-asistiranog zatvaranja rana i ortobioloških agenasa, dok Danilo Jeremić i saradnici saopštavaju prikaz dva slučaja revizione totalne artroplastike kolena, upotrebom implanta sa dizajnom rotirajuće šarke.

Na kraju, Jadran B. Erčić daje kratak pregled istorije klasifikovanja i lečenja jednog od najčešćih preloma u koštano-zglobnoj traumatologiji – preloma donjeg okrajka žbice na tipičnom mestu.

U ime Uredništva i u svoje lično ime, ljubazno vas pozivam na saradnju sa našim časopisom, uz najlepše želje za lično i porodično zdravlje.

*S poštovanjem,
Zamenik glavnog i odgovornog urednika
Prof. dr Goran Tulić*

Aleksandra Petrović et al. present a case of complex open foot injury treatment through the combined use of reconstructive surgical techniques, vacuum-assisted wound closure, and orthobiologic agents, while Danilo Jeremić et al. report two cases of revision total knee arthroplasty using a rotating hinge implant design.

Finally, Jadran B. Erčić offers a brief overview of the history of classification and treatment of one of the most common fractures in bone and joint traumatology – distal radius fracture at a typical site.

On behalf of the Editorial Board and in my personal capacity, I kindly invite you to contribute to our journal, while extending my best wishes for your personal health and that of your family.

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

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ORIGINALNI RAD

ORIGINAL ARTICLE

CHALLENGES IN MANAGING THE HEALTH WORKFORCE FOR UNIVERSAL HEALTH COVERAGE IN ANGOLA

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SAŽETAK

Uvod: Upravljanje ljudskim resursima u zdravstvu je od suštinskog značaja za postizanje univerzalne pokrivenosti zdravstvenom zaštitom, posebno u zemljama koje se suočavaju sa značajnim strukturnim izazovima, kao što je Angola.

Cilj: Ova studija ima za cilj da opiše izazove u upravljanju zdravstvenim kadrom koji se javljaju u procesu ostvarivanja univerzalne pokrivenosti zdravstvenom zaštitom u Angoli.

Materijali i metode: Izvršen je narativni pregled literature zasnovan na sekundarnim izvorima, uključujući naučnu literaturu i zvanične izveštaje objavljene na engleskom i portugalskom jeziku u periodu od 2019. do 2023. godine. Podaci su prikupljeni i iz dokumenata nacionalnih i međunarodnih zdravstvenih organizacija, sa fokusom na statistiku stanovništva, zdravstvene indikatore i informacije o zdravstvenom kadru.

Rezultati: Angola ima više od 36,7 miliona stanovnika, a projekcije pokazuju da bi se taj broj mogao udvostručiti do 2050. godine. Stopa pokrivenosti uslugama zdravstvene zaštite iznosi približno 45%, što znači da oko 20 miliona ljudi nema osnovni pristup zdravstvenoj zaštiti. Kada je reč o zdravstvenim indikatorima, 15% stanovništva ima katastrofalne zdravstvene troškove, a 30% živi u ekstremnom siromaštvu. Očekivani životni vek pri rođenju je 62,1 godina (2021.). Incidencija tuberkuloze dostigla je 339 slučajeva na 100.000 stanovnika, u 2023. godini, dok je incidencija malarije iznosila 235,9 slučajeva na 1.000 stanovnika, u 2022. godini. Smrtnost dece mlađe od pet godina iznosila je 66,87 na 1.000 živorođene dece, a neonatalna smrtnost je bila 26,03 na 1.000 živorođene dece, u istoj godini. Maternalna smrtnost iznosila je 221,9 na 100.000 živorođenih beba, u 2020. godini. Glavni uzroci smrti u 2021. godini su bile respiratorne infekcije, malarija i tuberkuloza. Očekuje se da će do 2025. godine, 1,6 miliona ljudi više imati bolje zdravstveno stanje, a 2,7 miliona više će biti pokriveno uslugama osnovne zdravstvene zaštite, u poređenju sa 2018. godinom. U 2021. godini, nacionalna zdravstvena mreža sastojala se od 6.930 ustanova (3.162 javnih i 3.768 privatnih zdravstvenih ustanova) i više od 100.000 zdravstvenih radnika, uključujući 7.716 lekara, 51.216 medicinskih sestara i 12.177 tehničara. Gustina raspoređenosti zdravstvenog kadra na 10.000 stanovnika je bila: 2,48 lekara, 16,45 sestara i 3,91 tehničar.

Zaključak: Univerzalna pokrivenost zdravstvenom zaštitom u Angoli ne može se postići bez značajnih i stalnih ulaganja u obrazovanje, zadržavanje i pravičnu raspodelu zdravstvenih radnika. Neophodno je obezbediti prisustvo ovih stručnjaka u urbanim i ruralnim područjima, kao i u ekonomski ugroženim regionima. Jačanje upravljanja ljudskim resursima je od ključnog značaja za rešavanje zdravstvenih i društvenih izazova u zemlji.

Cljučne reči: upravljanje, ljudski resursi u zdravstvu, univerzalna pokrivenost zdravstvenom zaštitom, Angola

ABSTRACT

Introduction: Human resource management in health is essential to achieving universal health coverage, particularly in countries facing significant structural challenges, such as Angola.

Study aim: This study aims to describe the challenges in managing the health workforce for universal health coverage in Angola.

Materials and methods: A narrative literature review was conducted using secondary sources, including scientific literature and official reports published in English and Portuguese between 2019 and 2023. Data were collected from documents issued by national and international health organizations, focusing on population statistics, health indicators, and information regarding the health workforce.

Results: Angola has a population of over 36.7 million, which is projected to double by 2050. The health service coverage rate is approximately 45%, leaving about 20 million people without basic access. In terms of health indicators, 15% of the population faces catastrophic health expenditures, while 30% live in extreme poverty. In 2021, life expectancy at birth was 62.1 years. In 2023, tuberculosis incidence reached 339 cases per 100,000 inhabitants, while in 2022, malaria incidence was 235.9 cases per 1,000 inhabitants. Under-five mortality was 66.87 per 1,000 live births in 2022, and neonatal mortality was 26.03 per 1,000 live births in the same year. Maternal mortality stood at 221.9 per 100,000 live births in 2020. The main causes of death in 2021 were respiratory infections, malaria, and tuberculosis. By 2025, it is estimated that 1.6 million more people will have better health conditions, and 2.7 million more people will be covered by essential health services, as compared to 2018. In 2021, the national health network comprised 6,930 facilities (3,162 public and 3,768 private healthcare facilities) and more than 100,000 health professionals, including 7,716 physicians, 51,216 nurses, and 12,177 technologists. The density of healthcare workers per 10,000 inhabitants was 2.48 doctors, 16.45 nurses, and 3.91 technologists.

Conclusions: Universal health coverage in Angola cannot be achieved without significant and sustained investment in the training, retention, and equitable distribution of health professionals. It is essential to ensure the presence of these professionals in both urban and rural areas, as well as in economically disadvantaged regions. Strengthening human resource management is crucial to addressing the country's health and social challenges.

Keywords: management, human resources for health, universal health coverage, Angola

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RESUMO

Introdução: gestão de recursos humanos em saúde é essencial para alcançar a cobertura universal de saúde, especialmente em países que enfrentam desafios estruturais significativos, como Angola.

Objetivos: Este estudo tem como objetivo descrever os desafios na gestão da força de trabalho em saúde para a cobertura universal de saúde em Angola.

Métodos: Foi realizada uma revisão narrativa com base em fontes secundárias, incluindo literatura científica e relatórios oficiais publicados em inglês e português entre 2019 e 2023. Os dados foram coletados a partir de documentos emitidos por organizações nacionais e internacionais de saúde, com foco em estatísticas populacionais, indicadores de saúde e informações sobre a força de trabalho em saúde.

Resultados: Angola possui uma população de mais de 36,7 milhões de habitantes, com projeções que indicam a duplicação desse número até 2050. A taxa de cobertura dos serviços de saúde é de aproximadamente 45%, deixando cerca de 20 milhões de pessoas sem acesso básico. Em relação aos indicadores de saúde, 15% da população enfrenta gastos catastróficos com saúde, e 30% vive em extrema pobreza. A expectativa de vida ao nascer era de 62,1 anos em 2021. A incidência de tuberculose alcançou 339 casos por 100.000 habitantes em 2023, enquanto a malária teve uma incidência de 235,9 casos por 1.000 habitantes em 2022. A mortalidade em menores de cinco anos foi de 66,87 por 1.000 nascidos vivos e a mortalidade neonatal foi de 26,03 por 1.000 nascidos vivos, ambas em 2022. A mortalidade materna foi de 221,9 por 100.000 nascidos vivos em 2020. As principais causas de morte em 2021 foram infecções respiratórias, malária e tuberculose. Até 2025, estima-se que 1,6 milhão de pessoas terão melhores condições de saúde e que 2,7 milhões estarão cobertas por serviços essenciais de saúde, em comparação com 2018. Em 2021, a rede nacional de saúde era composta por 6.930 unidades (3.162 públicas e 3.768 privadas) e mais de 100.000 profissionais de saúde, incluindo 7.716 médicos, 51.216 enfermeiros e 12.177 técnicos. A densidade por 10.000 habitantes era de 2,48 médicos, 16,45 enfermeiros e 3,91 técnicos.

Conclusões: A cobertura universal de saúde em Angola não pode ser alcançada sem investimentos significativos e sustentados na formação, retenção e distribuição equitativa de profissionais de saúde. É essencial garantir a presença desses profissionais tanto em áreas urbanas quanto rurais, e em regiões economicamente desfavorecidas. O fortalecimento da gestão de recursos humanos é crucial para enfrentar os desafios sociais e de saúde do país.

Palavras-chave: gestão, recursos humanos em saúde, cobertura universal de saúde, Angola

UVOD

Univerzalna pokrivenost zdravstvenom zaštitom (UPZ) jedan je od glavnih globalnih ciljeva definisanih u okviru Ciljeva održivog razvoja (COR) Ujedinjenih nacija, posebno u okviru COR 3, koji teži da obezbedi zdrav život i promoviše dobrobit za sve ljude, u svim životnim dobima. UPZ podrazumeva pravičan pristup kvalitetnim zdravstvenim uslugama, pri čemu pojedinci ne trpe finansijske teškoće. Da bi se ovaj cilj ostvario, neophodno je postojanje dovoljnog broja ravnomerno raspoređenog kvalifikovanog zdravstvenog kadra [1].

Međutim, mnogi zdravstveni sistemi širom sveta – kako u razvijenim, tako i u zemljama u razvoju – suočavaju se sa ozbiljnim izazovima u upravljanju ljudskim resursima u zdravstvu. Povećana potražnja za zdravstvenim uslugama, u kombinaciji sa budžetskim ograničenjima i neefikasnim modelima upravljanja, dovela je do značajnog nedostatka kadrova u različitim kontekstima [2]. Svetska zdravstvena organizacija (SZO) procenjuje da će, do 2030. godine, svetu nedostajati između 10 i 15 miliona zdravstvenih radnika [1,2]. Međunarodni centar za migraciju medicinskih sestara (engl. *International Centre on Nurse Migration – ICNM*) predviđa manjak od 13 miliona medicinskih sestara u istom periodu [3]. Ovaj nedostatak ne pogađa samo zemlje sa niskim prihodima. U Evropi, na primer, 18 od 30 zemalja je prijavilo manjak medicinskih sestara, dok je 13 zemalja prijavilo deficit lekara opšte prakse [4].

Nedavna istraživanja pokazuju da će biti potrebno dodatnih 43 miliona zdravstvenih radnika – 31 milion medicinskih sestara i više od 6 miliona lekara – kako bi se ostvarila univerzalna pokrivenost zdravstvenom zaštitom na globalnom nivou [4]. Najveći nedostaci kon-

INTRODUCTION

Universal Health Coverage (UHC) is one of the main global goals defined within the United Nations Sustainable Development Goals (SDGs), specifically within SDG 3, which aims to ensure healthy living and promote well-being for all people at all ages. UHC implies equitable access to quality health services without financial hardship for individuals. To achieve this goal, it is essential to have a sufficient number of evenly distributed qualified health workers [1].

However, many health systems around the world, both in developed and developing countries, are facing serious challenges in managing human resources in healthcare. The growing demand for health services, combined with budget constraints and inefficient management models, has led to a significant workforce shortage in various contexts [2]. The World Health Organization (WHO) estimates that by 2030, there will be a global shortage of between 10 and 15 million health workers [1,2]. The International Centre on Nurse Migration (ICNM) predicts a shortage of 13 million nurses during the same period [3]. This shortage does not affect only low-income countries. In Europe, for example, 18 out of 30 countries have reported a shortage of nurses, while 13 countries have reported a deficit of general practitioners [4].

Recent studies have shown that an additional 43 million health workers – 31 million nurses and over 6 million doctors – will be needed, in order to achieve universal coverage globally [4]. The most severe shortages have been recorded in Sub-Saharan Africa, South-east Asia, North Africa, and the Middle East. Currently, more than 130 countries face a shortage of doctors,

centrisani su u Podsaharskoj Africi, Jugoistočnoj Aziji, Severnoj Africi i na Bliskom Istoku. Trenutno više od 130 zemalja ima manjak lekara, a više od 150 suočava se sa deficitom medicinskih sestara [4]. Međunarodna konkurencija u potražnji zdravstvenih radnika dodatno otežava njihovo zadržavanje u zemljama sa niskim prihodima, naročito zbog migracije u razvijene zemlje koje nude bolje uslove rada i višu zaradu [5,6]. Ovu situaciju dodatno komplikuju finansijski izazovi sa kojima se suočavaju mnogi javni zdravstveni sistemi koji nisu u mogućnosti da obezbede adekvatne uslove rada, što utiče na motivaciju i zadržavanje zdravstvenih radnika [5].

Problemi nedostatka zdravstvenog kadra i lošeg upravljanja ovim resursom su česti, kako u razvijenim tako i u zemljama u razvoju, s tendencijom pogoršanja u narednim godinama, što zahteva inovativna i fleksibilna rešenja [7].

U kontekstu Angole, ovi izazovi su još izraženiji. Angola, zemlja u Podsaharskoj Africi sa oko 36,7 miliona stanovnika, suočava se sa dubokim regionalnim nejednakostima u pristupu zdravstvenim uslugama i raspodeli zdravstvenih radnika [4,8]. Pokrivenost zdravstvenim uslugama i dalje je ograničena, a zdravstveni indikatori ukazuju na visoke stope smrtnosti majki, dece i smrti koje se mogu sprečiti. Zdravstveni sistem Angole ima ozbiljne poteškoće zbog nedostatka kvalifikovanih kadrova, kako po broju, tako i po stručnosti, što ugrožava kapacitet sistema da odgovori na osnovne potrebe stanovništva.

Prema podacima Ministarstva zdravlja (port. *Ministério da Saúde da República de Angola – MINSA*), Angola beleži značajan deficit zdravstvenih radnika u poređenju sa međunarodnim standardima, što pogađa sve provincije [9]. Primer za to je provincija Kabinda, gde je odnos medicinskih sestara prema lekarima 8,6 prema 1 [9,10].

Ova situacija je prepoznata u Nacionalnom planu razvoja zdravstva (pt. *Plano Nacional de Desenvolvimento Sanitário – PNDS*) (2012–2025), koji ističe nedostatak ljudskih resursa kao faktor rizika za održivost sistema. Kao odgovor, Nacionalni program za upravljanje ljudskim resursima u zdravstvu definisao je strategije kao što su jačanje upravljanja i planiranja, unapređenje raspodele i obuke (osnovne i kontinuirane) zdravstvenih radnika i razvoj veština rukovođenja [11]. Ipak, efikasnost ovih mera je ograničena zbog niskih plata, nedostatka podsticaja i neprivlačnih uslova rada.

Godine 2012, samo 44,6% stanovništva je imalo stalni pristup zdravstvenim uslugama, dok je 2017. godine taj broj iznosio tek polovinu ukupnog stanovništva [8,9,11]. Iako su zabeleženi pomaci u pogledu infrastrukture i stručnog obrazovanja, neujednačena distribucija lekara, medicinskih sestara i tehničara, kao i teškoće u njihovom zadržavanju u ruralnim i udaljenim

and over 150 are experiencing a deficit of nurses [4]. International competition for health workers further complicates retention in low-income countries, particularly due to migration to developed nations offering better working conditions and higher salaries [5,6]. This situation is further exacerbated by financial challenges faced by many public health systems, which are often unable to provide adequate working conditions. This, consequently, impacts both the motivation and retention of health workers [5].

The issues of health workforce shortages and poor management of this resource are common in both developed and developing countries, with a tendency to worsen in the coming years, which calls for innovative and flexible solutions [7].

In the context of Angola, these challenges are even more pronounced. Angola, a Sub-Saharan African country with a population of approximately 36.7 million, faces deep regional inequalities regarding access to health services and the distribution of health workers [4,8]. Health services coverage remains limited, and health indicators show high rates of maternal and child mortality, as well as high rates of preventable deaths. Angola's health system is struggling due to a shortage of qualified personnel, both in terms of numbers and expertise, which undermines the system's capacity to meet the basic needs of the population.

According to data provided by the Ministry of Health (Pt. *Ministério da Saúde da República de Angola – MINSA*), Angola is experiencing a significant shortage of health workers in all its provinces, as compared to international standards [9]. An example of this is the province of Cabinda, where the nurse-to-doctor ratio is 8.6 to 1 [9,10].

This situation has been recognized by the National Health Development Plan (Pt. *Plano Nacional de Desenvolvimento Sanitário – PNDS*) (2012–2025), which highlights the shortage of human resources as a risk factor for the sustainability of the system. In response, the Human Resources for Universal Health Coverage in Angola program has defined strategies, including strengthening management and planning, improving the distribution and training (both basic and continuous) of health workers, and developing leadership skills [11]. However, the effectiveness of these measures is limited due to low salaries, lack of incentives, and unattractive working conditions.

In 2012, only 44.6% of the population had regular access to health services, while in 2017, this was true for only half of the total population [8,9,11]. Although there has been progress in terms of infrastructure and professional training, the uneven distribution of doctors, nurses, and technologists, as well as the difficulties in retaining medical professionals in rural and re-

oblastima, i dalje su ozbiljna prepreka za postizanje univerzalne pokrivenosti zdravstvenom zaštitom u Angoli.

Cilj ovog rada je da opiše izazove u upravljanju zdravstvenim kadrovima u kontekstu ostvarivanja univerzalne pokrivenosti zdravstvenom zaštitom u Angoli.

MATERIJALI I METODE

Ova studija predstavlja narativni, deskriptivni pregled literature, zasnovan na analizi sekundarnih podataka preuzetih iz naučne literature i zvaničnih dokumenata, sa ciljem da opiše izazove u upravljanju zdravstvenim kadrom koji se javljaju u procesu ostvarivanja univerzalne pokrivenosti zdravstvenom zaštitom u Angoli.

Pretraživanje dokumenata sprovedeno je između februara i aprila 2025. godine, korišćenjem baza podataka *PubMed*, *SciELO* i *Google Scholar*, kao i institucionalnih portala Svetske zdravstvene organizacije (<https://data.who.int/countries/024>) i regionalne AFRO i AHO baze (<https://aho.afro.who.int/data-and-statistics/af>). Takođe su konsultovani dokumenti Ministarstva zdravlja Angole (*MINSA*) i Nacionalnog instituta za statistiku (pt. *Instituto Nacional de Estatística – INE*).

U sklopu strategije pretraživanja, primenjeni su deskriptori na portugalskom i engleskom jeziku, koji su kombinovani pomoću Bulovih operatora, a uključivali su termine: *human resources in health*, *health workforce*, *health workers*, *health governance*, *universal health coverage*, *health system Angola*, *gestão de recursos humanos em saúde* i *cobertura universal de saúde Angola*¹.

U pregled literature su uključeni dokumenti objavljeni između 2019. i 2024. godine, na portugalskom ili engleskom jeziku, koji se direktno bave upravljanjem ljudskim resursima u zdravstvu u kontekstu univerzalne pokrivenosti zdravstvenom zaštitom u Angoli ili u zemljama sa sličnim socioekonomskim uslovima. Isključeni su dokumenti koji nisu bili direktno relevantni za datu temu ili nisu bili iz priznatih institucionalnih izvora.

Podaci su organizovani na osnovu kompletne analize odabranih dokumenata, uz izdvajanje informacija metodom traženja podataka bez unapred definisane hipoteze (engl. *data fishing*) i uz primenu tematske kategorizacije. Analiza je sprovedena kvalitativno i deskriptivno, sa fokusom na identifikaciju obrazaca i nedostataka u vezi sa distribucijom obučenošću, zadržavanjem, i kontinuiranom edukacijom zdravstvenih radnika, kao i u vezi sa regionalnim nejednakostima i predlozima javnih politika.

1 Termini na engleskom i portugalskom imaju sledeće značenje (redom kojim su navedeni u tekstu): ljudski resursi u zdravstvu, zdravstveni kadar, zdravstveni radnici, upravljanje zdravstvom, univerzalna pokrivenost zdravstvenom zaštitom, zdravstveni sistem Angole, upravljanje ljudskim resursima u zdravstvu, univerzalna pokrivenost zdravstvenom zaštitom u Angoli (prim. prev.)

mote areas, remain significant obstacles to achieving universal health coverage in Angola.

This paper aims to describe the challenges in health workforce management in the context of achieving universal health coverage in Angola.

MATERIALS AND METHODS

This study presents a narrative, descriptive review of the literature, based on the analysis of secondary data obtained from scientific literature and official documents, with the aim of describing the challenges in health workforce management that arise in the process of achieving universal health coverage in Angola.

The document search was conducted between February and April 2025, using the *PubMed*, *SciELO*, and *Google Scholar* databases, as well as the World Health Organization institutional portals (<https://data.who.int/countries/024>) and the regional AFRO and AHO databases (<https://aho.afro.who.int/data-and-statistics/af>). Documents issued by the Ministry of Health of Angola (*MINSA*) and the National Institute of Statistics (Pt. *Instituto Nacional de Estatística – INE*) were also consulted.

As part of the search strategy, descriptors in Portuguese and English were used and were combined with Boolean operators. They included the following terms: *human resources in health*, *health workforce*, *health workers*, *health governance*, *universal health coverage*, *health system Angola*, *gestão de recursos humanos em saúde*¹, and *cobertura universal de saúde Angola*².

The literature review included documents published between 2019 and 2024, in Portuguese or English, that directly address human resources management in health in the context of universal health coverage in Angola or countries with similar socioeconomic conditions. Documents that were not directly relevant to the topic or not issued by recognized institutional sources were excluded.

The data were organized based on a comprehensive analysis of the selected documents, with information extracted using the method of data fishing (i.e., data dredging – searching for data without a predefined hypothesis) and applying thematic categorization. The analysis was conducted qualitatively and descriptively, with a focus on identifying patterns and shortcomings related to the distribution, training, retention, and continuous education of health workers, as well as regional inequalities and public policy recommendations.

The results are presented in tables and graphs. Where applicable, quantitative data from official reports are shown as mean values with a 95% confidence interval (95% CI).

1 human resources management in health

2 universal health coverage in Angola

Rezultati su predstavljeni tabelarno i grafički. Tamo gde je to primenljivo, kvantitativni podaci iz zvaničnih izveštaja prikazani su kao srednje vrednosti sa intervalom poverenja od 95% (95% CI).

REZULTATI

Godine 2023, populacija Angole procenjena je na približno 36,7 miliona, sa predviđenim rastom na 74,3 miliona do 2050. godine, uz godišnju stopu rasta od 3,8% [8].

Tabela 1. Univerzalna pokrivenost zdravstvenom zaštitom u Angoli i regionalna poređenja (2022)

Pokazatelj / Indicator	Angola / Angola (2022)	Mauricijus / Mauritius (2022)	Afrički prosek / Africa average (2022)
Indeks pokrivenosti zdravstvenim uslugama / UHC (Universal Health Coverage) service coverage index	45	91	45
Populacija bez osnovne okrivnosti zdravstvenom zaštitom / Population without basic health coverage	20 miliona / million	1 milion / million	200 miliona / million
Katastrofalni zdravstveni troškovi (%) / Catastrophic health expenditures (%)	15%	5%	20%
Populacija u ekstremnom siromaštvu (%) / Population living in extreme poverty (%)	30%	2%	30%

Izvor: World Health Organization. Angola: country profile. Geneva: WHO; 2025 [8]

Iako je Angola napravila značajan napredak u pokrivenosti zdravstvenim uslugama, ostvarivši povećanje sa 35% u 2015. godini na 45% u 2022. godini [7], ovo je i dalje slabije od Mauricijusa, koji je postigao indeks od 91.

U Angoli, oko 20 miliona ljudi još uvek nema potpunu pokrivenost osnovnim zdravstvenim uslugama, što odražava ekonomske izazove i potrebu za većim ulaganjima u sektor zdravstva. Na Mauricijusu, samo 1 milion ljudi se nalazi u ovoj situaciji, u poređenju sa 200 miliona, što se uočava u afričkom proseku.

U Angoli, 15% stanovništva se suočava sa katastrofalnim zdravstvenim troškovima, što ukazuje na to da mnogi građani Angole troše veliki deo svojih prihoda na zdravstvenu zaštitu. Na Mauricijusu taj broj je 5%, dok je afrički prosek 20%.

Oko 30% stanovništva Angole živi u ekstremnom siromaštvu. Na Mauricijusu taj broj iznosi 2%, u poređenju sa 30%, što je afrički prosek.

Podaci Svetske zdravstvene organizacije odražavaju realnost prikazanu ispod.

Pokazatelj	Vrednost
Očekivani životni vek pri rođenju (2021)	62,1 godina
Incidencija tuberkuloze (2023)	339 na 100.000 stanovnika
Incidencija malarije (2022)	235,9 na 1.000 stanovnika
Smrtnost dece (<5 godina, 2022)	66,87 na 1.000 živorođenih
Neonatalna smrtnost (2022)	26,03 na 1.000 živorođenih
Maternalna smrtnost (2020)	221,9 na 100.000 živorođenih
Glavni uzroci smrti (2021)	Donje respiratorne infekcije, malarija, tuberkuloza

Izvor: World Health Organization. Angola: country profile. Geneva: WHO; 2025 [8]

RESULTS

In 2023, the population of Angola was estimated at approximately 36.7 million, with a projected increase to 74.3 million by 2050, reflecting an annual growth rate of 3.8% [8].

Although Angola has made significant progress in health service coverage, increasing from 35% in 2015 to 45% in 2022 [7], this is still lower than Mauritius, which achieved an index of 91.

Table 1. Universal health coverage in Angola and regional comparisons (2022)

Pokazatelj / Indicator	Angola / Angola (2022)	Mauricijus / Mauritius (2022)	Afrički prosek / Africa average (2022)
Indeks pokrivenosti zdravstvenim uslugama / UHC (Universal Health Coverage) service coverage index	45	91	45
Populacija bez osnovne okrivnosti zdravstvenom zaštitom / Population without basic health coverage	20 miliona / million	1 milion / million	200 miliona / million
Katastrofalni zdravstveni troškovi (%) / Catastrophic health expenditures (%)	15%	5%	20%
Populacija u ekstremnom siromaštvu (%) / Population living in extreme poverty (%)	30%	2%	30%

Source: World Health Organization. Angola: country profile. Geneva: WHO; 2025 [8]

In Angola, around 20 million people still lack full coverage of basic health services, reflecting economic challenges and the need for greater investment in the health sector. In Mauritius, only 1 million people are in this situation, compared to 200 million, which is the African average.

In Angola, 15% of the population faces catastrophic health expenditures, indicating that many Angolan citizens spend a large portion of their income on healthcare. In Mauritius, this figure is 5%, while the African average is 20%.

About 30% of Angola's population lives in extreme poverty. In Mauritius, that number is 2%, compared to 30%, which is the African average.

World Health Organization data reflect the reality shown below.

Indicator	Value
Life expectancy at birth (2021)	62.1 years
Incidence of tuberculosis (2023)	339 per 100,000 population
Incidence of malaria (2022)	235.9 per 1,000 population
Child mortality (<5 years, 2022)	66.87 per 1,000 live births
Neonatal mortality (2022)	26.03 per 1,000 live births
Maternal mortality (2020)	221.9 per 100,000 live births
Main causes of death (2021)	Lower respiratory tract infections, malaria, and tuberculosis

Source: World Health Organization. Angola: country profile. Geneva: WHO; 2025 [8]

In Angola, life expectancy at birth increased by 12.8 years, from 49.4 (48.2–50.4) years in 2000 to 62.1

U Angoli, očekivani životni vek pri rođenju je produžen za 12,8 godina, sa 49,4 (48,2–50,4) godina, u 2000. godini, na 62,1 (61,2–63,1) godina, u 2021. godini. U Africi, očekivani životni vek pri rođenju je produžen za 10,6 godina, sa 53 (52,1–53,8) godina, u 2000. godini, na 63,6 (62,6–64,6) godina, u 2021. godini [8].

Incidencija tuberkuloze u Angoli je iznosila 339 na 100.000 stanovnika u 2023. godini, dok je incidencija malarije bila oko 235,9 na 1.000 stanovnika u 2022. godini.

Stopa smrtnosti dece (< 5 godina) u Angoli je iznosila 66,87 na 1.000 živorođene dece u 2022. godini, dok je stopa neonatalne smrtnosti bila 26,03 na 1.000 živorođene dece.

Maternalna smrtnost u Angoli je značajno smanjena, sa 827 smrti na 100.000 živorođenih, u 2000. godini, na 241 smrt na 100.000 živorođenih, u 2017. godini, što odražava značajan napredak [8]. Međutim, maternalna smrtnost i dalje predstavlja ozbiljan problem, sa 221,9 smrti na 100.000 živorođenih, zabeleženih u 2020. godini.

Vodeći uzroci smrti u Angoli uključuju donje respiratorne infekcije, malariju i tuberkulozu.

U Angoli, broj dodatnih ljudi koji bi trebalo da imaju bolje zdravlje i veće blagostanje procenjuje se na

(61.2–63.1) years in 2021. In Africa, life expectancy at birth increased by 10.6 years, from 53 (52.1–53.8) years in 2000 to 63.6 (62.6–64.6) years in 2021 [8].

The incidence of tuberculosis in Angola was 339 per 100,000 population in 2023, while the incidence of malaria was around 235.9 per 1,000 population in 2022.

The under-five mortality rate in Angola was 66.87 per 1,000 live births in 2022, while the neonatal mortality rate was 26.03 per 1,000 live births.

Maternal mortality in Angola was significantly reduced from 827 deaths per 100,000 live births in 2000 to 241 deaths per 100,000 live births in 2017, reflecting significant progress [8]. However, maternal mortality remains a serious issue, with 221.9 deaths per 100,000 live births recorded in 2020.

The leading causes of death in Angola include lower respiratory tract infections, malaria, and tuberculosis.

In Angola, the number of additional people expected to experience improved health and well-being is estimated at -1.6 million (-7.3 million – 2.8 million) by 2025, as compared to 2018 [8].

In Angola, the number of additional people expected to be covered by basic health services and protected from financial hardship is estimated at 2.7

Tabela 2. Zdravstvene ustanove nacionalne zdravstvene službe po provincijama i po vrstama, 2021.

Provincije / Provinces	Centri za majku i dete / Mother and child facilities	Zdravstvene stanice / Primary health care units	Domovi zdravlja / Community health care centers	Opštinske bolnice / Municipal hospitals	Opšte bolnice / General hospitals	Specijalizovane bolnice / Specialized hospitals	Centralne bolnice / Central hospitals	Ukupno / Total
Bengo / Bengo	1	69	18	7	1	1	0	97
Benguela / Benguela	6	133	74	12	1	1	0	227
Bie / Bié	5	127	37	9	1	0	1	180
Kabinda / Cabinda	1	76	19	8	1	1	0	106
Kvando Kubango / Cuando Cubango	1	83	20	6	1	1	0	105
Severna Kvanza / North Cuanza	1	99	30	6	1	1	0	129
Južna Kvanza / South Cuanza	8	247	30	12	1	2	0	300
Kunene / Cunene	1	107	28	6	1	0	0	143
Huambo / Huambo	14	168	51	13	2	0	0	248
Huíla / Huíla	7	191	56	13	1	4	0	272
Luanda / Luanda	18	285	77	15	2	12	12	421
Severna Lunda / North Lunda	5	72	29	9	1	0	0	116
Južna Lunda / South Lunda	2	77	14	6	1	3	0	103
Malanže / Malanje	4	129	26	10	1	0	0	170
Mošiko / Moxico	7	102	28	6	1	3	0	147
Namibe / Namibe	8	86	25	6	1	0	0	126
Ujiže / Uíge	20	268	34	15	1	2	0	340
Zaire / Zaire	4	69	34	10	1	2	0	120
Ukupno / Total	105	2,183	644	167	18	32	13	3,162

Izvor: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Table 2. National health service facilities by province and type, 2021

Provincije / Provinces	Centri za majku i dete / Mother and child facilities	Zdravstvene stanice / Primary health care units	Domovi zdravlja / Community health care centers	Opštinske bolnice / Municipal hospitals	Opšte bolnice / General hospitals	Specijalizovane bolnice / Specialized hospitals	Centralne bolnice / Central hospitals	Ukupno / Total
Bengo / Bengo	1	69	18	7	1	1	0	97
Benguela / Benguela	6	133	74	12	1	1	0	227
Bie / Bié	5	127	37	9	1	0	1	180
Kabinda / Cabinda	1	76	19	8	1	1	0	106
Kvando Kubango / Cuando Cubango	1	83	20	6	1	1	0	105
Severna Kvanza / North Cuanza	1	99	30	6	1	1	0	129
Južna Kvanza / South Cuanza	8	247	30	12	1	2	0	300
Kunene / Cunene	1	107	28	6	1	0	0	143
Huambo / Huambo	14	168	51	13	2	0	0	248
Huíla / Huíla	7	191	56	13	1	4	0	272
Luanda / Luanda	18	285	77	15	2	12	12	421
Severna Lunda / North Lunda	5	72	29	9	1	0	0	116
Južna Lunda / South Lunda	2	77	14	6	1	3	0	103
Malanže / Malanje	4	129	26	10	1	0	0	170
Mošiko / Moxico	7	102	28	6	1	3	0	147
Namibe / Namibe	8	86	25	6	1	0	0	126
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Zaire / Zaire	4	69	34	10	1	2	0	120
Ukupno / Total	105	2,183	644	167	18	32	13	3,162

Source: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

-1,6 miliona (-7,3 miliona – 2,8 miliona) do 2025. godine, u poređenju sa 2018. godinom [8].

U Angoli, broj dodatnih ljudi koji bi trebalo da budu pokriveni osnovnim zdravstvenim uslugama i koji ne bi prolazili kroz finansijske poteškoće procenjuje se na 2,7 miliona (1,5 miliona – 3,8 miliona) do 2025. godine, u poređenju sa 2018. godinom [8].

Zdravstvena mreža Angole

Dostupni podaci su 2019. godine su pokazivali ukupno 2.793 javne zdravstvene ustanove u zemlji [9,11]. Do 2021. godine, taj broj se povećao na 3.162 javne zdravstvene ustanove [12], sa raspodelom kakva je prikazana u Tabeli 2.

Prema podacima Nacionalnog instituta za statistiku (2024), mrežu zdravstvenog sektora čine 3.162 zdravstvene ustanove koje su u funkciji, uključujući 13 nacionalnih bolnica, 32 specijalizovane bolnice, 18 opštih bolnica, 167 opštinskih bolnica, 105 centara za majku i dete, kao i 3.768 privatnih zdravstvenih ustanova.

Zdravstveni kadar

Prema podacima SZO, Angola je među zemljama koja ima više od 100.000 zdravstvenih radnika, uključujući lekare, medicinske sestre, babice, farmaceute i druge radnike. Međutim, ovaj broj je i dalje niži od onog za-

million (1.5 million – 3.8 million) by 2025, as compared to 2018 [8].

Healthcare network of Angola

In 2019, available data showed a total of 2,793 public health facilities in the country [9,11]. By 2021, that number had increased to 3,162 public health facilities [12], with a distribution as shown in Table 2.

According to data from the National Institute of Statistics (2024), the healthcare sector network consists of 3,162 operational health facilities, including 13 national hospitals, 32 specialized hospitals, 18 general hospitals, 167 municipal hospitals, 105 mother and child centers, as well as 3,768 private health-care facilities.

Health workforce

According to WHO data, Angola is among the countries with more than 100,000 health workers, including doctors, nurses, midwives, pharmacists, and other personnel. However, this number is still lower than that recorded in five countries in the African region with a higher number of health workers: Nigeria (940,193), South Africa (456,042), Algeria (329,494), Ethiopia (250,893), and the Democratic Republic of the Congo (224,002) [13,14].

Tabela 3. Privatne zdravstvene ustanove registrovane u zemlji, po provincijama, 2021.

Provincije / Provinces	Klinike / Clinics	Medicinski centri / Medical centers	Ordinacije / Medical practices	Specijalizovane ordinacije / Specialized medical practices	Laboratorije / Laboratories	Sestrinske stanice / Nursing stations	Ukupno / Total
Bengo / Bengo	1	7	1	0	5	7	21
Benguela / Benguela	8	79	11	10	33	57	198
Bie / Bie	1	4	4	0	0	31	38
Kabinda / Cabinda	8	127	1	7	15	28	186
Kvando Kubango / Cuando Cubango	0	17	3	0	0	40	60
Severna Kvanza / North Cuanza	0	17	3	0	0	23	43
Južna Kvanza / South Cuanza	3	48	22	0	3	54	130
Kunene / Cunene	0	28	7	1	1	12	27
Huambo / Huambo	17	28	10	3	2	118	178
Huíla / Huíla	15	76	7	16	15	102	231
Luanda / Luanda	94	998	371	200	108	420	2,191
Severna Lunda / North Lunda	4	14	0	0	0	97	115
Južna Lunda / South Lunda	2	14	7	0	0	18	41
Malanže / Malanje	0	9	0	0	3	14	25
Mošiko / Moxico	1	9	1	0	1	79	91
Namibe / Namibe	1	6	18	4	2	8	39
Ujiže / Uíge	3	23	9	2	0	40	77
Zaire / Zaire	1	29	5	0	0	42	77
Ukupno / Total	159	1,510	478	243	188	1,190	3,768

Izvor: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Table 3. Private healthcare facilities registered in the country, by province, 2021

Source: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Tabela 4. Raspodela lekara, medicinskih sestara, dijagnostičkih/terapeutskih tehničara, administrativnog osoblja i ostalih radnika u javnom zdravstvenom sektoru, po provincijama, 2021.

Table 4. Distribution of doctors, nurses, diagnostic/therapeutic technicians, administrative staff, and other workers in the public health sector, by province, 2021

Provincije / Provinces	Lekari / Doctors	Medicinske sestre / Nurses	Dijagnostički/ Terapeutski tehničari / Diagnostic/Therapeutic Technologists	Administrativni radnici / Administrative staff	Ostali radnici / Other	Ukupno / Total
Stopa na 10.000 stanovnika / Rate per 10,000 population						
Bengo / Bengo	3.07	23.41	6.70	4.43	7.50	45.11
Benguela / Benguela	1.70	15.28	2.49	3.67	3.08	26.22
Bie / Bié	1.61	15.33	1.61	2.52	7.82	28.89
Kabinda / Cabinda	2.45	14.15	2.79	4.79	7.65	31.83
Kvando Kubango / Cuando Cubango	1.97	15.25	3.81	8.77	6.58	36.38
Severna Kvanza / North Cuanza	2.38	20.17	3.91	10.24	13.53	50.23
Južna Kvanza / South Cuanza	0.63	8.40	1.06	3.80	6.39	20.28
Kunene / Cunene	1.17	10.05	2.44	5.99	2.38	22.03
Huambo / Huambo	1.63	16.93	2.16	4.81	4.66	30.18
Huíla / Huíla	1.13	6.81	1.60	2.96	2.47	14.97
Luanda / Luanda	0.79	7.56	2.34	2.20	5.37	18.26
Severna Lunda / North Lunda	1.56	12.02	1.61	5.17	7.59	27.95
Južna Lunda / South Lunda	1.73	14.84	2.23	6.33	5.18	30.30
Malanže / Malange	2.09	16.57	3.21	2.30	8.29	32.46
Mošiko / Moxico	1.30	17.30	2.53	4.22	5.75	31.10
Namibe / Namibe	2.28	20.49	7.94	7.72	4.98	43.41
Uíje / Uíge	1.47	7.60	1.37	3.61	3.85	17.90
Zaire / Zaire	2.04	12.69	2.36	3.94	5.19	26.22
Centralna uprava (pt. Órgão Central) / Central authority (Pt. Órgão Central)	1.64	4.73	2.06	2.05	3.14	13.63
Ukupno / Total	1.80	12.85	2.90	4.29	6.15	28.00

Izvor: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Source: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

beleženog u pet zemalja u Afričkom regionu sa većim brojem zdravstvenih radnika: Nigerija (940.193), Južna Afrika (456.042), Alžir (329.494), Etiopija (250.893) i Demokratska Republika Kongo (224.002) [13,14].

Angola je 2011. godine imala 3.541 doktora, 34.301 medicinsku sestru, 6.414 tehničara (dijagnostički ili terapeutski tehničari) i 9.640 drugih radnika u zdravstvu (administrativni radnici, radnici na održavanju čistoće, i dr.) [15]. Do 2021. godine, kao što prikazuju tabele u nastavku teksta, ovi brojevi su značajno porasli, dostigavši 7.716 lekara, 51.216 medicinskih sestara, 12.177 tehničara i 47.577 ostalih radnika (administrativni radnici, radnici na održavanju čistoće, i dr.) [12].

U pogledu zdravstvenih ljudskih resursa koji direktno pružaju usluge, na 10.000 stanovnika dolazi 2,48 lekara – od čega je 72,72% iz javnog sektora, 12,97 iz privatnog sektora i 14,31 iz ostalih sektora (Nacionalna policija Angole (pt. *Polícia Nacional de Angola*), Oružane snage Angole (pt. *Forças Armadas Angolanas*), nevladi-

In 2011, Angola had 3,541 doctors, 34,301 nurses, 6,414 technologists (diagnostic or therapeutic technologists), and 9,640 other health workers (administrative staff, cleaners, etc.) [15]. By 2021, as shown in the tables below, these numbers had increased significantly, reaching 7,716 doctors, 51,216 nurses, 12,177 technologists, and 47,577 other workers (administrative staff, janitorial staff, etc.) [12].

In terms of human resources directly providing services in healthcare, there are 2.48 doctors per 10,000 inhabitants, of whom 72.72% are from the public sector, 12.97% from the private sector, and 14.31% from other sectors (the National Police of Angola (pt. *Polícia Nacional de Angola*), the Armed Forces of Angola (pt. *Forças Armadas Angolanas*), and non-governmental organizations). Additionally, there are 16.45 nurses and 3.91 diagnostic/therapeutic technicians per 10,000 inhabitants [12].

Tabela 5. Raspodela lekara, medicinskih sestara, dijagnostičkih/terapeutskih tehničara, administrativnog osoblja i ostalih radnika u privatnom zdravstvenom sektoru, po provincijama, 2021.

Table 5. Distribution of doctors, nurses, diagnostic/therapeutic technicians, administrative staff, and other workers in the private health sector, by province, 2021

Provincije / Provinces	Lekari / Doctors	Medicinske sestre / Nurses	Dijagnostički/ Terapeutski tehničari / Diagnostic/Therapeutic Technologists	Administrativni radnici / Administrative staff	Ostali radnici / Other	Ukupno / Total
Stopa na 10.000 stanovnika / Rate per 10,000 population						
Bengo / Bengo	0.04	2.14	0.52	0.99	2.18	5.88
Benguela / Benguela	0.51	2.15	0.49	0.86	0.61	4.63
Bie / Bié	0.05	1.25	0.05	0.15	1.14	2.64
Kvando Kubango / Cuando Cubango	0.03	0.28	0.02	0.05	0.05	0.44
Severna Kvanza / North Cuanza	0.32	2.18	0.62	0.81	1.63	5.56
Južna Kvanza / South Cuanza	0.15	1.32	0.45	0.34	0.34	2.76
Huambo / Huambo	0.07	0.52	0.23	0.57	0.38	1.76
Huíla / Huíla	0.3	0.57	0.48	0.06	0.02	1.42
Luanda / Luanda	0.58	1.12	0.47	0.71	1.03	3.88
Južna Lunda / South Lunda	0.18	0.63	0.37	0.42	0.30	1.89
Malanže / Malange	0.16	0.61	0.56	0.43	0.53	2.29
Mošiko / Moxico	0.17	1.71	0.23	0.87	0.00	2.97
Namibe / Namibe	0.06	0.17	0.14	0.20	0.26	0.83
Ujiže / Uíge	0.26	3.36	0.50	0.47	1.48	6.07
Zaire / Zaire	0.43	3.33	0.44	1.54	0.28	6.02
Ukupno / Total	0.36	1.32	0.44	0.60	0.88	3.60

Izvor: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Source: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

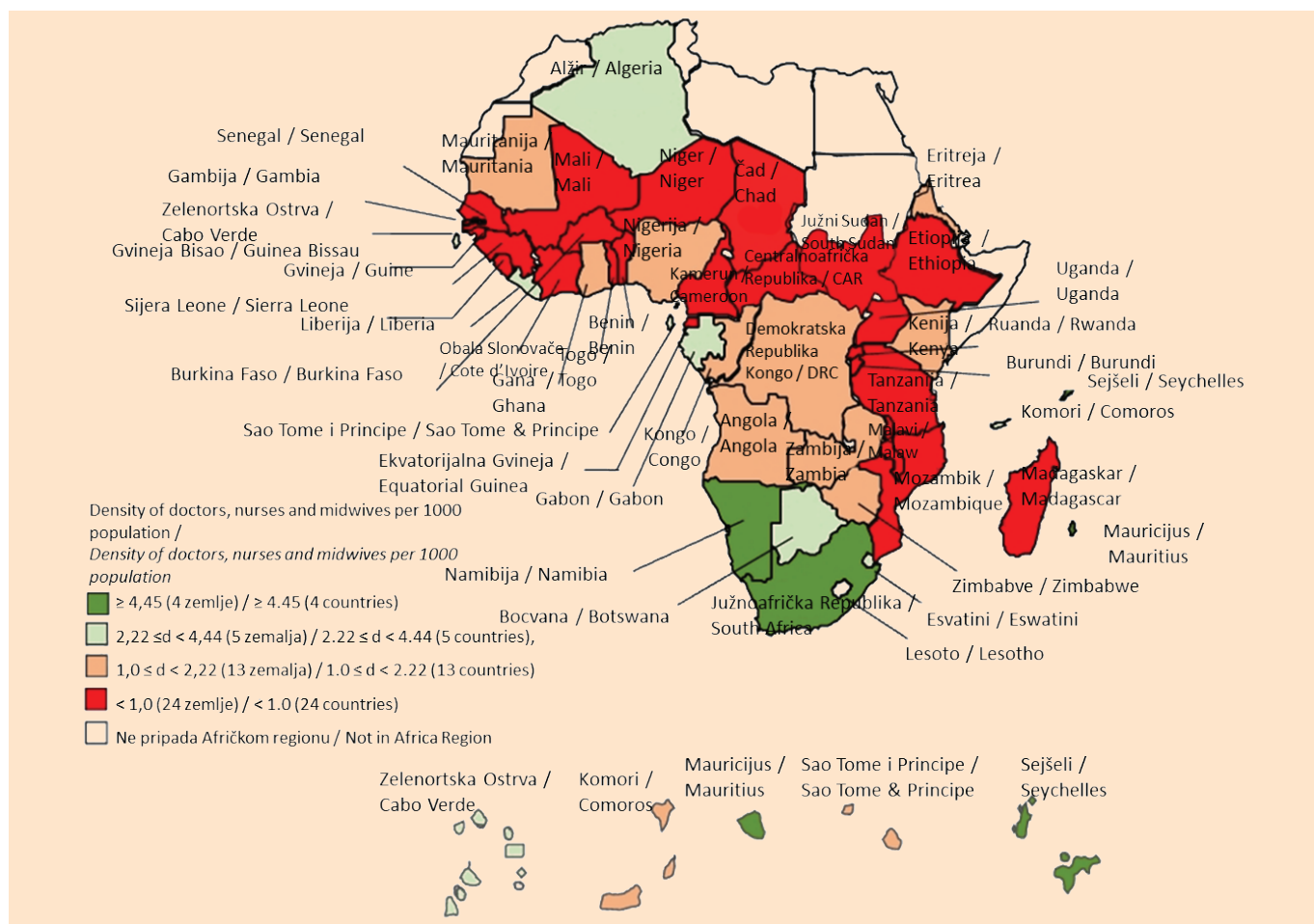
Tabela 6. Raspodela lekara, medicinskih sestara, dijagnostičkih/terapeutskih tehničara, administrativnog osoblja i ostalih radnika u drugim sektorima (Nacionalna policija Angole, Oružane snage Angole, nevladine organizacije), po provincijama, 2021.

Table 6. Distribution of doctors, nurses, diagnostic/therapeutic technicians, administrative staff, and other workers in other sectors (National Police of Angola, Armed Forces of Angola, NGOs), by province, 2021

Provincije / Provinces	Lekari / Doctors	Medicinske sestre / Nurses	Dijagnostički/ Terapeutski tehničari / Diagnostic/Therapeutic Technologists	Administrativni radnici / Administrative staff	Ostali radnici / Other	Ukupno / Total
Stopa na 10.000 stanovnika / Rate per 10,000 population						
Bengo / Bengo	0.09	0.09	0.09	0.09	0.09	0.43
Benguela / Benguela	0.02	0.60	0.09	0.19	0.13	1.03
Bie / Bié	0.01	0.28	0.00	0.32	0.87	1.47
Kvando Kubango / Cuando Cubango	0.17	4.45	0.19	0.13	1.05	5.98
Severna Kvanza / North Cuanza	0.02	0.41	0.08	0.13	0.36	1.00
Južna Kvanza / South Cuanza	0.02	0.41	0.08	0.13	0.36	1.00
Huambo / Huambo	0.18	2.74	0.26	1.26	0.17	4.63
Huíla / Huíla	0.18	1.22	0.18	0.03	3.01	4.62
Luanda / Luanda	1.12	5.65	1.96	3.74	7.03	19.49
Severna Lunda / North Lunda	0.17	1.50	0.09	0.08	0.08	1.76
Južna Lunda / South Lunda	0.17	1.50	0.09	0.08	0.08	1.76
Malanže / Malange	0.08	0.40	0.04	0.02	0.08	0.60
Mošiko / Moxico	0.12	5.41	0.14	1.24	0.25	7.16
Zaire / Zaire	0.28	3.25	0.33	0.32	1.89	6.06
Ukupno / Total	0.41	2.81	0.71	1.45	2.63	8.02

Izvor: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]

Source: Instituto Nacional de Estatística (Angola). Anuário Estatístico Sanitário 2021. Luanda: INE; 2024 [12]



Slika 1. Gustina raspoređenosti lekara, medicinskih sestara i babica na 1.000 stanovnika u Afričkom regionu u 2018. godini
COR – Ciljevi održivog razvoja; MCR – Milenijumski ciljevi razvoja

Izvor: World Health Organization. The state of the health workforce in the WHO African Region, 2021. Brazzaville: WHO Regional Office for Africa; 2021 [14]

Figure 1. Density of doctors, nurses, and midwives per 1,000 population in the Africa region in 2018
SDG – Sustainable Development Goals; MDG – Millennium Development Goals

Source: World Health Organization. The state of the health workforce in the WHO African Region, 2021. Brazzaville: WHO Regional Office for Africa; 2021 [14]

ne organizacije), kao i 16,45 medicinskih sestara i 3,91 dijagnostičkih/terapeutskih tehničara [12].

Slika 1 pokazuje da su, u 2018. godini, 24 zemlje u Afričkom regionu imale gustinu raspoređenosti zdravstvenog kadra manju od 1,0 lekara, medicinskih sestara i babica na 1.000 stanovnika, dok se ova vrednost u 13 zemalja kretala između 2,22 i manje od 1,0 lekara, medicinskih sestara i babica na 1.000 stanovnika.

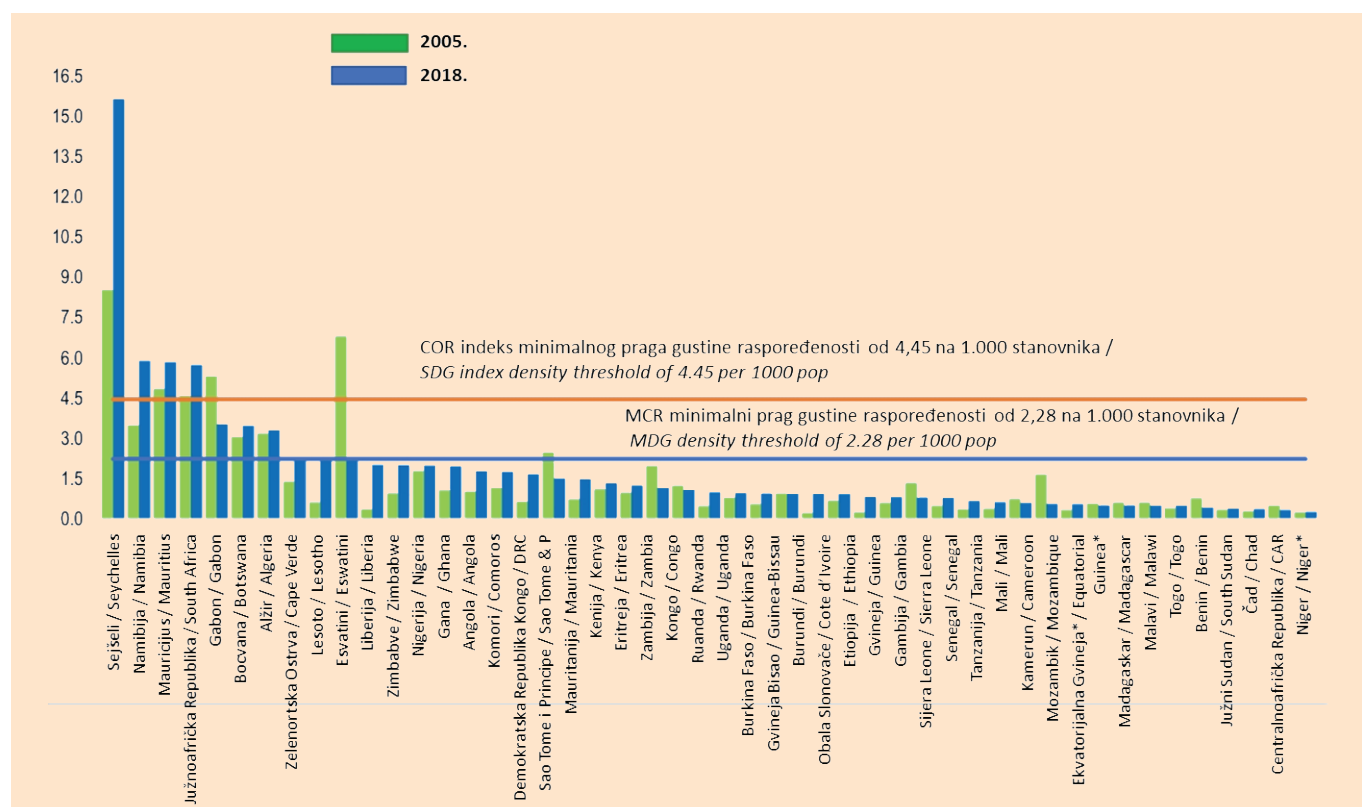
Devet zemalja (Alžir, Bocvana, Zelenortska ostrva, Gabon, Lesoto, Mauricijus, Namibija, Sejšeli i Južnoafrička Republika) od 47 u regionu, imala je gustinu raspoređenosti lekara, medicinskih sestara i babica na 1.000 stanovnika koja je dostigla ili premašila minimalni prag gustine raspoređenosti definisan Milenijumskim ciljevima razvoja (MCR) od 2,28 doktora, medicinskih sestara i babica na 1.000 stanovnika.

Takođe, naše istraživanje pokazuje da su, od 2018. godine, samo četiri zemlje (Sejšeli, Namibija, Mauricijus i Južnoafrička Republika) dostigle ili premašile indeks minimalnog praga gustine raspoređenosti definisan

Figure 1 shows that, in 2018, 24 countries in the Africa Region had a health workforce density of fewer than 1.0 doctors, nurses, and midwives per 1,000 inhabitants, while in 13 countries this value ranged between 2.22 and below 1.0 per 1,000 inhabitants.

Nine countries (Algeria, Botswana, Cape Verde, Gabon, Lesotho, Mauritius, Namibia, Seychelles, and South Africa) out of 47 in the region had a density of doctors, nurses, and midwives per 1,000 inhabitants that reached or exceeded the minimum threshold defined by the Millennium Development Goals (MDGs) of 2.28 doctors, nurses, and midwives per 1,000 inhabitants.

Furthermore, our research shows that as of 2018, only four countries (Seychelles, Namibia, Mauritius, and South Africa) had reached or exceeded the minimum threshold density index defined by the Sustainable Development Goals (SDGs) of 4.45 per 1,000 inhabitants (Figure 2), while in Angola that same year, the index was only 1.54 per 1,000 inhabitants [14].



Slika 2. Gustina raspoređenosti lekara, medicinskih sestara i babica na 1.000 stanovnika, 2005. i 2018. godine, u Afričkom regionu

Izvori: World Health Organization. Human resources for health: data and statistics for the WHO African Region. Brazzaville: WHO Regional Office for Africa; 2025 [13]; World Health Organization. The state of the health workforce in the WHO African Region, 2021. Brazzaville: WHO Regional Office for Africa; 2021 [14]

Figure 2. Density of doctors, nurses, and midwives per 1,000 population, in 2005 and 2018, in the Africa Region

Sources: World Health Organization. Human resources for health: data and statistics for the WHO African Region. Brazzaville: WHO Regional Office for Africa; 2025 [13]; World Health Organization. The state of the health workforce in the WHO African Region, 2021. Brazzaville: WHO Regional Office for Africa; 2021 [14]

Ciljevima održivog razvoja od 4,45 na 1.000 stanovnika (Slika 2), dok je ovaj indeks u Angoli iste godine iznosio samo 1,54 na 1.000 stanovnika [14].

DISKUSIJA

Naša studija je istraživala izazove u upravljanju zdravstvenim kadrom u procesu ostvarivanja univerzalne pokrivenosti zdravstvenom zaštitom u Angoli. Rezultati pokazuju da se Angola suočava sa izraženim strukturnim izazovima u postizanju univerzalne pokrivenosti zdravstvenom zaštitom, posebno u kontekstu demografskih promena koje karakteriše brz rast stanovništva. Stanovništvo Angole, procenjeno na 36,7 miliona u 2023. godini, ima projekciju da dostigne 74,3 miliona do 2050. godine, sa godišnjom stopom rasta od 3,8% [8]. Ovaj rast zahteva proporcionalno širenje zdravstvenog sistema, što predstavlja značajan pritisak na infrastrukturu, ljudske resurse i finansiranje zdravstva.

Iako je porasla sa 35%, u 2015. godini, na 45%, u 2022. godini, stopa pokrivenosti zdravstvenim uslugama i dalje ostaje ispod proseka potrebnog za obezbeđivanje punog pristupa stanovništvu. Istovremeno, zemlje poput Mauricijusa beleže mnogo više pokaza-

DISCUSSION

The present study examined the challenges in managing the health workforce in the process of achieving universal health coverage in Angola. The results show that Angola faces significant structural challenges in reaching universal health coverage, particularly in the context of demographic changes characterized by rapid population growth. Angola's population, estimated at 36.7 million in 2023, is projected to reach 74.3 million by 2050, with an annual growth rate of 3.8% [8]. This growth requires a proportional expansion of the health system, which places substantial pressure on infrastructure, human resources, and healthcare financing.

Although it increased from 35%, in 2015, to 45%, in 2022, the health coverage rate still remains below the average required to ensure full access to healthcare for the population. At the same time, countries such as Mauritius report significantly higher rates (91%), which is an illustration of regional disparities. Approximately 20 million people in Angola, representing more than half of the population, still lack access to basic health services.

telje (91%), što ukazuje na regionalne nejednakosti. Približno 20 miliona stanovnika Angole, što predstavlja više od polovine populacije, još uvek nema pristup osnovnim zdravstvenim uslugama.

Takođe, Angola pokazuje visok nivo socioekonomske ranjivosti: 30% stanovništva živi u ekstremnom siromaštvu, dok se 15% suočava sa katastrofalnim zdravstvenim troškovima, što ograničava pristup zdravstvenoj nezi i ugrožava pravičnost sistema. Očekivani životni vek pri rođenju, iako je poboljšán sa 49,4 godina, u 2000. godini, na 62,1 godinu, u 2021. godini, i dalje je nizak u poređenju sa drugim delovima Afrike.

Pokazatelji morbiditeta i mortaliteta dodatno otkrivaju ranjivost zdravstvenog sistema u Angoli – visoka incidencija tuberkuloze (339 slučajeva na 100.000 stanovnika u 2023. godini) i malarije (235,9 slučajeva na 1.000 stanovnika u 2022. godini); visoka stopa smrtnosti dece mlađe od pet godina (66,87/1.000) i visoka stopa neonatalne smrtnosti (26,03/1.000) u 2022. godini; visoka stopa smrtnosti majki od 221,9 na 100.000 živorođenih u 2020. godini. Glavni uzroci smrti u 2021. godini bile su respiratorne infekcije, malarija i tuberkuloza.

Što se tiče infrastrukture, Angola je 2021. godine imala 3.162 javne i 3.768 privatnih zdravstvenih ustanova, što ukupno čini 6.930 zdravstvenih ustanova u zemlji [12]. Međutim, geografska raspodela tih usluga je izrazito neravnomerna, sa velikim prazninama u provincijama kao što su Bengo, Kabinda, Kunene, Južna Lunda i Namibe, koje imaju najmanji apsolutni broj javnih bolničkih ustanova. Ova razlika ukazuje na duboke nejednakosti u pristupu bolničkoj nezi, naročito u udaljenim i manje urbanizovanim oblastima. Takva situacija ugrožava pravičnost sistema i predstavlja strukturni izazov prisutan širom zemlje.

Kada su u pitanju ljudski resursi, uprkos određenim naprecima, brojke su i dalje ispod neophodnog nivoa. U 2021. godini, Angola je imala: 7.716 lekara (2,48 na 10.000 stanovnika), 51.216 medicinskih sestara (16,45 na 10.000 stanovnika) i 12.177 dijagnostičkih/terapeutskih tehničara (3,91 na 10.000 stanovnika) [12]. Ova gustina raspoređenosti je ispod minimalnog praga od 4,45 zdravstvenih radnika (lekara, sestara i babica) na 1.000 stanovnika, kako preporučuje SZO za postizanje univerzalne pokrivenosti zdravstvenom zaštitom [14]. Situaciju dodatno pogoršava asimetrična geografska raspodela: oko 85% lekara koncentrisano je u Luandi i urbanim centrima, dok su ruralna područja često bez odgovarajuće zdravstvene zaštite [16].

Nedostatak kvalifikovanih stručnjaka, ograničena kontinuirana edukacija i nedovoljni podsticaji za rad u udaljenim oblastima identifikovani su kao ključne prepreke. Nacionalni plan za razvoj zdravstva (PNDS 2012–

Additionally, Angola exhibits a high level of socio-economic vulnerability: 30% of the population lives in extreme poverty, while 15% faces catastrophic health expenditures, limiting access to healthcare and undermining the equity of the system. Life expectancy at birth, although improved from 49.4 years in 2000 to 62.1 years in 2021, remains low, as compared to other parts of Africa.

Morbidity and mortality indicators further reveal the vulnerability of Angola's health system – a high incidence of tuberculosis (339 cases per 100,000 population in 2023) and of malaria (235.9 cases per 1,000 population in 2022); a high under-five mortality rate (66.87 per 1,000) and a high neonatal mortality rate (26.03 per 1,000) in 2022; as well as a high maternal mortality rate of 221.9 per 100,000 live births in 2020. The leading causes of death in 2021 were respiratory infections, malaria, and tuberculosis.

In terms of infrastructure, Angola had 3,162 public and 3,768 private healthcare facilities in 2021, totaling 6,930 healthcare facilities nationwide [12]. However, the geographical distribution of these services is highly uneven, with significant gaps in provinces such as Bengo, Cabinda, Cunene, South Lunda, and Namibe, which have the lowest absolute number of public hospital facilities. This disparity highlights deep inequalities in access to hospital care, particularly in remote and less urbanized areas. Such a situation undermines the equity of the system and represents a structural challenge present across the country.

In terms of human resources, despite some progress, the numbers remain below the necessary level. In 2021, Angola had: 7,716 doctors (2.48 per 10,000 population), 51,216 nurses (16.45 per 10,000 population), and 12,177 diagnostic/therapeutic technicians (3.91 per 10,000 population) [12]. This density is below the minimum threshold of 4.45 health workers (doctors, nurses, and midwives) per 1,000 population, as recommended by the WHO for achieving universal health coverage [14]. The situation is further worsened by the uneven geographical distribution: around 85% of doctors are concentrated in Luanda and urban centers, while rural areas are often left without adequate healthcare [16].

The lack of qualified professionals, the limited continuing education, and the insufficient incentives for working in remote areas have been identified as key obstacles. The National Health Development Plan (PNDS 2012–2025) recognizes these shortcomings and proposes strategies to strengthen human resource management. However, the implementation of these strategies faces budgetary and structural constraints.

2025.) prepoznaje ove nedostatke i predlaže strategije za jačanje upravljanja ljudskim resursima, ali njegova implementacija nailazi na budžetska i strukturna ograničenja.

S obzirom na prikazane podatke, postaje jasno da postizanje univerzalne pokrivenosti zdravstvenom zaštitom u Angoli zavisi direktno od kontinuiranih ulaganja u obuku, raspodelu i valorizaciju zdravstvenih radnika, kao i od proširenja infrastrukture i jačanja upravljanja u zdravstvu. Podrška međunarodnih organizacija poput SZO, Svetske banke, UNICEF-a i Globalnog fonda, koje već sprovode projekte obuke zdravstvenih stručnjaka, biće od ključnog značaja za ubrzanje ovog procesa.

ZAKLJUČAK

Zaključeno je da, uprkos značajnom napretku u zdravstvenom sektoru u Angoli, kao što je povećanje broja zdravstvenih ustanova i zdravstvenih stručnjaka, zemlja se i dalje suočava sa važnim strukturnim izazovima u nastojanju da postigne univerzalnu pokrivenost zdravstvenom zaštitom. Niska efektivna pokrivenost zdravstvenim uslugama, veliki teret zaraznih bolesti i alarmantni pokazatelji smrtnosti kod dece i majki ukazuju na hitnu potrebu za efikasnijim i održivijim politikama.

Jedna od najozbiljnijih tačaka koje su identifikovane jeste nejednakost u raspodeli ljudskih resursa u zdravstvu, kako između urbanih i ruralnih oblasti, tako i između ekonomski bogatijih i siromašnijih oblasti. Ovo ugrožava pravičan pristup zdravstvenoj zaštiti i produbljuje zdravstvene nejednakosti.

Da bi Angola napredovala ka potpunoj univerzalnoj pokrivenosti zdravstvenom zaštitom, neophodno je strateški ulagati u obrazovanje, zadržavanje kadrova i bolju raspodelu zdravstvenih radnika, sa naglaskom na pravičnost i efikasnost sistema. Takođe, ključno je ojačati mehanizme upravljanja i rukovođenja ljudskim resursima, osiguravajući da ulaganja u infrastrukturu budu praćena čvrstim i kontekstualizovanim politikama upravljanja ljudskim resursima.

Ova analiza, dakle, ukazuje na potrebu za integrisanim pristupom koji kombinuje širenje mreže zdravstvenih usluga, kvalifikaciju radne snage i javne politike zasnovane na podacima i dokazima, s ciljem da se smanje nejednakosti i poboljšaju zdravstveni ishodi stanovništva Angole.

Izjave zahvalnosti: Autorka zahvaljuje Laboratoriji za jačanje kapaciteta i performansi zdravstvenog sistema i kadrova za zdravstvenu pravičnost – Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija.

Sukob interesa: Nije prijavljen.

Given the presented data, it becomes clear that achieving universal health coverage in Angola directly depends on continued investment in the training, distribution, and recognition of healthcare workers, as well as the expansion of infrastructure and the strengthening of health governance. Support from international organizations such as the WHO, the World Bank, UNICEF, and the Global Fund, which are already implementing training projects for health professionals, will be crucial in accelerating this process.

CONCLUSION

It has been concluded that, despite significant progress in Angola's health sector, such as the increase in the number of healthcare facilities and health professionals, the country still faces major structural challenges in its efforts to achieve universal health coverage. Low effective coverage of health services, a high burden of infectious diseases, and alarming child and maternal mortality indicators point to an urgent need for more efficient and sustainable policies.

One of the most serious issues identified is the inequality in the distribution of human resources in healthcare, both between urban and rural areas and between economically wealthier and poorer regions. This undermines equitable access to healthcare and deepens health disparities.

For Angola to advance toward full universal health coverage, strategic investment is essential in education, workforce retention, and better distribution of health professionals, with a focus on equity and system efficiency. It is also critical to strengthen human resource management and governance mechanisms, ensuring that infrastructure investments are accompanied by strong and context-specific human resource policies.

This analysis, therefore, highlights the need for an integrated approach that combines the expansion of the healthcare network, workforce qualification, and data- and evidence-based public policies, with the goal of reducing inequalities and improving health outcomes for the population of Angola.

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ULOGA ZDRAVSTVENOG INFORMACIONOG SISTEMA U TRANSFORMACIJI I EFIKASNOSTI ZDRAVSTVENOG SISTEMA ANGOLE: IZAZOVI I MOGUĆNOSTI

ORIGINALNI RAD

ORIGINAL ARTICLE

THE ROLE OF HEALTH INFORMATION SYSTEMS IN TRANSFORMING AND ENHANCING THE EFFICIENCY OF ANGOLA'S HEALTH SYSTEM: CHALLENGES AND OPPORTUNITIES

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SAŽETAK

Zdravstveni informacijski sistemi (ZIS) su sistemi koji prikupljaju, čuvaju, obrađuju i obezbeđuju informacije o zdravlju korisnika, kao i o upravljanju, organizaciji, strukturi i funkcionisanju zdravstvenog sistema, a u vezi sa donošenjem odluka za dostizanjem zdravstvenih ciljeva zemlje. Ciljevi istraživanja su da se opiše delotvornost zdravstvenog informacijskog sistema Angole (ZIS Angola) – i utvrde izazovi za implementaciju i korišćenje ZIS-a od strane korisnika. U istraživanju, korišćena je bibliografska metoda i analiza dokumenata, koje kombinuju pregled relevantne literature o ulozi ZIS-a u Angoli i preporučene strategije za njegovu transformaciju i efikasnost uz uporednu analizu indikatora. U istorijskom metodu akcenat je bio na razumevanju porekla, razvoja i evolucije ZIS-a. U deduktivno-induktivnoj metodi ispitana je hipoteza o delotvornosti ZIS-a Angole. Za deskriptivnu kvalitativnu i kvantitativnu analizu, korišćeni su SZO standardni indikatori u zdravstvenim informacijskim sistemima, kao što su indikatori zdravstvene politike (npr. strateški planovi i implementacija zdravstvenih informacijskih sistema), pružanja zdravstvenih usluga (npr. pristup i korišćenje) i performansi zdravstvenog sistema (vreme odziva i kvalitet usluge), kao i indikatori koji opisuju obrazovne (npr. IT obuka za zdravstvene radnike) i finansijske (ulaganja u zdravstvenu zaštitu i u zdravstvene informacione i komunikacione tehnologije) aspekte. Rezultati pokazuju da je ZIS Angola unapređen prelaskom na platformu DHIS2, što je poboljšalo dostupnost podataka i upravljanje zdravstvenim uslugama, ali postoje izazovi kao što su ograničeni resursi, nedostatak infrastrukture, neravnomerna raspodela osoblja i nedovoljna IT obuka. Indikatori pristupa i korišćenja zdravstvenih usluga, vreme odziva i kvalitet usluge ukazuju na skroman napredak, dok finansijska ulaganja ostaju nedovoljna za dalji razvoj sistema.

Zaključak: ZIS Angola ima potencijal za značajno unapređenje upravljanja zdravstvenim sistemom i kvaliteta usluga, ali je neophodno kontinuirano ulaganje u ljudske resurse, infrastrukturu i obuku, kao i ravnomernija distribucija stručnjaka, kako bi se postigla veća delotvornost i poboljšala zdravstvena pokrivenost i efikasnost sektora u Angoli.

Ključne reči: informacijski sistem, zdravstveni indikatori, zdravstveni menadžment, javno zdravlje

ABSTRACT

Health Information Systems (HIS) are systems designed to collect, store, process, and provide information on both individual and population health, as well as on the management, organization, structure, and functioning of the health system. Their primary purpose is to support decision-making aimed at achieving national health goals. The research objectives were to describe the effectiveness of the Health Information System of Angola (HIS Angola), and to identify challenges for implementing and using HIS by users. The research was based on the assumption that the current form of the HIS provides only a minimal set of data necessary for formulating proposals for actions, policies, and practices aimed at improving the quality, financing, and management of health services, as well as reducing inequalities in access to health care. The research employed a bibliographic method and documentary analysis, combining a review of relevant literature on the role of the HIS in Angola and recommended strategies for its transformation and effectiveness, with a comparative analysis of health system indicators. The historical-logical method was used to explore the origin, development, and evolution of the HIS, while the deductive-inductive method was applied to examine the hypothesis regarding the effectiveness of Angola's HIS. For the descriptive qualitative and quantitative analysis, we will use standard WHO indicators related to health information systems. These include indicators on health policy (e.g., strategic plans and implementation of HIS), health service delivery (e.g., access and utilization), and health system performance (e.g., response time and service quality). Additionally, we will consider indicators reflecting educational (e.g., IT training for health professionals) and financial (e.g., investments in health care and health information and communication technologies) aspects. The results indicate that Angola's Health Information System (HIS) has improved through the transition to the DHIS2 platform, leading to enhanced data availability and better management of health services. However, significant challenges persist, including limited resources, inadequate infrastructure, uneven distribution of health personnel, and insufficient IT training. Indicators related to health service access and utilization, response time, and service quality suggest only modest progress, while financial investments remain inadequate to support further development of the system. Conclusion: Angola's HIS has the potential to significantly enhance health system management and service quality. However, to achieve greater effectiveness and improve health coverage and efficiency, sustained investment is needed in human resources, infrastructure, and training, along with a more equitable distribution of health professionals.

Keywords: information system, health indicators, health management, public health

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RESUMO

Sistemas de Informação em Saúde (SIS) são sistemas responsáveis pela recolha, armazenamento, processamento e fornecimento de informações relacionadas com a saúde dos utentes, assim como com a gestão, organização, estrutura e funcionamento do sistema de saúde. Estas informações são essenciais para apoiar a tomada de decisões com o objectivo de alcançar as metas de saúde de um país. Os objectivos da pesquisa foram descrever a efectividade do Sistema de Informação em Saúde de Angola (SIS Angola) e identificar os desafios para a implementação e o uso do SIS pelos utentes. A hipótese da pesquisa era que o SIS, na sua forma actual, fornece um conjunto mínimo de informações necessárias para a formulação de propostas de ações, políticas e práticas que possam contribuir para a melhoria da qualidade, do financiamento e da gestão dos serviços de saúde, assim como para a redução das desigualdades no acesso à assistência à saúde. Na pesquisa, foram utilizados o método bibliográfico e a análise documental, que combinam uma revisão da literatura relevante sobre o papel do SIS em Angola e as estratégias recomendadas para a sua transformação e efectividade, com uma análise comparativa de indicadores. No método histórico-lógico, a ênfase foi compreender a origem, o desenvolvimento e a evolução do SIS. No método dedutivo-indutivo, examinou-se a hipótese da efectividade do SIS de Angola. Para a análise descritiva qualitativa e quantitativa, utilizaremos os indicadores padrão da OMS em sistemas de informação em saúde, como os indicadores de política de saúde (por exemplo, planos estratégicos e implementação de sistemas de informação em saúde), de prestação de serviços de saúde (por exemplo, acesso e utilização) e de desempenho do sistema de saúde (tempo de resposta e qualidade do serviço), assim como indicadores que descrevem as áreas educativas (por exemplo, formação em Tecnologias de Informação para profissionais de saúde) e financeira (por exemplo, investimentos em informação em saúde). Os resultados mostram que o Sistema de Informação em Saúde (SIS) de Angola foi aprimorado com a transição para a plataforma DHIS2, o que melhorou a disponibilidade de dados e a gestão dos serviços de saúde. No entanto, persistem desafios, como recursos limitados, falta de infraestrutura, distribuição desigual de pessoal e treinamento insuficiente em TI. Os indicadores de acesso e utilização dos serviços de saúde, tempo de resposta e qualidade do serviço indicam um progresso modesto, enquanto os investimentos financeiros permanecem insuficientes para o desenvolvimento do sistema. Conclui-se que o SIS Angola tem potencial para aprimorar significativamente a gestão do sistema de saúde e a qualidade dos serviços, mas é necessário um investimento contínuo em recursos humanos, infraestrutura e treinamento, além de garantir uma distribuição mais equitativa de profissionais de saúde, para alcançar maior efectividade e melhorar a cobertura e a eficiência do sector de saúde em Angola.

Palavras-chave: Sistema de informação; Indicadores de saúde; Gestão em saúde; Saúde pública.

UVOD

Zdravstvenim organizacijama se mora upravljati na strateškoj osnovi koja, s obzirom na složenost i višestrukost zdravstvenih usluga, mora biti zasnovana na integrisanom modelu informacija i znanja. Na ovaj način je strateški menadžment prisutan u organizacijama u zdravstvenom sektoru, i podrazumeva stalnu upotrebu informacionih tehnologija i informacionih sistema [1]. Od nastanka elektronskih informacionih sistema posle Prvog svetskog rata do danas posebna pažnja u medicini posvećuje se digitalnim standardima i zdravstvenim informacionim sistemima (ZIS) [2], koji omogućavaju brz i bezbedan tok informacija, kao i stalni pristup i pretragu podataka od strane zdravstvenih radnika radi održavanja kvaliteta zdravstvene nege [3].

Zdravstveni informacioni sistemi predstavljaju ključnu komponentu odgovora na rastuće zahteve za zdravstvenom zaštitom, pri čemu kvalitet usluga značajno utiče na očuvanje zdravlja, a razvoj i upotreba ZIS-a imaju važnu ulogu u njegovom unapređenju [4]. Naime, dobro izgrađene i dobro vođene komponente ZIS-a, kao što su prikupljanje, skladištenje, obrada i analiza zdravstvenih podataka, omogućavaju donošenje odluka zasnovanih na podacima i efikasno upravljanje raspoloživim resursima, što predstavlja suštinski deo pružanja dobre zdravstvene zaštite [5]. Prema Svetskoj zdravstvenoj organizaciji, cilj zdravstvenih informacionih sistema je proizvodnja relevantnih informacija koje omogućavaju transparentno i zasnovano donošenje odluka u zdravstvenom sistemu [6,7]. Iz perspektive zdravstvenih radnika, ZIS olakšava prikupljanje i upravljanje informacijama o pacijentima u različitim uslovi-

INTRODUCTION

Health organizations must be strategically managed, taking into account the complexity and diversity of health services. This requires an integrated model of information and knowledge, where strategic management relies on the continual use of information technologies and systems [1]. Since the emergence of electronic information systems after the First World War, particular attention in medicine has been devoted to digital standards and health information systems (HIS) [2]. These systems facilitate the fast and secure flow of information, while ensuring continuous access to and retrieval of data by healthcare professionals, thereby supporting the quality of healthcare delivery [3].

Health information systems are a key component in responding to the growing demands for healthcare, as service quality plays a crucial role in preserving health. The development and effective use of HIS significantly contribute to improving that quality [4]. Well-designed and effectively managed components of HIS, such as the collection, storage, processing, and analysis of health data, enable data-driven decision-making and efficient resource management, both of which are essential for delivering high-quality healthcare [5]. According to the World Health Organization, the primary goal of health information systems is to generate relevant information that supports transparent, evidence-based decision-making within the health system [6,7]. From the perspective of healthcare professionals, HIS facilitate the collection and management of patient data across various healthcare settings [8]. In addition to supporting clinical care, HIS also contribute

ma [8]. Pored toga, ZIS podržava istraživanje, nastavu i kontrolu bolesti, kao i praćenje kvaliteta usluga [9]. Međutim, uspešno funkcionisanje ZIS-a zahteva ispunjenost političkih, administrativnih, organizacionih i finansijskih preduslova, kao i odgovarajuće zakonske okvire za zaštitu podataka i njihovo deljenje.

Uprkos potrebi za kvalitetnim informacijama, mnogi zdravstveni informacioni sistemi u zemljama u razvoju suočavaju se sa izazovima kao što su: nedostatak resursa, ograničena infrastruktura i potreba za većom koordinacijom [4]. Iako ZIS nudi značajne mogućnosti za poboljšanje kvaliteta usluga, optimizaciju administrativnih procesa i jačanje odgovora na vanredne situacije u domenu javnog zdravlja, njegova efikasna primena suočava se sa preprekama, kao što su nedostatak obuke, problemi tehnološke infrastrukture ili nedoknade, otpor promenama, i pravna zaštita podataka [4]. Istraživanje o načinima prevazilaženja ovih izazova je od suštinskog značaja za kretanje ka otpornijem, pristupačnijem i efikasnijem zdravstvenom sistemu.

Ciljevi istraživanja su da se opiše delotvornost postojećeg zdravstvenog informacionog sistema Angole, i utvrde izazovi za implementaciju i korišćenje ZIS-a od strane korisnika.

Pretpostavka u istraživanju je da ZIS, u trenutnoj formi, obezbeđuje minimalan skup informacija neophodnih za formulisanje predloga akcija, politika i praksi kojima se može doprineti unapređenju kvaliteta, finansiranja i upravljanja zdravstvenim uslugama, kao i smanjivanju nejednakosti u pristupu zdravstvenoj zaštiti.

METOD RADA

U istraživanju je primenjen pregled relevantne literature o ulozi ZIS u Angoli za kvalitativnu analizu dokumenata o preporučenim strategijama za njegovu transformaciju i efikasnost, indikatori koji opisuju IT obuku za zdravstvene radnike i finansijske aspekte (ulaganja u zdravstvenu zaštitu i u zdravstvene informacione i komunikacione tehnologije), uporedo sa kvantitativnom analizom raspoloživih zdravstvenih indikatora u ZIS Angole. U kvalitativnoj analizi primenjen je istorijsko-logički metod sa akcentom na razumevanju porekla, razvoja i evolucije ZIS-a. Uz pomoć deduktivno-induktivne metode ispitana je hipoteza o delotvornosti ZIS-a Angole.

Za deskriptivnu kvantitativnu analizu ZIS-a Angole, izabrani su SZO standardni kvalitativni i kvantitativni indikatori, kao što su:

1. Zdravstvene politike (npr. strateški planovi i implementacija zdravstvenih informacionih sistema),
2. Zdravstveno stanje stanovnika:
 - a. Stopa obuhvata vakcinacijom;
 - b. Broj umrlih majki na 100.000 živorođenih,

to research, education, disease surveillance, and the monitoring of service quality [9]. However, their effective functioning depends on the fulfillment of several preconditions, including political, administrative, organizational, and financial support, as well as the establishment of appropriate legal frameworks for data protection and sharing.

Despite the growing need for high-quality information, many health information systems in developing countries face significant challenges, including limited resources, inadequate infrastructure, and insufficient coordination [4]. While HIS offer substantial opportunities to enhance service quality, optimize administrative processes, and strengthen responses to public health emergencies, their effective implementation is often hindered by obstacles such as inadequate training, insufficient technological infrastructure, reimbursement issues, resistance to change, and gaps in legal frameworks for data protection [4]. Research aimed at overcoming these challenges is essential for building a more resilient, accessible, and efficient healthcare system.

The objectives of this research are to evaluate the effectiveness of Angola's existing health information system and to identify the key challenges faced by users in its implementation and utilization.

The central assumption of the study is that, in its current form, HIS Angola provides at least a minimum set of essential information needed to formulate actionable proposals, policies, and practices aimed at improving the quality, financing, and management of health services, as well as reducing disparities in access to healthcare.

METHODOLOGY

The research employed a review of relevant literature on the role of HIS in Angola to conduct a qualitative analysis of documents outlining recommended strategies for its transformation and improved efficiency. This included indicators related to IT training for healthcare workers and financial aspects, such as investments in healthcare and in health information and communication technologies, alongside a quantitative analysis of the available health indicators within Angola's HIS. The qualitative analysis employed the historical-logical method, with a focus on understanding the origin, development, and evolution of HIS. The deductive-inductive method was used to examine the hypothesis regarding the effectiveness of Angola's HIS.

For the descriptive quantitative analysis of Angola's HIS, WHO-standard qualitative and quantitative indicators were selected, such as:

1. Health policies (e.g., strategic plans and implementation of health information systems);
2. Population health status:

- c. Stopa mortaliteta novorođenčadi na 1.000 živorođenih,
 - d. Procenat populacije sa dijagnozom hroničnih bolesti, kao što su dijabetes i hipertenzija,
 - e. Broj novih slučajeva zaraznih bolesti, kao što su malarija, tuberkuloza i HIV/AIDS, na 100.000 stanovnika.
3. Pružanje zdravstvenih usluga (npr. pristup i korišćenje) i performanse zdravstvenog sistema (pokriivenost prenatalnom zdravstvenom zaštitom):
- a. Obezbeđenost kadrovima: Broj lekara na 10.000 stanovnika; broj medicinskih sestara na 10.000 stanovnika;
 - b. Indikatori strukture zaposlenih: % zaposlenih lekara; % medicinskih sestara zaposlenih u bolnici i proporcija broja medicinskih sestara po jednom lekaru;
 - c. Procenat stanovništva koji ima pristup osnovnim zdravstvenim uslugama, uključujući medicinske konsultacije i bolnice;
 - d. Ukupan broj konsultacija jednog lekara u primarnoj zdravstvenoj zaštiti;
 - e. Procenat trudnica koje primaju adekvatnu prenatalnu zdravstvenu zaštitu;
 - f. Stopa hospitalizacije: broj hospitalizacija na 100 stanovnika;
 - g. Stopa popunjenosti bolničkih kreveta.

Obrađeni podaci su prikazani u tabelarnom i grafičkom obliku, što olakšava njihovu vizualizaciju u kontekstu transformacije i efikasnosti zdravstvenog sistema Angole.

REZULTATI

Karakteristike zdravstvenog sistema, i delotvornost ZIS-a Angole

Jedinstveni zdravstveni sistem u Angoli uspostavljen je 1975. godine (zakon 9/75) i fokusiran je na primarnu zdravstvenu zaštitu, prevenciju bolesti, promociju zdravlja, negu u zajednici, uključivanje stanovništva u donošenje odluka, kao i zaštitu najugroženijih grupa. Civilna registracija i vitalna statistika (CRVS) su osnovni izvori podatka ne samo za zdravstveni sektor već i za administrativni sistem [10]. Zbog dugogodišnje kolonijalne vladavine i građanskog rata u Angoli koji je trajao 27 godina nakon sticanja nezavisnosti 1975. godine, dugi niz godina nije vršen popis stanovništva. Prvo nacionalno demografsko i zdravstveno istraživanje u Angoli, i četvrto istraživanje višestrukih indikatora (rađanja, zdravlja dece i majki, ishrane i zaraznih bolesti) sprovedeno je između oktobra 2015. i marta 2016. godine, i ono danas obezbeđuje važne informacije za pra-

- a. Vaccination coverage rate;
 - b. Maternal mortality rate per 100,000 live births;
 - c. Neonatal mortality rate per 1,000 live births;
 - d. Percentage of the population diagnosed with chronic diseases, such as diabetes and hypertension;
 - e. Number of new cases of infectious diseases, such as malaria, tuberculosis, and HIV/AIDS, per 100,000 population.
3. Healthcare service delivery (e.g., access and utilization) and health system performance (e.g., coverage of prenatal care):
- a. Human resource availability: number of physicians per 10,000 population; number of nurses per 10,000 population;
 - b. Workforce structure indicators: % of employed physicians; % of nurses employed in hospitals; and the nurse-to-physician ratio;
 - c. Percentage of the population with access to basic healthcare services, including medical consultations and hospital care;
 - d. Total number of consultations per physician in primary healthcare;
 - e. Percentage of pregnant women receiving adequate prenatal care;
 - f. Hospitalization rate: number of hospitalizations per 100 population;
 - g. Hospital bed occupancy rate.

The analyzed data are presented in both tabular and graphical formats, facilitating their visualization in the context of the transformation and efficiency of Angola's health system.

RESULTS

Characteristics of the Health System and the Effectiveness of Angola's HIS

Angola's distinctive health system, established in 1975 under Law 9/75, is focused on primary health care, disease prevention, health promotion, community-based care, inclusive decision-making, and the protection of vulnerable populations. Civil Registration and Vital Statistics (CRVS) serve as fundamental data sources not only for the health sector but also for the broader administrative system [10]. Due to Angola's prolonged colonial history and the 27-year civil war that followed its independence in 1975, the country went many years without conducting a population census. The first National Demographic and Health Survey, along with the fourth Multiple Indicator Survey, covering births, child and maternal health, nutrition, and infectious diseases, was carried out between October 2015 and March 2016. These data now serve as a vital resource for mon-

ćenje napretka i procenu uspeha zdravstvenih politika i programa [11].

Zdravstvenim informacionim sistemom u Angoli upravlja autonomna kancelarija u okviru Ministarstva zdravlja: Kancelarija za studije, planiranje i statistiku (GEPE). Ministarstvo zdravlja od 2015. godine prenosi svoj informacioni sistem na okružni softver (engl. *District Health Information Software2 (DHIS2)*) kako bi podaci bili vidljiviji i kako bi se osigurala veća podrška donošenju odluka. Platforma DHIS2 je promovisana uz podršku partnera kao što su SZO, USAID i UNICEF. Na ovoj platformi, podaci se u Zdravstvenim jedinicama prikupljaju i izveštavaju u papirnom formatu. Oni se zatim agregiraju i prijavljuju u sistem na nivou grada. Neki programi i dalje koriste paralelne sisteme izveštavanja, jer imaju za cilj prikupljanje specifičnih informacija koje se ne mogu dobiti putem formalnog sistema izveštavanja. Jedan primer za to su podaci koji se odnose na kontrolu zanemarenih tropskih bolesti, koji se takođe prikupljaju tokom masovnih kampanja distribucije lekova. U ovim slučajevima, podaci se prikupljaju iz škola i zajednica, a zatim se objedinjuju na nivou okruga, pri čemu se veći deo procesa još uvek obavlja na papiru. Svi ovi sistemi su od suštinskog značaja za podršku zdravstvenim politikama zasnovanim na dokazima, olakšavajući efikasnu alokaciju resursa i praćenje zdravstvenih indikatora u realnom vremenu.

Prema izveštaju Luande o zdravstvenom sektoru u Angoli, koji je objavila ambasada Indije u Angoli u maju 2022. godine, Angola je zemlja sa višim srednjim prihodima sa 33 miliona stanovnika i 67 procenata urbanog stanovništva. Očekivani životni vek pri rođenju u Angoli je 63,1 godina. Prema polu, stanovništvo čini 49,4% muškaraca i 50,6% žena. Siromaštvo se procenjuje na oko 48,4 odsto, prema najnovijim podacima iz 2019, koristeći 1,9 dolara po osobi dnevno. Prema podacima Svetske banke, 2020. godine samo 2,96% bruto domaćeg proizvoda Angole je izdvojeno za zdravstvenu potrošnju. Isti izvor kaže da je Vlada Angole podržala oko 42% ukupnog budžeta za zdravstveni sektor u 2018. godini, dok su ostatak podržali multilateralni i bilateralni partneri koji sarađuju u Angoli u oblasti zdravstvene zaštite. Međutim, varijabilnost u bruto domaćem proizvodu, često pod uticajem promenljivih cena nafte, utiče na sposobnost vlade da investira u delotvorne sisteme prikupljanja i analize podataka. Angola ima veliku radnu snagu sa 52% stanovništva u starosnoj grupi od 15 do 64 godine, i visoku stopu fertiliteta od 5,6 živorođenih po ženi. Prema Nacionalnom strateškom planu za zanemarene tropske bolesti u Angoli (2021–2025) i Nacionalnom institutu za statistiku, mapiranja epidemiološke situacije obavljena u periodu od 2014. do 2018–2019. godine omogućila su ažurira-

iting progress and assessing the effectiveness of health policies and programs [11].

Angola's health information system is overseen by an autonomous body within the Ministry of Health-the Office of Studies, Planning, and Statistics (GEPE). Since 2015, the Ministry of Health has been transitioning its health information system to the District Health Information Software 2 (DHIS2) platform, aiming to enhance data visibility and strengthen support for decision-making. The implementation of DHIS2 has been supported by key partners, including WHO, USAID, and UNICEF. On the DHIS2 platform, data are initially collected in paper format at Health facilities, then aggregated and submitted to the central system at the municipal or provincial level. However, some programs continue to use parallel reporting systems to capture specialized data that are not accommodated by the standard reporting framework. One example is data related to the control of neglected tropical diseases, which are also collected during mass drug administration campaigns. In such cases, data are gathered from schools and communities and then aggregated at the district level, much of it still recorded and processed manually on paper. Together, these systems play a critical role in supporting evidence-based health policy-making by enabling efficient resource allocation and real-time monitoring of key health indicators.

According to the *Luanda Report on the health sector in Angola*, published by the Embassy of India in May 2022, Angola is classified as an upper-middle-income country, with a population of 33 million, 67% of whom reside in urban areas. The country's life expectancy at birth is 63.1 years. By gender, the population is composed of 49.4% men and 50.6% women. Poverty affects an estimated 48.4% of the population, based on 2019 data using the international poverty line of \$1.90 per person per day. According to World Bank figures, only 2.96% of Angola's gross domestic product was allocated to health expenditure in 2020. According to the same source, the Government of Angola financed approximately 42% of the total health sector budget in 2018, with the remainder covered by multilateral and bilateral partners engaged in health cooperation. However, fluctuations in gross domestic product, often driven by volatile oil prices, continue to impact the government's capacity to invest consistently in robust data collection and analysis systems. Angola has a sizable labor force, with 52% of the population aged between 15 and 64, alongside a high fertility rate of 5.6 live births per woman. According to the National Strategic Plan for Neglected Tropical Diseases (2021–2025) and data from the National Institute of Statistics, epidemiological mapping conducted between 2014 and 2018–2019

nje podataka o tropskim bolestima, najpre šistosomijazi, koja su od suštinskog značaja za planiranje masovnih kampanja dehelmintizacije [12,13].

Program "Jačanje angolskog zdravstvenog sistema" odigrao je ključnu ulogu u podršci vladi Angole u institucionalizaciji nacionalnih politika zdravlja i razvoju alata za jačanje ZIS-a [14]. Ovaj Program je podržao stvaranje DHIS2 korisničkog priručnika i pratećeg tehničkog priručnika. Kada je uveden, radilo se na ažuriranju informacija, politika i protokola u oblastima kao što su HIV, planiranje porodice i malarija i vakcinacija, ali je kasnije proširen na informacije o tuberkulozi i aktivnostima zajednice, kao što su one koje sprovodi ADECOS (Agenti za razvoj zajednice i zdravlje) [10]. Od 2019. godine, Nacionalni program za kontrolu zanemarenih raznih bolesti (PNCDTN) radi na integraciji ovih podataka u DHIS2, obezbeđujući da se sve informacije evidentiraju u sistemu, omogućavajući kontinuirano praćenje i efikasno konsultovanje rezultata. Ovakvi naponi su bili od suštinske važnosti da bi se obezbedilo prikupljanje podataka i korišćenje informisanog donošenja odluka, kako na centralnom tako i na lokalnom nivou.

Na centralnom nivou, kroz program Jačanje angolskog zdravstvenog sistema uspostavljena je centralizovana baza podataka zasnovana na DHIS2 za Ministarstvo zdravlja, što je omogućilo praćenje 125 zdravstvenih indikatora [15]. Da bi poboljšalo upravljanje informacijama u zdravstvenim ustanovama, Ministarstvo zdravlja Angole koristi skup podataka pod nazivom Health Maps, kojim upravlja GEPE Odeljenje za istraživanje i projekte. Ove mape uključuju geografske informacije o zdravstvenim ustanovama, kao i podatke o broju stručnjaka, infrastrukturi, dostupnim uslugama, bolničkim krevetima, ambulantnim i drugim transportnim vozilima u svakoj opštini.

Važno je istaći da su i na opštinskom nivou pomoci bili značajni. U Huambu, na primer, Program Jačanje angolskih zdravstvenih sistema obučio je 52 zdravstvene jedinice i Pokrajinsku direkciju za zdravstvo da koriste digitalne alate, kao što je Excel, za izradu mesečnih izveštaja, što je rezultiralo smanjenjem grešaka u izveštavanju i poboljšanim kvalitetom podataka. U Luandi je Program uspeo da smanji procenat grešaka u izveštajima o registraciji HIV-a sa 9,05% na 1,58% u ciljnim zdravstvenim jedinicama, demonstrirajući uticaj efikasnog korišćenja ZIS-a. Program je takođe doprineo poboljšanju blagovremenog podnošenja mesečnih izveštaja o planiranju porodice, sa povećanjem usklađenosti sa 40% na 92% [15]. Pored toga, Program je uložio napore da se opštinski i okružni menadžeri obuče korišćenju podataka u formulisanju zdravstvenih planova i budžeta. Huambo je kroz Program postala prva provincija u zemlji koja je razvila zdravstvene

updated critical information on tropical diseases, particularly schistosomiasis, which is essential for the effective planning of mass deworming campaigns [12,13].

The program "Strengthening the Angolan Health System" has played a key role in supporting the Angolan government with the institutionalization of national health policies and the development of tools to enhance the Health Information System (HIS) [14]. This program supported the development of the DHIS2 User Manual along with its accompanying technical guide. Upon its introduction, the program focused on updating information, policies, and protocols in key areas such as HIV, family planning, malaria, and immunization. It was subsequently expanded to include data on tuberculosis and community-based activities, including those conducted by ADECOS (Agents for Community Development and Health) [10]. Since 2019, the National Program for the Control of Neglected Communicable Diseases (PNCDTN) has been working to integrate its data into the DHIS2 platform, ensuring comprehensive recording of information to enable continuous monitoring and efficient access to results. These efforts have been crucial in supporting informed decision-making at both central and local levels.

At the central level, the program *Strengthening the Angolan Health System* established a centralized DHIS2-based database for the Ministry of Health, enabling the monitoring of 125 key health indicators [15]. To enhance information management at health facilities, the Ministry utilizes a dataset known as Health Maps, maintained by the GEPE Research and Projects Department. These maps provide geographic information on health facilities, alongside detailed data on staffing levels, infrastructure, available services, hospital beds, ambulances, and other transport vehicles within each municipality.

Significant improvements were also achieved at the municipal level. In Huambo, for example, the program Strengthening the Angolan Health System trained 52 health units and the Provincial Directorate of Health to use digital tools, such as Excel, for generating monthly reports. This training led to a reduction in reporting errors and a marked improvement in data quality. In Luanda, the program successfully decreased errors in HIV registration reports within target health units from 9.05% to 1.58%, highlighting the positive impact of effective HIS utilization. The program also contributed significantly to improving the timely submission of monthly family planning reports, with compliance rising from 40% to 92% [15]. Additionally, it focused on training municipal and district managers in data utilization for health planning and budgeting. As a result, Huambo became the first province in Angola to develop comprehensive health plans for all its

planove za sve svoje opštine. Naime, Program je podržao razvoj petogodišnjeg pokrajinskog zdravstvenog plana i 11 opštinskih zdravstvenih planova.

Prema najnovijoj proceni SZO, Angola je napravila značajan korak u jačanju svog zdravstvenog sistema, isporukom tehnološke opreme GEPE-u, uz podršku Evropske unije (EU). U okviru to donacije, šest laptopova, od kojih pet finansira EU, namenjeno je unapređenju mogućnosti ZIS-a. Ova donacija je deo veće inicijative koja uključuje isporuku 64 laptopa i 354 pametna telefona za tehničku opremu Ministarstva zdravlja [16]. Pored toga, GEPE, uz podršku SZO, radi na reviziji Nacionalnog plana razvoja zdravstva i Strateškog plana Nacionalnog zdravstvenog informacionog sistema (PESIS), kao deo napora za jačanje ZIS-a u zemlji. Međutim, Angola se i dalje suočava sa izazovima u poboljšanju dostupnosti informacija o ključnim razvojnim indikatorima, kao što su ciljevi održivog razvoja (SDG) za zdravlje, registraciju rođenja i uzroke smrti, koji su propisno sertifikovani od strane bolnica na osnovu glavne dijagnostičke kategorije (ICD-10/11), između ostalih [17]. SZO podrška je stoga usmerena ka operacionalizaciji Nacionalnog zdravstvenog informacionog sistema (NHIS), i razvoju novog strateškog plana za nacionalni zdravstveni informacioni sistem 2024–2030, koji će pružiti strateške smernice za jačanje nacionalnog zdravstvenog sistema.

Uz napredak tehnologije i kontinuirani razvoj zdravstvenog sektora u zemlji, Ministarstvo zdravlja Angole (MINSa), u partnerstvu sa SZO i uz finansijsku podršku Evropske unije, pokrenulo je proces prikupljanja podataka za Strateški Plan Nacionalnog ZIS-a 2024–2030. Cilj je unapređenje kvaliteta zdravstvenih usluga u Angoli, uz učešće stručnjaka iz različitih vladinih odeljenja, agencija UN i međunarodnih organizacija, pod vođstvom GEPE i Regionalne kancelarije SZO za Afriku [18]. Među inicijativama, SZO je posvećena obučavanju nacionalnog tima o metodologiji za reviziju nacionalnog zdravstvenog informacionog sistema, osiguravajući da zemlja ostvari održiv napredak u jačanju svog zdravstvenog informacionog sistema.

Izazovi za implementaciju i korišćenje ZIS-a

Iz perspektive Caneca, uzimajući u obzir istorijske, društvene, političke i ekonomske uslove u zemlji, rasprava o zdravstvenom sektoru ukazuje na to da su izazovi značajni, ali i dostignuća vredna pažnje, naročito nakon godina građanskog rata. Nakon rekonstrukcije zemlje, zdravstveni sistem Angole se suočio sa poteškoćama u efikasnom organizovanju zdravstvenih informacija [19]. Nedostatak pouzdanih podataka ometao je formulisanje politike javnog zdravlja zasnovane na dokazima. Uništenje infrastrukture i nedostatak funk-

municipalities. Specifically, the program supported the creation of a five-year provincial health plan alongside 11 municipal health plans.

According to the latest WHO assessment, Angola has made significant progress in strengthening its health system through the provision of technological equipment to GEPE, supported by the European Union (EU). This donation includes six laptops, five of which were financed by the EU, aimed at enhancing the capacity and effectiveness of HIS. This donation is part of a broader initiative that includes the provision of 64 laptops and 354 smartphones to support the technical infrastructure of the Ministry of Health [16]. Additionally, with support from WHO, GEPE is engaged in revising the National Health Development Plan and the Strategic Plan for the National Health Information System (PESIS), as part of ongoing efforts to strengthen HIS nationwide. Despite these advances, Angola continues to face challenges in improving the availability and quality of data on key development indicators, such as the Sustainable Development Goals (SDGs) related to health, birth registration, and certified causes of death based on hospital diagnoses following ICD-10/11 classifications, among others [17]. WHO support is therefore focused on operationalizing the National Health Information System (NHIS) and developing a new strategic plan for 2024–2030, which will provide comprehensive guidance for strengthening the national health system.

With advancing technology and ongoing development in Angola's health sector, the Ministry of Health (MINSa), in partnership with WHO and with financial support from the European Union, has initiated data collection for the Strategic Plan of the National Health Information System (NHIS) 2024–2030. This effort aims to enhance the quality of health services across the country, involving experts from various government ministries, UN agencies, and international organizations, under the leadership of GEPE and the WHO Regional Office for Africa [18]. Among its initiatives, WHO is committed to training the national team on auditing methodologies for the health information system, ensuring sustainable progress in strengthening Angola's health data infrastructure.

Challenges in implementing and utilizing HIS

From Caneca's perspective, considering Angola's historical, social, political, and economic context, the health sector faces significant challenges, yet notable achievements have been made-especially following years of civil war. During the country's reconstruction, Angola's health system struggled to efficiently organize and manage health information [19]. The absence of reliable data has impeded the development of evidence-based

cionalnog sistema zdravstvene zaštite istakli su hitnu potrebu za efikasnijim ZIS-om, sposobnim da obezbedi pouzdane podatke za donošenje odluka i poboljšanje pružanja zdravstvenih usluga.

ZIS ima kvantitativne podatke – opis zdravstvenog statusa i mortaliteta stanovništva tokom vremena, analizu uzročnosti zdravstvenih problema, kvantifikaciju povezanosti zdravstvenih ishoda i faktora rizika ili zaštitnih faktora i procenu efikasnosti programa javnog zdravlja i zdravstvenih intervencija. Ipak, u ZIS Angole nedostaje kohezija zbog fragmentiranog razvoja nastalog pod administrativnim i ekonomskim pritiscima tokom vremena [20]. Prema Sanjuluci, bolnička zdravstvena zaštita u Angoli nije efikasna. Ne postoji adekvatno prikupljanje niti generisanje podataka o finansiranju zdravstva, niti o zdravstvenim rashodima, što otežava praćenje pravičnosti [21]. Fragmentacija ZIS-a u Angoli rezultira nedovoljno povezanim prikazom zdravstvenog stanja pacijenata, jer bolnice, laboratorije i stručnjaci ne razmenjuju informacije zbog čuvanja podataka u različitim, nepovezanim bazama podataka. Stoga je neophodno da Angola unapredi svoj ZIS kako bi on postao relevantan alat za informisanje menadžera i planera u zdravstvenom sistemu, kao i da doprinese povećanju efikasnosti upravljanja zdravstvenim ustanovama.

Ovi izazovi, kao što su nedostatak pouzdanih podataka i fragmentacija operacija u sistemu, počeli su da se rešavaju uz podršku Nacionalnog instituta za statistiku, koji je odigrao ključnu ulogu u integraciji podataka iz različitih izvora, olakšavajući razvoj ZIS-a koji je koherentniji i efikasan. Stoga je zdravstveni informacioni sistem, podržan od strane Nacionalnog instituta za statistiku, bio ključni odgovor za rešavanje nedostataka u prikupljanju podataka i praćenju zdravstvenih indikatora. Nacionalni institut za statistiku u Angoli odigrao je ključnu ulogu u integraciji podataka iz različitih izvora, omogućavajući bolje razumevanje zdravstvene situacije u zemlji.

Posvećenost Angole jačanju zdravstvenog sistema evidentirana je u izveštajima o specijalizovanoj obuci stručnjaka u vezi sa implementacijom i korišćenjem zdravstvenih informacionih sistema u Angoli. Dodatna edukacija je bila usmerena na jačanje znanja o prevenciji i kontroli infekcija povezanih sa zdravstvenom zaštitom. U 2023. godini održano je pet radionica u provincijama Huambo, Uíge, Luanda, Cunene i Moxico, na kojima je obučeno 260 tehničara sa fokusom na usavršavanje praktičnih veština i znanja potrebnih za efikasno upravljanje zdravstvenih rizicima [22]. Štaviše, Ministarstvo zdravlja Angole, uz podršku SZO, sprovelo je obuku o epidemiološkoj obaveštajnoj službi i korišćenju DHIS2, sistema upravljanja zdravstvenim informacijama, sa ci-

public health policies. The destruction of infrastructure and the breakdown of the healthcare system have underscored the urgent need for a more efficient HIS that can deliver accurate data to support decision-making and enhance the delivery of health services.

HIS provides quantitative data, including descriptions of population health status and mortality trends over time, analyses of the causes of health problems, quantification of relationships between health outcomes and risk or protective factors, and evaluations of the effectiveness of public health programs and interventions. However, Angola's HIS suffers from a lack of cohesion, resulting from fragmented development shaped by administrative and economic pressures over the years [20]. According to Sanjuluca, hospital healthcare in Angola remains inefficient. There is inadequate collection and generation of data on health financing and expenditures, which hampers effective monitoring of equity [21]. The fragmentation of Angola's Health Information System (HIS) results in a poorly connected representation of patients' health status, as hospitals, laboratories, and specialists do not share information due to data being stored in separate, disconnected databases. Therefore, it is essential for Angola to strengthen its HIS, transforming it into a valuable tool for health system managers and planners, while also enhancing the efficiency of health institution management.

Challenges such as unreliable data and system fragmentation began to be addressed with the support of the National Institute of Statistics, which played a pivotal role in integrating data from multiple sources. This integration facilitated the development of a more coherent and efficient Health Information System (HIS). Consequently, HIS, backed by the National Institute of Statistics, became a crucial tool in closing gaps in data collection and monitoring of health indicators, enabling a clearer understanding of Angola's health situation.

Angola's commitment to strengthening its health system is documented in reports detailing specialized training for experts on the implementation and use of health information systems. Additional training focused on enhancing knowledge of the prevention and control of healthcare-associated infections. In 2023, five workshops were conducted across the provinces of Huambo, Uíge, Luanda, Cunene, and Moxico, where 260 technicians received training aimed at improving the practical skills and expertise necessary for effective health risk management [22]. Furthermore, with support from WHO, the Angolan Ministry of Health conducted training on epidemiological intelligence and the use of DHIS2, a health information management system, to enhance disease surveillance and health data management. Epidemiological intelligence is an

ljem poboljšanja nadzora nad bolestima i upravljanja zdravstvenim podacima. Epidemiološka obaveštajna služba predstavlja pristup usmeren na unapređenje nadzora javnog zdravlja, koristeći napredne podatke i tehnologije za analizu rizika i podršku u donošenju odluka. Umesto da samo prati bolesti, epidemiološka obaveštajna služba teži da predvidi rizike i pruži tačne informacije kako bi zaštitila zdravlje stanovništva.

Prema analizi opšteg državnog budžeta, koju je sproveo UNICEF Angola, opšti državni budžet za 2024. procenjen je na 24,7 milijardi kwanzas, od čega je 5,5 odsto (oko 1,36 milijardi kwanza) izdvojeno za zdravstvo. Budžet za zdravstvo za 2024. godinu predstavlja nominalno povećanje od 1,3 odsto u odnosu na 2023. godinu. Prema iznetim podacima, značajan deo budžeta je usmeren na izgradnju, prekvalifikaciju i opremanje zdravstvene infrastrukture, što ima za cilj proširenje pristupa i kvaliteta usluga u različitim regionima zemlje [23]. Štaviše, budžet takođe naglašava važnost ljudskog kapitala, sa resursima dodeljenim za obuku i kvalifikaciju zdravstvenih radnika. Programi usmereni na borbu protiv pothranjenosti dece, vakcinaciju protiv malarije i druge aktivnosti javnog zdravlja dobijaju značajna ulaganja, usklađujući se sa prioritetima vlade za poboljšanje zdravlja stanovništva. Međutim, alokacija za zdravstvene informacione i komunikacione tehnologije, iako prisutna, i dalje je ograničena, što sugerise da ovoj oblasti treba posvetiti više pažnje kako bi se poboljšalo upravljanje zdravstvenim uslugama i njihova efikasnost.

Glavni cilj ZIS-a u Angoli je poboljšanje prikupljanja, obrada, analiza i širenje zdravstvenih informacija za unapređenje koordinacije i dostupnosti, kvaliteta i efikasnosti zdravstvenih intervencija. Trenutno, upravljanje ZIS-om predstavlja jedan od glavnih izazova za zdravstvene ustanove u celini, a posebno za bolnice, naročito kada teže unapređenju kliničkih i administrativnih procesa donošenja odluka zasnovanih na informacionim tehnologijama [21]. Stoga, kako Angola bude napredovala u obnovi svog zdravstvenog sistema, jačanje ZIS-a biće od ključnog značaja kako bi se osiguralo da politike javnog zdravlja budu zasnovane na dokazima, poboljšavajući jednakost, dostupnost i efikasnost usluga.

Indikatori u ZIS Angole

Analizom je potvrđeno da postojeći ZIS Angole poseduje 125 zdravstvenih indikatora neophodnih za formisanje predloga akcija, politika i praksi kojima se može doprineti unapređenju kvaliteta, finansiranja i upravljanja zdravstvenim uslugama, kao i smanjivanju nejednakosti u pristupu zdravstvenoj zaštiti.

Iako je DHIS2 osnovni alat za upravljanje zdravstvenim podacima, direktan pristup podacima koji se uno-

approach that strengthens public health surveillance by leveraging advanced data analytics and technologies for risk assessment and decision-making support. Beyond merely tracking diseases, epidemiological intelligence aims to predict health risks and deliver accurate information to safeguard population health.

According to an analysis of the general state budget conducted by UNICEF Angola, the 2024 budget is estimated at 24.7 billion kwanzas, with approximately 5.5 percent (around 1.36 billion kwanzas) allocated to health. This represents a nominal increase of 1.3 percent in the health budget compared to 2023. A significant portion of these funds is dedicated to the construction, refurbishment, and equipping of health infrastructure, aimed at expanding access to and improving the quality of services across various regions of the country [23]. Moreover, the budget underscores the importance of human capital, allocating resources for the training and professional development of health workers. Significant investments are directed towards programs combating child malnutrition, malaria vaccination, and other public health initiatives, reflecting government priorities to improve population health. However, funding for health information and communication technologies, while included, remains limited, indicating a need for greater focus in this area to enhance the management and efficiency of health services.

The primary goal of HIS in Angola is to enhance the collection, processing, analysis, and dissemination of health data to improve coordination, accessibility, quality, and efficiency of health interventions. Currently, managing the HIS remains one of the major challenges faced by healthcare institutions overall-and hospitals in particular-especially as they seek to leverage information technologies to support more effective clinical and administrative decision-making [21]. Therefore, as Angola continues to rebuild its health system, strengthening HIS will be essential to ensure that public health policies are evidence-based, thereby enhancing the equity, accessibility, and efficiency of health services.

Health indicators within Angola's HIS

The analysis confirmed that Angola's HIS includes 125 health indicators, which are essential for developing proposals for actions, policies, and practices aimed at improving the quality, financing, and management of health services, as well as reducing inequalities in access to healthcare.

Although DHIS2 serves as a fundamental tool for managing health data, direct access to the system is restricted. Only authorized users, such as healthcare technicians and managers, are permitted to access de-

se u sistem je ograničen. Samo ovlašćeni korisnici, kao što su zdravstveni tehničari i menadžeri, mogu pristupiti detaljnim i osjetljivim informacijama, obezbeđujući privatnost i bezbednost podataka.

Stoga Kancelarija za studije, planiranje i statistiku Ministarstva zdravlja Angole, kao delegirano telo Nacionalnog instituta za statistiku, objavljuje Godišnjak zdravstvene statistike, koji je rezultat rada zdravstvenih tehničara uključenih u zdravstveni informacioni sistem na svim nivoima. Ovaj dokument predstavlja zdravstvene indikatore stanovništva Angole i služi kao zvanična referenca za menadžere, partnere i širu javnost.

Godišnjak zdravstvene statistike za 2021. godinu, dostupan u štampanoj i digitalnoj verziji na veb stranici Nacionalnog instituta za statistiku, pruža sveobuhvatan

tailed and sensitive information, thereby ensuring data privacy and security.

Therefore, the Office of Studies, Planning and Statistics of the Ministry of Health of Angola, acting as a delegated body of the National Institute of Statistics, publishes the *Yearbook of health statistics*. This publication reflects the work of health technicians engaged in HIS at all levels. It presents key health indicators for Angola's population and serves as an official reference for policymakers, partners, and the general public.

The *Yearbook of Health Statistics 2021*, available in both print and digital formats on the website of the National Institute of Statistics, offers a comprehensive and detailed overview of the country's health landscape and serves as a vital tool for decision-making.

Tabela 1. Grupe pokazatelja Zdravstvenog informacionog sistema Angole

1. Demografski pokazatelji • Ukupna populacija; • Indeks maskuliniteta (broj muškaraca na 100 žena) • Gruba stopa mortaliteta; • Stopa smrtnosti novorođenčadi; • Očekivano trajanje života pri rođenju.
2. Pokazatelji ljudskih resursa i infrastrukture • Broj lekara na 10.000 stanovnika; • Broj medicinskih sestara na 10.000 stanovnika; • Javne i privatne zdravstvene jedinice u zemlji.
3. Indikatori zdravstvenih usluga • Ukupan broj obavljenih konsultacija; • Konsultacije koje se obavljaju u bolnicama, domovima zdravlja i punktovima; • Glavne specijalnosti koje pohađaju; • Stopa popunjenosti bolnica; • Prosečna dužina boravka u bolnici; • Promet bolničkih kreveta.
4. Indikatori morbiditeta • Stopa incidencije: meri pojavu novih slučajeva bolesti u populaciji tokom određenog perioda. • Stopa smrtnosti: označava procenat smrtnih ishoda među osobama sa dijagnostikovanom određenom bolešću. • Smrti: broj smrtnih slučajeva uzrokovanih specifičnom bolešću ili stanjem. • Novi slučajevi: odnosi se na broj novih slučajeva dijagnostikovane bolesti tokom određenog perioda. • Bolesti koje treba prijaviti, sa glavnim uzrocima morbiditeta, u opadajućem redosledu: - o Akutne respiratorne bolesti (teška upala pluća kod dece mlađe od 5 godina), - o Dijareja sa dehidracijom kod dece mlađe od pet godina, - o Teške akutne respiratorne infekcije kod dece starije od 5 godina. - o Malaria: Glavni uzrok morbiditeta u zemlji.
5. Indikatori mortaliteta • Stopa smrtnosti majki na 100.000 živorođenih; • Stopa mortaliteta od bolesti koje treba prijaviti na 100.000 stanovnika; • Stopa mortaliteta usled teške neuhranjenosti dece mlađe od 5 godina po pokrajinama na 100.000 stanovnika.

Table 1. Indicator groups in Angola's HIS

1. Demographic indicators • Overall population; • Masculinity ratio (number of males per 100 females); • Crude mortality rate; • Infant mortality rate; • Life expectancy at birth.
2. Indicators of human resources and infrastructure • Number of physicians per 10,000 Inhabitants; • Number of nurses per 10,000 Inhabitants; • Total number of public and private health facilities in the country.
3. Health services indicators • Total number of consultations performed; • Number of consultations conducted in hospitals, health centers, and health posts; • Primary medical specialties attended; • Hospital occupancy rate; • Average length of hospital stay; • Hospital bed turnover rate.
4. Morbidity indicators • Incidence Rate: Measures the number of new cases of a disease occurring in a population during a specific period. • Mortality Rate: Indicates the percentage of deaths among individuals diagnosed with a particular disease. • Deaths: The total number of fatalities caused by a specific disease or condition. • New Cases: Refers to the number of newly diagnosed cases of a disease within a defined time frame. • Notifiable Diseases – Main Causes of Morbidity (in descending order): - o Acute respiratory diseases (severe pneumonia in children under 5 years), - o Diarrhea with dehydration in children under 5 years, - o Severe acute respiratory infections in children over 5 years, - o Malaria, the leading cause of morbidity in the country.
5. Mortality indicators • Maternal mortality rate per 100,000 live births; • Mortality rate from notifiable diseases per 100,000 inhabitants; • Mortality rate due to severe malnutrition among children under 5 years, by province, per 100,000 inhabitants.

i detaljan pregled zdravstvene situacije u zemlji i predstavlja važno sredstvo za donošenje odluka. Prema Godišnjaku zdravstvene statistike za 2021, zdravstveni indikatori u Angoli su grupisani u poglavlja koja pokrivaju različite dimenzije Sistema [13]. Ovi pokazatelji su izvučeni iz zdravstvenog informacionog sistema i nacionalnog zdravstvenog sistema, a dopunjeni su demografskim podacima Nacionalnog instituta za statistiku (Tabela 1).

Analiza pokazatelja u 2020. i 2021. godini

Bolji obuhvat vakcinacijom kao što su BCG (78,8%) i Rotavirus (68,5%) sugeriraju veću posvećenost i efikasnost u kampanjama vakcinacije koje se odnose na ove imunizacije. S druge strane, niske stope obuhvata vakcinacijom protiv žute groznice (44,0%), tetanusa i difterije -TT2 (trudnice 1,7%) ukazuju na prepreke u pristupu zdravstvenim uslugama, logističke propuste i moguće nedostatke u programima za specifične grupe, kao što su trudnice. Umereni obuhvat vakcinama u 2021. godini, kao što su hepatitis B (57,5%) i poliomijelitis (62,0% neaktivan i 64,2% oralni), pneumokokna konjugovana vakcina sa tri serotipa (Pneumo 3) (58,4%), pojačava potrebu za intenziviranjem napora za proširenjem vakcinacije.

Kao što prikazuje Tabela 2, najčešći direktni uzroci maternalnog mortaliteta uključuju krvarenje (77,59 smrtnih slučajeva u 2020. i 29,32 u 2021.), toksemiju

According to the publication, Angola's health indicators are organized into chapters reflecting various dimensions of the health system [13]. These indicators are derived from the Health Information System and the broader national health system, and are complemented by demographic data provided by the National Institute of Statistics (Table 1).

Indicator analysis for 2020-2021

Higher coverage rates for vaccines such as BCG (78.8%) and Rotavirus (68.5%) indicate stronger commitment and effectiveness in the implementation of vaccination campaigns targeting these diseases. In contrast, low coverage for yellow fever (44.0%) and TT2 vaccination among pregnant women (1.7%) points to challenges in healthcare access, logistical shortcomings, and weaknesses in targeted immunization programs for vulnerable groups, particularly pregnant women. Moderate coverage levels in 2021 for vaccines such as hepatitis B (57.5%), poliomyelitis (62.0% inactivated and 64.2% oral), and the pneumococcal conjugate vaccine (Pneumo 3) (58.4%) underscore the need to intensify efforts aimed at expanding immunization outreach.

As shown in Table 2, the most common direct causes of maternal mortality were hemorrhage (77.59 deaths in 2020 and 29.32 in 2021), toxemia (37.10 in

Tabela 2. Stopa maternalnog mortaliteta na 100.000 živorođene dece, direktni i indirektni uzroci smrti, 2020. i 2021. godine

Table 2. Maternal Mortality Rate per 100,000 Live Births by Direct and Indirect Causes, 2020 and 2021

Uzroci / Causes	Premiune osobe u 2020. / Recorded deaths in 2020	Premiune osobe u 2021. / Recorded deaths in 2021
Direktni uzroci smrti / Direct causes of death		
Krvarenje / Hemorrhage	77.59	29.32
Toksemija / Toxemia	37.10	54.15
Abortus / Abortion	11.76	59.08
Puerperalna infekcija / Puerperal infection	8.10	14.77
Ruptura Materice / Uterine rupture	14.11	11.13
Ektopična trudnoća / Ectopic pregnancy	1.31	3.85
Drugi uzroci / Other causes	37.88	82.62
Međuzbir / Subtotal	187.84	254.93
Indirektni uzroci smrti / Indirect causes of death		
Malarija / Malaria	19.07	61.64
HIV/AIDS / HIV/AIDS	4.96	7.71
Tuberkuloza / Tuberculosis	1.04	4.07
Hepatitis / Hepatitis	1.04	1.93
Drugi uzroci / Other causes	25.08	73.63
Međuzbir / Subtotal	51.20	148.97
Ukupno / Total	239.04	403.90

Izvor: Izveštaji pokrajinskih uprava i bolnica, Nacionalno odeljenje za statistiku, GEPE-MINSA / 2019.

Source: Reports from Provincial Administrations and Hospitals; National Department of Statistics, GEPE-MINSA (2019).

(37,10 u 2020. i 54,15 u 2021.), i abortus (11,76 u 2020. i 59,08 u 2021. godini), dramatično povećanje slučajeva abortusa između 2020 i 2021. Pored toga, puerperalne infekcije, ruptura materice i vanmaterična trudnoća takođe su doprinele smrtnosti majki, sa ukupno 187,84 direktnih smrti u 2020. i 1.254,93 u 2021. godini. Indirektni uzroci, kao što su malarija (19,7 u 2020. i 61,64 u 2021.) i HIV/AIDS (4,96 u 2020. i 7,71 u 2021.), beleže značajan porast iz godine u godinu. Štaviše, tuberkuloza i hepatitis su takođe među važnim indirektnim uzrocima, što ukazuje na potrebu za integrisanom zdravstvenom politikom koja se efikasno bavi ovim bolestima kako bi se smanjio uticaj na zdravlje majki. Međutim, važno je istaći da se dvostruko povećao ukupan broj smrtnih slučajeva kod majki, sa 239,04 u 2020. na 403,90 u 2021. godini.

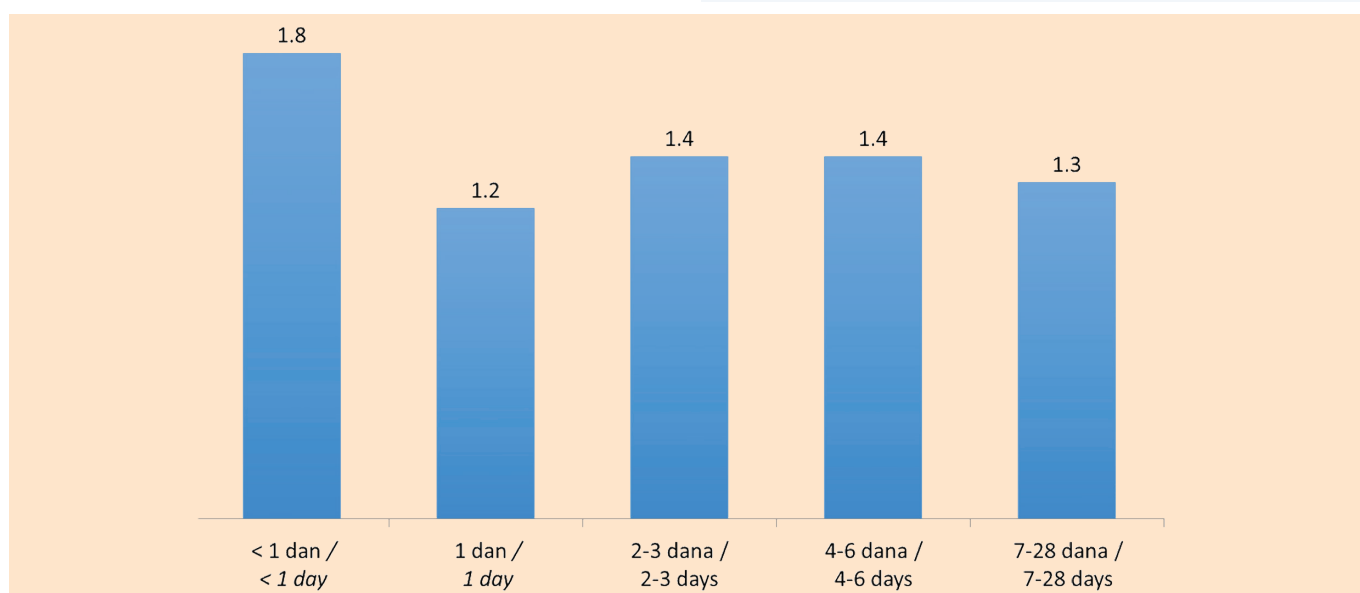
Grafikon 1 prikazuje stope neonatalne smrtnosti u različitim periodima ranog života. Najviša stopa je zabeležena u prvih 24 sata života (1,8). Ukupna stopa neonatalne smrtnosti iznosila je je 7,03 na 1.000 živorođenih, što otkriva visok nivo rizika u neonatalnom periodu i ističe potrebu za poboljšanjem kvaliteta zdravstvene zaštite novorođenčadi.

Prema izveštajima Nacionalne uprave za javno zdravlje u Angoli i Zdravstveno-statističkom godišnjaku za 2021. godinu, ukupna populacija Angole u 2020. iznosila je 33.428.486 stanovnika, a stopa novih slučajeva visokog krvnog pritiska bila je 929,6 na 100.000 stanovnika. Procenat hipertenzivne populacije iznosio je 0,93% u 2020. i 0,94% u 2021. godini, što ukazuje na mali porast slučajeva hipertenzije i odražava mogući trend porasta prevalencije ovog hroničnog stanja u zemlji. Što se tiče dijabetesa melitusa, stopa novoobolelih

2020 and 54.15 in 2021), and abortion (11.76 in 2020 and 59.08 in 2021), with a dramatic increase in abortion-related deaths between the two years. Other contributing factors included puerperal infections, uterine rupture, and ectopic pregnancy. In total, direct maternal deaths rose significantly from 187.84 in 2020 to 1,254.93 in 2021. Indirect causes of maternal mortality, such as malaria (19.7 in 2020 and 61.64 in 2021) and HIV/AIDS (4.96 in 2020 and 7.71 in 2021), showed marked year-on-year increases. Tuberculosis and hepatitis also remained significant contributors, underscoring the need for an integrated health policy that addresses these coexisting conditions to mitigate their impact on maternal health. Notably, the total number of maternal deaths nearly doubled, rising from 239.04 in 2020 to 403.90 in 2021.

Figure 1 shows the neonatal mortality rates across different periods of early life. The highest rate was recorded within the first 24 hours of life (1.8). The overall neonatal mortality rate was 7.03 per 1,000 live births, indicating a high level of risk during the neonatal period and highlighting the need to improve the quality of newborn healthcare.

According to the Angola National Public Health Administration and the 2021 Health Statistical Yearbook, Angola's total population in 2020 was 33,428,486. The incidence rate of new hypertension cases was 929.6 per 100,000 inhabitants. The prevalence of hypertension slightly increased from 0.93% in 2020 to 0.94% in 2021, suggesting a potential upward trend in this chronic condition. Regarding diabetes mellitus, the incidence rate of new cases was 53.81 per 100,000 in 2020 and slightly decreased to 52.66 in 2021. However,



Grafikon 1. Stopa mortaliteta novorođenčadi na 1.000 živorođenih

Izvor: Izveštaji Pokrajinskih direkcija, Narodne bolnice, Odeljenja za statistiku GEPE-MINSA/2019. Obuhvata nacionalne i pokrajinske bolnice.

Figure 1. Infant mortality rate per 1,000 live births

Source: Reports from Provincial Directorates and National Hospitals; Department of Statistics, GEPE-MINSA (2019). Data includes both national and provincial hospitals.

u 2020. godini iznosila je 53,81 na 100.000 stanovnika, a u 2021. godini 52,66, dok je procenat stanovništva sa dijabetesom bio 0,97% u 2020. i 1,88% u 2021. godini [13].

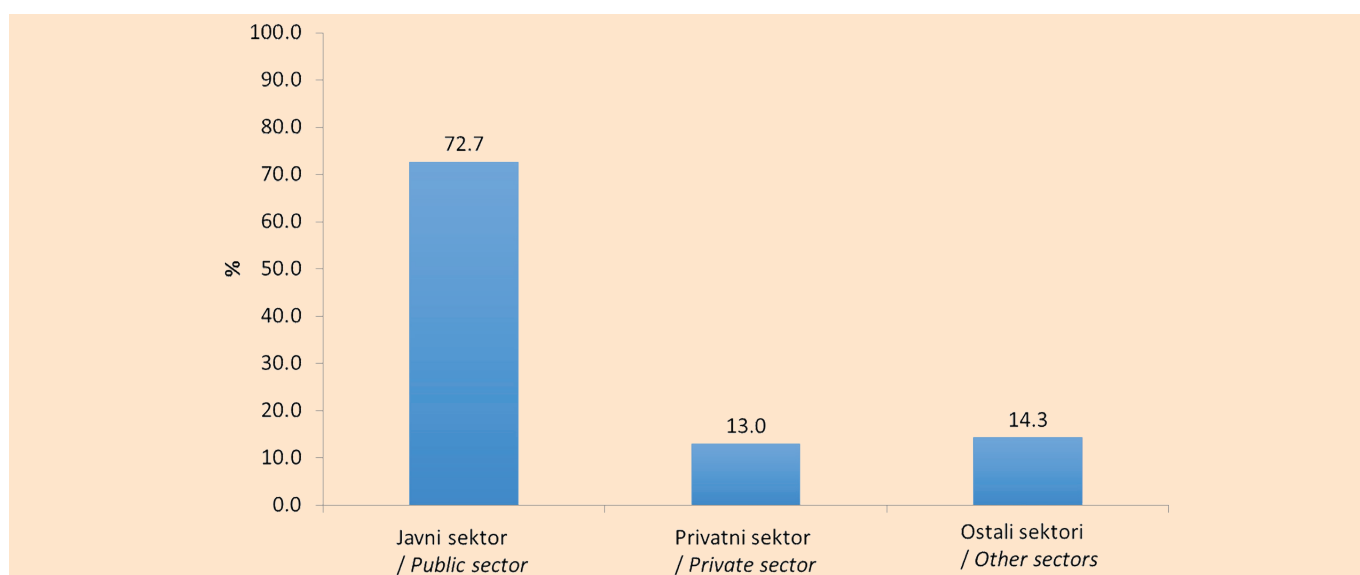
U istom periodu, u 2020. godini malarija je zabeležila alarmantan broj od 22.974,06 novih slučajeva na 100.000 stanovnika, što ukazuje na perzistenciju ove bolesti u zemlji, koja i dalje predstavlja jedan od glavnih problema javnog zdravlja (Tabela 2). U 2021. godini, broj slučajeva malarije je ostao visok, što ukazuje da, uprkos naporima da se ona kontroliše i spreči, bolest nastavlja da pogađa veliki deo populacije. Što se tiče tuberkuloze, vidimo da ona i dalje predstavlja zdravstveni problem, sa 192,94 novih slučajeva u 2020. Iako postoji blagi pad u 2021. sa 182,01 novih slučajeva na 100.000 stanovnika, ova stopa i dalje pokazuje da je tuberkuloza stalni izazov, posebno u regionima sa lošijom infrastrukturom zdravstvene zaštite gde rano otkrivanje i odgovarajući tretman mogu biti ograničeni. Još jedan relevantan podatak je HIV/AIDS, sa 89,71 novim slučajem u 2020. godini i 115,24 slučaja na 100.000 stanovnika u 2021 [13]. Iako je broj novih slučajeva HIV-a opao, epidemija i dalje predstavlja jedan od glavnih izazova javnog zdravlja u Angoli. Za njeno uspešno suzbijanje neophodni su snažne mere prevencije, obrazovanje i dostupnost efikasnih politika lečenja, kao i unapređenje zdravstvene infrastrukture, pristupa ranoj dijagnozi i sprovođenje edukativnih kampanja koje podstiču korišćenje preventivnih metoda. Takođe, važno je proširiti obuhvat tretmanom, naročito u ruralnim i ugroženim sredinama.

Prema Nacionalnoj upravi za ljudske resurse, Angola ima samo 2,48 lekara i 16,45 medicinskih sestara na 10.000 stanovnika, i nejednaku distribuciju ovih stručnjaka između ruralnih i urbanih područja. Prema podacima iz Zdravstvenog statističkog godišnjaka An-

the proportion of the population living with diabetes rose notably from 0.97% in 2020 to 1.88% in 2021 [13].

During the same period, malaria recorded an alarming incidence of 22,974.06 new cases per 100,000 inhabitants in 2020, highlighting the disease's persistence as one of the country's major public health challenges (Table 2). In 2021, malaria case numbers remained high, demonstrating that despite ongoing control and prevention efforts, the disease continues to affect a substantial portion of the population. Tuberculosis also remains a significant health concern, with 192.94 new cases per 100,000 inhabitants in 2020. Although there was a slight decline to 182.01 new cases per 100,000 in 2021, tuberculosis continues to pose challenges-particularly in areas with limited health-care infrastructure, where early diagnosis and effective treatment may be insufficient. Additionally, HIV/AIDS showed an increase, with 89.71 new cases per 100,000 in 2020 rising to 115.24 in 2021 [13]. Although the number of new HIV cases has declined, the epidemic remains one of Angola's most pressing public health challenges. Successfully controlling it requires robust prevention strategies, comprehensive education, and the widespread availability of effective treatment. Equally important are improvements in healthcare infrastructure, enhanced access to early diagnosis, and the implementation of educational campaigns that promote preventive measures. Expanding treatment coverage, particularly in rural and vulnerable communities, is also crucial to curbing the epidemic.

According to the National Human Resources Administration, Angola has only 2.48 doctors and 16.45 nurses per 10,000 inhabitants, with a marked disparity in their distribution between rural and urban areas. Data from the 2021 Health Statistical Yearbook of Ango-



Grafikon 2. Udeo zaposlenih lekara po sektorima (%)

Figure 2. Share of doctors employed across different sectors (%)

gole za 2021. godinu, postoji i nejednaka distribucija strukture zaposlenih lekara između javnog, privatnog i drugih sektora (Grafikon 2). Od ukupnog broja zaposlenih lekara, njih 5.610 (72,7%) radi u javnom sektoru, što ukazuje na važnost javnog zdravstvenog sistema kao glavnog poslodavca ovih stručnjaka u zemlji. S druge strane, privatni sektor zapošljava 12,96% lekara, dok 14,3% radi u drugim sektorima.

Prema izveštajima pokrajinske administracije i zdravstveno-statističkom godišnjaku za 2021, distribucija medicinskih sestara u javnom sektoru u Angoli pokazuje da je ukupan broj zaposlenih medicinskih sestara značajan, sa 40.006 medicinskih sestara koje rade u javnom sektoru. Ova radna snaga predstavlja suštinu osnovu za funkcionisanje sistema javnog zdravlja, s obzirom da su medicinske sestre često odgovorne za pružanje direktne nege stanovništvu i podršku medicinskim aktivnostima. Odnos medicinskih sestara prema broju lekaru u javnom sektoru je 7,13 medicinskih sestara po lekaru, što ukazuje na relativno uravnoteženu raspodelu za zadovoljenje operativnih zahteva u bolnicama i domovima zdravlja [13]. Ovaj odnos je od ključnog značaja za to da lekari dobiju potrebnu podršku u brizi o pacijentima, ali takođe ukazuje na potrebu za unapređenjem obuke i zapošljavanja medicinskih sestara u oblastima sa nedostatkom usluga, posebno u ruralnim regionima.

Prema Nacionalnom strateškom planu za zane-marene tropske bolesti (PEN-DTNs) 2021–2025, koji je zasnovan na informacijama iz Nacionalnog plana razvoja Angole, podaci pokazuju da je 2012. godine samo 44,6% stanovništva imalo pristup fiksnim zdravstvenim uslugama. Fiksne zdravstvene usluge u Angoli odnose se na usluge koje se nude u stalnim i fizičkim jedinicama, kao što su bolnice, zdravstveni centri, klinike i zdravstvene stanice, koje posluju na utvrđenim lokacijama i sa fiksnom strukturom. Ova činjenica je odraz ograničenja zdravstvenog sistema, posebno nakon perioda građanskog rata i značajnih oštećenja infrastrukture [12]. U 2017. godini pristup je povećan na oko 50%, što predstavlja napredak, ali uprkos tome, i dalje je polovina stanovništva bez adekvatne pokrivenosti, posebno u najudaljenijim regionima. Stoga, ovo skromno povećanje ukazuje na to da su, uprkos naporima, strukturne barijere, kao što su oskudica resursa, nedostatak infrastrukture i nedostatak osoblja, i dalje značajni izazovi koje treba prevazići da bi se unapredio pristup zdravstvenim uslugama. Sa ukupno 5.610 lekara u javnom sektoru, svaki lekar je tokom analiziranog perioda (2021. godine) u proseku obavio 3.664 konsultacije u primarnoj zdravstvenoj zaštiti, što je ekvivalentno brojcima od preko 10 konsultacija po stručnjaku na dan, imajući u vidu godinu dana neprekidnog rada.

la also reveals an uneven allocation of employed doctors across public, private, and other sectors (Figure 2). Of the total 5,610 employed doctors, 72.7% work in the public sector, emphasizing the critical role of the public health system as the primary employer of medical specialists in the country. In contrast, 12.96% of doctors are employed in the private sector, while 14.3% work in other sectors.

According to provincial administration reports and the 2021 Health Statistical Yearbook, Angola's public sector employs a substantial nursing workforce, with 40,006 nurses actively working in public health facilities. This workforce forms a vital pillar of the public health system, as nurses frequently provide direct patient care and support medical services. The nurse-to-doctor ratio in the public sector stands at 7.13 to 1, reflecting a relatively balanced distribution that helps meet the operational needs of hospitals and health centers [13]. This relationship is crucial for ensuring that physicians receive the necessary support in patient care. However, it also highlights the urgent need to enhance the training and deployment of nurses in underserved areas, particularly in rural regions. According to the National Strategic Plan for Neglected Tropical Diseases (PEN-DTNs) 2021–2025, which draws on data from Angola's National Development Plan, only 44.6% of the population had access to fixed health services in 2012. In Angola, fixed health services refer to care provided at permanent, physical facilities such as hospitals, health centers, clinics, and health stations, all operating from fixed locations with established infrastructure. This low coverage reflects the ongoing limitations of the health system, especially in the aftermath of the civil war, which caused extensive damage to healthcare infrastructure [12]. By 2017, access to fixed health services had increased to approximately 50%, marking progress; however, half of the population, particularly those in the most remote areas, still lacked adequate coverage. This modest improvement underscores the persistent structural barriers such as limited resources, inadequate infrastructure, and staff shortages that continue to hinder expanded healthcare access. In the public sector, with a total of 5,610 doctors, each physician conducted an average of 3,664 primary healthcare consultations during 2021. This workload amounts to over 10 consultations per doctor per day, assuming continuous year-round work, highlighting the substantial demand placed on healthcare specialists.

According to data from provincial administration reports, national hospitals, and the 2021 Health Statistical Yearbook of Angola, a substantial number of pregnant women received prenatal care in 2021, though

Tabela 3. Stopa hospitalizacija i bolnički kapaciteti

Specijalnosti / Specialties	Broj hospitalizacija na 100 stanovnika / Hospitalizations per 100 inhabitants		Stopa popunjenosti bolničkih kreveta / Hospital bed occupancy rate
	2020	2021	2021
Medicina ¹ / Medicine ¹	1.09	1.05	61.30%
Hirurgija ² / Surgery ²	0.16	0.13	65.85%
Ginekologija ³ / Gynecology ³	0.35	0.35	59.20%
Akušerstvo ⁴ / Obstetrics ⁴	56.14	57.48	69.50%
Pedijatrija ⁵ / Pediatrics ⁵	3.11	3.11	78.05%
Ortopedija ² / Orthopedics ²	0.05	0.05	63.44%
Drugi ² / Other ²	0.01	0.12	65.21%

Izvor: Izveštaji pokrajinskih uprava i narodnih bolnica.

Napomene:

- (1) Stanovništvo starosti 15 i više godina
- (2) Ukupno stanovništvo
- (3) Žensko stanovništvo starosti 15 i više godina
- (4) Trudnice
- (5) Stanovništvo starosti 0-14 godina

Table 3. Hospitalization Rates and Hospital Capacity

Source: Reports from Provincial Administrations and Public Hospitals.

Notes:

- (1) Population aged 15 years and older
- (2) Total population
- (3) Female population aged 15 and older
- (4) Pregnant women
- (5) Population aged 0-14 years

Prema podacima iz izveštaja pokrajinskih uprava, nacionalnih bolnica i Zdravstveno-statističkog godišnjaka 2021. godine u Angoli, značajan broj trudnica dobio je negu tokom trudnoće, ali i dalje postoji potreba za unapređenjem obuhvata i pristupa ovim uslugama. U 2021. godini obavljeno 1.373.062 konsultacija u Angoli u vezi sa prenatalnom zdravstvenom uslugom u domovima zdravlja i punktovima, dok je u bolnicama obavljeno 1.184.045 konsultacija. Ukupan broj konsultacija iznosio je 2.557.107 [13], što predstavlja značajan napor da se trudnicama pruži pomoć, ali razlika između broja akušerskih konsultacija u domovima zdravlja i bolnicama sugeriše da mnoge žene i dalje traže negu u složenijim zdravstvenim jedinicama, što može biti u vezi sa komplikacijama u trudnoći ili sklonošću ka specijalizovanijoj nezi.

Kao oblast sa najvećom potražnjom bolničkih usluga izdvaja se akušerstvo, sa stopama od 56,14 hospitalizacija na 100 žena u reproduktivnom dobu u 2020. godini i 57,48 u 2021. godini. Ovaj podatak odražava kontinuiranu potrebu za negom tokom trudnoće i porođaja, što ukazuje na važnost ove specijalnosti u zdravstvenom sistemu. Interna medicina ima stabilne stope, sa 1,09 u 2020. i 1,05 u 2021. godini, što ukazuje na konzistentan obrazac hospitalizacija u vezi sa opštim kliničkim stanjima. Specijalnosti kao što je ginekologija beleže niže stope hospitalizacije, sa 0,35 u obe godine. Pedijatrija je takođe stabilna, sa 3,11 hospitalizacija u obe godine, što ukazuje na stalnu potražnju za medicinskim uslugama kod dece. S druge strane, ortopedija ima stope od 0,05 u obe godine, što pokazuje veoma nisku učestalost hospitalizacija.

Što se tiče popunjenosti bolničkih kreveta u različitim medicinskim specijalnostima u 2021. godini, po-

there remains a need to further improve coverage and access. That year, a total of 1,373,062 prenatal consultations were conducted at health centers and health posts, while hospitals recorded 1,184,045 consultations. Together, these amounted to 2,557,107 prenatal consultations [13], reflecting significant efforts to support maternal health. However, the higher number of consultations in hospitals compared to health centers suggests that many women still seek care at more complex facilities, possibly due to pregnancy complications or a preference for specialized services.

Obstetrics stands out as the specialty with the highest demand for hospital services, with hospitalization rates of 56.14 per 100 women of reproductive age in 2020 and 57.48 in 2021. This highlights the ongoing need for care related to pregnancy and childbirth, underscoring the critical role of this specialty within the health system. Internal medicine maintained stable hospitalization rates, at 1.09 in 2020 and 1.05 in 2021, reflecting a consistent pattern of admissions for general clinical conditions. Gynecology recorded lower hospitalization rates, remaining steady at 0.35 for both years. Pediatrics also showed stable demand, with hospitalization rates of 3.11 in both years, indicating sustained need for child healthcare services. Conversely, orthopedics had very low hospitalization rates of 0.05 in both years, suggesting infrequent hospital admissions in this specialty.

Regarding hospital bed occupancy across medical specialties in 2021, data in Table 3 highlight increasing pressure on the health system, particularly in pediatrics, obstetrics, and surgery. This situation underscores

daci prikazani u **Tabeli 3.** ukazuju na sve veći pritisak na zdravstvene sisteme, uglavnom u oblastima pedijatrije, akušerstva i hirurgije, kao i na potrebu više efikasne strategije upravljanja bolnicom kako bi se garantovao kvalitet nege i dostupnost kreveta za pacijente.

Moguće je primetiti da odoljenje za internu medicinu ima stopu popunjenosti od 61,30%, što ukazuje na razumnu potražnju za kontinuiranom medicinskom negom, verovatno u vezi sa hroničnim bolestima i drugim stanjima koja zahtevaju produženo praćenje. Hirurgija, zauzvrat, ima stopu od 65,85%. Ginekologija, s druge strane, ima popunjenost od 59,20%, što je relativno niža vrednost, koja ukazuje na to da su hospitalizacije u ovoj specijalnosti ređe. S druge strane, akušerstvo se, sa stopom od 69,50%, izdvaja kao tražena specijalnost, verovatno zbog značajnog broja porođaja i potrebe za specijalizovanom negom tokom trudnoće i posle porođaja. Pedijatrija ima najveću stopu popunjenosti kreveta, 78,05%, što sugerise da su pedijatrijske bolničke usluge preopterećene, verovatno zbog infekcija i drugih stanja koja pogađaju decu, što povećava potrebu za poboljšanjima u pedijatrijskoj infrastrukturi kako bi se rešila velika potražnja. Ortopedija, sa druge strane, takođe ima značajnu stopu od 63,44%, dok druga kategorija, sa 65,21%, pokazuje visoku stopu, verovatno zbog varijacije u vrstama slučajeva koji se ne uklapaju u određene specijalnosti.

DISKUSIJA

Tokom skoro 40 godina nezavisnosti i građanskog rata, od 1961. do 2002. godine, socioekonomska infrastruktura Angole, uključujući puteve, škole i zdravstvene ustanove, bila je uništena, a pružanje javnih usluga ozbiljno narušeno. Slaba sposobnost zemlje da reaguje na zarazne bolesti rezultirala je velikim opterećenjem bolesti, pri čemu je zemlja zabeležila izbijanje žute groznice 2016. i kolere 2017–2018, što je imalo značajan uticaj na zdravstvene usluge, kao što je obustavljanje rutine zdravstvene usluge [10]. Zemlja je ostala bez funkcionalnog sistema zdravstvene zaštite (njene stope smrtnosti majki i novorođenčadi bile su i još su gore od onih u uporedivim zemljama), sa nekim od najnižih stopa upisa u osnovno obrazovanje (bruto i neto) u poređenju sa podsaharskom Afrikom.

Zdravstveno stanje stanovništva Angole karakteriše visoka stopa smrtnosti majki i novorođenčadi, veliki teret zaraznih bolesti i sve veći broj hroničnih i degenerativnih bolesti, kao i preranog mortaliteta koji se može sprečiti, kao što je prethodno navedeno [24]. Od 2005. godine, iako su učestalost dece sa malom telesnom težinom i plodnost značajno smanjeni, ključni indikatori poput smrtnosti novorođenčadi i dece mlađe od pet godina, smrtnosti majki i prevalencije HIV-a deluju

the need for more effective hospital management strategies to ensure quality care and maintain bed availability for patients. The internal medicine department recorded an occupancy rate of 61.30%, reflecting steady demand for ongoing medical care, likely related to chronic illnesses and conditions requiring extended follow-up. Surgery showed a higher occupancy rate of 65.85%. Gynecology had a comparatively lower rate of 59.20%, indicating less frequent hospitalizations in this specialty. Obstetrics stood out with the highest occupancy rate of 69.50%, likely due to the significant volume of births and the specialized care required during pregnancy and postpartum. Pediatrics has the highest hospital bed occupancy rate at 78.05%, indicating that pediatric services are under considerable strain—likely driven by infections and other conditions affecting children. This highlights an urgent need to strengthen pediatric infrastructure to meet growing demand. Orthopedics also shows a substantial occupancy rate of 63.44%, while the “Other” category records a high rate of 65.21%, which may reflect a diverse range of cases that do not fall neatly within specific specialties.

DISCUSSION

During nearly four decades of independence and civil war (1961–2002), Angola's socioeconomic infrastructure, including roads, schools, and health facilities, was devastated, severely disrupting public service delivery. The country's limited capacity to manage infectious diseases has contributed to a high disease burden, as evidenced by major outbreaks such as yellow fever in 2016 and cholera in 2017–2018, both of which significantly disrupted routine health services [10]. The country was left without a functioning health care system, reflected in maternal and infant mortality rates that were, and remain, among the highest compared to similar countries, and recorded some of the lowest gross and net primary school enrollment rates in sub-Saharan Africa.

The health status of the Angolan population is marked by high maternal and infant mortality, a heavy burden of infectious diseases, rising rates of chronic and degenerative conditions, and significant levels of preventable premature mortality [24]. Since 2005, while the incidence of underweight children and fertility rates have declined considerably, key indicators, such as infant and under-five mortality, maternal mortality, and HIV prevalence, have shown little improvement and remain high relative to the regional average [14]. Vaccines are among the most powerful tools available for protecting lives and preventing diseases like polio. By reducing the incidence of vaccine-preventable illnesses, they ease the burden on the healthcare

stagnirajuće, ali su i dalje visoki u poređenju sa regionalnim prosekom [14]. Vakcina je jedno od najmoćnijih sredstava koje imamo na raspolaganju da zaštitimo živote i sprečimo bolesti kao što je dečija paraliza, ublažavajući pritisak na naš zdravstveni sistem i omogućavajući da se dragoceni resursi usmere na lečenje drugih stanja koja vakcine ne mogu da spreče [17]. Uprkos stalnim naporima, Angola se i dalje suočava sa brojnim izazovima u obezbeđivanju imunizacije stanovništva. Prema podacima SZO, nalazi se među tri zemlje u afričkom regionu sa najvećim brojem dece koja nisu primila nijednu dozu vakcine (deca sa nultom dozom). Procenjuje se da je oko pola miliona dece nevakcinisano protiv bolesti koje pokrivaju Penta 1 i Penta 3 vakcine. S druge strane, Angola treba da pojača imunizaciju dece protiv dečje paralize zbog tekuće epidemije izazvane uvozom virusa iz susednih zemalja.

Veliki broj konsultacija u vezi sa prenatalnom zdravstvenom zaštitom ukazuje na to da veliki deo ženske populacije ima pristup nezi tokom trudnoće, ali razlika između broja akušerskih konsultacija u domovima zdravlja i bolnicama sugerise da mnoge žene i dalje traže negu u složenijim zdravstvenim jedinicama, što može biti u vezi sa komplikacijama u trudnoći ili sklonošću ka specijalizovanijoj nezi. Međutim, iako je broj konsultacija značajan, i dalje je ključno nastaviti sa ulaganjem u proširenje pristupa prenatalnoj nezi, posebno u udaljenijim područjima, kao i poboljšanje kvaliteta nege u zdravstvenim ustanovama kako bi se osiguralo da sve trudnice dobiju uputstva, praćenje i negu neophodnu za zdravu trudnoću. Dvostruko veći broj smrtnih slučajeva majki u 2021. godini je alarmantan i ističe hitnu potrebu za poboljšanjem pristupa zdravstvenim uslugama, posebno za trudnice koje se suočavaju sa komplikacijama ili su izložene rizičnim stanjima kao što su malarija i HIV. Javne politike usmerene na adekvatno obrazovanje, prevenciju i lečenje, posebno u ranjivim regionima, od suštinskog su značaja za preokretanje ovog negativnog trenda i obezbeđivanje bezbednosti majki u zemlji. Ove stope ukazuju na potrebu za hitnim fokusom na uslove rađanja i neonatalnu negu, jer se mnogi od ovih smrtnih slučajeva mogu sprečiti odgovarajućim porođajnim intervencijama, kao što su specijalizovana medicinska nega i poboljšani zdravstveni uslovi za majke i novorođenčad. Štaviše, smrtnost novorođenčadi u period između 7 i 28 dana života naglašavaju važnost postnatalne nege za sprečavanje komplikacija u prvim nekoliko dana života, kao što su infekcije i respiratorna stanja. Vredi napomenuti da povećanje smrtnosti u prvim danima života naglašava važnost efikasnijih programa zdravlja majke i deteta, uključujući jačanje neonatoloških jedinica, obuku zdravstvenih radnika i povećanje pristupa kvalitetnim medicinskim uslugama

system and free up critical resources for treating conditions that cannot be prevented through immunization [17]. Despite ongoing efforts, Angola continues to face significant challenges in achieving widespread immunization coverage. According to WHO data, it ranks among the three African countries with the highest number of zero-dose children (those who have not received even a single vaccine). An estimated half a million children remain unvaccinated against diseases targeted by the Penta 1 and Penta 3 vaccines. In addition, Angola must urgently strengthen polio immunization efforts in response to an ongoing outbreak fueled by virus importation from neighboring countries.

The high number of prenatal consultations suggests that a substantial portion of the female population has access to pregnancy care. However, the disparity between consultations at health centers and hospitals indicates that many women still seek care at higher-level facilities, possibly due to complications or a preference for specialized services. While the overall number of consultations is encouraging, it remains essential to expand access to antenatal care in remote areas and enhance the quality of services across all health facilities, ensuring that every pregnant woman receives adequate guidance, monitoring, and care for a healthy pregnancy. The doubling of maternal deaths in 2021 is deeply alarming and underscores the urgent need to improve access to health services, particularly for pregnant women facing complications or high-risk conditions such as malaria and HIV. Effective public policies focused on education, prevention, and treatment, especially in vulnerable regions, are essential to reverse this trend and safeguard maternal health. These high mortality rates also point to an urgent need to strengthen birth conditions and neonatal care, as many maternal and newborn deaths are preventable through timely interventions, skilled medical assistance, and improved health infrastructure. Additionally, elevated infant mortality between 7 and 28 days of life highlights the critical importance of postnatal care in preventing early-life complications, such as infections and respiratory illnesses. It is worth noting that the rise in mortality during the early days of life underscores the urgent need for more effective maternal and child health programs. This includes strengthening neonatal care units, enhancing the training of healthcare workers, and expanding access to quality medical services for women and children, particularly in vulnerable areas. According to UNICEF's 2015 report *Children and Women in Angola*, malaria, diarrhea, acute respiratory infections, and measles remain among the leading causes of death in children under five. Public health policies must therefore ad-

za žene i decu u ugroženim područjima. Štaviše, prema izveštaju Dečjeg fonda Ujedinjenih nacija (UNICEF) iz 2015. godine pod nazivom „Deca i žene u Angoli“, malarija, dijareja, akutne respiratorne infekcije i boginje spadaju među glavne uzroke smrti dece mlađe od 5 godina. Međutim, javnozdravstvena politika treba da razmotri ne samo poboljšanje uslova tokom porođaja, već i kontinuitet nege u prvim danima nakon rođenja, kao i intenziviranje prevencije navedenih bolesti, koje su česti uzroci smrtnosti odojčadi. U Angoli, malarija, tuberkuloza i HIV su perzistentne bolesti u zemlji, i predstavljaju glavne probleme javnog zdravlja. Međutim, analiza prevalencije hroničnih bolesti u Angoli otkriva značajne podatke koji ukazuju na potrebu kontinuiranog fokusiranja na javno zdravlje, posebno u vezi sa stanjima kao što su visok krvni pritisak i dijabetes melitus. Iako je broj obolelih od dijabetesa još uvek relativno nizak, neophodno je strogo praćenje ove bolesti, s obzirom na njen sve veći uticaj na javno zdravlje, tako da ranom otkrivanju, adekvatnom lečenju i politikama javne prevencije treba dati prioritet kako bi se smanjio uticaj ovog stanja na zdravlje stanovništva, kao i poboljšao kvalitet života obolelih pacijenata. Pokazatelji pristupa konsultacijama i bolničkim uslugama beleže skromno povećanje, ali strukturne barijere, poput oskudice resursa, nedostatka infrastrukture i nedostatka osoblja, i dalje predstavljaju značajne izazove koje treba prevazići kako bi se unapredio pristup zdravstvenim uslugama.

Državno finansiranje zdravstva ostaje relativno nisko i predstavlja 5% ukupne javne potrošnje, ali je pravičnije i efikasnije pošto se javna potrošnja na primarnu zdravstvenu zaštitu utrostručila.

Ljudski resursi su važni za razvoj održivog sistema javnog zdravlja tokom vremena kroz razvoj i održavanje visoko kvalifikovane radne snage sa odgovarajućom tehničkom obukom, naučnim veštinama i specijalizovanim znanjem [25]. Angola ima samo 2, 48 lekara i 16,45 medicinskih sestara na 10.000 stanovnika, što je značajno niže u odnosu na druge zemlje sa snažnijim zdravstvenim sistemima, gde Svetska zdravstvena organizacija preporučuje u proseku 10 lekara na 10.000 stanovnika kako bi se garantovala adekvatna briga za stanovništvo.

Iako je obezbeđenost medicinskim sestrama povoljnija, još uvek je nedovoljna da garantuje efikasan i kvalitetan obuhvat celokupne populacije. Štaviše, nejednaka distribucija ovih stručnjaka između ruralnih i urbanih područja takođe predstavlja dodatni izazov za osiguravanje jednakog pristupa zdravstvenim uslugama svih građana. Istraživanje ukazuje na važnost nastavka ulaganja u kvalifikacije i obuku ovih stručnjaka, pored optimizacije distribucije medicinskih sestara kako bi se smanjile nejednakosti u pristupu zdravstvenim uslugama između različitih regiona zemlje.

dress not only the conditions surrounding childbirth but also ensure continuity of care in the immediate postnatal period and intensify efforts to prevent these common, yet largely avoidable, causes of infant mortality. In Angola, malaria, tuberculosis, and HIV remain widespread and continue to pose major public health challenges. At the same time, the growing prevalence of chronic non-communicable diseases, particularly hypertension and diabetes mellitus, highlights the need for sustained attention to public health strategies. Although diabetes prevalence is still relatively low, its rising impact calls for strict monitoring, early detection, effective treatment, and robust prevention policies to reduce its burden and improve the quality of life for those affected. While indicators show modest improvements in access to consultations and hospital services, significant structural barriers persist, including limited resources, inadequate infrastructure, and a shortage of healthcare personnel. Overcoming these obstacles is essential to ensuring broader and more equitable access to health services.

Although state funding for health remains relatively low, at just 5% of total public expenditure, it has become more equitable and efficient, with public investment in primary health care having tripled.

Human resources are critical for building a sustainable public health system by developing and maintaining a highly qualified workforce equipped with the necessary technical training, scientific expertise, and specialized knowledge [25]. Angola currently has only 2.48 doctors and 16.45 nurses per 10,000 inhabitants and these figures fall well below those of countries with stronger health systems. The World Health Organization recommends an average of 10 doctors per 10,000 inhabitants to ensure adequate population health care.

Although the number of nurses is relatively more favorable, it remains insufficient to ensure efficient, high-quality coverage for the entire population. Additionally, the uneven distribution of healthcare professionals between rural and urban areas presents a significant barrier to equitable access to health services. Research highlights the importance of continued investment in the training and qualification of nurses, alongside efforts to optimize their distribution, in order to reduce regional disparities and improve access to care across the country.

The fact that two-thirds of doctors work in the public sector reflects the government's commitment to providing affordable medical services to the broader population. While the private sector and other providers are smaller in number, they serve important roles catering to specific groups, such as the upper middle

Činjenica da dve trećine lekara radi u javnom sektoru, odražava posvećenost vlade zadovoljavanju potreba stanovništva kroz pristupačne medicinske usluge. Iako su brojevi u privatnom sektoru i drugim sektorima znatno manji, ovi segmenti igraju važnu ulogu u opsluživanju specifičnih niša, kao što su viša srednja klasa i kompanije ili organizacije koje nude medicinsku negu svojim zaposlenima. S druge strane, dominacija javnog sektora ukazuje na zavisnost stanovništva od javnog zdravstvenog sistema u pristupu medicinskim uslugama. Međutim, disparitet u raspodeli lekara može uticati na kvalitet i dostupnost nege, posebno u ruralnim ili udaljenim oblastima, gde je broj dostupnih javnih lekara često nedovoljan da zadovolji potražnju.

Postoji značajan pritisak na lekare u primarnoj zdravstvenoj zaštiti, što ukazuje na veliki obim posla i potencijalni rizik od profesionalnog sagorevanja, što može ugroziti kvalitet pružene nege, jer profesionalci svakodnevno treba da brinu o velikom broju pacijenata.

Vredi napomenuti da odnos između broja lekara i obima konsultacija naglašava hitnu potrebu za povećanjem broja lekara u javnom sektoru kako bi se smanjio obim posla po stručnjaku i poboljšala efikasnost nege. Štaviše, strategije kao što je proširenje pristupa zdravstvenoj zaštiti preko drugih stručnjaka, kao što su obučene medicinske sestre, i digitalizacija procesa mogu pomoći u ublažavanju ovog pritiska.

ZIS u Angoli je bio osnovno sredstvo u podršci formisanju javnih zdravstvenih politika, posebno u borbi protiv zanemarenih tropskih bolesti. Međutim, ZIS u Angoli, kojim upravlja Kancelarija za studije, planiranje i statistiku (GEPE) Ministarstva zdravlja, je prošao kroz značajnu tranziciju od 2015. godine, implementacijom platforme DHIS2, koja ima za cilj da podatke učini dostupnijim i vidljivijim zdravstvenim menadžerima. Ova modernizacija ZIS-a je značajna u odnosu na 2015. godinu, jer sa prelaskom na platformu DHIS2 ZIS omogućava snažniju podršku za donošenje odluka na različitim nivoima zdravstvenog sistema, kao što je istaknuto u Nacionalnom strateškom planu za zanemarene tropske bolesti u Angoli (PEN-DTN 2021–2025) [12]. Jačanjem ZIS-a ne samo da se podržava operacionalizacija zdravstvenih politika, već i informisano donošenje odluka o raspodeli resursa i obuci profesionalaca, čime se direktno doprinosi poboljšanju zdravstvenog sistema Angole. Ovo je usko povezano sa ekonomskim učinkom zemlje i nivoima ulaganja u održivost ovih inicijativa [26]. Ipak, potrebe za boljim donošenjem odluka u javnom zdravstvu mogu se zadovoljiti upotrebom kombinacije šest ključnih podsistema zdravstvenih informacija: popis stanovništva, ankete domaćinstava, nadzor javnog zdravlja, praćenje vitalnih događaja, statistika zdravstvenih usluga i praćenje resursa. U većini zemalja u ra-

class and companies offering healthcare to their employees. This dominance of the public sector underscores the population's reliance on public health services for medical care. However, disparities in the geographic distribution of doctors, particularly in rural and remote areas, limit the availability and quality of care, as the number of public doctors in these regions often falls short of demand.

Doctors in primary health care face significant workload pressures, managing a high volume of patients daily. This intense demand increases the risk of professional burnout, which can ultimately compromise the quality of care provided.

It is worth mentioning that the ratio between the number of doctors and the volume of consultations underscores the urgent need to increase the number of public sector doctors to reduce individual workloads and enhance care efficiency. Additionally, strategies like expanding healthcare access through trained nurses and implementing digital health solutions can help ease this pressure and improve service delivery.

The Health Information System in Angola has been a crucial tool in supporting the formulation of public health policies, particularly in the fight against neglected tropical diseases. Managed by the Office of Studies, Planning and Statistics (GEPE) within the Ministry of Health, Angola's HIS has undergone a significant transformation since 2015 with the implementation of the DHIS2 platform. This modernization has improved data accessibility and visibility for health managers. The transition to DHIS2 marks a substantial advancement, enabling stronger decision-making support across different levels of the health system, as emphasized in the National Strategic Plan for Neglected Tropical Diseases in Angola (PEN-DTN 2021–2025) [12]. Strengthening HIS not only facilitates the implementation of health policies but also enables informed decision-making regarding resource allocation and workforce training, thereby directly contributing to the improvement of Angola's health system. This progress is closely linked to the country's economic performance and the level of investment dedicated to sustaining these initiatives [26]. Effective public health decision-making relies on the integration of six key health information subsystems: censuses, household surveys, public health surveillance, vital event monitoring, health service statistics, and resource tracking. In most developing countries, except for targeted disease-specific programs, public health surveillance primarily depends on passive reporting from health facilities designed to cover the entire population [27]. Additionally, sample-based surveys are conducted to manage costs.

zvoju, nadzor javnog zdravlja se osim za specifične programe kod određenih bolesti sprovodi putem pasivnog izveštavanja iz zdravstvenih ustanova, koje je dizajnirano da obuhvati celu populaciju [27]. Istraživanja se takođe sprovode na uzorku kako bi se ograničili troškovi.

S obzirom na to da je poslednjih godina značaj razmene informacija u donošenju odluka dobio veću pažnju u literaturi [28], važno je istaći da su rezultati ovog istraživanja zasnovani na javno dostupnim informacijama, bilo da su to procene ili prikupljeni originalni podaci, dok informacije iz internih dokumenata iz zdravstvenog sektora nisu obuhvaćene.

Pored podataka koje je ZIS Angole već prikupio, dostupni su SZO globalni zdravstveni podaci [29]. Među njima, podaci zdravstvenih usluga igraju ključnu ulogu u upravljanju pacijentima, administraciji ustanove, nadzoru bolesti i praćenju pružanja usluga i korišćenja resursa [18]. Dok se rutinski podaci o zdravstvenim ustanovama prikupljaju i izveštavaju na redovnoj osnovi putem rutinskih zdravstvenih informacionih sistema [30], postoje i drugi izvori podataka o pacijentima koji se potencijalno pribavljaju za željenu svrhu, kao što su elektronski zdravstveni kartoni, ankete pacijenata, potraživanja, administrativni podaci, informacije o društvenim determinantama zdravlja, registri bolesti, potrošnja lekova, i laboratorijski podaci, nadzor nad bolestima, epidemiološka ispitivanja, klinička ispitivanja i recenzirana istraživanja (publikacije u naučnim časopisima koje su prošle proces recenzije, što znači da su stručnjaci iz iste oblasti pregledali, komentarisali i odobrili rad pre objavljivanja) [31]. Informacije o funkcionisanju ZIS-a Angole mogu se dobiti od različitih sektora i agencija koje su odgovorne za generisanje, sintezu, analizu i korišćenje podataka na državnom, regionalnom i globalnom nivou [6]. Njihove informacije su korisne kada zemlja nastoji da proceni efikasnost sistema zdravstvene zaštite, a potom i postigne univerzalnu zdravstvenu pokrivenost (UHC) i ciljeve održivog razvoja (SDG) [17], kao i za unapređenje kvaliteta rada zdravstvenih radnika [4].

Bolje informisanje takođe može poboljšati efikasnost u upravljanju farmaceutskim resursima. Na primer, implementacija podnacionalnog informacionog sistema u južnoafričkoj provinciji Istočni Kejp dovela je do poboljšanja pristupa farmaceutskim proizvodima, uz smanjenje zaliha osnovnih lekova za 39 procenata. Ovakva poboljšanja nesumnjivo dovode do boljih zdravstvenih ishoda, što može rezultirati povećanjem produktivnosti i, posledično, povećanjem stope rasta bruto domaćeg proizvoda [27].

Godišnje izveštavanje iz ZIS-a oblikuje naš utisak o relativnom napretku zdravstvenog sistema zemlje, mogućnostima koje se nude građanima i usmerava sadržaj nacionalnog i globalnog političkog diskursa [32]. Teh-

Given the growing recognition in recent years of the importance of information exchange in decision-making [28], it is important to note that this research relies solely on publicly available data, whether estimates or original collected data, and does not include information from internal health sector documents.

In addition to the data collected by Angola's HIS, global health data from WHO are also available [29]. Among these, health services data play a crucial role in patient management, facility administration, disease surveillance, and monitoring of service delivery and resource utilization [18]. While routine health facility data are regularly collected and reported through routine health information systems [30], other valuable sources of patient data exist. These include electronic health records, patient surveys, claims and administrative data, information on social determinants of health, disease registries, drug consumption records, laboratory results, epidemiological studies, clinical trials, and peer-reviewed research-publications vetted by experts in the field prior to publication [31]. Information on the functioning of Angola's HIS can be obtained from various sectors and agencies responsible for data generation, synthesis, analysis, and utilization at national, regional, and global levels [6]. This information is invaluable for assessing the effectiveness of the healthcare system, advancing toward universal health coverage (UHC) and the Sustainable Development Goals (SDGs) [17], and enhancing the quality of work among health professionals [4].

Improved information management can also enhance the efficiency of pharmaceutical resource management. For example, implementing a subnational information system in South Africa's Eastern Cape province improved access to essential medicines while reducing drug stockpiles by 39 percent. Such advancements not only lead to better health outcomes but also boost productivity, ultimately contributing to higher gross domestic product growth rates [27].

Annual reports from Angola's HIS shape our understanding of the country's health system progress, the opportunities available to citizens, and influence both national and global health policy discussions [32]. The technological advancement of Angola's HIS should be aligned with health priorities and the goal of universal health coverage [33]. Data from the HIS highlight that primary health care services-such as immunization-are crucial for improving health outcomes and promoting health equity [34], underscoring the need for optimal allocation of scarce resources [35]. Moreover, strengthening HIS is a priority to support informed decision-making on effective policies, services, and

nološki napredak ZIS-a Angole treba usaglasiti sa zdravstvenim prioritetima i univerzalnom zdravstvenom pokrivenosti [33]. Zdravstveni indikatori iz ZIS-a su pokazali da su usluge primarne zdravstvene zaštite, kao što je imunizacija, od ključne važnosti za poboljšanje zdravlja i zdravstvenu pravednost [34], da je neophodno optimalno alocirati oskudne resurse [35]. Štaviše, jačanje ZIS-a je prioritet, kako bi se generisale dobre odluke o efektivnim politikama, uslugama i ponašanju [36]. U ispunjavanju ove funkcije, ZIS Angole mora biti zasnovan ne samo na svim dostupnim i relevantnim informacijama [37], već na potpunim, visokokvalitetnim podacima iz izvora zasnovanih na populaciji i ustanovama [38,39], jer se one tiču zdravlja i bezbednosti pacijenata [40].

ZIS Angole nije savršen, ali njegovi mehanizmi za prikupljanje, obradu, analizu i prenos informacija, kao i za istraživanje, planiranje i kontrolu bolesti, treba da se unapređuju kako bi se bolje strukturirao, operacionalizovao, nadzirao, pratio i procenjivao učinak i kvalitet zdravstvenih usluga [9], kao i brzina, sigurnost i troškovi zdravstvene zaštite u brizi o pacijentima [41]. Osim toga, neophodno je da se prikupljaju tačne i pouzdane informacije jer su one osnova za donošenje odluka u svim gradivnim elementima zdravstvenog sistema i od suštinskog su značaja za razvoj i implementaciju politike upravljanja i regulacije, istraživanja u zdravstvu, razvoja ljudskih resursa, zdravstvenog obrazovanja i obuke, usluga i finansiranje.

ZAKLJUČAK

Moderan ZIS Angole uspostavilo je Ministarstvo zdravlja 2015. godine, i on obuhvata 125 zdravstvenih indikatora koji su grupisani u sledeće kategorije: demografske, ljudskih resursa i infrastrukture, zdravstvenih usluga, morbiditeta i mortaliteta. ZIS Angole čini skup komponenti koje funkcionišu kao mehanizam za prikupljanje, obradu, analizu i prenos zdravstvenih podataka kojima se može poboljšati briga o pacijentima, identifikovati zdravstveni trendovi u populaciji u nekim situacijama, ili uočiti rizične populacije. Zdravstvenim informacionim sistemom Angole rukovodi Kancelarija za studije, planiranje i statistiku Ministarstva zdravlja, koja koordinira prikupljanje, obradu, analizu i diseminaciju zdravstvenih podataka, koji su u saradnji sa Svetskom zdravstvenom organizacijom i finansijskom podrškom Evropske unije počeli da pripremaju Strateški plan za Nacionalni zdravstveni informacioni sistem za period 2024-2030. Ovaj plan ima za cilj da poboljša kvalitet i dostupnost zdravstvenih informacija, olakšavajući donošenje odluka zasnovanih na dokazima. Ovi naponi moraju da budu usmereni na izazove kao što su nedostatak pouzdanih podataka, nedovoljna digitalna infrastruktura, fragmentacija Sistema (sistem ima nisku koheziju zbog

health behaviors [36]. To fulfill this role, Angola's HIS must rely not only on all available and relevant information [37] but also on comprehensive, high-quality data from both population-based and facility-based sources [38,39], particularly those related to patient health and safety [40].

Although Angola's HIS is not without flaws, its mechanisms for collecting, processing, analyzing, and transmitting information, as well as for supporting research, planning, and disease control, require significant improvement. Enhancing these functions is essential to better structure, operationalize, monitor, and evaluate the performance and quality of health services [9], as well as to improve the speed, safety, and cost-effectiveness of patient care [41]. Moreover, the collection of accurate and reliable data is fundamental for informed decision-making across all components of the health system. It underpins the development and implementation of management and regulatory policies, health research, human resource development, education and training, service delivery, and financing.

CONCLUSION

Angola's modern Health Information System (HIS) was established by the Ministry of Health in 2015 and comprises 125 health indicators organized into key categories: demographic data, human resources and infrastructure, health services, morbidity, and mortality. HIS Angola functions as an integrated mechanism for collecting, processing, analyzing, and transmitting health data to improve patient care, monitor population health trends, and identify at-risk groups. The system is managed by the Office for Studies, Planning, and Statistics within the Ministry of Health, which oversees data collection, analysis, and dissemination. In collaboration with the World Health Organization and with financial support from the European Union, this office has initiated the development of the Strategic Plan for the National Health Information System covering the period 2024–2030. This plan aims to enhance the quality and accessibility of health information to support evidence-based decision-making. Efforts must address key challenges such as the lack of reliable data, insufficient digital infrastructure, fragmentation within the system (resulting from its piecemeal development over time) hospital inefficiencies, and inadequate information system management. If left unresolved, these issues undermine the effective monitoring and evaluation of health plans and programs, as well as the management of preventive, diagnostic, curative, and rehabilitative care.

fragmentiranog razvoja tokom vremena), bolnička neefikasnost i neadekvatno upravljanje informacionim sistemom. Nerešene, ove poteškoće dovode u pitanje efikasno sprovođenje praćenja i evaluacije zdravstvenih planova i programa, kao i upravljanje preventivnom, dijagnostičkom, kurativnom i rehabilitacionom zaštitom.

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ISPITIVANJE *IN VITRO* OSETLJIVOSTI *BORRELIA AFZELII*, UZROČNIKA LAJMSKE BORELIOZE, NA SUPERNATANTE *LACTIPLANTIBACILLUS PLANTARUM* I *SACCHAROMYCES BOULARDII*

ORIGINALNI RAD

ORIGINAL ARTICLE

IN VITRO SUSCEPTIBILITY OF *BORRELIA AFZELII*, THE CAUSATIVE AGENT OF LYME BORRELIOSIS, TO THE SUPERNATANTS OF *LACTIPLANTIBACILLUS PLANTARUM* AND *SACCHAROMYCES BOULARDII*

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SAŽETAK

Uvod: Lajmska borelijoza (LB) je multisistemsko oboljenje koje uzrokuju bakterije iz kompleksa *Borrelia burgdorferi* sensu lato, a prenose je ubodom krpelji roda *Ixodes*. Terapija antibioticima zahteva dugotrajno lečenje, dok trenutno na tržištu ne postoji topikalni proizvod za profilaktičku primenu nakon uboda krpelja koji bi sprečio lokalnu infekciju i dalju diseminaciju patogena u sistemsku cirkulaciju.

Cilj rada: Cilj studije bio je da se *in vitro* ispita uticaj supernatana probiotičkih mikroorganizama *Saccharomyces boulardii* i *Lactiplantibacillus plantarum* i njihovih mešavina na rast i pokretljivost *Borrelia afzelii*.

Materijali i metode: Korišćen je soj *B. afzelii*, prethodno izolovan iz krpelja vrste *Ixodes ricinus*, koji je umnožen do koncentracije 1–2 x 10⁶ borelija/mL u Barbour-Stoeckner-Kelly-H hranljivoj podlozi. Za ispitivanje osetljivosti testiranog soja na probiotičke mikroorganizme korišćena je modifikovana bujon mikrodiluciona metoda za borelije. Minimalne inhibitorne koncentracije (MIK) određene su posmatranjem broja i pokretljivosti borelija nakon 72 sata inkubacije pod anaerobnim uslovima u prisustvu supernatana, a u poređenju sa pozitivnom kontrolom – netretiranom kulturom *B. afzelii*.

Rezultati: MIK je definisana kao najniža koncentracija testiranog supernatanta pri kojoj borelije nisu bile pokretne a njihov broj je bio smanjen u odnosu na pozitivnu kontrolu. Definisane su sledeće MIK vrednosti: medijana 12,5% za *S. boulardii* i 6% za *L. plantarum*, dok je najniža MIK vrednost (medijana 0,8%) definisana za mešavinu supernatanta probiotičkih mikroorganizama.

Zaključak: Supernatanti *S. boulardii* i *L. plantarum* pokazali su antimikrobno dejstvo na *B. afzelii*, dok je mešavina ovih supernatana pokazala efektivniji inhibicioni efekat na rast i pokretljivost borelija. Dobijeni rezultati daju nam osnovu za dalja istraživanja molekularnih mehanizama inhibitornog dejstva probiotičkih mikroorganizama na rast borelija.

Ključne reči: Lajmska borelijoza, *Borrelia afzelii*, osetljivost, *in vitro*, probiotički mikroorganizmi, minimalne inhibitorne koncentracije

ABSTRACT

Introduction: Lyme borreliosis (LB) is a multisystem disorder caused by bacteria of the *Borrelia burgdorferi* sensu lato complex, transmitted to humans through the bite of *Ixodes* spp. ticks. Standard treatment typically involves prolonged antibiotic therapy. Currently, no topical product is available on the market for prophylactic use following a tick bite.

Aim: The aim of the study was to investigate *in vitro* the effects of supernatants derived from the probiotic microorganisms *Saccharomyces boulardii* and *Lactiplantibacillus plantarum*, and their mixtures, on the growth and motility of *Borrelia afzelii*.

Materials and methods: To test the susceptibility of *B. afzelii* to probiotic microorganisms, a modified broth microdilution method adapted for *Borrelia* species was employed. Minimum inhibitory concentrations (MICs) were determined by evaluating both the number and motility of *B. afzelii* after 72 hours of incubation with supernatants under anaerobic conditions, compared to a positive control consisting of untreated *B. afzelii* culture.

Results: The MIC was defined as the lowest concentration of the tested supernatant at which borrelia were non-motile and their number was reduced compared to the positive control. The following median MIC values were determined: 12.5% for *S. boulardii*, 6% for *L. plantarum*, and the lowest median MIC value of 0.8% was defined for the supernatant mixture of probiotic microorganisms.

Conclusion: The mixture of *S. boulardii* and *Lactiplantibacillus plantarum* exhibited the strongest inhibitory effect on the growth and motility of *B. afzelii*. These results provide a foundation for further investigation into the molecular mechanisms of the inhibitory activity of probiotic microorganisms against *Borrelia* species.

Keywords: Lyme borreliosis, *Borrelia afzelii*, susceptibility, *in vitro*, probiotic microorganisms, minimum inhibitory concentrations

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UVOD

Lajmska borelijoza (LB) je zoonoza čije uzročnike ubodom prenose inficirani krpelji roda *Ixodes*. Uzročnici LB su spiralne bakterije iz kompleksa *Borrelia burgdorferi* sensu lato (s.l.) [1,2]. Primarni vektori u Evropi su krpelji vrste *Ixodes ricinus* [3]. Budući da LB predstavlja multisistemsko oboljenje ljudi i životinja, bolest se može ispoljiti različitim kliničkim manifestacijama kao što su: kožne lezije, mišićno-skeletne, neurološke, okularne i/ili kardiovaskularne manifestacije, dok u nekim slučajevima, infekcija prolazi asimptomatski ili čak u kasnijim fazama LB može biti pogrešno dijagnostikovana zbog kompleksnosti kliničkih znakova i simptoma [2,4].

Kompleks *B. burgdorferi* s.l. obuhvata do sada 21 imenovanu vrstu borelija. Dok je u Severnoj Americi glavni uzročnik LB vrsta *Borrelia burgdorferi* sensu stricto (s.s.), u Evropi je prisutan veći diverzitet borelija sa pet potvrđenih patogenih vrsta: *Borrelia afzelii*, *Borrelia garinii*, *B. burgdorferi* s.s., *Borrelia spielmanii* i *Borrelia bavariensis*. Vrste *Borrelia lusitaniae*, *Borrelia valaisiana* i *Borrelia bissettii* su takođe izolovane ili detektovane kod ljudi, ali njihov patogeni potencijal nije u potpunosti razjašnjen [2].

Dok su u većini evropskih zemalja u krpeljima najzastupljenije vrste borelija *B. afzelii*, *B. garinii* i *B. valaisiana* [5], u Srbiji je najdominantnija vrsta *B. lusitaniae*, praćena vrstama *B. afzelii*, *B. bavariensis*, *B. garinii*, *B. valaisiana* i *B. burgdorferi* s.s. [6,7]. Najčešća klinička manifestacija lajmske bolesti u Srbiji je *erythema migrans*, koja je zabeležena u 93,2% slučajeva, slede neurološke, mišićno-skeletne, i kardiološke manifestacije, u 2,8%, 2,4%, odnosno 1,1% slučajeva [8].

Generalno, tok LB se može podeliti u tri kliničke faze. Prva faza – rana lokalizovana infekcija – najčešće se manifestuje kao kožna lezija *erythema migrans*, karakteristična crvena promena u obliku koncentričnog kruga na mestu uboda inficiranog krpelja koja se obično javlja sedam dana nakon infekcije. Ova lezija može biti praćena različitim simptomima uključujući groznicu, glavobolju, bolove u mišićima i zglobovima, kao i uvećanjem limfnih čvorova [1,2,9]. Druga faza – rana diseminovana infekcija – razvija se nekoliko nedelja do nekoliko meseci nakon uboda i ako se antibiotska terapija ne sprovede u prvoj fazi, borelije iz primarne kožne lezije mogu da diseminuju i tako zahvate nervni sistem, kožu, zglobove i srce. Treća faza – kasna diseminovana infekcija se javlja nekoliko meseci ili čak nekoliko godina nakon uboda inficiranog krpelja i može dovesti do teških neuroloških, reumatoloških i dermatoloških komplikacija [1,2]. Iako sve patogene vrste borelija mogu izazvati *erythema migrans* i diseminovati u cirkulaciju, *B. afzelii* najčešće ostaje lokalizovana na koži i često se povezuje sa kožnim manifestacijama koje

INTRODUCTION

Lyme borreliosis (LB) is a zoonosis, the causative agents of which are transmitted through the bite of infected ticks of the genus *Ixodes*. The causative agents of LB are spiral-shaped bacteria from the *Borrelia burgdorferi* sensu lato (s.l.) complex [1,2]. The primary vectors in Europe are ticks of the species *Ixodes ricinus* [3]. Since LB is a multisystemic disease affecting both humans and animals, it can present with various clinical manifestations, such as skin lesions, musculoskeletal, neurological, ocular, and/or cardiovascular symptoms. In some cases, the infection may be asymptomatic, while in later stages, LB can be misdiagnosed due to the complexity of its clinical signs and symptoms [2,4].

The *Borrelia burgdorferi* sensu lato (s.l.) complex currently comprises 21 named *Borrelia* species. While in North America the primary causative agent of LB is *Borrelia burgdorferi* sensu stricto (s.s.), Europe exhibits greater *Borrelia* diversity, with five confirmed pathogenic species: *Borrelia afzelii*, *Borrelia garinii*, *B. burgdorferi* s.s., *Borrelia spielmanii*, and *Borrelia bavariensis*. In addition, *Borrelia lusitaniae*, *Borrelia valaisiana*, and *Borrelia bissettii* have also been isolated or detected in humans, although their pathogenic potential has not yet been fully elucidated [2].

While *B. afzelii*, *B. garinii*, and *B. valaisiana* are the most common *Borrelia* species found in ticks across most European countries [5], in Serbia the dominant species is *B. lusitaniae*, followed by *B. afzelii*, *B. bavariensis*, *B. garinii*, *B. valaisiana*, and *B. burgdorferi* s.s. [6,7]. The most common clinical manifestation of Lyme disease in Serbia is *erythema migrans*, observed in 93.2% of cases, followed by neurological (2.8%), musculoskeletal (2.4%), and cardiac (1.1%) manifestations [8].

In general, the course of LB can be divided into three clinical stages. The first stage-early localized infection-most commonly presents as *erythema migrans*, a characteristic red skin lesion in the form of a concentric circle that appears at the site of the infected tick bite, typically around seven days after infection. This lesion may be accompanied by a range of symptoms, including fever, headache, muscle and joint pain, and swollen lymph nodes [1,2,9]. The second stage-early disseminated infection-develops several weeks to several months after the tick bite. If antibiotic therapy is not administered during the first stage, *Borrelia* from the primary skin lesion can disseminate throughout the body, potentially affecting the nervous system, skin, joints, and heart. The third stage-late disseminated infection-occurs several months or even years after the bite of an infected tick and can lead to severe neurological, rheumatological, and dermatological complications [1,2]. Although all pathogenic *Borrelia* species

se javljaju u trećoj fazi poput *acrodermatitis chronica atrophicans* (ACA) prisutnih isključivo u Evropi dok se *B. burgdorferi* s.s. povezuje sa reumatološkim manifestacijama, posebno lajmskim artritisom, koji je učestaliji u Severnoj Americi nego u Evropi. Vrste *Borrelia garinii* i *B. bavariensis* najčešće uzrokuju neurološke simptome, lajmsku neuroboreliozu, koji se javljaju u drugoj i trećoj fazi lajmske borelioze [2].

Nakon postavljanja dijagnoze, trajanje i doza antibiotske terapije (oralna ili intravenska) određuju se u zavisnosti od faze bolesti, starosti pacijenta, i njegovog imunološkog statusa, a u terapiji se najčešće koriste doksiciklin, amoksiciklin, ceftriakson, cefuroksim, i azitromicin, u vremenskom periodu od 10 do 30 dana u zavisnosti od oblika i faze bolesti [1]. Najbolja zaštita od LB jeste izbegavanje uboda krpelja i detaljan pregled kože nakon boravka u prirodi. Preventivna upotreba antibiotika nakon uboda krpelja se ne preporučuje iz razloga što nije svaki krpelj inficiran borelijama i neće svaki inficirani krpelj da prenese patogen nakon uboda. U Evropi ne postoje vodiči i/ili smernice za takvu namenu. Takođe, na tržištu do sada nije plasiran topikalni proizvod koji bi se primenjivao na koži nakon uboda krpelja i tako sprečio transfer borelija u kožu. Ne postoji ni preparat koji bi se koristio za lokalni tretman *erythema migrans* u cilju sprečavanja dalje diseminacije borelija u sistemsku cirkulaciju. Za razliku od patogenih vrsta borelija, koje mogu izazvati lokalne i sistemske manifestacije LB i zahtevaju antibiotsku terapiju, probiotski mikroorganizmi su pokazali pozitivne efekte na zdravlje ljudi [10,11]. Određeni sojevi proizvode antimikrobne supstance, poput organskih kiselina, bakteriocina, peptida i polisaharida, koje se tokom kultivacije oslobađaju u supernatante [12]. Probiotski kvasac *Saccharomyces boulardii* za sada nepoznatim mehanizmima, *in vitro* inhibira rast nekih patogenih i uslovno patogenih mikroorganizama poput *Candida albicans*, *Escherichia coli*, *Salmonella enterica* serovar Typhi, *Shigella dysenteriae*, *Vibrio cholerae*, *Salmonella enteritidis* [12,13]. Takođe, određene vrste bakterija mlečne kiseline među kojima je *Lactiplantibacillus plantarum*, sprečavaju kolonizaciju patogena kompeticijom za hranljive materije i adhezivna mesta, modifikacijom uslova sredine koja postaje nepovoljna za rast patogena, proizvodnjom antimikrobnih jedinjenja i modulacijom imunskog odgovora [14,15].

Transformacija bakterija tokom vremena i velika i/ili povećana potrošnja antibiotika širom sveta značajno doprinose porastu antimikrobne rezistencije, što predstavlja ozbiljnu pretnju po javno zdravlje na globalnom nivou. Samo tokom 2019. godine, antimikrobna rezistencija je bila odgovorna za smrt najmanje 1,27 miliona ljudi širom sveta, što jasno pokazuje da predstavlja

can cause erythema migrans and disseminate into the circulation, *B. afzelii* most often remains localized to the skin and is commonly associated with late-stage skin manifestations, such as *acrodermatitis chronica atrophicans* (ACA), a condition found exclusively in Europe. *Borrelia burgdorferi* s.s. is primarily associated with rheumatological manifestations, particularly Lyme arthritis, which is more frequently observed in North America than in Europe. *Borrelia garinii* and *B. bavariensis* are most often linked to neurological symptoms, including Lyme neuroborreliosis, which may occur during the second and third stages of the disease [2].

Following diagnosis, the duration and dosage of antibiotic therapy, administered either orally or intravenously, are determined based on the stage of the disease, the patient's age, and immune status. The most commonly used antibiotics include doxycycline, amoxicillin, ceftriaxone, cefuroxime, and azithromycin, typically prescribed for a period of 10 to 30 days, depending on the clinical form and stage of the disease [1]. The best protection against Lyme borreliosis (LB) is to avoid tick bites and to carefully examine the skin after spending time outdoors. Prophylactic antibiotic use following a tick bite is not recommended, as not every tick is infected with *Borrelia*, and not every bite from an infected tick results in transmission of the pathogen. Currently, there are no guidelines or recommendations for prophylactic antibiotic use after tick bites in Europe. To date, there is no topical product available on the market that can be applied to the skin after a tick bite to prevent the transmission of *Borrelia*. Similarly, no preparation exists for the local treatment of erythema migrans aimed at preventing further dissemination of *Borrelia* into the systemic circulation. Unlike pathogenic *Borrelia* species, which cause both local and systemic manifestations of LB requiring antibiotic therapy, probiotic microorganisms have demonstrated beneficial effects on human health [10,11]. Certain strains produce antimicrobial substances, such as organic acids, bacteriocins, peptides, and polysaccharides, that are released into the culture supernatant during cultivation [12]. The probiotic yeast *Saccharomyces boulardii* has been shown *in vitro* to inhibit the growth of various pathogenic and opportunistic microorganisms, including *Candida albicans*, *Escherichia coli*, *Salmonella enterica* serovar Typhi, *Shigella dysenteriae*, *Vibrio cholerae*, and *Salmonella enteritidis* [12,13]. Additionally, certain lactic acid bacteria, including *Lactiplantibacillus plantarum*, help prevent pathogen colonization by competing for nutrients and adhesion sites, altering environmental conditions to inhibit pathogen growth, producing antimicrobial compounds, and modulating the immune response [14,15].

ozbiljan rizik za zdravlje ljudi u svim životnim dobima [16]. Zbog ograničenja u lečenju lajmske borelioze, neophodno je razviti bezbedne i delotvorne alternativne pristupe, kao što je topikalni preparat na bazi biološki aktivnih komponenti, koji bi se profilaktički primenjivao nakon uboda krpelja ili na mestu primarne kožne lezije, s ciljem da spreči dalju diseminaciju borelija i time značajno smanji ili eliminiše potrebu za primenom antibiotika.

Cilj ove studije bio je da se *in vitro* ispita rast, razmnožavanje i pokretljivost *B. afzelii* u prisustvu supernatanata *S. boulardii*, *L. plantarum* i njihovih mešavina kao i da se odrede vrednosti njihovih minimalnih inhibitornih koncentracija (MIK).

MATERIJAL I METODE

U studiji je testiran soj *B. afzelii* RS163_11i, prethodno izolovan iz krpelja vrste *I. ricinus* [6], a koji je deo kolekcije izolata Instituta za medicinska istraživanja, Instituta od nacionalnog značaja za Republiku Srbiju, Univerziteta u Beogradu. Soj je čuvan na -80 °C u brucela-glicerol bujonu, rekultivisan u Barbour-Stoenner-Kelly-H (BSK-H) (HiMedia, India) podlozi i inkubiran na 33 °C do postizanja koncentracije borelija od 1–2 × 10⁶/mL, dok je za određivanje broja borelija/mL primenjena Neubauer komora za brojanje (Brand GmbH & Co. KG, Wertheim, Germany) u kombinaciji sa mikroskopiranjem u tamnom polju [17].

Za pripremu supernatanata korišćene su liofilizovane kulture iz komercijalno dostupnog probiotskog preparata, iz kojih su zatim izolovane čiste kulture *S. boulardii* i *L. plantarum* pripremljene na Katedri za mikrobiologiju i imunologiju, Farmaceutskog fakulteta Univerziteta u Beogradu.

Serije dvostrukih razblaženja supernatanta *S. boulardii*, *L. plantarum* i njihovih mešavina su pripremljene u BSK-H podlozi. Zapremina svakog testiranog supernatanta i njihove mešavine iznosila je 100 µL (početna maksimalna koncentracija 100%) koja je u opadajućim koncentracijama mešana sa 100 µL kulture ispitivanog soja *B. afzelii*, koncentracije 1–2 × 10⁶ borelija/mL, a samostalno služila kao pozitivna kontrola, dok je kao negativna kontrola korišćena BSK-H podloga. Od svakog testiranog probiotskog mikroorganizma (*S. boulardii*, *L. plantarum* i njihove mešavine), pripremljeno je po 10 serijskih dvostrukih razblaženja u opadajućim koncentracijama (od 100% do 0,2%), dok je mešavina supernatanata pripremljena u odnosu 1:1, dodavanjem po 50 µL svakog supernatanta u opadajućim koncentracijama počevši od maksimalne koncentracije, od 100% svakog probiotskog mikroorganizma.

Antibiotik ceftriakson je korišćen kao kontrolni antibiotik u bujon mikrodilucionoj metodi za borelije i te-

Bacterial evolution over time, combined with the widespread and increasing use of antibiotics globally, has significantly contributed to the rise of antimicrobial resistance, a major threat to public health worldwide. In 2019 alone, antimicrobial resistance was responsible for at least 1.27 million deaths globally, underscoring the serious risk it poses to human health across all age groups [16]. Due to the limitations in LB treatment, there is a need to develop safe and effective alternative approaches, such as a topical preparation based on biologically active components that can be applied prophylactically after a tick bite or at the site of the primary skin lesion. The goal is to prevent further dissemination of *Borrelia* infection and thereby significantly reduce or eliminate the need for antibiotic therapy.

The aim of this study was to investigate *in vitro* the growth, reproduction, and motility of *B. afzelii* in the presence of supernatants from *S. boulardii*, *L. plantarum*, and their mixtures, as well as to determine their minimum inhibitory concentration (MIC) values.

MATERIALS AND METHODS

The study tested the *B. afzelii* strain RS163_11i, previously isolated from *I. ricinus* ticks [6], and maintained within the isolate collection of the Institute for Medical Research, National Institute of the Republic of Serbia, University of Belgrade. The strain was preserved at -80 °C in Brucella-glycerol broth and subsequently recultivated in Barbour-Stoenner-Kelly H (BSK-H) medium (HiMedia, India). Cultivation was carried out at 33 °C until a *Borrelia* concentration of 1–2 × 10⁶ cells/mL was achieved. Cell counts were determined using a Neubauer counting chamber (Brand GmbH & Co. KG, Wertheim, Germany) under dark-field microscopy [17].

To prepare the supernatants, lyophilized cultures from a commercially available probiotic formulation were used as the source for isolating pure cultures of *S. boulardii* and *L. plantarum*. These isolates were prepared at the Department of Microbiology and Immunology, Faculty of Pharmacy, University of Belgrade.

Two-fold serial dilutions of *S. boulardii*, *L. plantarum*, and their mixed supernatants were prepared in BSK-H medium. For each test, 100 µL of the undiluted supernatant (initial concentration 100%) or its dilution was mixed with 100 µL of the *B. afzelii* culture (1–2 × 10⁶ cells/mL). The *B. afzelii* culture without supernatant served as a positive control, while BSK-H medium without the addition of bacteria was used as a negative control. For each tested probiotic microorganism (*S. boulardii*, *L. plantarum*, and their mixtures), ten serial two-fold dilutions were prepared, ranging from 100% to 0.2% concentration. The mixed supernatant was prepared in a 1:1 ratio by combining 50 µL of each in-

stiran u rasponu 8–0,016 µg/mL kao što je prethodno opisano [18].

Antimikrobna aktivnost supernatanata i kontrolnog antibiotika ceftriaksona je ispitivana primenom modifikovane bujon mikrodilucione metode za borelije, s obzirom na to da Evropski komitet za ispitivanje antimikrobne osetljivosti (*European Committee on Antimicrobial Susceptibility Testing – EUCAST*) i Institut za kliničke i laboratorijske standarde (*Clinical and Laboratory Standards Institute – CLSI*) ne definišu uputstva i kriterijume za izvođenje ove metode za borelije, kao ni granične vrednosti MIK za antibiotke [17]. Ukratko, za bujon mikrodilucionu metodu i određivanje MIK vrednosti antibiotika i testiranih supernatanata korišćene su sterilne plastične 96-mikrotitarske ploče. Prva kolona je služila kao pozitivna kontrola (kultura borelija), druga kolona kao negativna kontrola (BSK-H podloga), a od treće do 12. kolone bazeni su punjeni mešavinom borelija i testiranim supstancama u opadajućim koncentracijama [17]. Opseg testiranih koncentracija supernatanata probiotičkih mikroorganizama u mikrotitarskim pločama je bio od 50% do 0,1%, za mešavinu probiotičkih mikroorganizama od 25% do 0,05%, dok je za kontrolni antibiotik opseg bio od 168 µg/mL do 0,3 µg/mL [17]. Eksperimenti sa testiranim supstancama ponovljeni su dva puta u triplikatu. Nakon postavljanja mikrodilucionog testa, mikrotitarske ploče su inkubirane 72 sata na 33 °C u Gas-Pak posudi (BD GasPak™ EZ Container Systems) sa anaerobnim generatorom i indikatorom. Nakon inkubacije, određene su MIK vrednosti. Preparati su posmatrani mikroskopiranjem u tamnom polju i poređeni su broj i pokretljivost borelija u prisustvu testiranih supernatanata sa pozitivnom kontrolom i kontrolnim antibiotikom. MIK je definisana kao najniža koncentracija testiranog supernatanta probiotičkog mikroorganizma (*S. boulardii* i *L. plantarum*, ili njihove mešavine) i antibiotika u kokultivaciji sa *B. afzelii*, pri kojoj borelije nisu bile pokretne ili su bile slabo pokretne, a njihov broj je bio smanjen u odnosu na pozitivnu kontrolu.

STATISTIČKA ANALIZA

Za statističku obradu podataka korišćeni su neparametarski Kruskal-Wallis test i Mann-Whitney test, a podaci su prikazani kao medijana (min-max). Statističke hipoteze su testirane na nivou statističke značajnosti $p = 0,05$.

Rezultati su prikazani tabelarno. Svi podaci su obrađeni u R programskom okruženju (R Core Team, 2024).

REZULTATI

Nakon 72 sata inkubacije na 33 °C određene su vrednosti MIK za *S. boulardii*, *L. plantarum*, njihovu mešavinu kao i za kontrolni antibiotik ceftriakson. Kruskal-Wallis

dividual supernatant at corresponding dilution levels, starting from the maximum concentration of 100% for each strain.

Ceftriaxone was used as the reference antibiotic control in the broth microdilution method for *Borrelia*, and was tested at concentrations ranging from 8 to 0.016 µg/mL, as previously described [18]. The antimicrobial activity of the supernatants and the control antibiotic ceftriaxone was evaluated using a modified broth microdilution method adapted for *Borrelia*, as neither the European Committee on Antimicrobial Susceptibility Testing (EUCAST) nor the Clinical and Laboratory Standards Institute (CLSI) provide standardized guidelines or interpretive criteria for this method, including MIC breakpoints for *Borrelia* spp [17]. Briefly, the broth microdilution method for determining the MIC values of antibiotics and tested supernatants was performed using sterile 96-well microtiter plates. The first column served as a positive control containing *Borrelia* culture, while the second column served as a negative control with BSK-H medium. Wells in columns three through twelve were filled with mixtures of *Borrelia* culture and the tested substances at serially decreasing concentrations [17]. The tested concentration range of probiotic supernatants in the microtiter plates was 50% to 0.1% for individual strains, 25% to 0.05% for the mixed supernatants, and 168 µg/mL to 0.3 µg/mL for the control antibiotic ceftriaxone [17]. Each experiment was performed in duplicate, with three technical replicates per condition. Following the setup of the microdilution assay, the microtiter plates were incubated for 72 hours at 33 °C in a GasPak™ EZ anaerobic container system (BD), equipped with an anaerobic generator and indicator. After incubation, MIC values were determined. Dark-field microscopy was used to assess *Borrelia* cell count and motility, and results were compared between samples treated with the tested supernatants, the positive control (untreated *Borrelia* culture), and the control antibiotic. MIC was defined as the lowest concentration of the tested probiotic supernatants (*S. boulardii*, *L. plantarum*, or their mixture) or antibiotics during co-cultivation with *B. afzelii* at which the *Borrelia* cells were either non-motile or showed significantly reduced motility, accompanied by a decrease in their number compared to the positive control.

STATISTICAL ANALYSIS

Statistical analysis was performed using the non-parametric Kruskal-Wallis and Mann-Whitney tests. Data were presented as median (minimum–maximum), and statistical significance was determined at a p -value threshold of 0.05.

test je pokazao da postoji statistički značajna razlika između MIK vrednosti testiranih supernatanata (*S. boulardii*, *L. plantarum* i njihovih mešavina) ($p = 0,01$). Mann-Whitney test je pokazao da postoji statistički značajna razlika između MIK vrednosti supernatanta *S. boulardii* i mešavine supernatanata ($p = 0,02$) kao i između supernatanta *L. plantarum* i mešavine supernatanata ($p = 0,01$) dok statistički značajna razlika ne postoji između supernatanata *S. boulardii* i *L. plantarum* ($p = 0,68$). Statističkom analizom je pokazano da mešavina testiranih probiotskih supernatanata efikasnije inhibira rast i razmnožavanje *B. afzelii* u odnosu na pojedinične probiotske supernatante.

Najefikasniji supernatant u inhibiciji rasta, razmnožavanja i pokretljivosti *B. afzelii* bila je mešavina supernatanata probiotskih mikroorganizama pri MIK vrednosti medijane od 0,8%. Rezultati su predstavljeni u **Tabeli 1**.

Tabela 1. Raspon i medijana vrednosti minimalnih inhibitornih koncentracija (MIK) (%) supernatanta *Saccharomyces boulardii*, *Lactiplantibacillus plantarum* i njihovih mešavina na vrstu *Borrelia afzelii*

Vrsta supernatanta / Type of supernatant	Raspon MIK (%) vrednosti / MIC (%) range	Medijana MIK (%) / Median MIC (%) value
<i>Saccharomyces boulardii</i>	0.8% – 50%	12.5%
<i>Lactiplantibacillus plantarum</i>	1.6% – 25%	6%
Mešavina supernatanata / The mixture of supernatants	0.2% – 3.1%	0.8%

Pored definisanih MIK vrednosti za supernatante *S. boulardii*, *L. plantarum* i njihovu mešavinu, pri nižim koncentracijama supernatanata probiotskih mikroorganizama uočena je povećana pokretljivost i broj borelija u odnosu na pozitivnu kontrolu. Prisustvo supernatanta *S. boulardii*, *L. plantarum* i njihovih mešavina, uticalo je stimulatивно na broj i pokretljivost borelija u odnosu na pozitivnu kontrolu dok je *B. afzelii* bila najpokretljivija a njena brojnost najviše povećana u odnosu na pozitivnu kontrolu u prisustvu mešavine supernatanata pri vrednosti medijane od 0,1%. Rezultati su predstavljeni u **Tabeli 2**.

MIK vrednost za testirani kontrolni antibiotik na *B. afzelli* iznosio je 0,016 µg/mL (odnosno 0,3 µg/mL u mikrotitarskim pločama) što je u skladu sa prethodno

Tabela 2. Koncentracije (%) i vrednosti medijana (%) supernatanata *Saccharomyces boulardii*, *Lactiplantibacillus plantarum* i njihovih mešavina koje su stimulatивно delovale na rast i pokretljivost vrste *Borrelia afzelii*

Vrsta supernatanta / Type of supernatant	Raspon koncentracija (%) / Concentration range (%)	Medijana (%) / Median value (%)
<i>Saccharomyces boulardii</i>	0.1% – 6.3%	0.4%
<i>Lactiplantibacillus plantarum</i>	0.1% – 3.1%	0.2%
Mešavina supernatanata / The mixture of supernatants	0.1%	0.1%.

The results are presented in tabular form. All data analyses were conducted using the R programming environment (R Core Team, 2024).

RESULTS

After 72 hours of incubation at 33 °C, MIC values were determined for *S. boulardii*, *L. plantarum*, their mixture, and the control antibiotic ceftriaxone. The Kruskal-Wallis test revealed a statistically significant difference among the MIC values of the tested supernatants (*S. boulardii*, *L. plantarum*, and their mixture) ($p = 0.01$). Wilcoxon test showed significant differences between the MIC of *S. boulardii* and the mixture ($p = 0.02$), as well as between *L. plantarum* and the mixture ($p = 0.01$). No statistically significant difference was observed between the MIC values of the supernatants of *S. boulardii* and *L. plantarum* ($p = 0.68$). Statistical analysis demonstrated that the mixture of the tested probiotic supernatants

Table 1. Range and median values of minimum inhibitory concentrations (MIC, %) of supernatants from *Saccharomyces boulardii*, *Lactiplantibacillus plantarum*, and their mixtures against *Borrelia afzelii*

inhibited the growth and reproduction of *B. afzelii* more effectively than the individual supernatants alone.

The most effective supernatant in inhibiting the growth, reproduction, and motility of *B. afzelii* was the mixture of probiotic supernatants, with a median MIC value of 0.8%. The results are presented in **Table 1**.

In addition to the defined MIC values for the supernatants of *S. boulardii*, *L. plantarum*, and their mixture, lower concentrations of these probiotic supernatants were associated with increased *Borrelia* motility and cell numbers compared to the positive control. The presence of supernatants from *S. boulardii*, *L. plantarum*, and their mixture stimulated both the number and motility of *Borrelia* compared to the positive control. Notably, *B. afzelii* exhibited the greatest increase in

Table 2. Concentrations (%) and median values (%) of *Saccharomyces boulardii*, *Lactiplantibacillus plantarum*, and their mixed supernatants that exhibited a stimulatory effect on the growth and motility of *Borrelia afzelii*

objavljenim rezultatima i njegovom dokazanom inhibirajućem dejstvu na rast i razmnožavanje borelija.

DISKUSIJA

Saccharomyces boulardii je jedini eukariotski mikroorganizam koji se koristi u farmaceutskoj industriji u svrhu probiotika. Za sada su poznata dva mehanizma pomoću kojih *S. boulardii* deluje na patogene: vezivanjem za bakterije i njihove toksine, čime se olakšava njihova eliminacija i lučenje specifičnih proteina koji imaju ulogu u degradaciji toksina i/ili ćelijskih elemenata patogena [19]. Studija Rajkowske i Kunicka-Styczyńska [20] pokazala je da *S. boulardii* vezuje enteropatogene bakterije (*E. coli*, *S. enterica* var. *Typhimurium*, *Staphylococcus aureus*, *Campylobacter jejuni* i *Enterococcus faecalis*) olakšavajući njihovu eliminaciju iz organizma. Uočeno je da *S. boulardii* značajno smanjuje broj ćelija *Listeria monocytogenes*, *Pseudomonas aeruginosa* i *S. aureus*, a pored toga smanjuje i stopu rasta *L. monocytogenes* i *P. aeruginosa*.

Jedan od mehanizama kako *L. plantarum* kao i ostale bakterije mlečne kiseline utiču na patogene jeste proizvodnja različitih antimikrobnih jedinjenja, kao što su bakteriocin, vodonik peroksid, organske kiseline, aceton i masne kiseline [21,22]. Antimikrobni peptidi-bakteriocini, deluju baktericidno ili inhibiraju rast srodnih bakterija, uključujući patogene sojeve. Posebno niz pozitivnih svojstava, a neka od njih su dejstvo protiv patogena rezistentnih na antibiotike, uz odsustvo ili nisku toksičnost prema eukariotskim ćelijama [23]. Na primer, plantaricin PLNC8 $\alpha\beta$ -bakteriocin, koji proizvodi *L. plantarum* je pokazao antimikrobno dejstvo prema paradontalnom patogenu *Porphyromonas gingivalis* izazivanjem deformacije spoljašnje membrane i lize ćelija.

Upravo zbog pomenutog antimikrobnog dejstva oba probiotska mikroorganizma, polazna hipoteza je podrazumevala mogućnost postojanja antibakterijskog efekta, a glavni cilj studije je bio ispitati njihov inhibicioni efekat na uzročnika LB, bakteriju *B. afzelii*, *in vitro*, koji do sada nije ispitan. Poređenje naših rezultata, sa rezultatima prethodnih istraživanja nije u potpunosti adekvatno, jer je korišćena drugačija metodologija sa različitim test mikroorganizmima. Takođe, u okviru naše studije dobijeni su prvi preliminarni rezultati za borelije primenom bujon mikrodilucione metode, kojom do sada nisu bili testirani pomenuti probiotski mikroorganizmi. U studiji iz 2012. godine je metodom difuzije u agaru testiran antimikrobni potencijal supernatanta *S. boulardii* protiv *S. aureus*, *E. coli*, *C. albicans* i *Aspergillus niger* [12]. Njihovi rezultati su prikazani kao zone inhibicije (u milimetrima), što nije direktno uporedivo sa rezultatima dobijenim u našoj

motility and abundance in the presence of the mixed supernatants at a median concentration of 0.1%. These results are presented in Table 2.

The MIC value of the tested control antibiotic for *B. afzelii* was 0.016 $\mu\text{g/mL}$ (corresponding to 0.3 $\mu\text{g/mL}$ in microtiter plates), consistent with previously published data and confirming its established inhibitory effect on the growth and reproduction of *Borrelia*.

DISCUSSION

Saccharomyces boulardii is the only eukaryotic microorganism used as a probiotic in the pharmaceutical industry. To date, two mechanisms of its action against pathogens have been identified: it binds to bacteria and their toxins, promoting their elimination, and it secretes specific proteins involved in the degradation of toxins and/or pathogenic cellular components [19]. A study by Rajkowska and Kunicka-Styczyńska [20] demonstrated that *S. boulardii* binds to enteropathogenic bacteria (*E. coli*, *S. enterica* serovar *Typhimurium*, *Staphylococcus aureus*, *Campylobacter jejuni*, and *Enterococcus faecalis*), thereby facilitating their elimination from the body. The study also showed that *S. boulardii* significantly reduces the number of *Listeria monocytogenes*, *Pseudomonas aeruginosa*, and *S. aureus* cells, and additionally slows the growth of *L. monocytogenes* and *P. aeruginosa*.

One of the key mechanisms by which *L. plantarum* and other lactic acid bacteria affect pathogens is the production of a range of antimicrobial compounds, including bacteriocins, hydrogen peroxide, organic acids, acetone, and fatty acids [21,22]. Antimicrobial peptides known as bacteriocins exhibit bactericidal activity or inhibit the growth of related bacteria, including pathogenic strains. They possess several advantageous properties, notably their effectiveness against antibiotic-resistant pathogens and their low or negligible toxicity to eukaryotic cells [23]. For example, the bacteriocin plantaricin PLNC8 $\alpha\beta$, produced by *L. plantarum*, has demonstrated antimicrobial activity against the periodontal pathogen *Porphyromonas gingivalis* by inducing outer membrane deformation and cell lysis.

In light of the previously described antimicrobial properties of both probiotic microorganisms, the initial hypothesis suggested their potential antibacterial effect. The main objective of this study was to examine, for the first time, their inhibitory activity against *Borrelia afzelii*, the causative agent of LB, *in vitro*. However, comparisons with earlier studies are limited due to differences in methodology and the microbial strains tested. Additionally, this study provides the first preliminary results on *Borrelia* using the broth microdilution method, which had not previously been applied to the

studiji, s obzirom na razlike u primenjenoj metodologiji, korišćenim test organizmima i rezultatima koji su u našem slučaju predstavljeni procentima. Antimikrobna aktivnost supernatanta *L. plantarum* potvrđena je metodom tačkaste difuzije u agaru protiv sojeva *E. coli*, *L. monocytogenes*, *E. faecalis* i *P. aeruginosa*, pri čemu je veličina zone inhibicije korišćena kao pokazatelj intenziteta antimikrobnog delovanja [24]. U eksperimentu u kojem je primenjena bujonmikrodiluciona metoda [23], kao i u našoj studiji, korišćena je serija dvostrukih razblaženja različitih tipova plantaricina koji su bili predmet testiranja. Za razliku od navedenog rada, u našem ispitivanju korišćeni su celokupni supernatanti probiotskih mikroorganizama i *B. afzelii* iz kompleksa *B. burgdorferi* s.l., pri čemu je primenjena modifikovana mikrodiluciona metoda. S druge strane, bujon mikrodiluciona metoda za borelije nije standardizovana, tj. EUCAST i CLSI kao što je prethodno pomenuto, ne definišu smernice za izvođenje bujon mikrodilucione metoda za borelije, čak ni za ispitivanje osetljivosti borelija na antibiotike. S tim u vezi treba pomenuti da se ne definišu ni granične vrednosti MIK za antibiotike kada su u pitanju bakterije iz kompleksa *B. burgdorferi* s.l. Pored MIK koje smo utvrdili za ispitivane probiotske mikroorganizme, važan deo rezultata čine i podaci o procentualnim vrednostima koje su pokazale stimulativan uticaj na brojnost i pokretljivost borelija. Ovi nalazi predstavljaju prvi korak u razumevanju kako određeni probiotski sojevi mogu uticati na rast i ponašanje borelija u veštačkim uslovima. Time se otvara mogućnost daljeg usavršavanja BSK-H (Hi-Media) podloge – standardnog medijuma za njihovu kultivaciju, s ciljem da se ona učini efikasnijom za izolaciju i kultivaciju borelija iz različitih bioloških uzoraka. Iako je Sigma BSK-H podloga skupa, Hi-Media, koja ima isti sastav, predstavlja jeftiniju alternativu koja može značajno smanjiti troškove ispitivanja. Efikasnost podloge je ključna, jer uspešnost izolacije i kultivacije borelija zavisi upravo od njenog kvaliteta. U ovom kontekstu, prethodna istraživanja, poput studije Ružić-Sabljić i saradnika [25], pokazala je da Hi-Media podloga bolje stimuliše rast borelija. Naša istraživanja su dodatno potvrdila ove nalaze, pokazujući da dodavanje supernatanata probiotika borelijama utiče na njihov bolji rast i povećanu pokretljivost, čime se otvara nova perspektiva za primenu probiotika u optimizaciji laboratorijskih uslova za njihov rast. S druge strane, dobijene MIK vrednosti za supernatante *S. boulardii* i *L. plantarum* i njihovu mešavinu na *B. afzelii* (Tabela 1), predstavlja prvi do sada dobijen rezultat na borelijama sa ovim supernatantima, što pruža osnov za dalja istraživanja supernatanata i njihovog inhibitorynog efekta na rast, razmnožavanje i pokretljivost borelija.

probiotic microorganisms in question. In a 2012 study, the antimicrobial potential of *S. boulardii* supernatant was evaluated against *S. aureus*, *E. coli*, *C. albicans*, and *Aspergillus niger* using the agar diffusion method [12]. Their results were expressed as zones of inhibition (in millimeters), which are not directly comparable to the findings of our study due to differences in methodology, the test organisms used, and the way results were reported in our case, as percentages. The antimicrobial activity of *L. plantarum* supernatant was previously confirmed using the agar point diffusion method against *E. coli*, *L. monocytogenes*, *E. faecalis*, and *P. aeruginosa*, with the size of the inhibition zone serving as an indicator of antimicrobial intensity [24]. In the experiment where the broth microdilution method was used [23], as in our study, a series of two-fold dilutions of various types of plantaricins were tested. However, unlike that study, our research employed whole supernatants of probiotic microorganisms and *B. afzelii* from the *B. burgdorferi* s.l. complex, using a modified microdilution method. On the other hand, the broth microdilution method for *Borrelia* is not standardized; as previously mentioned, neither EUCAST nor CLSI provides guidelines for performing this method on *Borrelia*, including antibiotic susceptibility testing. It is important to note that MIC breakpoint values for antibiotics have not been established for bacteria within the *B. burgdorferi* s.l. complex. Alongside the MIC values we determined for the tested probiotic microorganisms, a significant part of our results includes percentage data indicating a stimulatory effect on the number and motility of *Borrelia*. These findings represent an initial step toward understanding how specific probiotic strains may influence the growth and behavior of *Borrelia* under controlled, *in vitro* conditions. This opens up the possibility for further optimization of the BSK-H medium (Hi-Media), the standard substrate for *Borrelia* cultivation, with the goal of enhancing its efficiency for isolating and growing *Borrelia* from various biological samples. While the Sigma BSK-H medium is expensive, Hi-Media offers a more affordable alternative with the same composition, potentially reducing testing expenses significantly. The effectiveness of the medium is critical, as successful isolation and cultivation of *Borrelia* depend heavily on its quality. In this regard, previous research, such as the study by Ružić-Sabljić et al. [25], demonstrated that the Hi-Media medium more effectively promotes the growth of *Borrelia*. Our research further supports these findings by demonstrating that the addition of probiotic supernatants to *Borrelia* enhances their growth and motility, thus opening new possibilities for using probiotics to optimize laboratory cultivation conditions. Moreover, the MIC values obtained for the supernatants of *S. boulardii*, *L. plantarum*, and their

Ako se uzmu u obzir mogući značaj dobijenih MIK rezultata probiotskih mikroorganizama i potencijalne smernice daljeg istraživanja, treba razmotriti dalje aspekte istraživanja – formulaciju topikalnog (profilaktičkog) preparata, koji bi se primenjivao nakon uboda krpelja i čime bi se sprečila oralna i/ili intravenska primena antibiotika. Trenutno lek za LB koji bi se koristio topikalno ili profilaktički ne postoji. Ipak, 2017. godine je sprovedena pilot klinička studija u kojoj su ispitanici, nakon uboda krpelja topikalno nanosili preparat 10% azitromicina u formi gela [26]. Rezultati ove studije nisu bili zadovoljavajući za preporuku azitromicin-gela u profilaktičke svrhe. Još jedna studija bavila se sličnom tematikom. Naime, postoje dokazi o efikasnosti topikalne primene kreme azitromicina u cilju prevencije nastanka LB. Ipak, efikasnost u pružanju 100% zaštite od infekcije nakon uboda krpelja je za sada ispitivana samo na miševima [27].

Sve ovo ukazuje na potrebu za razvojem topikalnog preparata sa drugačijom formulacijom i mehanizmom delovanja. S tim u vezi ideja o mogućnosti zamene antibiotika prirodnim proizvodima, koji ne izazivaju neželjene efekte i uzrokuju manji rizik od daljeg razvoja antimikrobne rezistencije, i ujedino doprinose smanjenju ili racionalizaciji njihove upotrebe, postaje sve relevantnija. Formulacija potencijalnog topikalnog probiotskog preparata, na bazi testiranih probiotskih mikroorganizama, mogla bi značajno doprineti prevenciji *erythema migrans*, kao i mogućem sprečavanju širenja borelija sistemskom cirkulacijom. U našem istraživanju, pokazano je da se pri određenim koncentracijama supernatanta probiotskih mikroorganizama brojnost i pokretljivost borelija smanjuje, ali bez ispitanih molekularnih mehanizama delovanja. Zbog toga bi u daljim istraživanjima trebalo proučavati komponente supernatanta kao i molekularne mehanizme kojima supernatanti (celi) i/ili njihove komponente inhibiraju rast i pokretljivost uzročnika LB – *B. afzelii*. Upravo iz tog razloga se dalja istraživanja u svrhu formulacije topikalnog preventivnog probiotskog preparata na bazi ispitivanih probiotskih mikroorganizama ostavljaju kao otvoreno polje za buduća istraživanja.

ZAKLJUČAK

Ovim istraživanjem je pokazano da supernatanti *S. bo-
ulardii* i *L. plantarum* imaju antimikrobno dejstvo na *B. afzelii*. Kombinacija supernatanta ova dva probiotska mikroorganizma imala je najefikasnije dejstvo pri njihovoj mešavini (MIK vrednost medijana 0,8%), što ih čini potencijalnim kandidatima za dalje istraživanje. Takođe, primećena je stimulacija rasta i veća pokretljivost borelija pri nižim koncentracijama supernatanta, odnosno njihovoj mešavini, pri koncentraciji vrednosti

mixture against *B. afzelii* (Table 1) represent the first such data reported for *Borrelia*. These results provide a foundation for future studies on the inhibitory effects of probiotic supernatants on the growth, reproduction, and motility of *Borrelia*.

Considering the potential significance of the obtained MIC results for probiotic microorganisms and future research directions, additional aspects warrant attention-specifically, the development of a topical (prophylactic) formulation to be applied after a tick bite, aimed at preventing the need for oral and/or intravenous antibiotic treatment. Currently, no topical or prophylactic drug for LB exists. However, in 2017, a pilot clinical study investigated the topical application of a 10% azithromycin gel following tick bites [26]. The results were unsatisfactory, and the study did not support recommending azithromycin gel for prophylactic use. Another study explored a similar approach, providing evidence for the effectiveness of topical azithromycin cream in preventing LB. However, this protective effect, achieving 100% prevention of infection after a tick bite, has so far only been demonstrated in mice [27].

All of this highlights the need to develop a topical preparation with a different formulation and mechanism of action. In this context, the prospect of replacing antibiotics with natural products, which do not cause side effects and pose a lower risk of promoting antimicrobial resistance, becomes increasingly relevant. Developing a topical probiotic formulation based on the tested probiotic microorganisms could play a significant role in preventing *erythema migrans* and potentially inhibiting the systemic spread of *Borrelia*. Our research demonstrated that at certain concentrations, probiotic microorganism supernatants reduce the number and motility of *Borrelia*, although the underlying molecular mechanisms were not investigated. Therefore, future studies should focus on identifying the active components within these supernatants and elucidating the molecular pathways through which the whole supernatants and/or their components inhibit the growth and motility of *B. afzelii*, the causative agent of LB. This highlights a promising area for further research aimed at developing a topical probiotic preventive formulation based on the tested probiotic strains.

CONCLUSION

This study demonstrated that the supernatants of *S. bo-
ulardii* and *L. plantarum* exhibit antimicrobial activity against *B. afzelii*. The mixed supernatants of these two probiotic microorganisms showed the strongest effect, with a median MIC value of 0.8%, highlighting their potential for further investigation. Interestingly, at lower concentrations, specifically around a median

medijane 0,1%, što takođe zahteva dodatna ispitivanja. Potencijalni smerovi daljih istraživanja uključuju analizu sastava supernatanta i proučavanje molekularnih mehanizama kojima bi se objasnila inhibicija rasta, razmnožavanja i pokretljivosti *B. afzelii*. To bi dalje iniciralo pre svega istraživanja za razvoj topikalnog profilaktičkog preparata koji bi se primenjivao nakon uboda krpelja i koji bi sprečavao pojavu *erythema migrans*. Samim tim bi se mogla smanjiti diseminacija borelija u sistemsku cirkulaciju, rizik od komplikacija koje sa sobom nosi LB, kao i upotreba antibiotika.

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of 0.1%, the supernatants and their mixture stimulated *Borrelia* growth and increased motility, indicating the need for additional research to better understand these effects. Potential directions for future research include analyzing the composition of the supernatants and investigating the molecular mechanisms underlying the inhibition of *B. afzelii* growth, reproduction, and motility. Such studies would primarily pave the way for developing a topical prophylactic preparation to be applied after a tick bite, aimed at preventing the onset of erythema migrans. This approach could help reduce the systemic dissemination of *Borrelia*, lower the risk of LB-related complications, and minimize the reliance on antibiotics.

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SNAGE I SLABOSTI REPRODUKTIVNOG BIOEKONOMSKOG TRŽIŠTA: UVIDI IZ PREGLEDA LITERATURE

PREGLEDNI RAD

REVIEW ARTICLE

STRENGTHS AND WEAKNESSES OF THE REPRODUCTIVE BIOECONOMY MARKET: INSIGHTS FROM THE LITERATURE REVIEW

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SAŽETAK

Uvod: Ekonomija je oblast koja obuhvata proizvode, usluge i trgovinu, a reproduktivna bioekonomija se odnosi na oblast reprodukcije i načine proizvodnje, usluga, kupaca i trgovine sa reproduktivnim ćelijama i tkivima. Svrha ovog istraživanja je da se identifikuju ključni faktori na tržištu reproduktivne bioekonomije koji je oblikuju, kako bi se prepoznale mogućnosti za unapređenje, i uočili potencijalni izazovi. U skladu s tim, cilj rada podrazumeva sprovođenje analize za opisivanje snaga, slabosti, mogućnosti i pretnji (SWOT analize) na tržištu reproduktivne bioekonomije, što će omogućiti formulisane strategijske smernice za dalji razvoj.

Metode: Sproveden je pregled literature objavljene od 2017. do 2024. Sprovedena je pretraga akademskih i naučnih radova korišćenjem baze podataka PubMed, Springer i Elsevier, kao i alata Google Scholar za identifikaciju dodatnih relevantnih izvora. Korišćen je sledeći string za pretragu: (“donacija reproduktivnih ćelija” ILI “donacija gameta” ILI “donacija jajnih ćelija” ILI “donacija sperme”) AND (“biomedicinski inženjering” ILI “biotehnologija proizvodnje gameta” ILI “kriobiologija gameta” ILI “banke gameta” ILI “gamete banks” ILI “gamete banks” OR “gamete banks” OR “gamete cross-border game”) roditeljstvo” ILI “uticaj karijere na reprodukciju” ILI “pojedinačni donator donira više banaka” ILI “netradicionalna porodica” ILI “altruizam” ILI “reproduktivni rad” ILI “bioetika u doniranju reproduktivnih ćelija”). Faktori koji imaju najveći uticaj na razvoj reproduktivnog bioekonomskog tržišta su identifikovani korišćenjem PRISMA vodiča za izveštavanje (engl. Preferred Reporting Items for Systematic reviews and Meta-Analyses), i klasifikovani uz pomoć SWOT instrumenta za stratešku analizu u snage, slabosti, mogućnosti i pretnje.

Rezultati: Pregledom literature pokazano je da su najuticajnije (i) snage reproduktivne bioekonomije: postojanje i razvoj biomedicinskog inženjerstva, razvoj novih tehnologija u biotehnologiji – kriobiologiji, distribucija i biodostupnost proizvoda – kriobanke; (ii) tržišne mogućnosti: prekogranična reproduktivna zdravstvena zaštita (eng., Cross Border Reproductive Care), transnacionalni program donacije gameta (eng., Transnational Gamete Donation) i raznolikost potrošača koji učestvuju na tržištu reproduktivne bioekonomije; ali i (iii) slabosti: odlaganje roditeljstva na starije životne dobi, regulisanje broja porodica po davaocu gde različiti standardi otežavaju praćenje, buduće formiranje složenije, netradicionalne, moderne porodice; kao i (iv) potencijalne pretnje u vidu nepoznatog kvaliteta i budućih rezultata, bioetičke dileme i da komercijalizacija reproduktivnog rada predstavlja pretnju altruizmu.

Zaključak: Rezultati ovog istraživanja su pokazali značajan potencijal reproduktivne bioekonomije za lečenje neplodnosti i diversifikaciju porodice. Neophodno je da regulatorni okvir bude transparentan, u skladu sa etičkim i normativnim propisima, pre sprovođenja programa doniranja reproduktivnog materijala, i uvođenja nacionalnog registra za domaću i strane državljane, sve potencijalne korisnike programa donacije.

Ključne reči: bioekonomija, biotehnologija, SWOT analiza, reproduktivno tržište, donacija gameta, PRISMA

ABSTRACT

Introduction: The economy is a field that includes products, services, and trade, and reproductive bioeconomy refers to the field of reproduction and the ways of production, services, customers, and trade of reproductive cells and tissues. This research aimed to identify the key factors that shape the reproductive bioeconomy market and pinpoint opportunities for improvement as well as potential challenges. Accordingly, the study objective includes implementing an analysis to determine the Strengths, Weaknesses, Opportunities, and Threats in the reproductive bioeconomy market (SWOT analysis); this will enable the formulation of strategic guidelines for further development.

Methods: A review of the literature published from 2017 to 2024 was carried out. A search of academic and scientific papers was conducted using the PubMed, Springer, and Elsevier databases, as well as the Google Scholar tool, to identify additional relevant sources. The following search string was used: (“donating reproductive cells” OR “gamete donation” OR “oocyte donation” OR “sperm donation”) AND (“biomedical engineering” OR “in vitro gamete production biotechnology” OR “gamete cryobiology” OR “gamete banks” OR “cross-border reproductive care” OR “Transnational gamete donation”) AND (“parenthood delay” OR “career impact on reproduction” OR “one donor donates to several banks” OR “non-traditional family” OR “altruism” OR “reproductive work” OR “bioethics in donating reproductive cells”). The factors that have the greatest impact on the development of the reproductive bioeconomy market have been identified using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guide, and classified with the help of the SWOT instrument for strategic analysis into strengths, weaknesses, opportunities, and threats.

Results: The review of the literature showed that the most influential forces of the reproductive bioeconomy are: (i) the strengths of the reproductive bioeconomy: the existence and development of biomedical engineering, the development of new technologies in biotechnology – Cryobiology, distribution and bioavailability of products – cryobanks; (ii) market opportunities: cross-border reproductive care (eng., Cross Border Reproductive Care), Transnational Gamete Donation Program (eng., Transnational Gamete Donation), and the diversity of consumers participating in the reproductive bioeconomy market; but also (iii) weaknesses: postponing parenthood to older ages, regulating the number of families per donor where different standards make monitoring difficult, the future formation of a complex, non-traditional, modern family; as well as (iv) potential threats in the form of unknown quality and future results, bioethical dilemmas, and that the commercialization of reproductive work poses a threat to altruism.

Conclusion: This research demonstrates significant potential for the reproductive bioeconomy in treating infertility and promoting family diversification. Before implementing the reproductive material donation program and establishing a national registry for domestic and foreign citizens who are potential beneficiaries of the donation program, the regulatory framework must be transparent and aligned with ethical and normative regulations.

Keywords: bioeconomy, biotechnology, SWOT analysis, reproductive market, gamete donation, PRISMA

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UVOD

Prema izveštaju Organisation for Economic Co-operation and Development (OECD), na srpskom - Organizacija za ekonomsku saradnju i razvoj [1], reproduktivna bioekonomija postaje sve značajnija za unapređenje zdravlja populacije. Ona obuhvata primenu biotehno- loških inovacija u oblasti reproduktivnog zdravlja, što dovodi do poboljšanog kvaliteta zdravstvene zaštite i povećanja uspešnosti u reproduktivnoj medicini. Uz razvoj reproduktivne bioekonomije, neophodno je prilagoditi javne zdravstvene politike kako bi se obezbedila njena dostupnost i etička primena. Globalna demografska kretanja ukazuju na starenje populacije i pad nataliteta u pojedinim zemljama [2]. Za održivi razvoj društva potrebni su inovativni pristupi u ključnim oblastima, kao što je reproduktivna bioekonomija [1].

Bioekonomija kombinuje biotehnologiju i prirodne biološke nauke, a biološki materijali i proizvodi predstavljaju priliku za održivi ekonomski rast [3]. Definicija „bioekonomije“ kaže da je to deo ekonomije koji koristi napredno biološko razumevanje u poslovne i industrijske svrhe za unapređenje ljudskog blagostanja [4]. Prema projektu Bioekonomija Organizacije za ekonomsku saradnju i razvoj, do 2030. godine biotehnologija kao deo bioekonomije se opisuje kao „svet u kome biotehnologija daje značajan doprinos ekonomskom outputu“, sa fokusom na korišćenje biotehnologije za generisanje ekonomskog rasta [5]. Današnja bioekonomija se smatra „biokapitalizmom“ [6]. Resursi bioekonomije se upravljaju tako da zamene proizvode dobijene iz neobnovljivih izvora (npr. fosilnih goriva) sa proizvodima dobijenim iz obnovljivih izvora, kao što su oni koji se uzgajaju (npr. biogorivo) [4]. Reprodutivna bioekonomija obuhvata način na koji reprodutivna tkiva, ćelije, usluge donacije, korisnici i radnici postaju deo globalnog biokapitalizma. Reprodutivni organi, jajne ćelije, spermatozoidi, embrioni i materice uključuju reprodutivni rad u komercijalizaciji jajnih ćelija, sperme, dobavljača tkiva i surogat majki, a tržišni akteri podstiču komercijalizaciju i nadoknadu za davaoce [7]. Strateški cilj reprodutivne bioekonomije je proširenje spektra proizvoda uzgajanih in vitro - od proizvodnje reprodutivnih ćelija [8] do novih tehnologija inženjeringa tkiva za proizvodnju materice iz matičnih ćelija [9]. Razvijaju se strategije za tehnološki napredak regenerativne medicine u oblasti biologije matičnih ćelija koje mogu generisati zdravlje i bogatstvo, primenjujući inženjersku tehnologiju i prirodne nauke. Ćelije se generišu de novo i imaju potencijal i sposobnost da regenerišu i zamene oštećena tkiva usled starosti, bolesti, traume ili urođenih mana [10].

Za medicinski tretman koji uključuje donaciju reprodutivnih ćelija, trenutni resursi reprodutivne bioekonomije su neobnovljivi i oslanjaju se na ograničenu

INTRODUCTION

According to the Organisation for Economic Co-operation and Development (OECD) report [1], the reproductive bioeconomy is becoming more significant in improving population health. It encompasses the application of biotechnological innovations in reproductive health, leading to improved quality of healthcare and increased success in reproductive medicine. Along with the development of the reproductive bioeconomy, public health policies must be adapted to ensure its availability and ethical implementation. Global demographics indicate an aging population and a decline in birth rates in some countries [2]. For the sustainable development of society, innovative approaches are necessary for key areas such as the reproductive bioeconomy [1].

The bioeconomy combines biotechnology and natural biological sciences, and biological materials and products offer an opportunity for sustainable economic growth [3]. The definition of “Bioeconomy” says that it is part of the economy that uses advanced biological understanding for business and industrial purposes to develop human well-being [4]. According to the Bioeconomy project of the Organization for Economic Co-operation and Development, until 2030, biotechnology as a bioeconomy is described as “a world where biotechnology supply with a significant contribution to the economic output,” focusing attention on the use of biotechnology to generate economic growth [5]. Today’s bioeconomy is considered “biocapitalism” [6]. The resources of the bioeconomy are managed to replace products obtained from non-renewable sources (e.g., fossil fuels) with products derived from renewable sources, such as those grown (e.g., biofuel) [4]. The reproductive bioeconomy encompasses how reproductive tissues, cells, donation services, customers, and workers become part of global biocapitalism. Reproductive organs, eggs, sperm, embryos, and wombs involve reproductive labour in the commercialisation of eggs, sperm, tissue suppliers, and surrogate mothers, and market supporters encourage commercialisation and compensation to suppliers [7]. The strategic goal of the reproductive bioeconomy is to expand the range of products grown in vitro from the production of reproductive cells [8] to new tissue engineering technologies for the production of the uterus from stem cells [9]. Strategies are being developed for the technological advancement of regenerative medicine in the area of stem cell biology that can generate health and wealth that applies engineering technology and natural sciences, cells are generated de novo and have the potential and ability to regenerate and replace damaged tissues damaged by age, disease or trauma, or birth defects [10].

For reproductive medical treatment involving reproductive cell donation, the current resources of the

ponudu donatora (donora reproduktivnih ćelija) kao dobavljača bioproizvoda [11]. Tretman uključuje specifične skupove (fenotipskih karakteristika) koji predstavljaju resurse reproduktivnih bioekonomija u zemljama poput Španije, Grčke, Češke i Danske, a način na koji funkcioniše uparivanje pacijenata i donora oblikuje pacijente kao potrošače izbora, dok uparivanje ima ključnu ulogu u marketingu, pa se bazeni reproduktivnih ćelija tretiraju kao konkurentski proizvodi u reproduktivnoj bioekonomiji, iako reproduktivni zakoni insistiraju da se nabavka reproduktivnih ćelija zasniva na altruističkoj donaciji sa malom finansijskom nadoknadom u vidu ekonomske kompenzacije do maksimalno 1000 evra, što je iznos dovoljan da se izbegne komercijalizacija transakcije [5]. Banke smrznutih reproduktivnih ćelija se globalno šire slanjem setova ćelija širom sveta u kriogenim kontejnerima, što je dovelo do širenja tržišta. Kao rezultat toga, banke povećavaju svoje zalihe donatora sa specifičnim fenotipovima kako bi zadovoljile potrebe transnacionalne industrije plodnosti [11]. Tržište plodnosti je vredna industrija koja se procenjuje na više milijardi dolara ili nekoliko miliona evra i uključuje donaciju gameta/embriona i surogat materinstvo [12]. Industrija plodnosti Danske generiše stotine miliona dolara [13]. Svaka zemlja ima zakonske regulative koje definišu postupak korišćenja resursa reproduktivne bioekonomije, ali ti zakoni ne diktiraju već oblikuju transnacionalnu industriju plodnosti [14].

Regulisanje bioetičkih dilema, reproduktivnih prava i roditeljstva, koje zavise od nacionalnih pravnih okvira i kulturnih specifičnosti, pruža uvid u etičke i normativne izazove u ovoj oblasti [15].

Propisi koji se odnose na nabavku i upotrebu reproduktivnih ćelija razlikuju se od zemlje do zemlje. Te razlike su dovele do ideje o proceni snaga i slabosti tržišta reproduktivne bioekonomije, posebno u vezi sa korišćenjem neobnovljivih donorskih reproduktivnih ćelija.

Cilj ove studije bio je da se sprovede sistematski pregled postojeće literature u vezi sa snagama, slabostima, mogućnostima i pretnjama trenutnog tržišta reproduktivne bioekonomije i da se izvrši SWOT analiza koja omogućava formulisane strateških smernica za dalji razvoj.

METODE

Strategija pretrage

Istraživanje i pregled literature sprovedeni su u periodu od januara do aprila 2024. godine. Pretraga je obuhvatila recenzirane članke objavljene na engleskom jeziku u akademskim časopisima, na osnovu kojih je formirana konačna referentna lista. Pregled akademskih i naučnih radova vršen je putem Google Scholar platforme, sa ciljem identifikacije što većeg broja recenziranih publikacija objavljenih u stručnim časopisima. Dodatne baze

reproductive bioeconomy are non-renewable, relying on a limited supply of donors (reproductive cell donors) as suppliers of bioproducts [11]. The treatment involves specific sets (of phenotypic characteristics) that represent the resources of reproductive bioeconomies in countries like Spain, Greece, the Czech Republic and Denmark, and how patient-donor matching works shapes patients as consumers of choice and how matching plays a key role in marketing so pools of reproductive cells are given the role of competing products in the reproductive bioeconomy, although reproductive laws insist that the procurement of reproductive cells is based on an altruistic donation with a small financial compensation in the form of economic compensation of a maximum of 1000 euros, which is a sum sufficient to avoid the commercialization of the transaction [5]. Frozen reproductive cell cryobanks are expanding globally by shipping sets of reproductive cells around the world in cryogenic containers, which has led to an expanding market. As a result, banks are increasing their reserves of donors with specific phenotypes to meet the needs of the transnational fertility industry [11]. The fertility market is a valuable industry estimated to be worth billions of dollars or several million euros and includes gamete/embryo donation and gestational surrogacy [12]. Denmark's fertility industry generates hundreds of millions of dollars [13]. Every country has legal regulations that define the procedure for using the resources of the reproductive bioeconomy, and these laws do not dictate but instead shape the transnational fertility industry [14].

The regulation of bioethical dilemmas, reproductive rights, and parenthood, which depend on national legal frameworks and cultural specificities, provides insights into the ethical and normative challenges in this area [15].

Regulations regarding the procurement and use of reproductive cells vary from country to country. These differences have led to the idea of assessing the strengths and weaknesses of the reproductive bioeconomy market, particularly in relation to the use of non-renewable donor reproductive cells.

This study aimed to conduct a systematic review of the existing literature regarding the strengths, weaknesses, opportunities, and threats of the current reproductive bioeconomy market, and to undertake a SWOT analysis that enables the formulation of strategic guidelines for further development.

METHODS

Search strategy

The research and literature review were conducted from January to April 2024. The search included peer-reviewed articles published in English in academic journals, based on which the final reference list was generated. A review

podataka koje su korišćene uključuju PubMed, Springer i Elsevier. Korišćen je sledeći niz ključnih reči za pretragu: SWOT analiza ILI bioekonomsko tržište I donacija reproduktivnih ćelija ILI donacija gameta ILI donacija jajnih ćelija ILI donacija sperme I (biomedicinski inženjering ILI biotehnologija proizvodnje gameta in vitro ILI kriobiologija gameta ILI banke gameta ILI prekogranična reproduktivna zaštita (CBRC) ILI transnacionalna donacija gameta I odlaganje roditeljstva ILI uticaj karijere na reprodukciju ILI jedan donor donira u više banaka ILI netradicionalna porodica ILI altruizam ILI reproduktivni rad ILI bioetika u donaciji reproduktivnih ćelija.

Kriterijumi za selekciju

Kriterijumi za uključivanje bili su publikacije koje su u svom tekstu sadržale opis ključnih pojmova i njihova objašnjenja, koja bi mogla doprineti njihovom uključivanju u SWOT analizu (snage, slabosti, mogućnosti, pretnje). Kriterijumi za isključenje su bili sledeći: po datumu objavljivanja – publikacije starije od 2017. godine su isključene, kao i one koje nisu pružale jasniji uvid u navedene snage, slabosti, mogućnosti i pretnje.

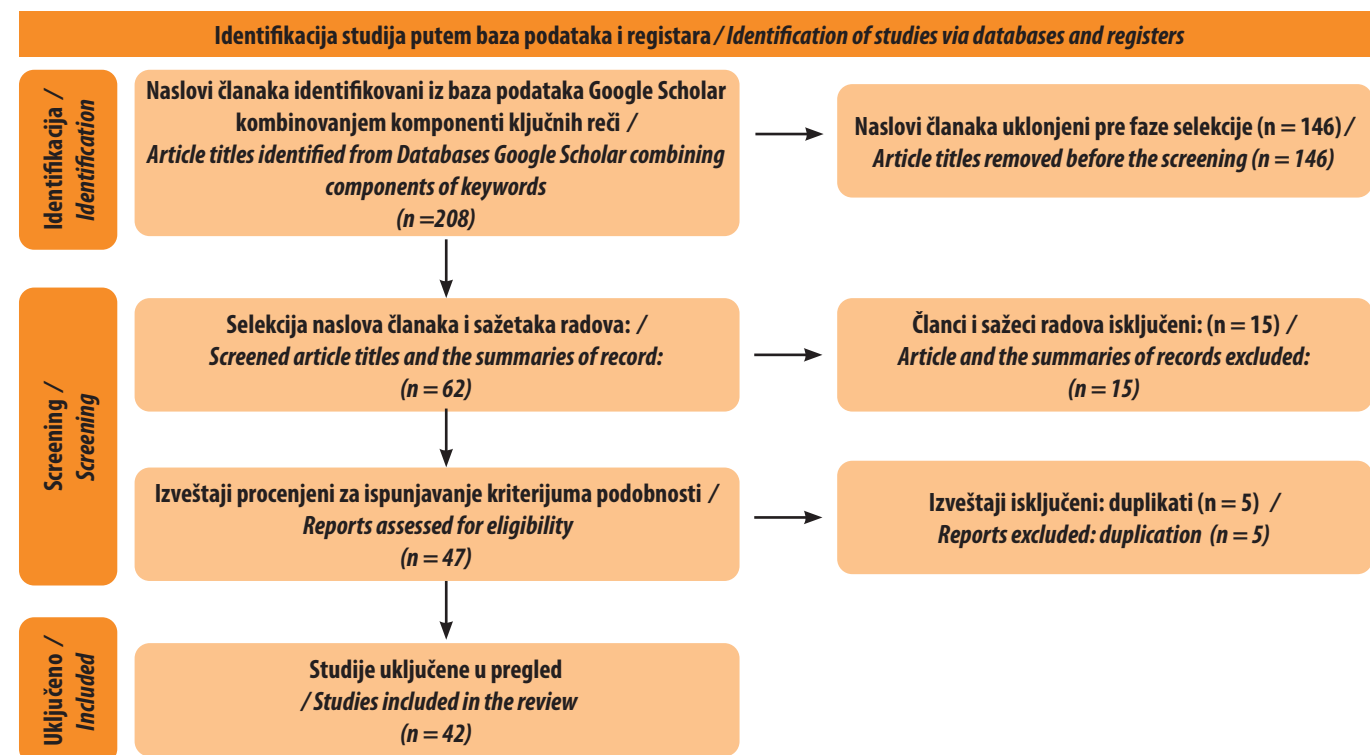
U skladu sa PRISMA smernicama [16] i pregledom PRISMA dijagrama toka (Slika 1), selekcija literature sprovedena je tako što su najpre analizirani naslovi. Za izvučene naslove izvršena je selekcija sažetaka svakog rada, nakon čega je procenjeno da li je sadržaj članka relevantan ili koristan za sistematski pregled. Ova pretraga je rezultirala analizom 208 naslova članaka, od

of academic and scientific works was conducted using Google Scholar to identify as many peer-reviewed publications as possible, published in academic journals. Additional database sources consulted included PubMed, Springer, and Elsevier. The following search string was used: SWOT analysis OR bioeconomic market AND donating reproductive cells OR gamete donation OR oocyte donation OR sperm donation AND (biomedical engineering OR in vitro gamete production biotechnology OR gamete cryobiology OR gamete banks OR cross-border reproductive care (CBRC) OR Transnational gamete donation AND parenthood delay OR career impact on reproduction OR one donor donates to several banks OR non-traditional family OR altruism OR reproductive work OR bioethics in donating reproductive cells.

Selection criteria

The criteria for inclusion were publications that contained in their text a description of keywords and their explanations that could help to include them in the SWOT analysis (strengths, weaknesses, opportunities, threats). The exclusion criteria were as follows: by publication date, publications older than 2017 were excluded, and those that could not give a clearer picture of the mentioned strengths, weaknesses, opportunities, and threats were excluded.

Following the PRISMA guide [16] and by reviewing the PRISMA flow diagram (Figure 1), we conducted the literature selection by initially analyzing the titles. For



Slika 1. Ilustrovani PRISMA dijagram toka izbora studija prema PRISMA vodiču [16]

Figure 1. Illustrated PRISMA flow diagram of study selection in accordance with the PRISMA guide [16]

kojih je 62 odabrano na osnovu naslova. Dodatnih 15 članaka je isključeno jer nisu sadržali podatke značajne za SWOT analizu i nisu nudili relevantne uvide u ključne aspekte programa donacije gameta i njihov uticaj na reproduktivnu medicinu. Takođe, uklonjeno je i pet duplikata. Na kraju, 42 članka su ispunila kriterijume selekcije i čine osnovu ovog rada.

Kvalitativna analiza

Ova studija sprovedla je kvalitativnu analizu sadržaja literature kako bi identifikovala faktore koji potencijalno podstiču rast i predstavljaju izazove za razvoj reproduktivne bioekonomije. U istraživanju je korišćena SWOT analiza kao metodološki okvir za organizaciju i tumačenje kvalitativnih podataka. SWOT analiza pomaže u identifikaciji snaga, slabosti, mogućnosti i pretnji unutar reproduktivne bioekonomije, nudeći strukturiran pristup za razumevanje potencijala i izazova u ovoj oblasti. Ova metoda je korisna za sintezu podataka iz naučnih izvora, jer omogućava integraciju složenih informacija i njihovu primenu u strateškom planiranju i razvoju sektora.

Uspostavljena je kategorizacija na pokretače rasta i izazove. Faktori koji su klasifikovani kao pokretači rasta obuhvataju sve aspekte koji pozitivno doprinose razvoju reproduktivne bioekonomije, dok faktori klasifikovani kao izazovi obuhvataju prepreke i rizike.

Prvi autor je sproveo pregled naslova, analizu i sintezu članaka navedenih u referencama. Prvi autor je pročitao pune tekstove 42 članka i razvrstao ih po SWOT tabelama. Delovi teksta članaka koji su se bavili pitanjima snaga, slabosti, mogućnosti i pretnji analizirani su prema uputstvima o tome zašto pripadaju određenoj tabeli i obeleženi simbolom +. Drugi i treći autor su pregledali i proverili sve prikupljene radove. Okvir za pretragu informacija kreiran je na osnovu SWOT analize, pri čemu su informacije iz svakog rada izvlačene i predstavljene u diskusiji od strane prvog autora, uz sugestije drugog i trećeg autora.

REZULTATI

Rezultati istraživanja prikazani su kroz četiri segmenta SWOT analize, korišćenjem relevantnih referenci iz literature:

1. Snage:
 - Razvoj novih biotehnologija i metoda krioprezervacije.
 - Povećana dostupnost bioekonomskih proizvoda putem biobanaka.
 - Odlaganje roditeljstva do kasnijeg životnog doba, sa medicinskim i društvenim posledicama.
2. Slabosti:
 - Visoki troškovi i tehnička ograničenja krioprezervacije.

the extracted titles, a screening of each record's summary was performed, after which it was determined whether the article's content would be relevant or helpful for a systematic review. This search resulted in an analysis of 208 article titles, from which 62 were selected based on their titles. An additional 15 articles were excluded because they did not contain data significant for the SWOT analysis and lacked relevant insights into the key aspects of donor gamete programs and their impact on reproductive medicine. Five duplicates were also removed. Consequently, 42 articles met the selection criteria, forming the basis of this paper.

Qualitative Analysis

This study conducted a qualitative content analysis of literature to identify factors that potentially promoted growth and posed challenges to the development of the reproductive bioeconomy. This research employed a SWOT analysis as a methodological framework for organizing and interpreting qualitative data. The SWOT analysis helps to identify strengths, weaknesses, opportunities, and threats within the reproductive bioeconomy, offering a structured approach to understanding the potential and challenges in this area. This method is beneficial for synthesising data from scientific references, as it allows for the integration of complex information and its application in strategic planning and development of the sector.

A categorization into growth drivers and challenges has been established. Factors classified as growth drivers include all aspects that positively contribute to the development of the reproductive bioeconomy, while factors classified as challenges involve obstacles and risks.

The first author did the title review, analysis, and synthesis of the articles listed in the references. The first author read the full texts of 42 articles and divided and grouped the titles into SWOT tables. The parts of the article text that addressed the questions on strengths, weaknesses, opportunities, and threats were examined based on the instructions on why they belonged in the given table and were assigned the symbol +. The second and third authors reviewed and cross-checked the texts of all retrieved papers. The information search framework was created based on SWOT analyses, requiring the extraction of information from each paper and its presentation in the discussion by the first author, with suggestions from the second and third authors.

RESULTS

The results of the research are presented through four segments of SWOT analysis, using relevant references from the literature:

3. Mogućnosti:

- Implementacija transnacionalnih programa kao što su CBRC i TGD.
- Aktivno učešće potrošača na tržištu reproduktivne bioekonomije.

4. Pretnje:

- Etnička pitanja, komercijalizacija reproduktivnih usluga i nepoznati dugoročni efekti novih tehnologija.

Svaka od tabela u prilogu pokriva specifične aspekte reproduktivne bioekonomije. Snage (Tabela 1): Ova tabela pruža pregled referenci koje ističu snage repro-

1. Strengths:

- Development of new biotechnologies and cryo-preservation methods.
- Increased availability of bioeconomic products through biobanks.
- Delaying parenthood until later in life, with medical and social consequences.

2. Weaknesses:

- High costs and technical limitations of cryopreservation.

3. Opportunities:

- Implementation of transnational programs such as CBRC and TGD.

Tabela 1. Studije uključene u sistematski pregled (Snage)

Naziv / Name	Godina / Year	Izvor / Source	Snage / Strengths	Razvoj biomedicinskog inženjeringa / Development of biome- dical engineering	Razvoj novih tehnologija u bioteh- nologiji – Kriobiologija / Development of new technologies in biotechnology – Cryobiology	Bioiskoristivost proiz- voda – Kriobanke / Bioavailability of products – Cryobanks	Odlaganje roditeljstva do poodmaklog životnog doba/ Postponing parenthood to advanced age
1 Razvoj biomedicinskih inženjerskih teh- nologija za reproduktivnu medicinu [18] / Developing biomedical engineering technolo- gies for reproductive medicine [18]	2022	Smart Med.	+	+			
2 Stvaranje veštačkih gameta i embriona iz matičnih ćelija u reproduktivnoj medicini [22] / Generation of artificial gamete and embryo from stem cells in reproductive medicine [22]	2020	Front Bioeng Biotechnol.	+	+			
3 Napredni bioinženjering matičnih ćelija muških zametnih ćelija za očuvanje plodnosti [23] / Advanced bioengineering of male germ stem cells to preserve fertility [23]	2021	JTissue Eng.	+	+			
4 Kriopolitika reprodukcije na ledu: Nova skandinavski ledena epoha [13] / The cryopolitics of reproduction on ice: A new Scandinavian ice age [13]	2019	Emerald Publishing Limited;	+		+	+	
5 Pregled krioprezervacije ljudskih jajnih ćelija u programima asistiranu reprodukcije: Trenutni izazovi i mogućnosti / Review of human oocyte cryopreservation in ART programs: Current challenges and opportunities [24]	2023	Cryobiology	+		+		
6 Jajkonomija: Vitifikacija i bioekonomije donacije jajnih ćelija u Sjedinjenim Amer- ičkim Državama i Španiji / Eggonomics: Vitification and bioeconomies of egg donation in the United States and Spain [11]	2023	Med Anthropol Q.	+		+		
7 Reprodukovanje beline i uspostavljanje srodstva u nordijskom kontekstu transnacionalne donaci- je jajnih ćelija: Usklađivanje donorki sa primaoci- ma koji putuju preko granica u Finskoj [12] / Reproducing whiteness and enacting kin in the Nordic context of transnational egg donation: Matching donors with cross-border traveller recipients in Finland [12]	2018	Soc Sci Med.	+			+	
8 Prilagođavanje kriobioloških tehnika socijal- no i ekonomski ugroženim populacijama - Deo 1: Strategije kriogene prezervacije [25] / Translation of cryobiological techniques to so- cially economically deprived populations-Part 1: Cryogenic preservation strategies [25]	2020	Journal of Medical Devices.	+			+	
9 Krioprezervacija jajnih ćelija i ovarijalnog tkiva u evropskim zemljama: zakonski okvir, praksa, skladištenje i upotreba [26] / Oocyte and ovarian tissue cryopreservation in European countries: statutory background, practice, storage and use [26]	2017	Hum Reprod Open.	+			+	

Table 1. Studies included in the systematic review (Strengths)

duktivne bioekonomije, uključujući razvoj novih biotehnologija, napredak u biomedicinskom inženjeringu i inovacije u krioprezervaciji.

Mogućnosti (Tabela 2): Tabela prikazuje mogućnosti identifikovane u literaturi, kao što su širenje primene bioekonomskih rešenja, razvoj održivih biotehnologija i unapređenje međunarodne saradnje u ovoj oblasti.

- Active participation of consumers in the reproductive bioeconomy market.

4. Threats:

- Ethical issues, commercialization of reproductive services, and the unknown long-term effects of new technologies.

Tabela 2. Studije uključene u sistematski pregled (Mogućnosti)

Table 2. Studies included in the systematic review (Opportunities)

Naziv / Name	Godina / Year	Časopis / Journal	Mogućnosti / Opportunities	Prekogranična repro- duktivna zaštita (CBRC) / Cross-border reproductive care (CBRC)	Transnacionalni program donacije gameta (TGD) / Transnational Gamete Donation Program (TGD)	Tip potrošača koji učestvuje na tržištu reproduktivne bioekonomije / Participating consumer type in the repro- ductive bioeconomy market
1 Prekogranična reproduktivna zaštita (CBRC): rastući globalni fenomen sa višedimenzionalnim implikacijama (sistematski i kritički pregled) / Cross border reproductive care (CBRC): a growing global phenomenon with multidimensional implications (a systematic and critical review) [27]	2018	J Assist Reprod Genet.	+	+		
2 Održivi pristupi medicinskom turizmu: Strategije za Centralnu Makedoniju / Grčku / Sustainable approaches to medical tourism: Strategies for Central Macedonia/Greece. Sustainability [28]	2023	Sustainability	+	+		
3 Globalizovane potrage za asistiranim začećem: Reproductivna putovanja zbog neplodnosti i nevoljne bezdetnosti [29] / Globalised quests for assisted conception: Reproductive travel for infertility and involuntary childlessness [29]	2019	Glob Public Health.	+	+		
4 Španski pravni reproduktivni pejzaž: Stvaranje bio-industrije [30] / Spanish legal reproscape: The making of a bio-industry [30]	2021	Law, Tech. & Hum.	+	+		
5 Višestruke mobilnosti u industriji plodnosti u Meksiku [31] / Multiple mobilities in Mexico's fertility industry [31]	2019	Mobilities.	+	+		
6 Bioekonomije: Život, tehnologija i kapital u 21. Veku [5] / Bioeconomies: Life, Technology, and Capital in the 21st Century [5]	2017	Book	+	+	+	
7 Procvat biznisa sa bebama: Ekonomske geografije asistirane reprodukcije [32] / The baby business booms: Economic geographies of assisted reproduction [32]	2018	Geogr Compass.	+	+		
8 „Dve zemlje – dve laboratorije”: Program transnacionalne donacije gameta (TGD) za podršku donaciji jajnih ćelija [33] / ‘Two countries-two labs’: the transnational gamete donation (TGD) programme to support egg donation	2020	Journal of Assisted Reproduction and Genetics	+		+	
9 Pregled krioprezervacije ljudskih jajnih ćelija u programima asistirane reprodukcije: Trenutni izazovi i mogućnosti [34] / Review of human oocyte cryopreservation in ART programs: Current challenges and opportunities [34]	2023	Cryobiology	+		+	
10 Transakcije jajnih ćelija preko granica u postsovjetskom prostoru [10] / Transacting oocytes across borders in the post-Soviet space [35]	2022	Cult Anthropol.	+		+	
11 Kriopolitika reprodukcije na ledu: Nova skandinavska ledena epoha [13] / The cryopolitics of reproduction on ice: A new Scandinavian ice age [13]	2019	Emerald Publishing Limite	+		+	
12 „Želela bih da joj platim”: Izazivanje altruističke razmene jajnih ćelija u Kanadi kroz moralne mozaike [37] / “I would want to pay her”: Challenging altruistic egg exchanges in Canada through moral patchworks [37]	2021	Soc Sci Med.	+			+
13 Karakteristike i namere heteroseksualnih parova koji uključuju transrodnog muškarca koji čeka donaciju sperme za začeće deteta [38] / Characteristics and intentions of heterosexual couples comprising a transgender man awaiting sperm donation to conceive a child [38]	2021	Andrology	+			+

Tabela 3. Studije uključene u sistematski pregled (slabosti)

Table 3. Studies included in the systematic review (Weaknesses)

	Naziv / Name	Godina / Year	Časopis / Journal	Slabosti / Weaknesses	Nedostatak regulative u vezi sa brojem porodica po donoru / Lack of regulation regarding the number of families per donor	Buduće formiranje složene, netradicionalne, moderne porodice / The future formation of a complex, non-traditional, modern family	Visoki troškovi i ograničenja krioprezervacije / High costs and limitations of cryopreservation
1	Vitrifikacija oocita za elektivno očuvanje plodnosti: SWOT analiza [39] / <i>Oocyte vitrification for elective fertility preservation: a SWOT analysis [39]</i>	2022	Reprod Biomed Online	+			
2	Odlaganje majčinstva: Razlozi, determinante, vreme potrebno za postizanje trudnoće i nivo anksioznosti kod majki [40] / <i>The delay of motherhood: Reasons, determinants, time used to achieve pregnancy, and maternal anxiety level [40]</i>	2019	PLoS One.	+			
3	Preporuke za dobru praksu u pružanju informacija onima koji su uključeni u reproduktivnu donaciju [41] / <i>Good practice recommendations for information provision for those involved in reproductive donation [41]</i>	2022	Human Reproduction Open	+	+		
4	Sperma na koju možete računati: Predlog saveznog regulatornog okvira za povećanje zaštite potrošača u industriji donacije sperme [42] / <i>Sperm you can bank on: A proposed federal regulatory scheme to increase consumer protection in the sperm donation industry [42]</i>	2021	Book	+	+		
5	„Mešati ili slagati?": Transnacionalna industrija plodnosti i poželjnost belaca [14] / <i>Mix or Match?": Transnational fertility industry and white desirability [14]</i>	2021	Med Anthropol.	+	+		
6	Pravni pejzaž reprodukcije u Španiji: Stvaranje bio-industrije [30] / <i>Spanish legal reproscape: The making of a bio-industry [30]</i>	2021	Law, Tech. & Hum.	+	+		
7	Emocije, otelotvorenje i reproduktivni kolonijalizam u globalnoj trgovini ljudskim jajnim ćelijama [43] / <i>Emotion, embodiment, and reproductive colonialism in the global human egg trade [43]</i>	2021	Gend Work Organ.	+	+		
8	SWOT analiza neregulirane donacije sperme [44] / <i>A SWOT analysis of unregulated sperm donation [44]</i>	2023	Reprod Biomed Online	+	+		
9	Kreativno postajanje porodicom u klinici za plodnost? Uparivanje donora sa neheteroseksualnim i samostalnim primaocima u komercijalnoj zaštiti. U: Kreativne porodice: Rod i tehnologije svakodnevnog života [45] / <i>Creatively becoming a family in the fertility clinic? Matching donors with non-heterosexual and single recipients in commercial care. In: Creative Families: Gender and Technologies of Everyday Life [45]</i>	2021	Springer International Publishing;	+		+	
10	Roditeljstvo uz pomoć tehnologije i moderne porodice u 21. veku. U: Moderne veze: Romansa, prijateljstvo i porodica u 21. veku [46] / <i>Technology-Assisted Parenthood and Modern Families in the 21st Century. In: Modern Relationships: Romance, Friendship, and Family in the 21st Century [46]</i>	2024	Book	+		+	
11	U: Sloboda naučnog istraživanja [47] / <i>Reproductive technologies and the family in the twenty-first century. In: The freedom of scientific research [47]</i>	2020	Manchester University Press;	+		+	
12	„Dve zemlje – dve laboratorije": Transnacionalni program donacije gameta (TGD) za podršku donaciji jajnih ćelija [33] / <i>'Two countries-two labs': the transnational gamete donation (TGD) programme to support egg donation [33]</i>	2020	Journal of Assisted Reproduction and Genetics.	+			+
13	Krioprezervacija oocita – trenutna situacija i buduće perspektive: narativni pregled [48] / <i>Oocyte cryopreservation-current scenario and future perspectives: a narrative review [48]</i>	2021	J Hum Reprod Sci	+			+

Tabela 4. Studije uključene u sistematski pregled (pretnje)

Table 4. Studies included in the systematic review (Threats)

	Naziv / Name	Godina / Year	Časopis / Journal	Pretnje / Threats	Nepoznat kvalitet i budući rezultati / Unknown quality and future results	Reproduktivni rad kao pretnja altruizmu / Reproductive work as a threat to altruism	Bioetičke dileme / Bioethical dilemmas
1	„Dve zemlje – dve laboratorije”: Transnacionalni program donacije gameta (TGD) za podršku donaciji jajnih ćelija [33] / <i>Two countries-two labs: the transnational gamete donation (TGD) programme to support egg donation [33]</i>	2020	Journal of Assisted Reproduction and Genetics	+	+		
2	Pregled krioprezervacije ljudskih oocita u programima asistirane reprodukcije: Trenutni izazovi i mogućnosti [34] / <i>Review of human oocyte cryopreservation in ART programs: Current challenges and opportunities [34]</i>	2023	Cryobiology	+	+		
3	Upravljanje krioskadištenjem reproduktivnih ćelija i tkiva u asistiranoj reprodukciji: stanje, potrebe, mogućnosti i potencijalni novi izazovi [49] / <i>Cryostorage management of reproductive cells and tissues in ART: status, needs, opportunities, and potential new challenges [49]</i>	2023	Reproductive BioMedicine Online	+	+		
4	Krioprezervacija gameta i embriona i njihove molekularne promene [50] / <i>Cryopreservation of gametes and embryos and their molecular changes [50]</i>	2021	Int J Mol Sci.	+	+		
5	Kriopolitika reprodukcije na ledu: Nova skandinavska ledena doba [13] / <i>The cryopolitics of reproduction on ice: A new Scandinavian ice age [13]</i>	2019	Emerald Publishing Limited;	+		+	
6	Ekonomske geografije asistirane reprodukcije [32] / <i>Economic geographies of assisted reproduction [32]</i>	2018	Geogr Compass.	+		+	
7	Ekonomija donacije jajnih ćelija u Španiji kao globalna/intimna kontakt zona [51] / <i>The Spanish egg donation economy as a global/intimate contact zone [51]</i>	2022	Documents d'Anàlisi Geogràfica.	+		+	
8	O (globalnim) lancima nege u vremenima krize: donacija jajnih ćelija i kućni rad u Španiji [52] / <i>On (global) care chains in times of crisis: egg donation and domestic work in Spain [52]</i>	2020	Tapuya: Latin Am Sci Technol Soc.	+		+	
9	Da li banka gameta treba da verifikuje nemedicinske informacije koje pruža donor? [53] / <i>Should a gamete bank verify the non-medical information provided by a donor? [53]</i>	2024	Hum Reprod.	+		+	
10	Preporuke za dobru praksu u pružanju informacija onima koji su uključeni u reproduktivnu donaciju [41] / <i>Good practice recommendations for information provision for those involved in reproductive donation [41]</i>	2022	Human Reproduction Open	+			+
11	Razvijajuća etika donacije sperme [54] / <i>The evolving ethics of sperm donation [54]</i>	2022	Johns Hopkins University	+			+
12	Pravo deteta da zna naspram prava roditelja da ne kažu: Stavovi parova koji se podvrgavaju tretmanima plodnosti prema donaciji gameta sa otkrivanjem identiteta [55] / <i>The child's right to know versus the parents' right not to tell: The attitudes of couples undergoing fertility treatments towards identity-release gamete donation [55]</i>	2023	J Reprod Infertil.	+			+
13	Pravo na zaborav naspram prava na otkrivanje identiteta donora gameta: etički i pravni aspekti [56] / <i>The right to be forgotten versus the right to disclosure of gamete donors' ID: ethical and legal considerations [56]</i>	2021	Acta Bioethica.	+			+
14	Anonimna donacija gameta i član 8. Evropske konvencije o ljudskim pravima: Argument za nespojivost [57] / <i>Anonymous gamete donation and Article 8 of the European Convention on Human Rights: The case for incompatibility [57]</i>	2022	Med Law Int.	+			+
15	Etika banke oocita za asistiranu reprodukciju uz pomoć treće strane: sistematski pregled [58] / <i>Ethics of oocyte banking for third-party assisted reproduction: a systematic review [58]</i>	2018	Hum Reprod Update.	+			+

Slabosti (Tabela 3): Ova tabela navodi slabosti identifikovane kroz pregled literature, kao što su tehnički, finansijski i regulatorni izazovi. Ove prepreke ukazuju na potrebu za dodatnim istraživanjima kako bi se postojeće barijere prevazišle.

Pretnje (Tabela 4): Tabela prikazuje pretnje identifikovane analizom literature, uključujući rizike vezane za etička pitanja, regulatorna ograničenja i nedostatak finansijskih sredstava.

Faktori rasta korisni za razvoj tržišta uključuju inovacije, tehnološki napredak, povećanu potražnju i nove mogućnosti poput krioprezervacije, bioekonomskih proizvoda dostupnih putem biobanaka i odlaganje roditeljstva za kasnije životno doba. Ovi pokretači stvaraju nove tržišne mogućnosti, kao što su programi prekogranične reproduktivne zaštite (CRC) i transnacionalne donacije gameta (TGD). Aktivno učešće potrošača na tržištu reproduktivne bioekonomije omogućava bolji pristup savremenim rešenjima i doprinosi globalnoj povezanosti u ovoj oblasti.

S druge strane, izazovi na tržištu uključuju prepreke, regulatorna ograničenja, etičke dileme, visoke troškove i druge faktore koji mogu usporiti rast ili otežati održavanje tržišta, kao i regulisanje broja porodica po donoru, što zahteva stroge zakonske okvire (Slika 2). Takođe, visoki troškovi i tehnička ograničenja krioprezervacije, uz složenost formiranja savremenih porodica, predstavljaju značajne izazove koji ometaju širu primenu ovih tehnologija. Potencijalne pretnje uključuju nepoznate dugoročne posledice, bioetičke dileme, rizik da reproduktivne usluge postanu isključivo komercijalizovane i narušavanje altruističkih principa u ovoj oblasti.

FAKTORI RASTA	IZAZOVI TRŽIŠTA
Snage: ◆ Razvoj biomedicinskog inženjeringa. ◆ Odlaganje roditeljstva do kasnijeg životnog doba. ◆ Razvoj novih tehnologija u biotehnologiji – kriobiologija. ◆ Biodostupnost proizvoda - kriobanke.	Slabosti: ◆ Nedovoljna regulativa u vezi sa brojem porodica po donoru. ◆ Potencijalno formiranje složene, netradicionalne, savremene porodice. ◆ Visoki troškovi i ograničenja povezana sa krioprezervacijom.
Mogućnosti: ◆ Prekogranična reproduktivna zaštita (CBRC). Program transnacionalne donacije gameta (TGD). ◆ Načini učešća na tržištu reproduktivne bioekonomije.	Pretnje: ◆ Nepoznat kvalitet i budući rezultati ◆ Reproductivni rad se posmatra kao pretnja altruizmu. ◆ Bioetičke dileme.

Slika 2. SWOT Analiza reproduktivne bioekonomije

Each of the tables in the appendix covers specific aspects of the reproductive bioeconomy. Strengths (Table 1): This table provides an overview of references that highlight the strengths of the reproductive bioeconomy, including the development of new biotechnologies, advancements in biomedical engineering, and innovations in cryopreservation.

Opportunities (Table 2): Table 3 focuses on opportunities identified in the literature, such as expanding the application of bioeconomic solutions, the development of sustainable biotechnologies, and the enhancement of international cooperation in this area.

Weaknesses (Table 3): This table lists the weaknesses identified through the literature review, such as technical, financial, and regulatory challenges. These obstacles indicate the need for further research to overcome existing barriers.

Threats (Table 4): Table 4 provides an overview of the literature, in which threats were identified through analysis, including risks associated with ethical issues, regulatory constraints, and inadequate financial resources.

Growth factors beneficial to market development include innovation, technological advances, increased demand, and new opportunities such as cryopreservation, bioeconomic products available through biobanks, and delaying parenthood to a later stage in life. These drivers create new market opportunities, such as cross-border reproductive care (CRC) and transnational gamete donation (TGD) programs. The active involvement of consumers in the reproductive bioeconomy market allows better access to modern solutions and contributes to global connectivity in this area.

GROWTH FACTORS	MARKET CHALLENGES
Strengths: ◆ Development of biomedical engineering. ◆ Postponing parenthood to advanced age. ◆ Development of new technologies in biotechnology – Cryobiology. ◆ Bioavailability of products – Cryobanks.	Weaknesses: ◆ Insufficient regulation concerning the number of families per donor. ◆ The prospective formation of a complex, non-traditional, modern family. ◆ High costs and limitations associated with cryopreservation.
Opportunities: ◆ Cross-border reproductive care (CBRC). Transnational Gamete Donation Program (TGD). ◆ Types of participation in the reproductive bioeconomy market.	Threats: ◆ Unknown quality and future results. ◆ Reproductive work is viewed as a threat to altruism. ◆ Bioethical dilemmas.

Figure 2. SWOT analysis of the reproductive bioeconomy

Ovi nalazi naglašavaju važnost uravnoteženja inovacija sa regulativama kako bi se obezbedio održiv i etički razvoj reproduktivne bioekonomije.

DISKUSIJA

Pregled literature i SWOT analiza su istakli ključne snage, mogućnosti, slabosti i pretnje unutar reproduktivne bioekonomije. Ovi rezultati podržavaju slične zaključke iz prethodnih radova, poput studije o bioekonomiji u Letoniji [17], koja je istakla regulatorne izazove i potrebu za podrškom inovacijama. Koherentnost rezultata ukazuje na univerzalne obrasce razvoja bioekonomije.

Rezultati istraživanja razmatraju se kroz četiri ključna segmenta SWOT analize, uz podršku referenci iz relevantnih naučnih časopisa. Sledeća diskusija kritički ispituje ova otkrića i njihova šira značenja za oblast.

SNAGE

Postojanje i kontinuirani razvoj biomedicinskog inženjeringa, zajedno sa napretkom u biotehnologiji, posebno u oblasti kriobiologije i proizvodnje veštačkih gameta, značajno su unapredili efikasnost donatorskih programa [19]. Primena ovih tehnologija u reproduktivnoj medicini dovela je do poboljšanja tehnika krioprezervacije, povećavajući održivost i dugovečnost čuvanih reproduktivnih ćelija. Ovo direktno doprinosi višim stopama uspeha tretmana asistiran reprodukcije i jača pouzdanost donatorskih programa. Dalje, integracija regenerativne biomedicine i personalizovanih terapijskih pristupa omogućava kreiranje individualizovanih strategija lečenja [20]. Time se omogućava precizniji odabir i optimizacija reproduktivnih ćelija, čime se poboljšavaju ishodi lečenja pacijenata. Klinike koje usvoje ove inovacije mogu poboljšati kvalitet svojih usluga, nudeći pacijentima šire mogućnosti za tretman neplodnosti. Odlaganje roditeljstva do kasnijih godina povećava zdravstvene rizike i izazove u demografskim trendovima. Iako tehnologije reproduktivne medicine omogućavaju produženje reproduktivnog potencijala, ograničenja ostaju izražena kod starijih pacijenata. Vitifikacija jajnih ćelija omogućava efikasniju organizaciju donatorskih programa i smanjuje liste čekanja [21]. Prednosti se prepoznaju u visokom standardu usluge koji se postiže primenom novih tehnologija u dijagnostici, kliničkoj terapiji i regenerativnoj medicini, uključujući kulturu ćelija i tkiva, što potvrđuju brojni istraživači [18, 22, 23]. Istraživači takođe ukazuju da je formiranje kriobanki, zahvaljujući tehnikama vitifikacije, smanjilo liste čekanja i eliminisalo potrebu za sinhronizacijom ciklusa donora i primaoca. Poštovanjem fenotipskog podudaranja između donora i pacijenata olakšava se ispunjavanje ključnog aspekta jačanja veze roditelj-dete [12, 13, 25, 26].

On the other hand, market challenges include obstacles, regulatory restrictions, ethical dilemmas, high costs, and other factors that can slow down growth or make it difficult to sustain a market, as well as regulating the number of families per donor, which requires strict legal frameworks (Figure 2). Moreover, the high costs and technical limitations of cryopreservation, along with the complexities of forming modern families, pose significant challenges that hinder the broader application of these technologies. Potential threats include unknown long-term outcomes, bioethical dilemmas, the risk of reproductive services becoming solely commercialized, and the erosion of altruistic principles in this field.

These findings emphasize the importance of balancing innovation with regulation to ensure the sustainability and ethical development of the reproductive bioeconomy.

DISCUSSION

The literature review and SWOT analysis highlighted key strengths, opportunities, weaknesses, and threats within the reproductive bioeconomy. These results support similar conclusions from previous works, such as the study on the bioeconomy in Latvia [17], which highlighted regulatory challenges and the need for support for innovation. The coherence of the results points to universal patterns of bioeconomy development.

The research results are discussed through four key segments of the SWOT analysis, supported by references from relevant scientific journals. The following discussion will critically examine these findings and their broader implications for the field.

Strengths

The existence and continuous development of biomedical engineering, along with advancements in biotechnology, particularly in cryobiology and artificial gamete production, have significantly improved the efficiency of donor programs [19]. Implementing these technologies in reproductive medicine has led to enhanced cryopreservation techniques, increasing the viability and longevity of stored reproductive cells. This directly contributes to higher success rates in assisted reproduction treatments and strengthens the reliability of donor programs. Furthermore, the integration of regenerative biomedicine and personalized therapy approaches within donor programs enables tailored treatment strategies [20]. This enables a more precise selection and optimization of reproductive cells, ultimately enhancing patient outcomes. By adopting these innovations, clinics can improve the quality of

Mogućnosti

Programi transnacionalne donacije gameta (TGD) i prekogranične reproduktivne zaštite (CBRC) omogućavaju prevazilaženje pravnih i društvenih ograničenja, čime se širi dostupnost usluga [27]. Španija, Češka, Grčka i Danska privlače korisnike zahvaljujući povoljnim zakonskim okvirima. Raznovrsnost tipova korisnika koji učestvuju na tržištu reproduktivne bioekonomije (heteroseksualni parovi, LGBT zajednice, transrodne osobe, samohrani roditelji) ukazuje na rastuće prihvatanje i prilagođavanje tržišta savremenim porodicama. Postoji značajan tržišni potencijal za međunarodnu ekspanziju usluga, što potvrđuju istraživanja o složenosti industrije prekogranične reproduktivne zaštite, posebno u zemljama gde postoji nedostatak donora ili gde postoje zakonska, etička ili verska ograničenja [27, 28, 29, 30]. Istraživanja pokazuju i da međunarodnu ekspanziju tržišta olakšava dobro organizovan transnacionalni trgovinski sistem [33, 34, 35].

Slabosti

Nedostatak jedinstvenih propisa u vezi sa brojem porodica po donoru predstavlja izazov, naročito u kontekstu globalizacije tržišta reproduktivnih ćelija. Razlike u nacionalnim standardima otežavaju praćenje donacija preko granica, čime se povećava rizik od slučajnih genetskih povezanosti među decom začetom donacijom. Takođe, neusaglašeni propisi stvaraju pravnu neizvesnost za reproduktivne banke i buduće roditelje, potencijalno ograničavajući efikasnost tržišta i pristup donorskim gametima u određenim regionima. Formiranje netradicionalnih porodica donosi izazove vezane za društveno prihvatanje i pravnu regulaciju [36], dok odsustvo genetske povezanosti može izazvati psihološke i socijalne prepreke.

Iako bi globalizacija donatorskih praksi mogla doprineti širenju reproduktivne bioekonomije, nedostatak jedinstvenih regulatornih standarda otežava praćenje ukupnog broja donacija i povezanih porodica, što stvara etičke i pravne prepreke daljem razvoju sektora [14, 43, 44]. Moderni oblici porodica, uključujući one zasnovane na donaciji gameta, često se suočavaju s pravnim ograničenjima jer tradicionalni zakonski okviri ne prate dinamične promene u tehnologijama i društvenim normama. Ta diskrepancija usporava razvoj tržišta i ograničava dostupnost usluga različitim grupama korisnika [45, 46, 47].

Pretnje

Nepoznat dugoročni kvalitet i ishodi krioprezervacije embriona, uključujući moguće epigenetske promene, predstavljaju ozbiljne izazove za zdravstvene ishode

their services, offering patients broader opportunities for infertility treatment. Postponing parenthood to later years increases health risks and challenges in demographic trends. Although reproductive medicine technologies allow for the extension of reproductive potential, limitations remain pronounced for older patients. Oocyte vitrification allows for a more efficient organization of donor programs and reduces waiting lists [21]. The advantages are recognized by the high standard of service achieved through new technologies in diagnostics, clinical therapy, and regenerative medicine, including cell and tissue culture, as confirmed by numerous researchers [18, 22, 23]. Researchers also indicate that the formation of cryobanks, thanks to vitrification techniques, has reduced the waiting list and eliminated the synchronisation of donor and recipient cycles, and by respecting the phenotypic match between donors and patients, it facilitates the fulfillment of an essential aspect of strengthening parent-child attachment, as researchers believe [12, 13, 25, 26].

Opportunities

Transnational gamete donation (TGD) and cross-border reproductive care (CBRC) programs allow for overcoming legal and social restrictions, thereby expanding the availability of services [27]. Spain, the Czech Republic, Greece, and Denmark attract users with favourable legal frameworks. The diversity of the type of consumers participating in the reproductive bioeconomy market (heterosexual couples, LGBT communities, transgender people, single parents) indicates a growing acceptance and adaptation of the market to the needs of modern families. There is significant market potential for expanding services internationally, as evidenced by research on the complexity of the cross-border reproductive care industry, particularly in countries where there is a shortage of donors or where there are restrictions, whether legal, ethical, or religious [27, 28, 29, 30]. Research also shows that international market expansion is facilitated by a well-organized transnational trade system [33, 34, 35].

Weaknesses

The lack of uniform regulations for the number of families per donor poses a challenge, particularly in the context of the globalisation of the reproductive cell market. Variations in national standards make it difficult to track donations across borders, increasing the risk of accidental genetic connections among donor-conceived individuals. Furthermore, inconsistent regulations create legal uncertainties for both reproductive banks and intended parents, potentially limiting market efficiency and access to donor gametes in certain

dece začete ovim tehnologijama, koji nisu dovoljno istraženi. Bioetičke dileme, poput anonimnosti donora i prava dece da znaju svoje genetsko poreklo, i dalje su nerešena pitanja u mnogim kontekstima. Komercijalizacija reproduktivnog rada ugrožava principe altruizma i potencijalno doprinosi eksploataciji ekonomski ranjivih osoba. Nepoznata bezbednost i kvalitet krio-prezerviranih ćelija, uz moguće epigenetske promene koje mogu uticati na razvoj embriona [32, 33, 49, 50], predstavljaju značajnu pretnju rastu tržišta reproduktivne bioekonomije. Takođe, komercijalizacija donacije reproduktivnih organa i ekonomski motivisano učešće donora [51, 52, 53] izazivaju etičke izazove koji mogu dovesti do regulatornih ograničenja i smanjenja poverenja pacijenata. Bioetičke dileme, poput anonimnosti donora i psiholoških posledica po potomstvo [54], dodatno komplikuju percepciju javnosti i potencijalno ograničavaju razvoj tržišta.

Ova studija možda nije u potpunosti sveobuhvatna, jer je obuhvatila samo radove objavljene na engleskom jeziku. Kako je ovo oblast u razvoju, moguće je da članci objavljeni nakon perioda istraživanja nisu uključeni. Ipak, prateći PRISMA smernice, možemo izvući sledeće preporuke. Iako tehnološki napredak i rastuće tržišne mogućnosti ukazuju na značajan progres, ove koristi treba kritički sagledati u svetlu postojećih izazova. Na primer, iako krio-prezervacija i regenerativna medicina unapređuju efikasnost donatorskih programa, dugoročne biološke i etičke implikacije ostaju neizvesne. Takođe, iako globalizacija reproduktivnih usluga povećava dostupnost, ona istovremeno otvara pitanja o regulatornim neusaglašenostima i etičkim dilemama. Zato je potreban uravnotežen pristup radi maksimizacije koristi uz minimizaciju rizika.

ZAKLJUČAK

Rezultati studije ukazuju na značajan potencijal reproduktivne bioekonomije u unapređenju lečenja neplodnosti i diverzifikacije porodica. Ipak, kreiranje nacionalnog registra predstavlja ključni regulatorni propust u nadzoru biomedicinski potpomognute oplodnje sa doniranim reproduktivnim ćelijama. Regulatorni okvir bi trebalo unaprediti u pravcu transparentnih i etičkih propisa koji bi obezbedili pristup, dostupnost i dobrobit svih učesnika (uključujući pravo dece začete donacijom da saznaju svoje genetsko poreklo). Kompromis se može postići ulaganjem u porodično orijentisane politike koje omogućavaju ženama koje odlažu roditeljstvo da se odluče na potomstvo ranije. Buduća istraživanja treba da se fokusiraju na dugoročne efekte tehnologija i standardizaciju međunarodnih praksi.

Sukob interesa: Nije prijavljen.

regions. The formation of non-traditional families presents challenges related to social acceptance and legal regulation [36], while the absence of a genetic connection can cause psychological and social obstacles.

Although the globalisation of donor practices could contribute to the expansion of the reproductive bioeconomic market, the lack of uniform regulatory standards makes it difficult to track the total number of donations and related families, which creates ethical and legal obstacles to the further development of this sector [14, 43, 44]. In addition, modern forms of families, including those based on gamete donation, often face legal constraints, as traditional legal frameworks do not keep pace with dynamic changes in reproductive technologies and social norms. This discrepancy between legal regulations and social needs slows market development and limits the availability of services for different groups of users [45, 46, 47]

Threats

The unknown long-term quality and outcomes of cryo-preservation of embryos, including possible epigenetic changes, pose significant challenges to the health outcomes of children born through these technologies, which are not sufficiently researched, and the existence of which is unknown. Bioethical dilemmas, such as donor anonymity and the right of children to know their genetic origin, remain unresolved issues in many contexts. The commercialization of reproductive labour threatens the principles of altruism and potentially contributes to the exploitation of economically vulnerable individuals. The unknown safety and quality of cryopreserved cells, along with possible epigenetic changes that may impact embryo development [32, 33, 49, 50], pose a significant threat to the growth of the bioeconomic market. In addition, the commercialisation of reproductive organ donation and economically motivated donor participation [51, 52, 53] challenge the ethical principles of altruism, which may lead to regulatory constraints and reduce patient trust. Bioethical dilemmas, such as donor anonymity and psychological consequences for offspring [54], further complicate public perception and potentially limit market development.

This study may not be as comprehensive as it could be, as it only reviewed publications in the English language. Given that this is an evolving field of research, it is possible that articles published after our study were not included in this review. Nonetheless, following the PRISMA guide, our recommended insights include the following. While technological advancements and expanding market opportunities suggest significant progress, these benefits must be critically examined in light of ongoing challenges. For instance, although

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18. cryopreservation techniques and regenerative medicine improve the efficiency of donor programs, the long-term biological and ethical implications remain uncertain. Additionally, while the globalisation of reproductive services increases accessibility, it also raises concerns about regulatory inconsistencies and ethical dilemmas. Therefore, a balanced approach is crucial to maximise benefits while mitigating potential risks.

CONCLUSION

The study results indicate the significant potential of the reproductive bioeconomy in improving infertility treatment and family diversification. However, the creation of a national registry is a key regulatory oversight for the control of biomedically assisted reproduction with donated reproductive cells. The regulatory framework should be changed in the direction of the need for transparent and ethical regulations to ensure transparency, accessibility, and the well-being of all participants (allowing access to children conceived from donation to choose to know about their genetic origin). A compromise can be achieved by investing in family-friendly policies, allowing women who delay childbearing to decide to have children earlier. Further research should focus on the long-term effects of technologies and the standardisation of international practices.

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ANTIISHEMIJSKA TERAPIJA U LEČENJU HRONIČNOG KORONARNOG SINDROMA

PREGLEDNI RAD

REVIEW ARTICLE

ANTIISCHEMIC THERAPY IN TREATING CHRONIC CORONARY SYNDROME

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SAŽETAK

Ishemija srčanog mišića ima, kao patofiziološku osnovu, neadekvatan odnos između snabdevenosti i potreba miokarda za oksigenisanom krvlju. Klinički se manifestuje kao anginozni bol sa tipičnom lokalizacijom, karakterom, intenzitetom i pratećim tegobama, pre svega netolerancijom napora. Dijagnostički algoritam obuhvata klinički pregled, neinvazivne i invazivne dijagnostičke procedure, uključujući koronarografiju kao zlatni standard. Konzervativno lečenje stabilne angine pectoris, sem modifikacije načina života i eliminisanja tradicionalnih faktora rizika, podrazumeva primenu savremenih lekova, među kojima je i ranolazin, koji se izdvojio svojim jedinstvenim mehanizmom dejstva, efikasnošću i bezbednošću. Ranolazin je efikasan u redukciji manifestacija ishemije i angine sa potencijalnim efektom na disfunkciju leve komore – pre svega dijasistolnu i električnu nestabilnost.

Ključne reči: ishemija miokarda, konzervativno lečenje angine pectoris, ranolazin

ABSTRACT

Myocardial ischemia is pathophysiologically based on the inadequate balance between the supply of oxygenated blood and the myocardial oxygen demand. Clinically, it presents as anginal pain with a typical localization, nature, intensity, and accompanying symptoms, primarily exercise intolerance. The diagnostic algorithm includes clinical examination, non-invasive and invasive diagnostic procedures, with coronary angiography as the gold standard. Conservative treatment of stable angina pectoris, in addition to lifestyle modification and elimination of traditional risk factors, involves the use of novel medications, including ranolazine, which stands out for its unique mechanism of action, effectiveness, and safety. Ranolazine is effective in reducing manifestations of ischemia and angina, with a potential effect on left ventricular dysfunction-primarily diastolic and electrical instability.

Keywords: myocardial ischemia, conservative treatment of angina pectoris, ranolazine

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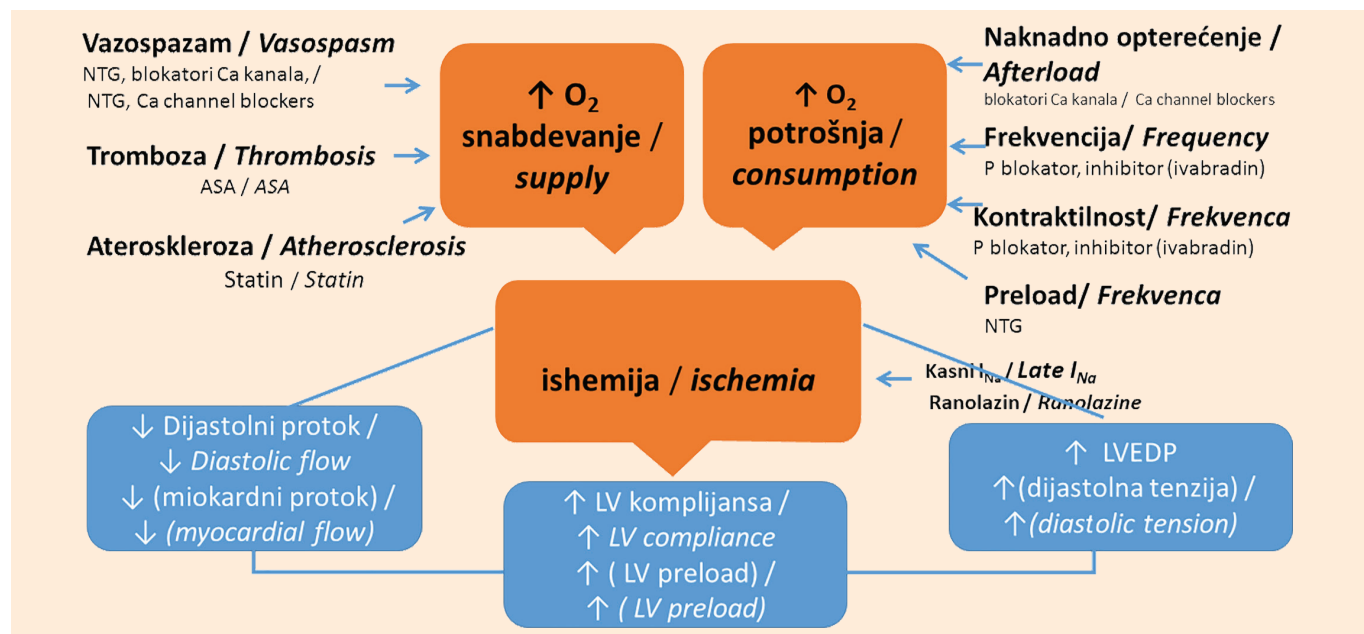
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STABILNA ANGINA PEKTORIS

Ishemija srčanog mišića ima, kao patofiziološku osnovu, neadekvatan odnos između snabdevenosti i potreba miokarda za oksigenisanom krvlju (Slika 1) [1].

STABLE ANGINA PECTORIS

The pathophysiological basis of myocardial ischemia lies in the inadequate balance between the supply of oxygenated blood to the myocardium and its demand for oxygen (Figure 1) [1].



Slika 1. Patofiziološka osnova ishemijske i mesta dejstva antianginoznih lekova

(Adapted from: Morrow DA, Boden WE. Chapter 57: Stable Ischemic Heart Disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. (2012). Saunders; pp 1210-1269)

Figure 1. Pathophysiological basis of ischemia and the sites of the action of antianginal drugs

(Adapted from: Morrow DA, Boden WE. Chapter 57: Stable Ischemic Heart Disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. (2012). Saunders; pp 1210-1269)

Ishemija srčanog mišića se klinički manifestuje kao anginozni bol sa tipičnom lokalizacijom, karakterom, intenzitetom i pratećim tegobama, pre svega netolerancijom napora [1]. Dvogodišnja studija praćenja, koju su sprovedi Mozaffarian i saradnici na skoro 9.000 pacijenata sa koronarnom arterijskom bolešću, potvrdila je da su simptomi angine pektoris nezavistan prediktor kardiovaskularnog mortaliteta, potencirajući fizičko ograničenje kao prediktor lošeg preživljavanja [2]. Dominantno, morfološki supstrat stabilne angine pektoris je stabilan, nekomplikovani aterosklerotski plak, koji sužava koronarnu arteriju.

Dijagnostički algoritam obuhvata klinički pregled, neinvazivne i invazivne dijagnostičke procedure, uključujući koronarografiju kao zlatni standard. Konzervativno lečenje stabilne angine pektoris, osim modifikacije načina života i eliminisanja tradicionalnih faktora rizika, podrazumeva primenu savremenih lekova, među kojima je i ranolazin, koji se izdvojio svojim jedinstvenim mehanizmom dejstva, efikasnošću i bezbednošću. Ranolazin je efikasan u redukciji manifestacija ishemijske i angine, sa potencijalnim efektom na disfunkciju leve komore, pre svega dijastolnu i električnu nestabilnost [1-5].

Myocardial ischemia clinically presents as anginal pain with a typical localization, nature, intensity, and accompanying symptoms, primarily exercise intolerance [1]. A two-year follow-up study conducted by Mozaffarian et al. on nearly 9,000 patients with coronary artery disease confirmed that angina pectoris symptoms were an independent predictor of cardiovascular mortality, emphasizing physical limitation as a predictor of poor survival [2]. The predominant morphological substrate of stable angina pectoris is a stable, uncomplicated atherosclerotic plaque that narrows the coronary artery.

The diagnostic algorithm includes clinical examination, non-invasive and invasive diagnostic procedures, with coronary angiography as the gold standard. Conservative treatment of stable angina pectoris, in addition to lifestyle modification and elimination of traditional risk factors, involves the use of modern medications, among which ranolazine stands out due to its unique mechanism of action, efficacy, and safety. Ranolazine is effective in reducing manifestations of ischemia and angina, with a potential effect on left ventricular dysfunction, particularly diastolic dysfunction and electrical instability [1-5].

Medikamentozna terapija stabilne angine pectoris – osnovni principi

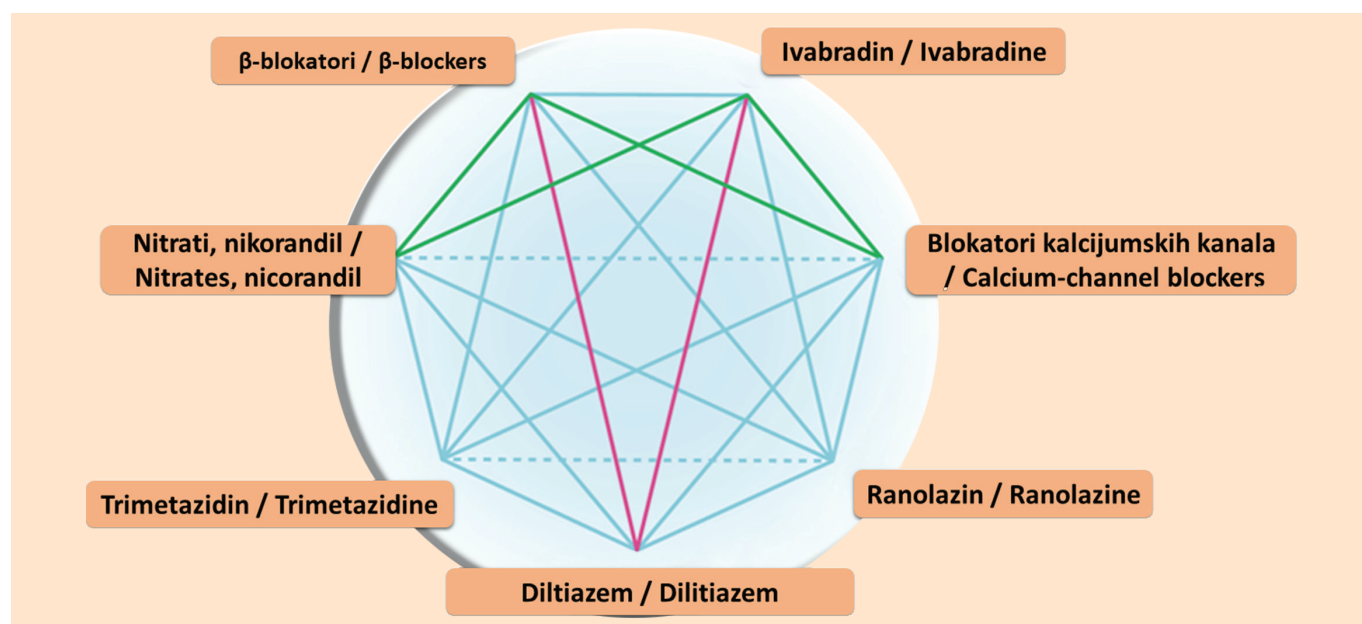
Konvencionalni antiishemijski lekovi smanjuju razvoj ishemije, primarno smanjujući determinante miokardnih zahteva za kiseonikom: broj srčanih otkucaja, krvni pritisak, predopterećenje, kontraktilnost. Veoma je bitna činjenica da ne postoji preklapanje između lekova koji poboljšavaju prognozu i lekova koji olakšavaju simptome, izuzev beta blokatora nakon infarkta miokarda. Prethodno rečeno govori u prilog hipotezi da simptomatska ishemija miokarda ne mora da bude bazičan mehanizam relevantan za prognozu, već da specifični mehanizmi koji utiču na funkciju trombocita i antiinflamatornu ili citokinima posredovanu neurohumoralnu aktivnost mogu da poboljšaju preživljavanje.

Aktuelne strategije lečenja su bazirane na ublažavanju simptoma pomoću lekova kroz uspostavljanje ravnoteže između snabdevanja miokarda kiseonikom i njegove potrošnje, što je relevantno za ishemiju miokarda i anginu pectoris. Svi agensi u ovoj kategoriji: beta blokatori, antagonisti kalcijumskih kanala, nitrati, aktivatori kalijumovih kanala, i blokatori sinusnog čvora, smanjuju zahteve miokarda za kiseonikom. Ovo se postiže kroz direktne efekte na srčani mišić ili indirektno, kroz kompleksne efekte na hemodinamske determinante. Antagonisti kalcijumskih kanala, nitrati i aktivatori kalijumovih kanala mogu dodatno da poboljšaju protok krvi i snabdevanje kiseonikom (Slika 2) [1-6].

Pharmacological treatment of stable angina pectoris – fundamental principles

Conventional anti-ischemic drugs reduce the development of ischemia, primarily by decreasing the determinants of myocardial oxygen demand: heart rate, blood pressure, preload, and contractility. It is important to note that there is no overlap between drugs that improve prognosis and those that alleviate symptoms, except for beta-blockers following myocardial infarction. The above supports the hypothesis that symptomatic myocardial ischemia is not necessarily the fundamental mechanism relevant to prognosis, but rather that specific mechanisms affecting platelet function and anti-inflammatory or cytokine-mediated neurohumoral activity may contribute to improved survival.

Current treatment strategies are based on symptom relief through pharmacological agents by restoring the balance between myocardial oxygen supply and demand, which is crucial for myocardial ischemia and angina pectoris. All pharmacological agents in this category – beta-blockers, calcium channel blockers, nitrates, potassium channel activators, and sinus node inhibitors – reduce myocardial oxygen demand. This is achieved either through direct effects on the myocardium or indirectly via complex effects on hemodynamic determinants. Calcium channel blockers, nitrates, and potassium channel activators can additionally improve blood flow and oxygen delivery (Figure 2) [1-6].



Slika 2. Individualizacija lečenja angine pectoris, tzv. diamond approach sa mogućim kombinacijama različitih klasa antianginoznih lekova (preporučene kombinacije – zelene linije; kombinacije koje se ne preporučuju – crvene linije; moguće kombinacije – plave pune linije; lekovi sa sličnom aktivnošću – plave isprekidane linije)

(Preuzeto iz: Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15(2):120-132.)

Figure 2. Individualization of angina pectoris treatment, the so-called diamond approach, with possible combinations of different classes of antianginal drugs (recommended combinations – green lines; combinations that are not recommended – red lines; possible combinations – blue solid lines; drugs with similar actions – blue dashed lines)

(From: Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, et al. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15(2):120-132.)

U patofiziološkom smislu, u toku miokardne ishemije, razvija se intracelularno opterećenje kalcijumom sa konsekvativnim razvojem ishemije, uključujući i sistolnu i dijasolnu disfunkciju miokarda i električnu nestabilnost [1-6]. Ranolazin nema klinički značajan uticaj na varijable miokardne potrebe za kiseonikom ali potencira njihov antiishemijski efekat prevenirajući intracelularno opterećenje kalcijumom, smanjujući na taj način rigidnost srčanog mišića koja dovodi do redukcije miokardne perfuzije [7-10].

Nedavna studija ističe da se dozno-zavisno poboljšanje miokardne ishemije pri submaksimalnom i maksimalnom opterećenju, postignuto ranolazinom kod pacijenata sa stabilnom koronarnom bolešću, pripisuje poboljšanju miokardnog protoka bez merljivog uticaja na srčane otkucaje i krvni pritisak [9]. Iz navedenog proizilazi da ranolazin može biti idealna komplementarna dopuna standardnoj antianginoznoj terapiji.

Medikamentozna terapija ishemije

Antianginozni efekat lekova se ostvaruje na različitim nivoima, delujući komplementarno – sa jedne strane na povećano snabdevanje miokarda kiseonikom (smanjenjem vazospazma, progresije ateroskleroze i tromboze), a sa druge strane na smanjenu potrošnju kiseonika (smanjenjem preopterećenja i naknadnog opterećenja, srčane frekvencije i kontraktilnosti) (Slike 1 i 2) [7-10].

Ishemija na ćelijskom nivou remeti funkciju Na kanala kardiomiocita, koja je odgovorna za prolongirano povećanje kasne Na struje i konsekvativno prekomerno povećanje intracelularne koncentracije Na i Ca. Prekomerna intracelularna koncentracija Ca remeti dijasolnu relaksaciju i dovodi do povećanja dijasolnog opterećenja i potrošnje kiseonika, te do redukcije miokardnog protoka i snabdevanja kiseonikom. Na ovaj način nastala miokardna hipoperfuzija doprinosi pogoršanju ishemije i angine (Slika 3) [1-2].

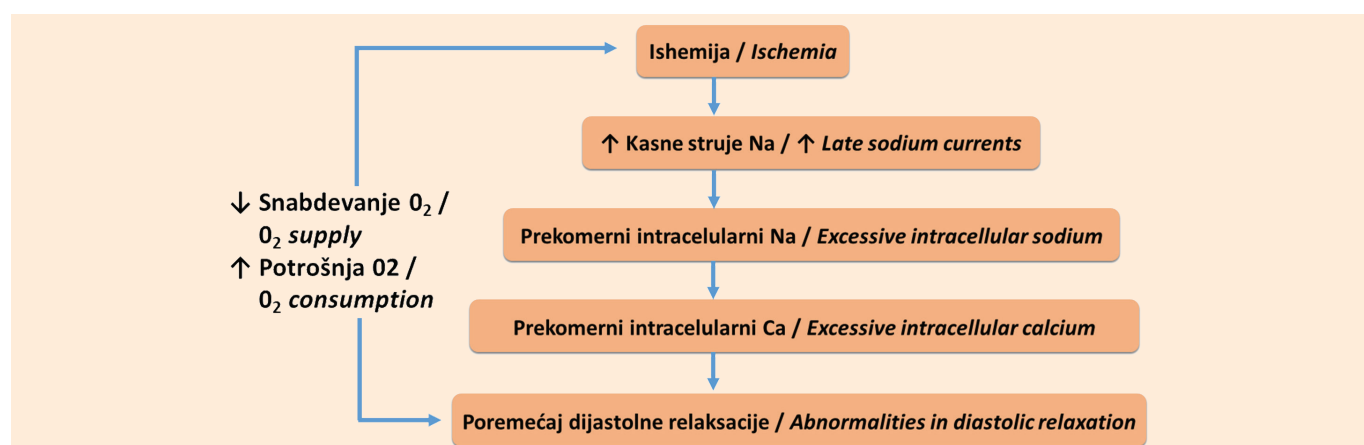
From a pathophysiological perspective, during myocardial ischemia, intracellular calcium overload develops, leading to the progression of ischemia, including both systolic and diastolic myocardial dysfunction, as well as electrical instability [1-6]. Ranolazine does not have a clinically significant impact on variables related to myocardial oxygen demand, however, it does enhance their anti-ischemic effect by preventing intracellular calcium overload. In doing so, it reduces myocardial stiffness that contributes to decreased myocardial perfusion [7-10].

A recent study emphasizes that the dose-dependent improvement in myocardial ischemia during submaximal and maximal exertion achieved with ranolazine in patients with stable coronary artery disease is attributed to enhanced myocardial perfusion, without a measurable effect on heart rate or blood pressure [9]. This suggests that ranolazine may serve as an ideal complementary addition to standard antianginal therapy.

Pharmacological treatment of ischemia

The antianginal effect of medications is achieved at different levels, acting in a complementary manner – on one hand, by increasing myocardial oxygen supply (by reducing vasospasm, atherosclerosis progression, and thrombosis), and on the other, by decreasing oxygen demand (by reducing preload and afterload, heart rate, and contractility) (Figures 1 and 2) [7-10].

At the cellular level, ischemia disrupts the function of sodium channels in cardiomyocytes, leading to a prolonged increase in late sodium current and consequently excessive intracellular accumulation of sodium and calcium. The elevated intracellular calcium concentration impairs diastolic relaxation, resulting in increased diastolic wall stress and oxygen consumption, as well as reduced myocardial perfusion and oxygen supply. The resulting myocardial hypoperfusion further contributes to the worsening of ischemia and angina (Figure 3) [1-2].

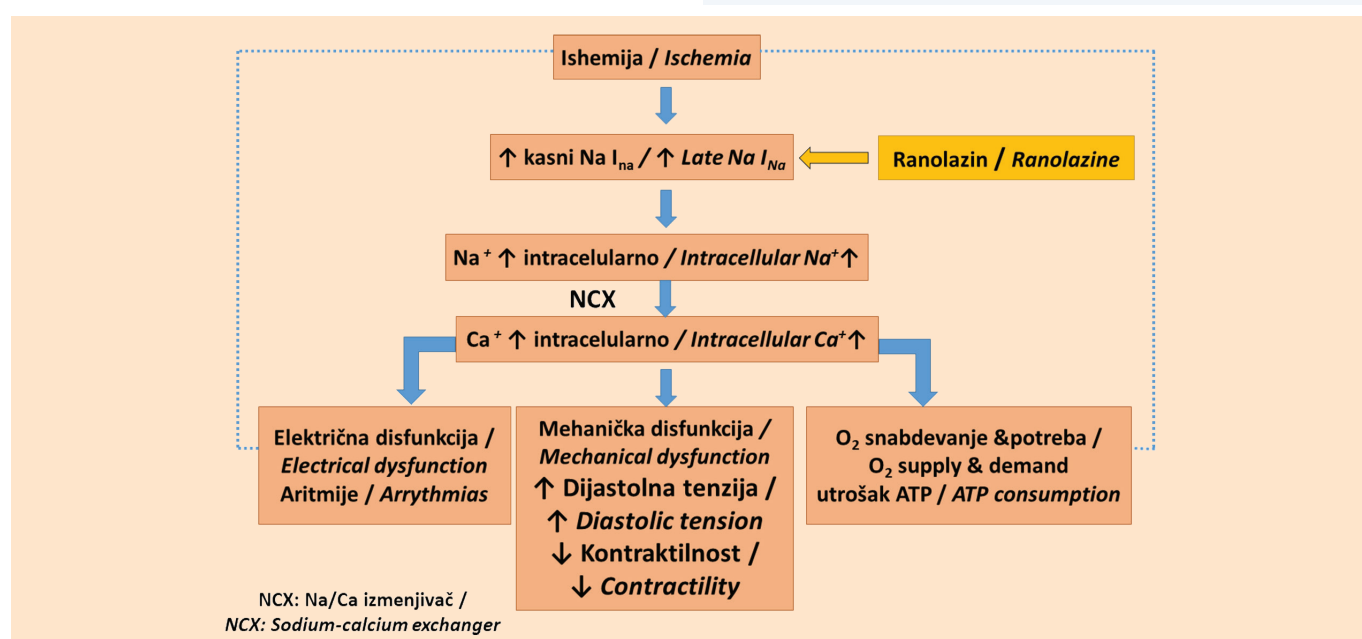


Slika 3. Patofiziologija miokardne hipoperfuzije

Figure 3. Pathophysiology of myocardial hypoperfusion

U ishemijom pogođenom miocitu, intracelularna koncentracija Na je povećana, što dovodi do povećanja intracelularnog nivoa Ca i posledične kontraktilne disfunkcije. Štaviše, povećano dijastolno opterećenje povećava mikrovaskularnu rezistenciju i potencira oštećenje energetske ravnoteže u ishemijom pogođenom miokardu. Formira se jedan začaran krug u kome dijastolna disfunkcija, koja se javlja kao posledica ishemije miokarda, povećava potrošnju energije i potencira energetski disbalans. Patološko pojačanje kasne Na struje doprinosi Na zavisnom opterećenju kalcijumom. Smanjenjem magnitude patološkog pojačanja kasne Na struje, ranolazin prevenira ili dovodi do smanjenja intracelularne koncentracije Ca i na taj način prekida značajan mehanizam u patofiziološkoj osnovi miokardne ishemije (Slika 4) [8].

In an ischemia-affected cardiomyocyte, intracellular sodium concentration increases, leading to elevated intracellular calcium levels and resulting in contractile dysfunction. Moreover, increased diastolic wall stress increases microvascular resistance and exacerbates the disturbance of the energy balance in the ischemic myocardium. This creates a vicious cycle wherein diastolic dysfunction – arising as a consequence of myocardial ischemia – increases energy consumption and further aggravates the energy imbalance. Pathological increase of the late sodium current contributes to sodium-dependent calcium overload. By reducing the magnitude of this pathological late sodium current increase, ranolazine prevents or decreases the intracellular calcium concentration, thereby interrupting a key mechanism in the pathophysiology of myocardial ischemia (Figure 4) [8].



Slika 4. Mehanizam antiishemijskog delovanja ranolazina
(Preuzeto iz: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6.)

Figure 4. Mechanism of the anti-ischemic action of ranolazine
(From: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6.)

Antiishemijski mehanizam, farmakokinetika i farmakodinamika ranolazina

Osnovu delovanja ranolazina predstavlja poboljšanje regionalnog koronarnog protoka u zoni ishemije. Antianginalno delovanje ranolazina se ostvaruje bez značajnijeg uticaja na frekvenciju i visinu arterijskog pritiska. U kliničkim studijama je registrovano zanemarljivo smanjenje srednje frekvencije (< 2 /min) i sistolnog pritiska (< 3 mmHg) [9-10]. Antianginalna efikasnost ne zavisi od pola i životnog doba, kao ni od komorbiditeta (pridruženog dijabetesa melitusa), ali je povezana za povoljnim metaboličkim profilom kod pacijenata sa šećernom bolešću (redukcija HbA1c) [9, 11-12]. Osnov-

Anti-ischemic mechanism, pharmacokinetics, and pharmacodynamics of ranolazine

The primary mechanism of ranolazine action is the improvement of regional coronary blood flow in the ischemic zone. Its antianginal effect is achieved without a significant impact on heart rate or arterial blood pressure. Clinical studies have reported only negligible reductions in average heart rate (< 2 bpm) and systolic blood pressure (< 3 mmHg) [9-10]. The antianginal efficacy of ranolazine is not dependent on gender, age, or comorbidities (such as diabetes mellitus), but it is associated with a favorable metabolic profile in diabetic patients (reduction in HbA1c levels) [9, 11-12]. The key

Tabela 1. Osnovne farmakokinetičke i farmakodinamske karakteristike ranolazina

Ranolazin	Farmakokinetika i farmakodinamika
Bioraspoloživost	35% – 50%
Maksimalna koncentracija	2–6 časova
Poluvreme eliminacije	7 časova
Stabilno delovanje	3 dana
Vezivanje za proteine plazme	62%
Ekskrecija	73% putem urina, 25% putem fecesa
Interakcije sa lekovima (Oprez potreban kod korišćenja drugih inhibitora CYP3A4 i lekova koji utiču na produženje QT intervala)	Moguća INTERAKCIJA sa digoksinom, simvastatinom, ciklosporinom, diltiazemom, verapamilom, ketokonazolom, makrolidima
Interakcije sa hranom	Ne preporučuje se unos grejpfruta.
Ekstenzivan hepatični metabolizam	5% doze se izlučuje nepromenjeno putem urina i fecesa
Primarni metabolizam	Preko CYP3A4
Minorni metabolizam	Preko CYP2D6
Maksimalna preporučena dnevna doza	2 x 750 mg

(Preuzeto i modifikovano iz: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6; Sažetak karakteristika leka Ranexa, februar 2021)

ne farmakokinetičke i farmakodinamske karakteristike ranolazina su date u **Tabeli 1**.

Antianginalna terapija u svakodnevnoj kliničkoj praksi

Cilj antianginalnih lekova je da obezbede adekvatno olakšanje simptoma angine kod pacijenata sa hroničnim koronarnim sindromom (engl. *chronic coronary syndrome - CCS*), delimično nezavisno od njihovog efekta ili nedostatka efekta na MACE (engl. *major adverse cardiac events*). Početna monoterapija, sa naknadnom eskalacijom na kombinaciju antianginalnih lekova u slučaju neadekvatnih ublažavanja simptoma, predstavlja racionalan pristup [13].

Prema aktuelnim evropskim vodičima, terapijski ciljevi u medikamentoznom lečenju stabilne angine pectoris mogu se podeliti u tri grupe:

1. neposredno kratkoročno olakšanje tegoba
2. simptomatska terapija
3. etiološko lečenje sa poboljšanjem prognoze [1-2,14].

U tom smislu, optimizacijom terapije se postiže poboljšanje kvaliteta života (ublažavanje simptoma), smanjenje mortaliteta i morbiditeta, redukcija progresije bolesti i indukcija regresije [1-2,14].

U ovom kontekstu, empirijski pristup započinjanja sa beta-blokatorom može se preporučiti kod mnogih pacijenata sa hroničnim koronarnim sindromom, osim ako ne postoje kontraindikacije ili ako su drugi lekovi

Table 1. Key pharmacokinetic and pharmacodynamic properties of ranolazine

Ranolazine	Pharmacokinetics and pharmacodynamics
Bioavailability	35% – 50%
Maximum concentration	2–6 hours
Elimination half-life	7 hours
Stable action	3 days
Plasma protein binding	62%
Route of elimination	73% renally; 25% in the feces
Drug interactions (Caution is necessary when using other CYP3A4 inhibitors and drugs that affect QT interval prolongation)	Possible INTERACTION with digoxin, simvastatin, cyclosporine, diltiazem, verapamil, ketoconazole, macrolides
Food interactions	Grapefruit consumption is not recommended.
Extensive hepatic metabolism	An estimated 5% of the dose is eliminated as unchanged drug, renally and in the feces.
Primary metabolism	Through CYP3A4
Minor metabolism	Through CYP2D6
Maximum recommended daily dose	2 x 750 mg

(Adapted and modified from: Hasenfuss G, Maier LS. Mechanism of action of the new anti-ischemia drug ranolazine. Clin Res Cardiol. 2008;97(4):222-6; Summary of drug characteristics for Ranexa, February 2021)

pharmacokinetic and pharmacodynamic properties of ranolazine are presented in **Table 1**.

Antianginal therapy in everyday clinical practice

The goal of antianginal drugs is to provide adequate relief of angina symptoms in patients with chronic coronary syndrome (CCS), somewhat independently of their effect or lack thereof on major adverse cardiac events (MACE). Initial monotherapy, followed by escalation to combination antianginal therapy in cases of inadequate symptom relief, represents a reasonable approach [13].

According to current European guidelines, therapeutic goals in the pharmacological treatment of stable angina pectoris can be categorized into three groups:

1. immediate short-term relief of symptoms
2. symptomatic therapy
3. etiological treatment with improved prognosis [1-2,14].

Therapy optimization leads to improved quality of life (symptom relief), reduced mortality and morbidity, slowed disease progression, and induction of regression [1-2,14].

In this context, an empirical approach of starting with a beta-blocker may be recommended for many patients with chronic coronary syndrome, unless there are contraindications or unless other drugs are more

prikladniji od beta-blokatora (npr. pacijenti sa niskim brojem otkucaja srca i/ili krvnim pritiskom) [15].

Preporučuje se da izbor antianginalnih lekova bude individualizovan i prilagođen karakteristikama pacijenta, uzimajući u obzir hemodinamski profil, prisustvo komorbiditeta, postojeću terapiju (komedikaciju), podnošljivost lekova, kao i osnovnu patofiziologiju angine. Takođe, važno je razmotriti lokalnu dostupnost i cenu terapije (razred preporuke: Ic).

U skladu sa aktuelnim preporukama, treba razmotriti dugodelujuće nitrate ili ranolazin kao dodatnu terapiju kod pacijenata kod kojih beta-blokatori i/ili antagonisti kalcijumskih kanala ne omogućavaju zadovoljavajuću kontrolu simptoma, ili kao deo inicijalne terapije kod pažljivo odabranih pacijenata (razred preporuke: IIa) [13-15].

Trenutna empirijska paradigma za izbor antianginalne terapije podrazumeva hijerarhijski, postupni pristup koji uključuje lekove prve linije (beta-blokatori, antagonisti kalcijumskih receptora) i lekove druge linije (nitrati dugog dejstva, nikorandil, ranolazin, ivabradin, trimetazidin). Ovaj pristup potencira koncept da medicinska terapija za kontrolu simptoma kod hroničnog koronarnog sindroma (CSS) treba da bude prilagođena hemodinamskom profilu svakog pacijenta (krvni pritisak, srčana frekvencija), komorbiditetima (naročito kod prisustva srčane slabosti), istovremenom uzimanju lekova koji imaju potencijalne interakcije sa antianginalnim lekovima, istovremeno uzimajući u obzir patofiziološku osnovu ishemije miokarda kod svakog pacijenta, kao i lokalnu dostupnost različitih lekova.

Za mnoge pacijente sa hroničnim koronarnim sindromom, početna terapija lekovima treba da uključuje beta blokator i/ili blokator kalcijumskih kanala (engl. *calcium channel blockers* – CCB). Ako se simptomi angine ne mogu uspešno kontrolisati početnom monoterapijom beta-blokatorom ili blokatorom kalcijumskih kanala, treba razmotriti kombinaciju beta-blokatora i dihidropiridina-blokatora kalcijumskih kanala (DHP-CCB), osim ako nije kontraindikovana (razred preporuke: IIa).

Drugi antianginalni lekovi (nitrati dugog dejstva, ranolazin, nikorandil, trimetazidin, ili ivabradin kod pacijenata sa sistolnom disfunkcijom leve komore) mogu se dodati uz beta-blokator i/ili CCB, ili kao deo početne kombinovane terapije kod adekvatno odabranih pacijenata kada je lečenje beta-blokatorom i/ili blokatorom kalcijumskih kanala kontraindikovano ili se slabo toleriše, ili kada su simptomi angine neadekvatno kontrolisani (Slika 5) (razred preporuke: IIa).

Kada je u pitanju izbor antianginalnih lekova, kratkodelujući nitrati se preporučuju za trenutno ublažavanje angine (razred preporuke: Ib). Kada su propisani nitrati dugog dejstva, treba razmotriti interval bez nitrata

suitable than beta-blockers (e.g., patients with a low heart rate and/or low blood pressure) [15].

It is recommended that the choice of antianginal drugs be individualized and tailored to the patient's characteristics, taking into account the hemodynamic profile, presence of comorbidities, current therapy (co-medication), drug tolerability, as well as the underlying pathophysiology of angina. Additionally, local availability and cost of medications should also be considered (recommendation grade: Ic).

Per current recommendations, long-acting nitrates or ranolazine should be considered as add-on therapy in patients whose symptoms are not adequately controlled by beta-blockers and/or calcium channel blockers, or as part of initial therapy in carefully selected patients (recommendation grade: IIa) [13-15].

The current empirical paradigm for selecting antianginal therapy involves a hierarchical, stepwise approach that includes first-line drugs (beta-blockers, calcium channel blockers) and second-line drugs (long-acting nitrates, nicorandil, ranolazine, ivabradine, trimetazidine). This approach emphasizes the concept that medical therapy for symptom control in chronic coronary syndrome (CCS) should be tailored to the hemodynamic profile of each patient (blood pressure, heart rate), comorbidities (especially in the presence of heart failure), concurrent use of medications with potential interactions with antianginal drugs, while also considering the pathophysiological basis of myocardial ischemia in each patient, as well as the local availability of different drugs.

For many patients with chronic coronary syndrome, initial drug therapy should include a beta-blocker and/or a calcium channel blocker (CCB). If angina symptoms cannot be adequately controlled with initial monotherapy with a beta-blocker or calcium channel blocker, a combination of a beta-blocker and a dihydropyridine calcium channel blocker (DHP-CCB) should be considered, unless contraindicated (recommendation grade: IIa).

Other antianginal drugs (long-acting nitrates, ranolazine, nicorandil, trimetazidine, or ivabradine in patients with left ventricular systolic dysfunction) can be added to beta-blockers and/or CCBs, or applied as part of initial combination therapy in appropriately selected patients when treatment with beta-blockers and/or calcium channel blockers is contraindicated or poorly tolerated, or when angina symptoms are inadequately controlled (Figure 5) (recommendation grade: IIa).

As to the choice of antianginal drugs, short-acting nitrates are recommended for immediate relief of angina (recommendation grade: Ib). When long-acting nitrates are prescribed, a nitrate-free or low-nitrate in-

ili sa niskim sadržajem nitrata da bi se smanjila tolerancija (razred preporuke: IIa). Nikorandil ili trimetazidin se mogu smatrati dodatnom terapijom kod pacijenata sa neadekvatnom kontrolom simptoma dok su na terapiji beta-blokatorima i/ili blokatorima kalcijumskih kanala, ili delom početnog lečenja kod pravilno odabranih pacijenata (razred preporuke: IIb).

Ivabradin treba smatrati dodatnom antianginalnom terapijom kod pacijenata sa sistolnom disfunkcijom leve komore (LVEF < 40%) i neadekvatnom kontrolom simptoma, ili delom početnog lečenja kod pravilno odabranih pacijenata (razred preporuke: IIa). Ivabradin se ne preporučuje kao dodatna terapija kod pacijenata sa CCS, LVEF > 40% i bez kliničke srčane insuficijencije (razred preporuke: IIIb). Ne preporučuje se kombinacija ivabradina sa ne-DHP-CCB (verapamil ili diltiazem) ili drugim jakim inhibitorima CYP3A4 (razred preporuke: IIIb) [13-15].

Nitrati se ne preporučuju kod pacijenata sa hipertrofičnom kardiomiopatijom ili u kombinaciji sa inhibitorima fosfodiesteraze (razred preporuke: IIIb). Ovi lekovi mogu zahtevati oprez ili mogu biti kontraindikovani kod određenih pacijenata sa niskim krvnim pritiskom, (beta-blokatori i DHP-CCB), dijabetes melitusom (beta-blokatori), poremećajima atrioventrikularne provodljivosti (beta-blokatori i ne-DHP-CCB), hroničnom opstruktivnom bolešću pluća (neselektivni beta-blokatori) [13-15].

Za inicijalnu terapiju treba razmotriti ivabradin, nikorandil, dugodelujuće nitrate, ranolazin ili trimetazidin kod pacijenata sa netolerancijom ili kontraindikacijama na beta-blokatore i/ili blokatore kalcijumskih kanala; ranolazin i trimetazidin kod pacijenata sa mikrovaskularnom anginom; nikorandil ili nitrati kod pacijenata sa spazmom koronarnih arterija (razred preporuke: IIb) [13-15].

Ovi lekovi mogu da izazovu poremećaj atrioventrikularne provodljivosti i treba da se primenjuju oprežno kod pacijenata sa perifernom arterijskom bolešću (engl. *peripheral arterial disease – PAD*) i hroničnom opstruktivnom bolešću pluća (HOBP). Blokatori kalcijumskih kanala zahtevaju oprez kod pacijenata sa srčanom insuficijencijom sa redukovanom ejekcionom frakcijom (engl. *heart failure with reduced ejection fraction – HFrEF*). Ranolazin i trimetazidin su racionalne alternative kao deo antianginalne kombinovane terapije kod pacijenata sa niskim otkucanjima srca [13-15].

Kod pacijenata sa srčanom insuficijencijom sa očuvanom ejekcionom frakcijom (engl. *heart failure with preserved ejection fraction – HFpEF*), pored diuretika za lečenje kongestije, preporučuju se SGLT2 inhibitori za poboljšanje ishoda (razred preporuke: I). Pored toga, beta-blokatori, dugodelujući nitrati, CCB, ivabradin, ranolazin, trimetazidin, nikorandil i njihove kombinacije treba da se razmotre kod pacijenata sa HFpEF i koronar-

terval should be considered to reduce tolerance (recommendation grade: IIa). Nicorandil or trimetazidine may be considered as add-on therapy in patients with inadequate symptom control while on beta-blockers and/or calcium channel blockers, or as part of initial therapy in appropriately selected patients (recommendation grade: IIb).

Ivabradine should be considered as additional antianginal therapy in patients with left ventricular systolic dysfunction (LVEF < 40%) and inadequate symptom control, or as part of initial treatment in appropriately selected patients (recommendation grade: IIa). Ivabradine is not recommended as add-on therapy in patients with CCS, LVEF > 40%, and no clinical heart failure (recommendation grade: IIIb). The combination of ivabradine with non-DHP CCBs (verapamil or diltiazem) or other strong CYP3A4 inhibitors is not recommended (recommendation grade: IIIb) [13-15].

Nitrates are not recommended in patients with hypertrophic cardiomyopathy or combined with phosphodiesterase inhibitors (recommendation grade: IIIb). These drugs may require caution or may be contraindicated in certain patients, such as those with low blood pressure (beta-blockers and DHP-CCBs), diabetes mellitus (beta-blockers), atrioventricular conduction disorders (beta-blockers and non-DHP-CCBs), or chronic obstructive pulmonary disease (non-selective beta-blockers) [13-15].

For initial therapy, ivabradine, nicorandil, long-acting nitrates, ranolazine, or trimetazidine should be considered in patients with intolerance or contraindications to beta-blockers and/or calcium channel blockers. Ranolazine and trimetazidine may be considered in patients with microvascular angina, while nicorandil or nitrates may be considered in patients with coronary artery spasm (recommendation grade: IIb) [13-15].

These drugs may cause atrioventricular conduction disturbances and should be used with caution in patients with peripheral arterial disease (PAD) and chronic obstructive pulmonary disease (COPD). Calcium channel blockers require caution in patients with heart failure with reduced ejection fraction (HFrEF). Ranolazine and trimetazidine are reasonable alternatives as part of combination antianginal therapy in patients with a low heart rate [13-15].

In patients with heart failure with preserved ejection fraction (HFpEF), in addition to diuretics for treating congestion, SGLT2 inhibitors are recommended to improve outcomes (recommendation grade: I). Additionally, beta-blockers, long-acting nitrates, calcium channel blockers (CCBs), ivabradine, ranolazine, trimetazidine, nicorandil, and their combinations should be considered in patients with HFpEF and coronary artery disease (CAD) for angina relief, though

nom arterijskom bolešću (KAB) za ublažavanje angine, ali bez efekta na srčanu slabost i krajnje ishode u koronarnom sindromu [13-15].

Redukovane doze rivaroksabana mogu se razmotriti kod pacijenata sa KAB i srčanom insuficijencijom, LVEF > 40% i sinusnim ritmom kada su pod visokim rizikom od moždanog udara, i sa malim rizikom od hemoragije [15].

Lečenje simptoma angine kod pacijenata sa neokludiranom anginom koronarne arterije/neokludiranom ishemijom koronarne arterije (engl. *angina with nonobstructive coronary arteries/ischemia with nonobstructive coronary arteries* - ANOCA/INOCA) predstavlja izazov jer pacijenti čine heterogenu grupu i nedostaju randomizovana ispitivanja. Jedna mala studija je pokazala da je stratifikovani algoritam antianginalne terapije zasnovan na koronarnom funkcionalnom testiranju doveo do ublažavanja simptoma angine i poboljšanja kvaliteta života u poređenju sa kontrolnom grupom lečenom standardnom terapijom.

Kod pacijenata sa mikrovaskularnom anginom i smanjenom rezervom koronarnog protoka (engl. *coronary flow reserve* – CFR) i/ili povećanim indeksom otpora mikrocirkulacije (engl. *index of microcirculatory resistance* – IMR), što može odražavati remodeliranje arteriola, koriste se beta-blokatori, CCB, ranolazin i inhibitori angiotenzin konvertujućeg enzima (engl. *angiotensin-converting enzyme inhibitors* – ACE-I). Kod ovih pacijenata, antiishemična terapija sa amlodipinom je dovela do značajnog poboljšanja.

U lečenju pacijenata sa epikardijalnim ili mikrovaskularnim spazmom nakon acetilholinskog testa (engl. *acetylcholine testing* – ACH testing), antagonist kalcijuma treba smatrati terapijom prve linije. Kod pacijenata sa teškom vazospastičnom anginom, može biti neophodna primena neuobičajeno visokih doza antagonista kalcijuma (npr. diltiazem u dozi od 2×200 mg dnevno ili čak do 960 mg dnevno), a u određenim slučajevima i kombinacija nedihidropiridina (kao što je diltiazem) i dihidropiridinskih blokatora kalcijumskih kanala (kao što je amlodipin).

Važno je napomenuti da, u maloj studiji tokom koje se u periodu od šest nedelja primenjivala oralna terapija diltiazemom u dozi do 360 mg dnevno ili placebo, kod pacijenata sa koronarnom mikrovaskularnom disfunkcijom (engl. *coronary microvascular dysfunction* – CMD), nije utvrđeno značajno poboljšanje simptoma ili kvaliteta života. Ipak, terapija diltiazemom je dovela do smanjenja prevalencije epikardijalnog spazma. Nikorandil, kombinovani vazodilatator koji deluje putem nitratno i kalijum zavisnih kanala, može predstavljati efikasnu alternativu, iako su neželjeni efekti česti (razred preporuke: IIb) [15].

without effect on heart failure progression or end outcomes in coronary syndrome [13-15].

Reduced doses of rivaroxaban may be considered in patients with coronary artery disease (CAD) and heart failure, LVEF > 40%, and sinus rhythm, who are at high risk of stroke and have a low risk of hemorrhage [15].

Managing angina symptoms in patients with angina with nonobstructive coronary arteries/ischemia with nonobstructive coronary arteries (ANOCA/INOCA) is challenging, as these patients represent a heterogeneous group and randomized trials are lacking. A small study showed that a stratified algorithm for antianginal therapy based on coronary functional testing led to symptom relief and improved quality of life compared to the control group treated with standard therapy.

In patients with microvascular angina and reduced coronary flow reserve (CFR) and/or increased index of microcirculatory resistance (IMR), which may reflect arteriolar remodeling, beta-blockers, CCB, ranolazine, and angiotensin-converting enzyme inhibitors (ACE-I) are administered. In these patients, anti-ischemic therapy with amlodipine has led to significant improvement.

In the treatment of patients with epicardial or microvascular spasm after acetylcholine testing (ACH testing), calcium antagonists should be considered as first-line therapy. In patients with severe vasospastic angina, the use of unusually high doses of calcium antagonists (e.g., diltiazem at a dose of 2×200 mg daily or even up to 960 mg daily) and in certain cases a combination of nondihydropyridines (such as diltiazem) and dihydropyridine calcium channel blockers (such as amlodipine) may be necessary.

It is important to note that, in a small study wherein oral therapy with diltiazem at a dose of up to 360 mg per day or a placebo was administered for six weeks, in patients with coronary microvascular dysfunction (CMD), no significant improvement in symptoms or quality of life was found. However, diltiazem therapy reduced the prevalence of epicardial spasm. Nicorandil, a combined vasodilator that acts via nitrate- and potassium-dependent channels, may represent an effective alternative, although side effects are common (recommendation grade: IIb) [15].

Combination treatment with ranolazine, an antianginal agent that improves myocyte relaxation and ventricular compliance by reducing sodium and calcium overload, has shown significant results. In patients with INOCA, spinal cord stimulation is an option for those with refractory complaints after drug therapy [15].

Due to inconsistencies in data collection over time, there is no clear and well-founded evidence to support the existence of clearly defined first- and second-line

Lečenje kombinacijom sa ranolazinom, antianginalnim agensom koji poboljšava relaksaciju miocita i ventrikularnu komplijansu smanjenjem preopterećenja natrijumom i kalcijumom, pokazalo je zapažene rezultate. Kod pacijenata sa neokludiranom ishemijom koronarne arterije, stimulacija kičmene moždine je opcija za one sa refraktornim tegobama nakon medikamentozne terapije [15].

Zbog nedoslednosti u prikupljanju podataka tokom vremena, ne postoje jasni i utemeljeni dokazi koji bi potkrepili postojanje jasno definisane antianginalne terapije prve i druge linije. I dalje nije dovoljno razjašnjeno da li dugodelujući nitrati, ranolazin, nikorandil, ivabradin, trimetazidin ili njihove kombinacije pružaju veće olakšanje simptoma angine u poređenju sa beta-blokatorima ili blokatorima kalcijumskih kanala [15].

Ranolazin u pivotalnim studijama i svakodnevnoj kliničkoj praksi

Do sada nisu sprovedena velika randomizovana ispitivanja koja bi direktno uporedila klasične, istorijski prve odobrene antianginalne lekove (beta-blokatore i blokatore kalcijumskih kanala – CCB) sa novijim antiishemijskim agensima kao što su ivabradin, nikorandil, ranolazin i trimetazidin. Noviji lekovi su uglavnom ispitivani u manjim studijama koje su procenjivale njihovu neinferornost u poređenju sa beta-blokatorima ili blokatorima kalcijumskih kanala, ili u većim ispitivanjima, gde su posmatrani kao dodatak standardnoj terapiji zasnovanoj na beta-blokatorima i/ili blokatorima kalcijumskih kanala. U prilog tezi da ranolazin treba dati pre beta blokatora kod hronične angine govori i nedavna studija sprovedena na 158 pacijenata sa anginoznim simptomima. U toj studiji, ranolazin je poboljšao toleranciju na fizički napor, smanjio naporom indukovanu ishemiju i anginu, pokazujući efikasnost najmanje jednaku atenololu, pri čemu nije imao uticaj na arterijski pritisak ni puls [16].

Jedna od pivotalnih studija koja je etablirala mesto ranolazina u lečenju pacijenata sa stabilnom anginom pectoris bila je dvostruko slepa, placebo kontrolisana studija sa ukrštanjem modaliteta lečenja u četiri perioda MARISA (*Monotherapy Assessment of Ranolazine in Stable Angina*) koja je uključila 175 pacijenata lečenih ranolazinom u dve dnevne doze kao monoterapijom angine. U poređenju sa placebo, ranolazin je pokazao održiv dožno zavisni efekat, povećao toleranciju na napor i smanjio naporom indukovanu ishemiju bez klinički merljivih hemodinamskih efekata, a da pri tom kratkoročno preživljavanje nije bilo kraće od očekivanog [17].

U skladu sa prethodno citiranom studijom su i rezultati CARISA studije (*Combination Assessment of Ranolazine in Stable Angina*) sprovedene na 450 pacijenata kod kojih je konvencionalnoj antiishemijskoj terapiji

antianginal terapiji. Whether long-acting nitrates, ranolazine, nicorandil, ivabradine, trimetazidine, or their combinations provide greater relief of angina symptoms compared to beta-blockers or calcium channel blockers remains unclear [15].

Ranolazine in pivotal studies and daily clinical practice

To date, no large, randomized trials have directly compared the classic, historically first-approved antianginal agents (beta-blockers and calcium channel blockers – CCBs) with newer anti-ischemic drugs such as ivabradine, nicorandil, ranolazine, and trimetazidine. Newer drugs have mostly been investigated in smaller studies evaluating their non-inferiority compared to beta-blockers or calcium channel blockers, or in larger trials, where they have been examined as an addition to standard therapy founded on beta-blockers and/or calcium channel blockers. A recent study conducted on 158 patients with angina symptoms also supports the thesis that ranolazine should be given rather than beta-blockers in chronic angina. In this study, ranolazine improved exercise tolerance, reduced exercise-induced ischemia and angina, showing efficacy at least equal to atenolol, with no effect on arterial pressure or heart rate [16].

One of the pivotal studies that established the role of ranolazine in the treatment of patients with stable angina pectoris was the double-blind, placebo-controlled, four-period crossover study MARISA (*Monotherapy Assessment of Ranolazine in Stable Angina*), which included 175 patients treated with ranolazine in two daily doses as monotherapy for angina. Compared to placebo, ranolazine demonstrated a sustained, dose-dependent effect, increased exercise tolerance, and reduced exercise-induced ischemia without clinically significant hemodynamic effects, and without any reduction in short-term survival compared to expectations [17].

Consistent with the previously cited study are the results of the CARISA study (*Combination Assessment of Ranolazine in Stable Angina*), conducted on 450 patients in whom ranolazine was added to conventional anti-ischemic therapy at standard doses, and in whom long-term survival was not shorter than expected. The same applies to the post-hoc CARISA analysis, which recorded improved exercise tolerance and symptom relief, along with a reduction in exercise-induced ischemia and hemodynamic neutrality in patients with more severe forms of angina who received ranolazine in addition to standard antianginal therapy, with maximum doses of beta-blockers and calcium channel antagonists [18].

u standardnim dozama dodat ranolazin i kod kojih dugo-oročno preživljavanje nije bilo kraće od očekivanog. Isto važi i za *post-hoc* CARISA analizu gde je zabeleženo poboljšanje tolerancije na napor i ublažavanje simptoma, uz smanjenje naporom indukovane ishemije i hemodinamsku inerciju kod pacijenata sa težom formom angine kojima je na standardnu antianginoznu terapiju maksimalnim dozama beta blokatora i kalcijumskih antagonista dodat ranolazin [18].

Značajno smanjenje učestalosti anginoznih napada, a samim tim i upotrebe nitroglicerina, zabeleženo je i u velikoj studiji Stouna i saradnika, gde je pacijentima na monoterapiji amlodipinom u maksimalnoj dnevnoj dozi dodat ranolazin. Interesantno je da su pacijenti sa težom formom angine imali značajniji efekat terapije bez hemodinamskih promena [19].

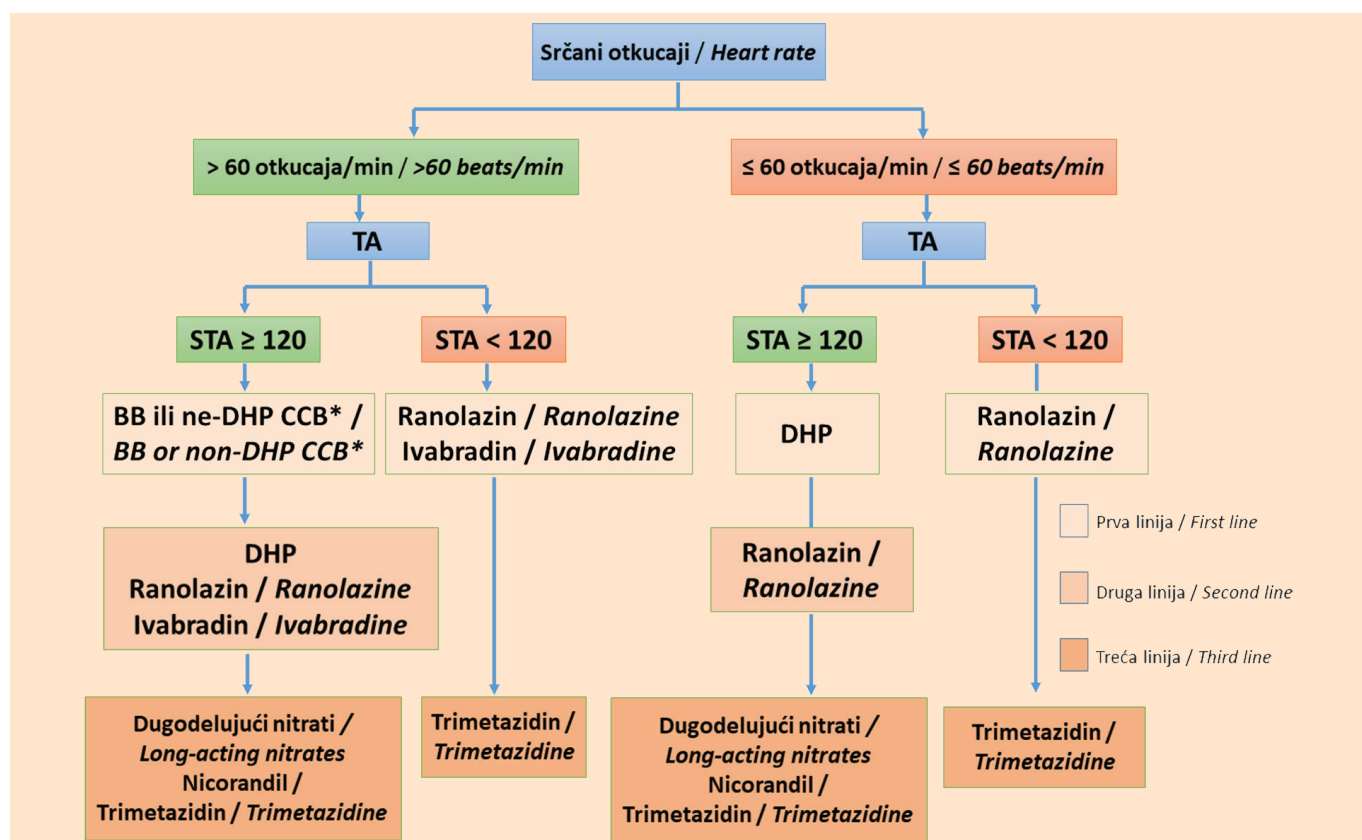
Antiishemijski efekat je konzistentan kroz sve podgrupe pacijenata sa hroničnom anginom, uključujući i pacijente sa dijabetesom, kod kojih je, osim održivog antianginoznog efekta u smislu smanjenja učestalosti ataka angine i korišćenja nitroglicerina tokom lečenja, zabeležen povoljniji metabolički profil i redukcija HbA1c, nezavisno od inicijalnih vrednosti (Slika 5) [12,20-21].

A significant reduction in the frequency of anginal attacks – and consequently, in the use of nitroglycerin – was also recorded in a large study by Stone et al., wherein ranolazine was added to the therapy of patients already receiving amlodipine monotherapy at the maximum daily dose. Interestingly, patients with more severe forms of angina experienced a more pronounced therapeutic effect without hemodynamic changes [19].

The anti-ischemic effect is consistent across all subgroups of patients with chronic angina, including patients with diabetes, in whom – besides the sustained antianginal effect in terms of reduced frequency of angina attacks and nitroglycerin use during treatment – a more favorable metabolic profile and a reduction in HbA1c were observed, regardless of baseline values (Figure 5) [12,20-21].

The results of the ROLE (Ranolazine Open Label Experience) study, which included 746 patients with chronic angina, confirmed the long-term safety of ranolazine use in this population. Treatment was associated with symptomatic improvement and good tolerance of therapy, with no observed increase in mortality [21].

In addition to patients with chronic angina, pa-



Slika 5. Preporuke za lečenje hroničnog koronarnog sindroma

*Normalna ejekciona frakcija; **Srčani otkucaji >70/min

TA = arterial blood pressure (Lat. tensio arterialis); BB = beta bloker;
CCB = kalcijumski antagonista; DHP = dihidropiridin; STA = sistolni arterijski krvni pritisak

Figure 5. Treatment recommendations for chronic coronary syndrome

*Normal ejection fraction; **Heart rate >70 bpm

TA = arterial blood pressure (Lat. tensio arterialis); BB = beta-blocker;
CCB = calcium channel blocker; DHP = dihydropyridine; STA = systolic arterial blood pressure

Rezultati ROLE (*Ranolazine Open Label Experience*) studije, koja je obuhvatila 746 pacijenata sa hroničnom anginom, potvrdili su dugoročnu bezbednost primene ranolazina u ovoj populaciji. Lečenje je bilo praćeno simptomatskim poboljšanjem i dobrom tolerancijom terapije bez zabeleženog povećanja mortaliteta [21].

Pored pacijenata sa hroničnom anginom, i pacijenti sa akutnom koronarnim sindromima bez elevacije ST segmenta imaju merljive dobrobiti kada se ranolazin doda standardnoj antiishemijskoj terapiji. Efekat je održiva redukcija simptoma ishemije, bez uticaja na kardiovaskularni morbiditet i mortalitet kod ovih bolesnika [22]. Zabeležen je pozitivan uticaj ranolazina na miokardnu perfuziju, pa i pacijenti sa endotelnom disfunkcijom ostvaruju jasno subjektivno i objektivno poboljšanje u smislu simptomatskog olakšanja tegoba i popravljavanja ishemijskog deficita [23].

O sveukupnoj koristi optimizacije antianginozne terapije ranolazinom svedoči i nedavna ekonomska metaanaliza koja je obuhvatila sedam studija. Ova analiza potvrđuje jasnu finansijsku korist za zdravstveni sistem kroz primenu ranolazina kao dodatka konvencionalnoj antiishemijskoj terapiji, bar u prvoj godini lečenja [24].

Osim kod HFrEF, koja najčešće nastaje kao komplikacija koronarne bolesti, merljivi su efekti ranolazina i kod HFpEF. Majer i saradnici su, u pilot studiji na 20 pacijenata sa HFpEF, lečenih intravenskom infuzijom ranolazina, registrovali akutno poboljšanje hemodinamskih (LVEDP, PCWP, MPAP) ali ne i parametara dijastralne funkcije. Sa druge strane, metaanaliza koja je obuhvatila osam randomizovanih studija sa prilično heterogenom populacijom sa HFpEF (ishemijska bolest srca, dijabetes, hipertrofična kardiomiopatija), osim poboljšanja hemodinamike kod pacijenata lečenih ranolazinom, ističe i pozitivan uticaj leka na parametre dijastralne funkcije (LVEDV, E/e') bez izazivanja hemodinamske i električne nestabilnosti [25-26].

Iako je poznato da ranolazin produžava QT interval u EKG zapisu, kao i da se produžetak korigovanog QT intervala (QTc) kreće od prosečnih 6 ms pa sve do 15 ms u 5 % pacijenata, kliničko iskustvo nije ukazalo na povećanje rizika od proaritmija ili napravnog umiranja kod pacijenata lečenih ranolazinom [4,17]. Štaviše, rezultati RAID studije koja je uključila pacijente sa ugrađenim implantabilnim kardioverter defibrilatorom (engl. *implantable cardioverter defibrillator* - ICD), jasno ističu efekat ranolazina na električnu nestabilnost u smislu smanjenja broja epizoda ventrikularne tahikardije kod visokorizičnih pacijenata, a naročitu korist su imali pacijenti sa nadograđenim biventrikularnim pejsmejkerom, tzv. CRT-om (engl. *cardiac resynchronization therapy*), pacijenti kod kojih nije zabeležena

tients with non-ST-segment elevation acute coronary syndromes also experience measurable benefits when ranolazine is added to standard anti-ischemic therapy. The effect is a sustained reduction of ischemic symptoms, without impact on cardiovascular morbidity and mortality in these patients [22]. A positive effect of ranolazine on myocardial perfusion has been observed, and even patients with endothelial dysfunction have achieved clear subjective and objective benefits in terms of symptom relief and improvement of ischemic deficit [23].

The overall benefit of optimizing antianginal therapy with ranolazine is substantiated by a recent economic meta-analysis that included seven studies. This analysis confirms a clear financial benefit for the health system through the application of ranolazine as an adjunct to conventional anti-ischemic therapy, at least in the first year of treatment [24].

In addition to HFrEF, which most often occurs as a complication of coronary disease, the effects of ranolazine are also measurable in HFpEF. In a pilot study involving 20 patients with HFpEF treated with intravenous ranolazine, Maier et al. registered an acute improvement in hemodynamic (LVEDP, PCWP, MPAP) but not diastolic function parameters. On the other hand, a meta-analysis that included eight randomized studies with a rather heterogeneous population with HFpEF (ischemic heart disease, diabetes, hypertrophic cardiomyopathy), in addition to the improvement of hemodynamics in patients treated with ranolazine, also highlights the positive effect of the drug on diastolic function parameters (LVEDV, E/e'), without causing hemodynamic and electrical instability [25-26].

Although it is known that ranolazine prolongs the QT interval in the ECG recording, and that the prolongation of the corrected QT interval (QTc) ranges from an average of 6 ms up to 15 ms in 5% of patients, clinical experience has not indicated an increase in the risk of proarrhythmias or sudden death in patients treated with ranolazine [4,17]. Moreover, the results of the RAID study, which included patients with an implantable cardioverter defibrillator (ICD), clearly highlight the effect of ranolazine on electrical instability in terms of reducing the number of episodes of ventricular tachycardia in high-risk patients, while particular benefits were observed in patients with an upgraded biventricular pacemaker, the so-called by CRT (cardiac resynchronization therapy), patients in whom atrial fibrillation was not recorded, and in patients without concomitant antiarrhythmic therapy [27].

Precisely because of its mechanism of action, ranolazine has the potential to prevent the occurrence of not only ventricular, but also atrial arrhythmias, such

atrijalna fibrilacija i pacijenti bez konkomitantne antiaritmijske terapije [27].

Upravo zbog svog mehanizma delovanja, ranolazin ima potencijal da prevenira nastanak, ne samo komorskih, već i pretkomorskih aritmija, kakva je atrijska fibrilacija (AF), i ima naročito značajno mesto u kontroli ritma kod pacijenata sa paroksizmalnom atrijskom fibrilacijom i različitim kliničkim stanjima.

Rezultati metaanalize Leelapatane i saradnika, koja je uključila pacijente sa AF i sistolnom disfunkcijom, jasno ističu sinergistički efekat ranolazina u kombinaciji sa amiodaronom na Na struje, što rezultira povećanjem učestalosti i brzine konverzije AF u sinusni ritam, uz optimalan bezbedonosni profil [28].

Konzistentan efekat u prevenciji nastanka postoperativne atrijske fibrilacije komparabilan efektu amiodarona, ranolazin pokazuje i kod hirurški revaskularizovanih pacijenata, bez razlike u učestalosti neželjenih događaja [29].

ZAKLJUČAK

Optimalna terapija angine se ne može zamisliti bez poslednje generacije antiishemijskih lekova sa ćelijskim mehanizmom delovanja, kojim se postiže smanjenje ishemije na nivou miocita. Ranolazin je prvi inhibitor kasne natrijumske struje, dokazano efikasan i bezbedan, kojim se postiže smanjenje učestalosti stenokardija, bolja tolerancija napora, unapređen kvalitet života i poboljšano preživljavanje uz pozitivan metabolički profil (redukcija HbA1C), a bez uticaja na hemodinamiku, odnosno puls i pritisak.

Ranolazin, dakle, nije „rezervni lek“; optimalan je za pojedine podgrupe pacijenata, kakvi su pacijenti sa dijabetesom, mikrovaskularnom bolešću, hipotenzijom i bradikardijom, gde se pokazao efikasan, kako u monoterapiji, tako i u kombinaciji sa beta blokatorom ili kalcijumskim antagonistom.

Sukob interesa: Nije prijavljen.

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as atrial fibrillation (AF), and has a particularly important place in rhythm control in patients with paroxysmal atrial fibrillation and various clinical conditions.

The results of the meta-analysis by Leelapatana et al., which included patients with AF and systolic dysfunction, clearly highlight the synergistic effect of ranolazine in combination with amiodarone on Na currents, resulting in an increase in the frequency and speed of conversion of AF to sinus rhythm, with an optimal safety profile [28].

Ranolazine has demonstrated a consistent effect in the prevention of postoperative atrial fibrillation comparable to the effect of amiodarone in surgically revascularized patients, without a change in the frequency of adverse events [29].

CONCLUSION

Optimum therapy of angina cannot be conceived without the latest generation of anti-ischemic drugs that have a cellular mechanism of action, which achieves reduction of ischemia at the myocyte level. Ranolazine is the first late sodium current inhibitor, proven effective and safe, which achieves a reduction in the frequency of angina pectoris, better exercise tolerance, improved quality of life, and improved survival, with a positive metabolic profile (reduction of HbA1C), without affecting hemodynamics, i.e. heart rate and blood pressure.

Ranolazine, therefore, is not a "backup drug"; it is optimal for certain patient subgroups, such as those with diabetes, microvascular disease, hypotension, and bradycardia, where it has proven effective both as monotherapy and in combination with a beta-blocker or calcium channel blocker.

Conflict of interest: None declared.

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INTERAKCIJA IZMEĐU MEZENHIMALNIH MATIČNIH ČELIJA I MAKROFAGA U INFLAMATORNOJ MIKROSREDINI

PREGLEDNI RAD

REVIEW ARTICLE

THE INTERACTION BETWEEN MESENCHYMAL STEM CELLS AND MACROPHAGES IN THE INFLAMMATORY MICROENVIRONMENT

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SAŽETAK

Mezenhimalne matične ćelije (MMĆ; engl. *mesenchymal stem cells - MSC*) su ćelije koje imaju veliki terapijski potencijal u regenerativnoj medicini, prevashodno zahvaljujući svojoj sposobnosti samoobnavljanja i diferencijacije u različite tipove ćelija. Imunomodulatorna svojstva ovih ćelija omogućavaju im da regulišu proces inflamacije, u zavisnosti od interakcije sa ćelijama imunskog sistema. Makrofagi, koji su deo urođenog imunskog sistema, mogu da ispoljavaju proinflamatorni M1 ili antiinflamatorni M2 fenotip i utiču na imunski odgovor i homeostazu tkiva. Mezenhimalne matične ćelije utiču na polarizaciju makrofaga, čime modulišu njihove efektorske funkcije. S druge strane, makrofagi mogu da utiču na potencijal za diferencijaciju mezenhimalnih matičnih ćelija i njihovu imunoregulatornu funkciju. Interakcija između mezenhimalnih matičnih ćelija i makrofaga, kao i njihova interakcija sa različitim imunskim i neimunskim ćelijama, ukazuje na složenost procesa unutar inflamatorne mikrosredine. Interakcija između ovih ćelija je od suštinskog značaja za proces reparacije tkiva. U ovom kratkom pregledu nastojaćemo da objasnimo značaj interakcije mezenhimalnih matičnih ćelija i makrofaga u nekim bolestima povezanim sa upalom, sa posebnim naglaskom na ključnu ulogu inflamatorne mikrosredine i terapijski potencijal ovih ćelija.

Ključne reči: MMĆ, makrofagi, inflamacija, imunski sistem

ABSTRACT

Mesenchymal stem cells (MSCs) are cells with significant therapeutic potential in regenerative medicine, primarily due to their capacity for self-renewal and differentiation into various cell types. The immunomodulatory properties of these cells enable them to regulate the inflammatory process, depending on their interaction with immune system cells. Macrophages, which are part of the innate immune system, can exhibit a pro-inflammatory M1 or an anti-inflammatory M2 phenotype, thereby influencing the immune response and tissue homeostasis. Mesenchymal stem cells affect macrophage polarization, thus modulating their effector functions. Conversely, macrophages can influence the differentiation potential of mesenchymal stem cells and their immunoregulatory function. The interaction between mesenchymal stem cells and macrophages, as well as their interaction with various immune and non-immune cells, highlights the complexity of processes within the inflammatory microenvironment. The interaction between these cells is essential for the tissue repair process. This brief review aims to analyze the importance of the interaction between mesenchymal stem cells and macrophages in certain inflammation-associated diseases, with special emphasis on the key role of the inflammatory microenvironment and the therapeutic potential of these cells.

Keywords: MSCs, macrophages, inflammation, immune system

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UVOD

Mezenhimalne matične ćelije (MMC; engl. *mesenchymal stem cells* – MSC) su multipotentne matične ćelije koje poseduju sposobnost samoobnavljanja i diferencijacije. Iako se MMC mogu izdvojiti iz gotovo svih tkiva u ljudskom telu, glavni izvori su koštana srž i masno tkivo. MMC se mogu diferencirati u više ćelijskih linija, uključujući osteoblaste, hondroците, miocyte i adipocyte, što omogućava njihovu primenu u regenerativnoj medicini i terapiji bolesti [1]. MMC mogu da komuniciraju sa imunskim ćelijama putem sekrecije regulatornih molekula i citokina, kao i putem direktnih međućelijskih kontakata [2]. Zbog svog uticaja na ćelije adaptivnog i urođenog imuniteta, naročito makrofage, primenjuju se u terapiji brojnih imunoloških poremećaja [3].

Poznato je da dolazi do akumulacije mezenhimalnih matičnih ćelija na mestu povrede gde one započinju proces reparacije zahvaljujući svojim izuzetnim imunomodulatornim svojstvima [4]. U zavisnosti od različitih stimulansa, mezenhimalne matične ćelije mogu biti proinflamatorne (MSC1) ili antiinflamatorne (MSC2). Kada se aktiviraju stimulusima kao što su hipoksija, citokinska mikrosredina i ligandi za receptore slične „*toll-u*“, MMC proizvode različite imunomodulatore, uključujući azot-monoksid (NO), indolamin 2,3-dioksigenazu (IDO), prostaglandin E2 (PGE2), interleukin (IL)-6 i IL-10 [5]. Poznato je da MMC igraju ključnu ulogu kao imunosupresivne ćelije putem produkcije molekula kao što su PGE2 i protein gena 6 stimulisan faktorom nekroze tumora (engl. *tumor necrosis factor-stimulated gene 6 protein* - TSG-6) [6].

Makrofagi, kao ćelije urođenog imunskog sistema, predstavljaju ključnu komponentu prve linije odbrane protiv patogena i ćelija tumora [7]. To su veoma plastične ćelije koje mogu poprimiti različite fenotipe aktivacije sa specifičnim efektorskim funkcijama kao odgovor na različite stimulse iz okolne mikrosredine. Iako su makrofagi standardno klasifikovani u dve kategorije – M1 proinflamatorni makrofagi i M2 antiinflamatorni makrofagi sa sposobnostima reparacije tkiva – najnovija dostignuća u tehnologijama sekvenciranja na nivou pojedinačnih ćelija otkrila su mnogo širi spektar stanja aktivacije makrofaga, koji prevazilazi ovu pojednostavljenu podelu [8]. Migracija makrofaga ka mestu inflamacije, gde vrše fagocitozu oštećenih ili mrtvih ćelija, od suštinskog je značaja za homeostazu i regeneraciju tkiva [7]. U početnoj fazi inflamatornog procesa, makrofagi pretežno ispoljavaju proinflamatorne karakteristike, odnosno M1-nalik fenotip, lučeći faktor nekroze tumora-alfa (engl. *tumor necrosis factor-alpha* – TNF- α), IL-1 β i IL-12.

Međutim, kako bi se sprečilo oštećenje tkiva u uslovima akutne inflamacije, M2-nalik makrofagi luče velike količine interleukina 10 (IL-10) i faktora rasta tumo-

INTRODUCTION

Mesenchymal stem cells (MSCs) are multipotent stem cells that possess self-renewal and differentiation capacities. Although MSCs can be obtained from almost all tissues within the human body, the main sources are the bone marrow and adipose tissue. MSCs can differentiate into multiple cell lineages, including osteoblasts, chondrocytes, myocytes, and adipocytes, which enables their applicability in regenerative medicine and disease therapy [1]. MSCs can interact with immune cells by secreting regulatory molecules and cytokines or via cell-to-cell contacts [2]. Due to their effect on adaptive and innate immune cells, especially macrophages, they have been applied in many immune disorders [3].

It is known that MSCs accumulate at the injured site and initiate the repair process due to their remarkable immunomodulatory properties [4]. Depending on different stimuli, MSCs can be proinflammatory (MSC1), or anti-inflammatory (MSC2). Once they are activated with stimuli such as hypoxia, the cytokine milieu, and toll-like receptor ligands, MSCs produce various immunomodulators, including nitric oxide (NO), indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), interleukin (IL)-6, and IL-10 [5]. MSCs are known to play a crucial role as immunosuppressive cells by producing molecules like PGE2 and tumor necrosis factor-stimulated gene 6 protein (TSG-6) [6].

Macrophages, as cells of the innate immune system, are an essential component of the first line of defense against pathogens and tumor cells [7]. These are highly plastic cells that can adopt different activation phenotypes with distinct effector functions as a result of diverse stimuli from the surrounding microenvironment. Although macrophages have traditionally been classified into two categories, M1 proinflammatory macrophages and M2 anti-inflammatory macrophages with tissue repair capabilities, recent advancements in single-cell technologies have revealed a wider range of macrophage activation states that extend beyond this simplified classification [8]. Their migration to the inflammatory site, where they perform phagocytosis of damaged or dead cells, is crucial for tissue homeostasis and regeneration [7]. In the initial phase of an inflammatory process, macrophages primarily exhibit pro-inflammatory characteristics, the M1-like phenotype, by secreting tumor necrosis factor α (TNF- α), IL-1 β , and IL-12.

However, to prevent tissue damage in acute inflammatory conditions, M2-like macrophages secrete copious amounts of IL-10 and tumor growth factor β (TGF- β), thus contributing to the resolution of inflammation and tissue regeneration, stimulating angiogenesis, and maintaining tissue homeostasis [9]. In

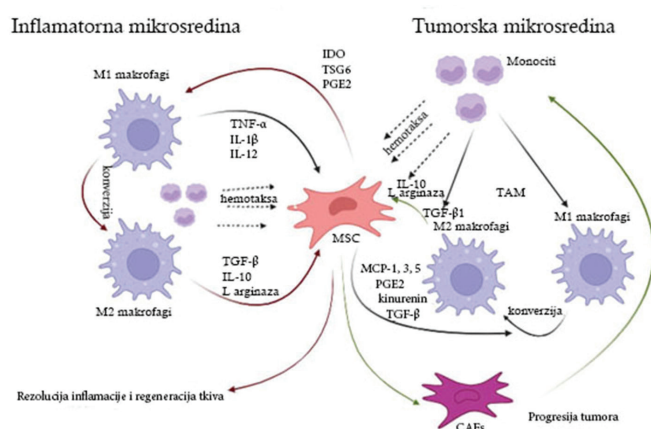
ra-beta (engl. *tumor growth factor-beta* – *TGF-β*), čime doprinose razrešenju inflamacije i regeneraciji tkiva, stimulišu angiogenezu i održavaju homeostazu tkiva [9]. Takođe, makrofagi imaju i ključnu ulogu u imunomodulaciji i prezentaciji antigena [10]. Oni aktiviraju druge imunske ćelije putem lučenja proinflammatoryh citokina kao što su IL-1β, *TNF-α*, IL-6, kao i drugih rastvorljivih faktora [7].

Interakcija između mezenhimalnih matičnih ćelija i makrofaga važna je u mnogim aspektima, uključujući reparaciju tkiva, imunske modulaciju i terapijske intervencije. Konkretno, MMĆ dovode do promene u polarizaciji makrofaga sa M1 proinflammatoryh na M2 antiinflammatoryh fenotip (Slika 1), što je pokazano na *in vitro* modelu koji su sprovedi Kim i saradnici [11]. Utvrđeno je da MMĆ mogu da prouzrokuju polarizaciju makrofaga i njihovu transformaciju od inflamatornog M1 u antiinflammatoryh M2 fenotip pomoću ciklooksigenaza-2-prostaglandin E2 (engl. *cyclooxygenase-2-prostaglandin E2* – *COX2-PGE2*) puta, kao i putem proizvoda indoleamin 2,3-dioksigenaze (IDO) i *TSG-6* [12]. MMĆ mogu biti fagocitovane od strane makrofaga i mogu pasivno da utiču na njihov profil, suzbijajući proizvodnju *TNF-α*, IL-1β, IL-6 i inducibilne azot oksid sintaze (iNOS), istovremeno podstičući proizvodnju IL-10 [13]. Takođe, MMĆ mogu da pojačaju fagocitozu makrofaga putem transfera mitohondrija u određenim bolestima, kao što su akutni respiratorni distres sindrom i sepsa [14]. Pored toga, u inflamatornoj mikrosredini MMĆ proizvode citokine kao što je monocitni hemoatraktantni protein-1 (engl. *monocyte chemoattractant protein-1* – *MCP-1*), makrofagni inflamatorni protein-1 alfa (engl. *macrophage inflammatory protein-1 alpha* – *MIP-1α*) i hemokin (C-C motiv) ligand 12 (engl. *C-C motif chemokine ligand 12* – *CCL12*), čime pospešuju hemotaksiju monocita i makrofaga koji imaju ulogu u zarastanju rana [15].

addition, macrophages also have a critical role in immunomodulation and antigen presentation [10]. They activate other immune cells via the secretion of proinflammatory cytokines such as IL-1β, *TNF-α*, IL-6, as well as other soluble factors [7].

The interaction between mesenchymal stem cells and macrophages is important in many respects, including tissue repair, immune modulation, and therapeutic intervention. Specifically, MSCs lead to changes in macrophage polarization from the M1 pro-inflammatory to the M2 anti-inflammatory phenotype (Figure 1), as Kim et al. demonstrated in an *in vitro* model [11]. It has been shown that MSCs can trigger macrophage polarization and transform them from an inflammatory M1 to an anti-inflammatory M2 phenotype via the cyclooxygenase-2-prostaglandin E2 (*COX2-PGE2*) pathway, the products of IDO, and *TSG-6* [12]. MSCs can be phagocytosed by macrophages and can passively affect the profile of macrophages, suppressing the production of *TNF-α*, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) and promoting the production of IL-10 [13]. MSCs can also enhance macrophage phagocytosis via mitochondrial transfer in some diseases, such as acute respiratory distress syndrome and sepsis [14]. Furthermore, in the inflammatory microenvironment, MSCs produce cytokines, such as monocyte chemoattractant protein-1 (*MCP-1*), macrophage inflammatory protein-1 alpha (*MIP-1α*), and C-C motif chemokine ligand 12 (*CCL12*), thus leading to the chemoattraction of monocytes and macrophages that play a role in wound healing [15].

In the inflammatory microenvironment, through cytokine production, MSCs influence monocyte chemotaxis, favoring M2 phenotypes, which consequently leads to immunosuppression and resolution of inflammation. In the tumor microenvironment, MSCs influ-



Slika 1. Interakcija između mezenhimalnih matičnih ćelija i makrofaga u inflamatornoj i tumorskoj mikrosredini

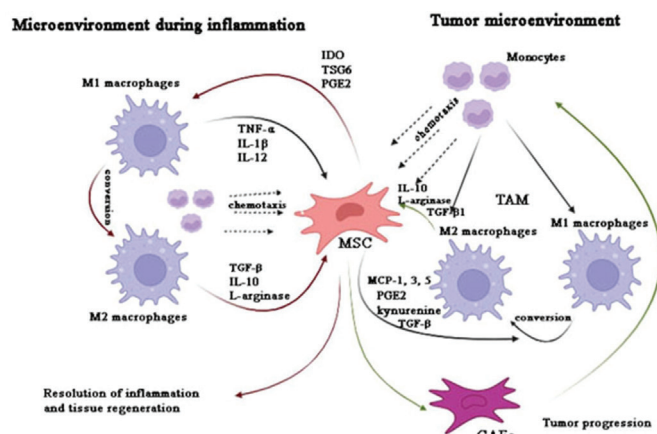


Figure 1. Interaction between mesenchymal stem cells and macrophages in inflammation and tumor microenvironments

U inflamatornoj mikrosredini, putem produkcije citokina, mezenhimalne matične ćelije utiču na hemotaksu monocita, favorizujući M2 fenotipove, što za posledicu ima imunosupresiju i razrešavanje inflamacije. U tumorskoj mikrosredini, MMC utiču na formiranje makrofaga povezanih sa tumorom (engl. *tumor-associated macrophages – TAM*), koji su pretežno M2 fenotipovi, a pod njihovim uticajem MMC mogu da se diferenciraju u fibroblaste povezane sa karcinomom (engl. *carcinoma-associated fibroblasts – CAF*), dodatno pospešujući progresiju tumora.

Interakcija između mezenhimalnih matičnih ćelija i makrofaga u inflamatornim stanjima – dijabetes melitus i psorijaza kao modeli bolesti

U hroničnim zapaljenskim stanjima koja dovode do hroničnih bolesti, kao što su dijabetes melitus (hronični metabolički poremećaj karakterisan niskogradusnom inflamacijom) i psorijaza (inflamatorno imunološko oboljenje kože), dolazi do narušavanja ravnoteže između M1-nalik i M2-nalik tipova makrofaga, što može imati za posledicu trajno oštećenje tkiva [16, 17]. Pokazano je da je insulinska rezistencija, koja se često javlja pre pojave dijabetesa tipa 2 (*diabetes mellitus* tip II – DMT2), u osnovi pokrenuta hroničnim, niskogradusnim inflamatornim stanjem [18]. Konkretno, *TNF-α* i *IL-1β* koje proizvode makrofagi u masnom tkivu, a koji ispoljavaju karakteristike M1 tipa makrofaga, identifikovani su kao ključni faktori u razvoju insulinske rezistencije [19]. Kod pacijenata sa dijabetesom tipa 1, izazvanim imunskim odgovorom, studije su pokazale povećan broj M1-nalik makrofaga. Istovremeno, dokazano je da miševi sa dijabetesom imaju povećan broj CD169+ ćelija sa sposobnošću zadržavanja matičnih ćelija. Takođe je pokazano da dijabetes utiče na oslobađanje matičnih ćelija putem faktora izvedenog iz stromalnih ćelija-1 (engl. *stromal cell-derived factor-1 – SDF-1*), koji luče M1-nalik makrofagi, što sprečava oslobađanje mezenhimalnih matičnih ćelija iz koštane srži, stvarajući tako začarani krug. Zbog ovog procesa, potencijal mezenhimalnih matičnih ćelija za regeneraciju krvnih sudova i drugih organa dodatno je oslabljen [20]. Stoga je hitno i važno iskoristiti potencijal ciljane terapije u kontrolisanju ravnoteže između makrofaga i mezenhimalnih matičnih ćelija i smanjenju komorbiditeta izazvanih osnovnom bolešću.

Novije studije su pokazale da mezenhimalne matične ćelije kod pacijenata sa psorijazom ispoljavaju određene abnormalnosti. Ove ćelije imaju smanjenu sposobnost regulacije inflamacije i regeneracije. Orciani i saradnici su pokazali da mezenhimalne matične ćelije izolovane iz psorijatičnih kožnih lezija ispoljavaju povećanu ekspresiju vaskularnog endotelnog faktora rasta (engl. *vascular endothelial growth factor – VEGF*) i

ence the formation of tumor-associated macrophages (TAMs), which are predominantly M2 phenotypes, and under their influence, MSCs may differentiate into carcinoma-associated fibroblasts (CAFs), further supporting tumor progression.

Interaction between mesenchymal stem cells and macrophages in inflammatory conditions – diabetes mellitus and psoriasis as disease model systems

In chronic inflammatory conditions that lead to chronic diseases, such as diabetes mellitus (a chronic metabolic disorder characterized by low-grade inflammation) and psoriasis (an inflammatory immune skin disease), there is a disrupted balance between M1-like and M2-like macrophage types, which can result in permanent tissue damage [16,17]. It has been shown that insulin resistance, which frequently occurs before the onset of type 2 diabetes (diabetes mellitus type II – DMT2), is fundamentally driven by a chronic, low-grade inflammatory state [18]. Specifically, *TNF-α* and *IL-1β* produced by adipose tissue macrophages, which exhibit characteristics of the M1 macrophage type, have been identified as key factors in the development of insulin resistance [19]. In patients with type 1 diabetes caused by an immune response, studies have shown increased M1-like macrophages. At the same time, it has been demonstrated that diabetic mice have increased CD169+ cells with stem cell retaining activity. It has also been shown that diabetes affects the release of stem cells via the stromal cell-derived factor-1 (SDF-1) secreted by M1-like macrophages, which prevents the release of MSCs from the bone marrow, resulting in a vicious cycle. Due to this process, the potential of MSCs to regenerate blood vessels and other organs is further impaired [20]. Therefore, it is urgent and important to utilize the potential of targeted therapies in controlling the balance between macrophages and MSCs and reducing comorbidities caused by the underlying disease.

Recent studies have shown that, in patients with psoriasis, MSCs exhibit abnormalities. These cells have a reduced ability to regulate inflammation and regeneration. Orciani et al. demonstrated that MSCs isolated from psoriatic skin lesions exhibit increased expression of vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS) [21]. Jiao et al. demonstrated that MSCs from skin lesions of psoriasis patients decreased the levels of *TGF-β* and its receptors, thus increasing the Th17/Treg ratio, which resulted in an immune imbalance in these patients [22]. MSCs isolated from the bone marrow of psoriasis patients also exhibited abnormalities. This aligns with

inducibilne azot oksid sintaze (*iNOS*) [21]. Žao i saradnici su pokazali da MMĆ iz kožnih lezija pacijenata sa psorijazom smanjuju nivoe TGF- β i njegovih receptora, čime se povećava odnos *Th17/Treg* ćelija, što ima za posledicu imunsku neravnotežu kod ovih pacijenata [22]. MMĆ izolovane iz koštane srži pacijenata sa psorijazom takođe su pokazale abnormalnosti. Ovo je u skladu sa istraživanjima koja ukazuju na to da je psorijaza povezana sa poremećenom hematopoezom [23].

Takođe je primećeno da je hronični psihološki stres jedan od glavnih faktora u razvoju psorijaze i da istovremeno dovodi do razvoja stresne eritropoeze, uz sledstvene promene unutar mikrosredine koštane srži [24,25,26]. Mezenhimalne matične ćelije i njihove interakcije sa ćelijama imunskog sistema mogu biti ključni učesnici u patogenezi ove bolesti.

Sa druge strane, psorijatične lezije pretežno sadrže M1-nalik makrofage za koje je pokazano da luče *TNF- α* i IL-23 [16]. Međutim, u mišjem modelu psorijaze dokazano je da M2 fenotip ima regulatornu ulogu [26]. Neke studije sugerišu da deplecija makrofaga smanjuje inflamaciju [27]. Nasuprot tome, druge studije na miševima pokazale su da stimulacija glukokortikoidnih receptora u makrofagima dovodi do polarizacije ka M1-nalik fenotipu putem fosforilacije prenosioca signala i aktivatora transkripcije 1 (engl. *signal transducer and activator of transcription 1* – *STAT1*), dok blokiranje ovog signalnog puta smanjuje inflamaciju, što dodatno ističe značaj stresa u razvoju psorijaze [28]. Postoji ograničen broj istraživanja koja naglašavaju značaj interakcije između MMĆ i makrofaga u patogenezi psorijaze. Ipak, studije ukazuju na terapijski potencijal MMĆ zasnovan na njihovoj sposobnosti da modulišu imunski odgovor regulacijom polarizacije makrofaga.

Interakcija između mezenhimalnih matičnih ćelija i makrofaga u tumorskoj mikrosredini

Neke hipoteze zastupaju stanovište da se karcinogeneza i rast tumora zasnivaju na hroničnoj inflamaciji, koja narušava ravnotežu između proinflammatory i antiinflammatory odgovora. Takva neravnoteža narušava adekvatan imunski odgovor u eliminaciji tumorskih ćelija, stvarajući time povoljne uslove za rast tumora [29]. Brojne savremene studije ističu značajnu ulogu mezenhimalnih matičnih ćelija, makrofaga i njihovih interakcija u razvoju tumora, što proizilazi iz njihovih imunomodulatornih sposobnosti. Pored interakcije sa T i B limfocitima tokom karcinogeneze, MMĆ takođe ostvaruju interakcije sa makrofagima, modulišući njihovu aktivnost. Za razliku od procesa inflamacije, gde prelazak sa M1-nalik na M2-nalik makrofage vodi ka razrešavanju inflamacije, u tumorskoj mikrosredini M2-nalik makrofagi doprinose progresiji raka (Slika 1).

research suggesting that psoriasis is associated with aberrant hematopoiesis [23].

It has also been noted that chronic psychological stress is one of the main factors in the development of psoriasis and that it simultaneously leads to the development of stress erythropoiesis with subsequent changes within the bone marrow microenvironment [24,25,26]. MSCs and their interactions with immune system cells may be the key players in the pathogenesis of this disease.

On the other hand, psoriatic lesions predominantly feature M1-like macrophages, which have been shown to secrete *TNF- α* and IL-23 [16]. However, in a mouse model of psoriasis, it has been demonstrated that the M2 phenotype plays a regulatory role [26]. Some studies suggest that macrophage depletion reduces inflammation [27]. In contrast, other studies on mice have demonstrated that the stimulation of glucocorticoid receptors in macrophages leads to M1-like macrophage polarization via phosphorylation of signal transducer and activator of transcription 1 (*STAT1*), whereas blocking this signaling pathway reduces inflammation, further highlighting the importance of stress in the development of psoriasis [28]. There is a limited body of research emphasizing the significance of MSC-macrophage interactions in the pathogenesis of psoriasis. Nonetheless, studies suggest a therapeutic potential of MSCs based on their ability to modulate the immune response by regulating macrophage polarization.

Interaction between mesenchymal stem cells and macrophages in the tumor microenvironment

Some hypotheses state that carcinogenesis and tumor growth are based on chronic inflammation, which disrupts the balance between proinflammatory and anti-inflammatory responses. Such an imbalance impairs an adequate immune response in eliminating tumor cells, thereby creating favorable conditions for tumor growth [29]. Many recent studies have highlighted the significant role of MSCs, macrophages, and their interactions in tumor development, due to their immunomodulatory capabilities. In addition to interacting with T and B lymphocytes during carcinogenesis, MSCs also establish interactions with macrophages, modulating their activity. Unlike the inflammation process, where the transition from M1-like to M2-like macrophage types leads to the resolution of the inflammatory process in the tumor microenvironment, M2-like macrophages contribute to cancer progression (Figure 1).

A special type of macrophage is present within the tumor microenvironment – tumor-associated macro-

Poseban tip makrofaga prisutan je u tumorskoj mikrosredini – makrofagi povezani sa tumorom (TAM). Ovi makrofagi mogu da ispoljavaju fenotipske karakteristike i M1-nalik i M2-nalik makrofaga i predstavljaju značajnu komponentu imunskog sistema i same tumorske mikrosredine [30]. Istraživanja su pokazala da M1-nalik makrofagi mogu da eliminišu tumorske ćelije putem fagocitoze ili aktivacijom T-ćelijskog odgovora [31].

Nasuprot tome, M2-nalik makrofagi imaju ključnu ulogu u progresiji tumora jer luče matriksne metaloproteinaze, čime omogućavaju migraciju tumorskih ćelija i stromalnih ćelija tumora. Takođe podstiču angiogenezu oslobađanjem angiogenih molekula i ekspresijom niza enzima uključenih u regulaciju angiogeneze [30]. M2-nalik makrofage karakteriše povećana ekspresija L-arginaze, IL-10 i liganda proteina programirane ćelijske smrti 1 (engl. *programmed cell death ligand 1* – PD-L1), što dovodi do imunosupresije i potiskivanja funkcije T-ćelija i kao krajnji rezultat podstiče rast tumora [32]. Makrofagi utiču na mezenhimalne matične ćelije da poprime fenotip fibroblasta povezanih sa karcinomom (CAF), čime dodatno pospešuju progresiju karcinoma.

Mezenhimalne matične ćelije, u kombinaciji sa izmenjenim uslovima unutar tumorske mikrosredine, doprinose formiranju makrofaga povezanih sa tumorom (TAM). MMĆ putem prostaglandina E2 (PGE2) i kinurenina, zajedno sa MIP-1 α i MIP-2 α , koje proizvode inflamatorni makrofagi, doprinose transformaciji inflamatornih M1-nalik makrofaga u alternativno aktivisane, imunosupresivne M2-nalik makrofage [34]. Na taj način, MMĆ i izmenjeni uslovi unutar tumorske mikrosredine modulišu aktivnost makrofaga.

Studije na modelima melanoma B16 F0 i limfoma EL4 pokazale su da egzozomi poreklom iz tumorskih ćelija utiču na mezenhimalne matične ćelije tako da pojačavaju infiltraciju makrofaga [35]. Nakon infiltracije makrofaga u tumorsku mikrosredinu, oni se pod uticajem MCP-1, MCP-3 i MCP-5 – produkata MMĆ – polarizuju u M2 tumorske fenotipove [36]. S druge strane, kod karcinoma dojke, produkti MMĆ – TGF- β , C1q i semaforini – doprinose M2 polarizaciji makrofaga [32]. Kao što je pokazano, hronični stres je jedan od faktora koji doprinosi razvoju karcinoma [37].

Jang i saradnici su pokazali da stres utiče na polarizaciju makrofaga, čime ima uticaj na razvoj karcinoma [38]. S druge strane, *in vivo* studije su pokazale da medijatori stresa utiču na međućelijsku interakciju između mezenhimalnih matičnih ćelija i makrofaga [39].

TERAPIJSKI POTENCIJAL

Tokom poslednjih godina značajna pažnja se posvećuje terapijskom potencijalu mezenhimalnih matičnih ćelija. Zbog svojih snažnih imunomodulatornih efekta-

phages (TAMs). These macrophages may exhibit phenotypic characteristics of both M1-like and M2-like macrophages and are a significant component of the immune system and the tumor microenvironment [30]. Research has shown that M1-like macrophages can eliminate tumor cells through phagocytosis or by activating the T-cell response [31].

In contrast, M2-like macrophages play a crucial role in tumor progression by secreting matrix metalloproteinases, facilitating the migration of tumor cells and tumor stromal cells. They also promote angiogenesis by releasing angiogenic molecules and expressing a range of enzymes involved in regulating angiogenesis [30]. M2-like macrophages are characterized by an increased expression of L-arginase, IL-10, and programmed cell death ligand 1 (PD-L1), which leads to immunosuppression and suppression of T-cell functions, ultimately promoting tumor growth [32]. Macrophages influence mesenchymal stem cells (MSCs) to acquire the carcinoma-associated fibroblast (CAF)-like phenotype, thereby promoting cancer progression.

MSCs, in combination with altered conditions within the tumor microenvironment, contribute to the formation of TAMs. MSCs, via PGE2 and kynurenine, with MIP-1 α and MIP-2 α produced by inflammatory macrophages, contribute to the conversion of inflammatory M1-like macrophages into alternatively activated, immunosuppressive M2-like macrophages [34]. In this way, MSCs and altered conditions within the tumor microenvironment modulate macrophage activity.

Studies on B16 F0 melanoma and EL4 lymphoma models have demonstrated that exosomes derived from tumor cells influence MSCs to enhance macrophage infiltration [35]. After macrophage infiltration within the tumor microenvironment, they polarize into the M2 tumor phenotypes under the influence of MCP-1, MCP-3, and MCP-5, which are products of MSCs [36]. On the other hand, in breast cancer, MSC products – TGF- β , C1q, and semaphorins, contribute to the M2 polarization of macrophages [32]. As has been shown, chronic stress is one of the factors contributing to cancer development [37].

Yang et al. demonstrated that stress influences macrophage polarization, impacting cancer development [38]. On the other hand, *in vivo* studies have shown that stress mediators affect the intercellular interaction between MSCs and macrophages [39].

THERAPEUTIC POTENTIAL

In recent years, there has been a significant focus on the therapeutic potential of MSCs. Due to their strong immunomodulatory effects, MSCs and their derivatives show great potential in treating various inflammato-

ta, MMĆ i njihovi derivati pokazuju veliki potencijal u lečenju različitih inflamatornih bolesti. Nakon primene, MMĆ migriraju ka mestima inflamacije, što dodatno ističe njihov potencijal u tretiranju takvih stanja [40]. Međutim, MMĆ dobijene iz različitih tkiva ispoljavaju različite citokine koji utiču na njihov imunomodulatorni potencijal [41].

Pored samih MMĆ, brojna istraživanja sprovedena su i o terapijskom potencijalu egzozoma mezenhimalnih matičnih ćelija. Egzozomi MMĆ se smatraju potencijalnim nosačima različitih citokina, imunomodulatora, pa čak i genske terapije. Studije su pokazale terapijski potencijal MMĆ u određenim inflamatornim oboljenjima kroz regulaciju aktivnosti makrofaga. Pokazano je da PGE2, koji proizvode mezenhimalne matične ćelije, utiče na makrofage tako što stimuliše produkciju IL-10 i inhibira diferencijaciju monocita u dendritske ćelije [42]. Produkcija PGE2 od strane MMĆ zavisi od signalizacije *TNF-α* i iNOS iz monocita/makrofaga, što ukazuje na složenost njihovog međusobnog odnosa [43].

In vivo i *in vitro* studije koje su ispitivale terapijsku efikasnost mezenhimalnih matičnih ćelija u zarastanju rana pokazale su da MMĆ ispoljavaju svoje imunomodulatorne efekte pretežno stimulacijom polarizacije makrofaga ka M2 fenotipu [44]. Brojne studije takođe potvrđuju terapijski potencijal MMĆ u lečenju psorijaze. Primena MMĆ ili egzozoma mezenhimalnih matičnih ćelija, intravenski ili subkutano, u mišjim modelima psorijaze dovela je do značajne imunomodulacije i antiinflamatornih efekata [45]. To se manifestovalo smanjenjem simptoma psorijaze, normalizacijom diferencijacije epidermisa, redukcijom angiogeneze i hiperproliferacije, kao i smanjenjem infiltracije imunskih ćelija u koži [42]. Pokazano je da MMĆ sprečavaju proliferaciju keratinocita inhibicijom produkcije *TNF-α* od strane monocita i makrofaga [46].

Sie i saradnici su pokazali da mezenhimalne matične ćelije izolovane iz pupčane vrpce smanjuju insulinsku rezistenciju reprogramiranjem makrofaga sa M1-nalik na M2-nalik tip kod pacova sa dijabetesom tip 2 [47]. Konkretno, MMĆ stimulišu M1-nalik makrofage da povećaju ekspresiju IL-6, što zatim dovodi do povećanja ekspresije IL-4 receptora, rezultujući fosforilacijom prenosioca signala i aktivatora transkripcije 6 (*STAT6*) u makrofagima i sledstvenom transformacijom makrofaga u M2-nalik fenotipove [47]. Sa druge strane, pokazano je da terapija mezenhimalnim matičnim ćelijama smanjuje infiltraciju makrofaga smanjenjem ekspresije *MCP-1* [48]. U dijabetičnoj nefropatiji, koštano-ćelijske MMĆ, MMĆ iz pupčane vrpce, kao i njihovi izvedeni egzozomi i mikroRNK, pokazali su sposobnost da pojačaju M2 polarizaciju makrofaga, što dovodi do proinflamatornog odgovora i smanjuje oštećenje

ry diseases. After application, MSCs migrate to sites of inflammation, which highlights their potential for treating such conditions [40]. However, MSCs obtained from different tissues express different cytokines that affect their immunomodulatory potential [41].

In addition to MSCs, numerous studies have been conducted on the therapeutic potential of MSC exosomes. MSC exosomes are considered to be potential carriers of various cytokines, immunomodulators, or even gene therapy. Studies have shown the therapeutic potential of MSCs in certain inflammatory diseases by regulating macrophage activity. It has been shown that PGE2, produced by MSCs influences macrophages by stimulating IL-10 production and inhibiting monocyte differentiation into dendritic cells [42]. The generation of PGE2 by MSCs is dependent upon *TNF-α* and iNOS signaling from monocytes/macrophages, indicating the complexity of their relationship [43].

In vivo and *in vitro* studies investigating the therapeutic efficacy of MSCs in wound healing have demonstrated that MSCs exert their immunomodulatory effects primarily through the stimulation of M2 macrophage polarization [44]. Many studies have also substantiated the therapeutic potential of MSCs in treating psoriasis. The administration of MSCs or MSC exosomes, intravenously or subcutaneously in psoriasis mouse models has resulted in significant immunomodulation and anti-inflammatory effects [45]. This manifested in the reduction of psoriasis symptoms, the normalization of epidermal differentiation, a reduction in angiogenesis and hyperproliferation, and a decrease in immune cell infiltration within the skin [42]. It has been shown that MSCs prevent keratinocyte proliferation by inhibiting *TNF-α* production by monocytes and macrophages [46].

Xie et al. have demonstrated that MSCs isolated from the umbilical cord reduce insulin resistance by reprogramming macrophages from the M1-like to the M2-like types in rats with type 2 diabetes mellitus [47]. Specifically, MSCs stimulate the M1-like macrophage phenotypes to increase IL-6 expression, which then leads to an increase in IL-4 receptor expression, resulting in the phosphorylation of signal transducer and activator of transcription 6 (*STAT6*) in macrophages and the subsequent transformation of macrophages into the M2-like phenotypes [47]. On the other hand, it has been shown that MSC treatment reduces macrophage infiltration by decreasing *MCP-1* expression [48]. In diabetic nephropathy, bone marrow MSCs, umbilical cord MSCs, and their derived exosomes and microRNAs have been shown to enhance macrophage M2 polarization, leading to a pro-inflammatory response and reducing kidney damage caused by diabetes [49].

bubrega izazvano dijabetesom [49]. Terapija mezenhimalnim matičnim ćelijama se takođe pokazala korisnom u regulaciji mitohondrijske disfunkcije stimulacijom arginaze 1 – markera M2-nalik makrofaga [49].

Manipulacija makrofagima, u smislu njihove aktivacije i deplecije, pokazala je potencijalne terapijske efekte u inflamaciji i karcinomu. Adaptivna terapija makrofagima pokazala se efikasnom u lečenju limfoma i karcinoma dojke. Ren i saradnici su pokazali da mezenhimalne matične ćelije povezane sa tumorom, koje obično podstiču rast tumora, gube svoju funkciju nakon specifične eliminacije makrofaga, te da je kod miševa koji imaju nedostatak C-C hemokinskog receptora tipa 2 (engl. *C-C chemokine receptor type 2* – CCR2), antitumorni efekat tumorskih mezenhimalnih matičnih ćelija bio smanjen [36]. Takođe je pokazano da dolazi do povećane proizvodnje MCP-1 nakon radioterapije, što rezultira pojačanom sposobnošću tumora da privlače mezenhimalne matične ćelije [50].

ZAKLJUČAK

Nesumnjivo je da su interakcije između makrofaga i mezenhimalnih matičnih ćelija ključne za regulaciju inflamatorne mikrosredine, sa značajnim uticajem na nastanak i progresiju bolesti, kao i na reparaciju i remodelovanje tkiva. Međutim, njihov međusobni odnos može da varira u zavisnosti od uslova mikrosredine. Studije ukazuju na to da modulacija ovih interakcija ima terapijski potencijal, a pristup koji je usmeren i prilagođen specifičnim uslovima mikrosredine mogao bi da donese delotvornije rezultate.

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MSCs therapy has also proven beneficial in regulating mitochondrial dysfunction by stimulating arginase 1, a marker of M2-like macrophages [49].

Macrophage manipulation, in terms of activation and depletion, has shown potential therapeutic effects in inflammation and cancer. Adaptive macrophage therapy has proven effective in treating lymphoma and breast cancer. Ren et al. (2012) demonstrated that cancer-associated MSCs, which typically promote tumor growth, lose their function after specific eradication of macrophages and that in C-C chemokine receptor type 2 (CCR2)-deficient mice, the antitumorigenic effect of tumor-associated MSCs was reduced [36]. It has been shown that there is an increased production of MCP-1 after radiation therapy, which results in enhanced ability of tumors to attract MSCs [50].

CONCLUSION

Undoubtedly, the interactions between macrophages and MSCs are crucial in regulating the inflammatory microenvironment, significantly influencing disease onset and progression, as well as tissue repair and remodeling. However, their relationship can vary depending on the microenvironment. Studies suggest that modulating these interactions holds therapeutic potential, and a targeted approach tailored to specific microenvironment conditions could yield more effective results.

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MELANOCITOM GLAVE OPTIČKOG NERVA UZ JUKSTAPAPILARNI NEVUS HORIOIDEJE: PRIKAZ SLUČAJA I PREGLED LITERATURE

PRIKAZ SLUČAJA

CASE REPORT

MELANOCYTOMA OF THE OPTIC NERVE HEAD COEXISTING WITH JUXTAPAPILLARY CHOROIDAL NEVUS: CASE REPORT AND LITERATURE REVIEW

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SAŽETAK

Uvod: Melanocitom glave optičkog nerva predstavlja retku, benignu pigmentovanu leziju koja nastaje od melanocita u području glave optičkog nerva. Iako je benigne prirode, melanocitom može predstavljati dijagnostički izazov zbog moguće sličnosti sa melanomom, kao i zbog potencijalnih komplikacija, uključujući defekte vidnog polja i, u retkim slučajevima, malignu transformaciju. Tačna dijagnoza se postavlja primenom pomoćnih dijagnostičkih metoda, poput fluoresceinske angiografije, optičke koherentne tomografije (OCT) i OCT-a sa povećanom dubinskom rezolucijom (EDI-OCT).

Prikaz slučaja: Četrdesetogodišnja pacijentkinja dolazi zbog pigmentovane promene na glavi levog optičkog nerva, koja je unazad 10 godina praćena u drugoj ustanovi. Oftalmološkim pregledom uočena je jasno ograničena, uzdignuta, sivo-crna lezija tipičnih kliničkih karakteristika melanocitoma. Uz melanocitom je primećen i jukstapapilarni horoidalni nevus. Dijagnostička obrada, koja je uključivala fluoresceinsku angiografiju i B-scan ultrasonografiju, potvrdila je benignu prirodu lezije. Pacijentkinji je preporučeno redovno praćenje kako bi se na vreme uočila eventualna progresija ili maligna transformacija.

Zaključak: Ovaj slučaj ističe važnost primene pomoćnih dijagnostičkih metoda i dugoročnog praćenja melanocitoma glave optičkog nerva. Koegzistencija jukstapapilarnog horoidalnog nevusa dodatno otežava dijagnostički proces, čime se naglašava potreba za redovnim kontrolama radi pravovremenog uočavanja mogućih komplikacija.

Ključne reči: melanocitom, horoidalni nevus, ultrazvučna dijagnostika, fluoresceinska angiografija

ABSTRACT

Introduction: Melanocytoma of the optic nerve head (melanocytoma papillae) is a rare, benign pigmented lesion originating from melanocytes within the optic nerve head. Despite its benign nature, melanocytoma can present diagnostic challenges due to its potential mimicry of melanomas and associated complications, including visual field defects and, in rare cases, malignant transformation. Accurate diagnosis relies on multimodal imaging, including fluorescein angiography, optical coherence tomography (OCT), and enhanced depth imaging-OCT (EDI-OCT).

Case report: A 40-year-old female presented with a pigmented lesion on the left optic nerve head, which had been monitored at another institution for the past 10 years. Ophthalmologic examination revealed a sharply demarcated, elevated, gray-black lesion with clinical features typical of melanocytoma. Adjacent to the melanocytoma, a juxtapapillary choroidal nevus was observed. The diagnostic workup, including fluorescein angiography and B-scan ultrasonography, confirmed the benign nature of the lesion. The patient was advised to undergo regular follow-up to monitor for potential progression or malignant transformation.

Conclusion: This case underscores the importance of auxiliary diagnostic methods and long-term surveillance in managing melanocytoma of the optic nerve head. The coexistence of a juxtapapillary choroidal nevus further complicates the diagnostic process, emphasizing the need for regular follow-up to enable the timely detection of potential complications.

Keywords: melanocytoma, choroidal nevus, ultrasonography, fluorescein angiography

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UVOD

Melanocitom glave optičkog nerva (melanocytoma papillae) je retka, benigna melanocitna lezija koja potiče od melanocita unutar glave optičkog nerva. Prvi su je opisali Limas i Ulrich 1962. godine. Melanocitom je histološki različit od melanoma, ali deli sličnu tamnu pigmentaciju zbog prisustva jako pigmentisanih, okruglih ili poligonalnih ćelija koje sadrže obilne granule melanina. Iako je obično asimptomatski, njegov klinički značaj ogleda se u mogućnosti izazivanja defekata vidnog polja, otoka optičkog diska i, u retkim slučajevima, maligne transformacije [1].

Ova lezija često koegzistira sa jukstapapilarnim horoidalnim nevusima, koji su pigmentisane, ravne lezije locirane u blizini optičkog diska. Studije sugerišu da je do 50% slučajeva melanocytoma povezano sa takvim nevusima, što dodatno komplikuje kliničku diferencijaciju od agresivnijih patologija, poput melanoma [2,3].

Napredak u tehnikama snimanja, kao što su fluoresceinska angiografija, optička koherentna tomografija (OCT), OCT sa poboljšanim prikazom dubine (EDI-OCT) i B-sken ultrasonografija, značajno je poboljšao sposobnost razlikovanja melanocytoma od lezija [4].

Iako su obično benigni, melanocitomi mogu pokazivati lokalno agresivno ponašanje, što može dovesti do kompresije optičkog nerva ili zahvatanja susednih struktura, poput retine i horioideje. Najčešće se dijagnostikuju kod osoba srednjih godina, bez značajne polne predispozicije [5,6]. Dugoročno praćenje je ključno kako bi se pratile moguće komplikacije, poput oštećenja vida, optičke neuropatije ili retkog, ali ozbiljnog rizika od maligne transformacije [7].

Ovaj prikaz slučaja predstavlja redak slučaj melanocytoma glave optičkog nerva sa koegzistirajućim jukstapapilarnim horoidalnim nevusom, naglašavajući dijagnostičke i terapijske izazove povezane sa ovom bolešću. Sveobuhvatan pregled literature pruža dodatni uvid u njegove kliničke, radiološke i histopatološke karakteristike, ističući značaj redovnog praćenja [8-10].

PRIKAZ SLUČAJA

Pacijentkinja, stara 40 godina, javila se našoj klinici sa poznatom anamnezom pigmentovane lezije na levom očnom dnu, koja je prvi put primećena pre više od 10 godina tokom rutinskog oftalmološkog pregleda. Pacijentkinja nije prijavila nikakve vizuelne simptome; njena medicinska anamneza bila je uredna, bez sistemskih oboljenja ili porodične istorije očnih bolesti. Oštrina vida bila je 1,0 na oba oka bez korekcije.

INTRODUCTION

Melanocytoma of the optic nerve head (melanocytoma papillae) is a rare, benign melanocytic lesion originating from melanocytes within the optic nerve head. Initially described by Limas and Ulrich in 1962, melanocytoma is histologically distinct from melanomas but shares a similar dark pigmentation due to heavily pigmented, round, or polygonal cells containing abundant melanin granules. While typically asymptomatic, its clinical significance lies in its potential to cause visual field defects, optic disc swelling, and, in rare cases, malignant transformation [1].

This lesion frequently coexists with juxtapapillary choroidal nevi, which are pigmented, flat lesions located near the optic disc. Studies suggest that up to 50% of melanocytoma cases are associated with such nevi, further complicating clinical differentiation from more aggressive pathologies such as melanoma [2,3].

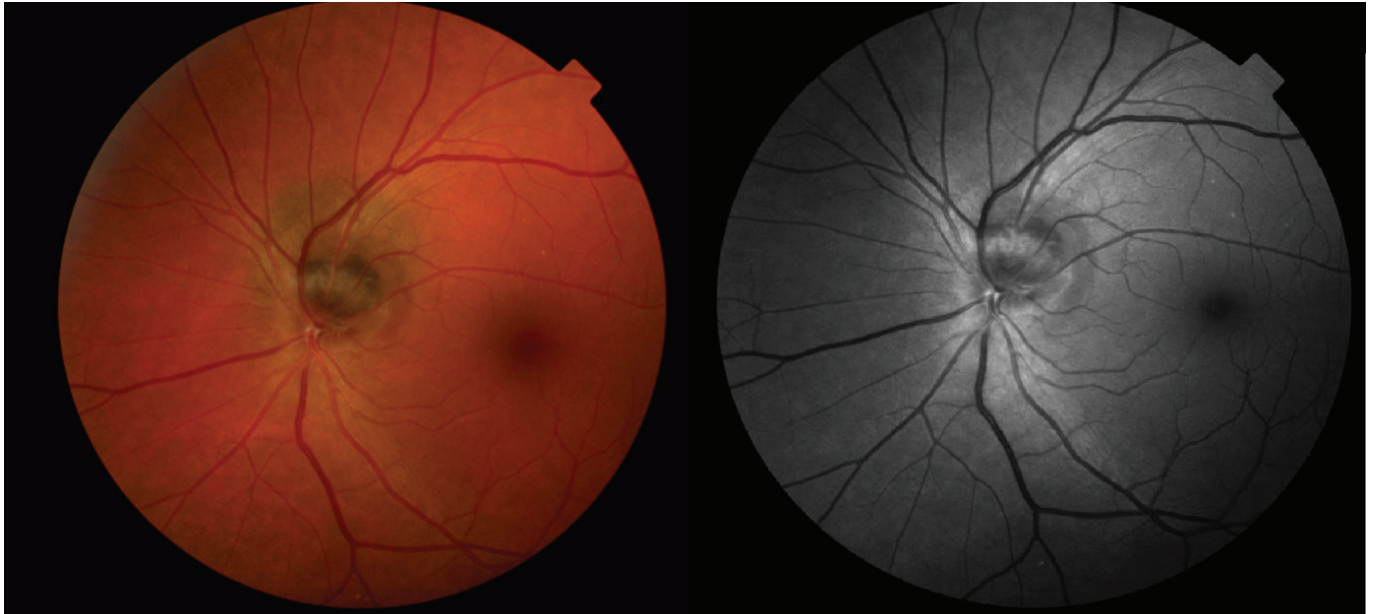
Advancements in imaging techniques, such as fluorescein angiography, optical coherence tomography (OCT), enhanced depth imaging-OCT (EDI-OCT), and B-scan ultrasonography have significantly improved the ability to distinguish melanocytoma from malignant lesions [4].

Although typically benign, melanocytomas can exhibit locally aggressive behavior, potentially leading to optic nerve compression or involvement of adjacent structures, such as the retina and choroid. They are most commonly diagnosed in middle-aged individuals with no significant gender predilection [5,6]. Long-term follow-up is crucial to monitor for complications, such as visual impairment, optic neuropathy, or the rare but serious risk of malignant transformation [7].

This report presents a rare case of melanocytoma of the optic nerve head with a coexisting juxtapapillary choroidal nevus, emphasizing the diagnostic and management challenges associated with this condition. A comprehensive literature review provides additional insights into its clinical, imaging, and histopathological features, highlighting the importance of multidisciplinary care in ensuring optimal outcomes for affected patients [8-10].

CASE REPORT

A 40-year-old female patient presented to our clinic with a known history of a pigmented lesion on the left optic nerve, first identified over 10 years ago during a routine ophthalmologic examination. The patient reported no visual symptoms; her medical history was unremarkable, with no systemic illnesses or family history of ocular diseases. Visual acuity was 20/20 bilaterally without correction.



Slika 1. Ova slika prikazuje fundus fotografiju melanocitoma lociranog na glavi optičkog nerva, praćenog jukstapapilarnim horoidalnim nevusom. Melanocitom je vidljiv kao jasno ograničena, uzdignuta, sivo-crna lezija na optičkom disku, što je u skladu sa njegovom karakterističnom pigmentacijom. Pored melanocitoma, horoidalni nevus izgleda kao ravno zelenkasto-braon polje sa jasnim granicama

Figure 1. The image presents a fundus photograph of a melanocytoma located on the optic nerve head, accompanied by a juxtapapillary choroidal nevus. The melanocytoma is visible as a sharply demarcated, elevated, dark gray-black lesion on the optic disc, consistent with its characteristic pigmentation. Adjacent to the melanocytoma, the choroidal nevus appears as a flat, greenish-brown area with distinct borders

Oftalmoskopski pregled otkrio je oštro ograničenu, prominentnu, sivo-crnu leziju na glavi optičkog nerva levog oka. Pored melanocitoma, uočen je jukstapapilarni horoidalni nevus, koji se prezentovao kao ravna, zelenkasto-smeđa lezija sa jasnim granicama. Nije bilo znakova edema optičkog diska, a retinalni sudovi su izgledali normalno (Slika 1). Automatska perimetrija pokazala je prisustvo malog, neprogresivnog centralnog skotoma.

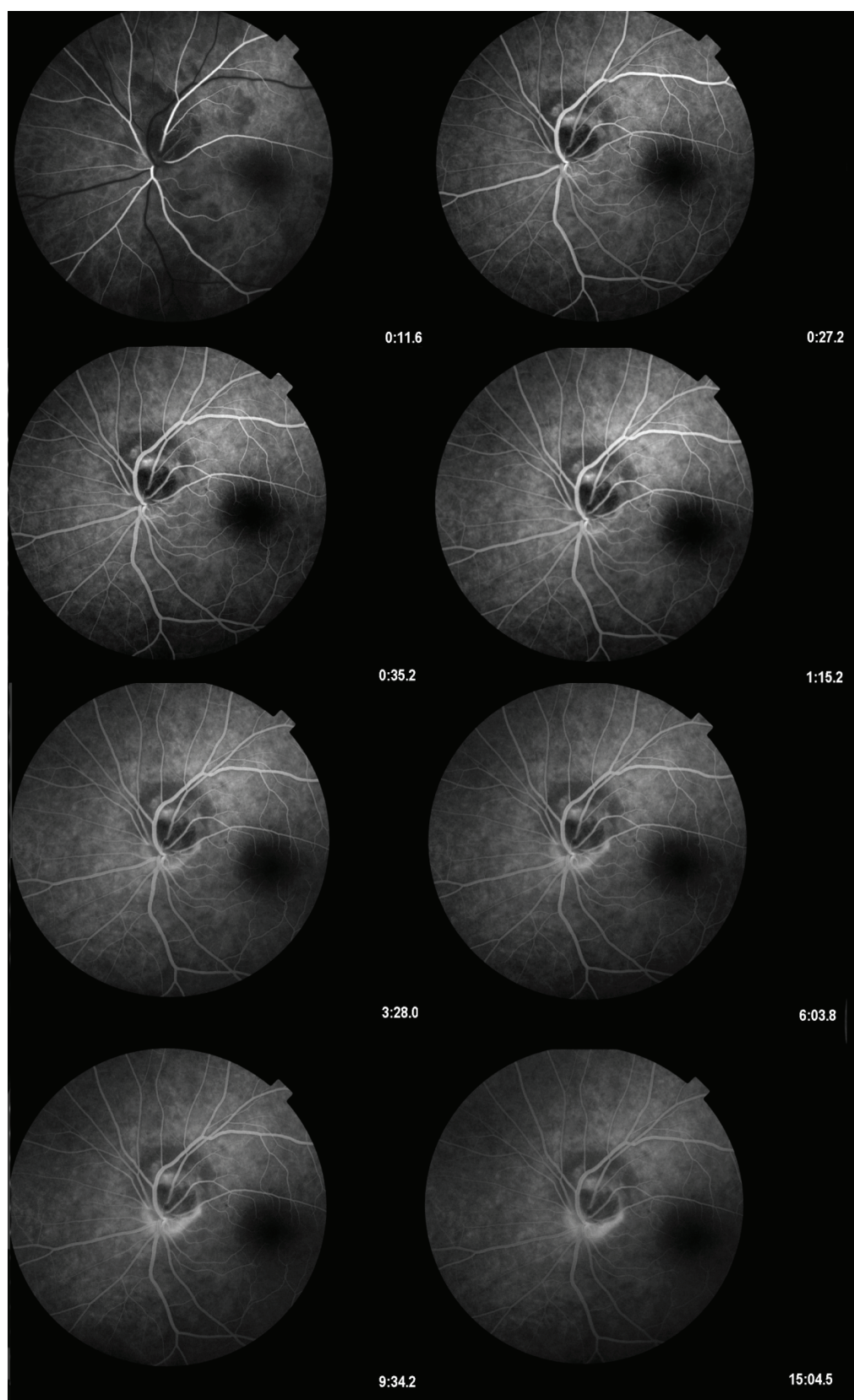
Fluoresceinska angiografija pokazala je potpunu blokadu fluorescencije koja odgovara melanocytomu, bez dokaza o curenju ili neovaskularizaciji (Slika 2). Jukstapapilarni nevus je tokom svih angiografskih faza ispoljavao postojanu hipofluorescenciju. Optička koherentna tomografija potvrdila je prisustvo izdignute lezije bez disrupcije slojeva retine. B-sken ultrasonografija otkrila je solidnu leziju srednje refleksivnosti.

S obzirom na benignu prirodu lezije i odsustvo vizuelnih simptoma ili komplikacija, pacijentkinji je savetovano redovno praćenje svakih šest meseci radi nadzora mogućeg napredovanja, uključujući povećanje lezije, gubitak vidnog polja ili znakove maligne transformacije. Pacijentkinja je edukovana o simptomima mogućih komplikacija, uključujući iznenadne promene vida, koje bi zahtevale hitnu medicinsku pomoć. Hirurška intervencija u ovoj fazi nije bila neophodna.

The ophthalmoscopic evaluation revealed a sharply demarcated, elevated, gray-black lesion on the optic nerve head of the left eye. Adjacent to the melanocytoma, a juxtapapillary choroidal nevus was noted, presenting as a flat, greenish-brown lesion with distinct borders. There were no signs of optic disc edema, and retinal vessels appeared normal (Figure 1). Automated perimetry revealed a small, non-progressive central scotoma.

Fluorescein angiography demonstrated a complete blockage of fluorescence corresponding to the melanocytoma, with no evidence of leakage or neovascularization (Figure 2). The juxtapapillary nevus exhibited persistent hypofluorescence throughout all angiographic phases. Optical coherence tomography confirmed the presence of an elevated lesion with shadowing effects but without disruption of the retinal layers. B-scan ultrasonography revealed a solid lesion with moderate internal reflectivity.

Given the benign nature of the lesion and the absence of visual symptoms or complications, the patient was advised to undergo regular follow-up examinations every six months to monitor for potential progression, such as enlargement, visual field loss, or signs of malignant transformation. The patient was educated about the symptoms of possible complications, including sudden vision changes, which would necessitate immediate medical attention. Surgical intervention was deemed unnecessary at this stage.



Slika 2. Ova slika prikazuje seriju snimaka fluoresceinske angiografije (FA) melanocitoma glave optičkog nerva, praćenog jukstapapilarnim horoidalnim nevusom. Angiografski niz ilustruje odsustvo curenja ili prebojavanja melanocitoma, što je u skladu sa njegovom benignom prirodom. Lezija se vidi kao tamna, jasno ograničena oblast na optičkom disku, koja blokira fluorescenciju. Pored melanocitoma, horoidalni nevus se prikazuje kao hipofluorescentna oblast

Figure 2. This image depicts a series of frames from fluorescein angiography (FA) of a melanocytoma of the optic nerve head, accompanied by a juxtapapillary choroidal nevus. The angiographic sequence illustrates the absence of leakage or staining over the melanocytoma, consistent with its benign nature. The lesion appears as a dark, sharply demarcated area on the optic disc, causing blockage of fluorescence. Adjacent to the melanocytoma, the choroidal nevus is visible as a hypofluorescent area

DISKUSIJA

Melanocitom glave optičkog nerva je retka, benigna lezija koja može oponašati agresivnija stanja, poput melanoma, što naglašava važnost tačne dijagnoze. Shields i saradnici su pokazali da se melanocitom javlja kod približno 1% opšte populacije, sa većom prevalencijom kod osoba tamnije pigmentacije [1,4]. Ove lezije obično ostaju stabilne, iako su u retkim slučajevima dokumentovani rast i maligna transformacija, sa procenjenom stopom transformacije od 1% [7].

Nekoliko prikaza slučajeva u literaturi ističe kliničku varijabilnost i dijagnostičke izazove melanocitoma. Burgos-Blasco i saradnici su predstavili slučaj pacijenta sa melanocitomom optičkog nerva, naglašavajući upotrebu multimodalnog snimanja, uključujući OCT i OCT angiografiju, za potvrdu dijagnoze i praćenje stabilnosti lezije tokom vremena [5]. U drugom slučaju, Kita i saradnici su opisali 38-godišnjeg pacijenta sa defektima vidnog polja uzrokovanim kompresijom optičkog nerva; praćenjem u periodu od pet godina utvrđeno je da lezija ostaje stabilna bez potrebe za intervencijom [9].

Mannat i saradnici su opisali redak slučaj melanocitoma koji se širio u peripapilarnu retinu, uzrokujući nakupljanje subretinalne tečnosti i blage vizuelne smetnje. Lezija je ostala stabilna bez znakova maligne transformacije tokom trogodišnjeg praćenja [6]. Takođe, Garza-Garza i saradnici su izvestili o seriji slučajeva u kojima su napredne tehnike snimanja, poput EDI-OCT, pružile neprocenljiv uvid u morfologiju i dubinu lezije, pomažući u diferencijaciji benignih od malignih promena [8]. Kao što se vidi u ovom slučaju, koegzistencija jukstapapilarnog horoidalnog nevusa komplikuje kliničku sliku.

Prema Gassu [2], prisustvo ovih nevusa povećava dijagnostički izazov, zahtevajući upotrebu multimodalnog snimanja za diferencijaciju. Fluoresceinska angiografija i OCT su ključni u prikazivanju karakteristične blokade fluorescencije i potvrđivanju benigne prirode lezije [3,5]. EDI-OCT dodatno poboljšava dijagnostičku preciznost pružajući slike visoke rezolucije glave optičkog nerva i okolnih struktura [6].

Histopatološke studije otkrivaju gusto raspoređene melanocyte sa obilnim granulama melanina i niskom mitotskom aktivnošću, što je u skladu sa benignim tokom bolesti [10]. Međutim, faktori poput rasta lezije, kompresije optičkog nerva ili defekata vidnog polja zahtevaju pažljivije praćenje i potencijalnu intervenciju. Nedavne studije naglašavaju značaj genetskog i molekularnog profilisanja u diferencijaciji melanocitoma od melanoma u dvosmislenim slučajevima [8].

Lečenje melanocitoma se prvenstveno zasniva na redovnom praćenju radi otkrivanja promena u morfologiji ili funkciji lezije. Shields i saradnici preporučuju

DISCUSSION

Melanocytoma of the optic nerve head is an uncommon, benign lesion that can mimic more aggressive conditions such as melanoma, highlighting the importance of accurate diagnosis. Shields et al. reported that melanocytoma occurs in approximately 1% of the general population, with a higher prevalence among individuals of darker pigmentation [1,4]. These lesions typically remain stable, although growth and malignant transformation have been documented in rare cases, with an estimated transformation rate of 1% [7].

Several case reports in the literature emphasize the clinical variability and diagnostic challenges of melanocytoma. Burgos-Blasco et al. presented a case of a patient with optic nerve melanocytoma, highlighting the use of multimodal imaging, including OCT and OCT angiography, to confirm the diagnosis and monitor lesion stability over time [5]. Another case by Kita et al. detailed a 38-year-old patient who experienced visual field defects due to optic nerve compression; follow-up revealed lesion stability over five years without intervention [9].

Mannat et al. described a rare instance of melanocytoma extending into the peripapillary retina, causing subretinal fluid accumulation and mild visual disturbances. The lesion remained stable with no signs of malignant transformation during a three-year follow-up [6]. Additionally, Garza-Garza et al. reported a series of cases where advanced imaging techniques, such as EDI-OCT, provided invaluable insights into lesion morphology and depth, aiding in differentiating benign from malignant lesions [8]. As seen in this case, the coexistence of juxtapapillary choroidal nevi complicates the clinical picture.

According to Gass [2], the presence of such nevi increases the diagnostic challenge, necessitating the use of multimodal imaging for differentiation. Fluorescein angiography and OCT are pivotal in demonstrating characteristic blockage of fluorescence and confirming the lesion's benign nature [3,5]. EDI-OCT further enhances diagnostic accuracy by providing high-resolution images of the optic nerve head and surrounding structures [6].

Histopathological studies reveal densely packed melanocytes with abundant melanin granules and low mitotic activity, consistent with a benign course [10]. However, factors such as lesion growth, optic nerve compression, or visual field defects warrant closer surveillance and potential intervention. Recent studies have emphasized the importance of genetic and molecular profiling to differentiate melanocytoma from melanoma in ambiguous cases [8].

Management of melanocytoma primarily involves regular monitoring to detect changes in lesion morphology or function. Shields et al. recommend fol-

kontrolne preglede od šest meseci tokom prve godine, a zatim godišnje ako lezija ostane stabilna [10]. Edukacija pacijenata o simptomima optičke neuropatije ili maligne transformacije ključna je za pravovremenu intervenciju. U slučajevima značajnog rasta, progresivnog gubitka vidnog polja ili dijagnostičke neizvesnosti, može biti neophodna hirurška ekscizija i histopatološki pregled.

ZAKLJUČAK

Melanocitom glave optičkog nerva je retka i obično benigna lezija, ali njegova mogućnost lokalne agresivnosti i retke maligne transformacije zahteva pažljivo i kontinuirano praćenje. Ovaj slučaj naglašava značaj multidisciplinarnog pristupa, koji uključuje napredne tehnike snimanja i redovne kontrole, kako bi se optimizovali ishodi lečenja i sprečile komplikacije. Temeljno razumevanje kliničkih i histopatoloških karakteristika lezije, potkrepljeno pregledom literature, ključno je za efikasno upravljanje ovim stanjem.

Sukob interesa: Nije prijavljen.

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low-up intervals of six months for the first year and annual evaluations thereafter if the lesion remains stable [10]. Patient education regarding optic neuropathy or malignant transformation symptoms is crucial for timely intervention. In cases of significant growth, progressive visual field loss, or diagnostic uncertainty, surgical excision, and histopathological examination may be necessary.

CONCLUSION

Melanocytoma of the optic nerve head is a rare and typically benign lesion, yet its potential for local aggressiveness and rare malignant transformation necessitates careful and continuous monitoring. This case underscores the importance of a multidisciplinary approach, incorporating advanced imaging techniques and regular follow-up, to optimize patient outcomes and prevent complications. A thorough understanding of the lesion's clinical and histopathological features, supported by a literature review, is essential for effective management.

Conflict of interest: None declared.

LEČENJE KOMPLEKSNE POVREDE STOPALA UPOTREBOM VACUUM ASSISTED CLOSURE I PLATELET-RICH FIBRIN METODE – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

COMPLEX FOOT INJURY TREATMENT USING VACUUM ASSISTED CLOSURE AND PLATELET-RICH FIBRIN METHOD – CASE REPORT

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SAŽETAK

Uvod: Saobraćajni traumatizam predstavlja jedan od vodećih uzroka smrti i povreda širom sveta. Prema podacima Svetske zdravstvene organizacije (SZO), više od 1,3 miliona ljudi godišnje izgubi život u saobraćajnim nesrećama, dok je između 20 i 50 miliona osoba povređeno. Veći deo povreda izazvanih saobraćajnim nesrećama obuhvata traume ekstremiteta, pri čemu su donji ekstremiteti najčešće povređeni kod pešaka i motociklista.

Prikaz slučaja: Prikazujemo slučaj pacijentkinje stare 77 godina koja je pretrpela saobraćajnu nezgodu kao pešak, zadobivši otvorene prelome II i III metatarsalne kosti leve noge (Gustillo tip II). Inicijalno je primenjeno hirurško lečenje odmah nakon povrede, koje je uključivalo obilnu lavažu, debridman i stabilizaciju preloma K-iglama, uz potkolenu gipsanu imobilizaciju i trojnu antibiotsku terapiju. Dalje, kompleksno lečenje je zahtevalo kombinovano lečenje metodom vacuum-assisted closure (V.A.C.) i platelet-rich fibrin (PRF) i tretmanima u hiperbaričnoj komori (HBO).

Zaključak: Pravovremeno operativno lečenje bilo je ključno za postizanje pozitivnog ishoda kod pacijentkinje starije životne dobi, čime je omogućeno zarađanje bez infekcija i funkcionalan oporavak. Multidisciplinarni pristup pokazao se neophodnim u ovom složenom slučaju, prilagođavajući terapiju specifičnim potrebama starijeg pacijenta i poboljšavajući sveobuhvatni oporavak.

Ključne reči: otvoreni prelom, defekt kože, hiperbarična komora

ABSTRACT

Introduction: Traffic accidents are one of the leading causes of death and injuries worldwide. According to the World Health Organization (WHO), more than 1.3 million people die annually in road accidents, while between 20 and 50 million suffer injuries. The majority of these injuries involve limb trauma, with the lower limbs being most commonly affected, particularly among pedestrians and motorcyclists.

Case report: This report presents the case of a 77-year-old female pedestrian involved in a road accident, sustaining open fractures of the second and third metatarsal bones of the left foot (Gustilo type II). Initial surgical treatment was performed immediately after the injury, including extensive irrigation, debridement, and fracture stabilization using K-wires, along with below-knee plaster immobilization and triple antibiotic therapy. Further complex treatment involved a combination of vacuum-assisted closure (V.A.C.), platelet-rich fibrin (PRF) application, and hyperbaric oxygen therapy (HBO).

Conclusion: Timely surgical intervention was crucial for achieving a positive outcome in an elderly patient, ensuring healing without infection and functional recovery. A multidisciplinary approach was essential in this complex case, adapting therapy to the specific needs of an elderly patient and improving overall recovery.

Keywords: open fracture, skin defect, hyperbaric oxygen therapy

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UVOD

Saobraćajni traumatizam predstavlja jedan od vodećih uzroka smrti i povreda širom sveta. Prema podacima Svetske zdravstvene organizacije (SZO), više od 1,3 miliona ljudi godišnje izgubi život u saobraćajnim nesrećama, dok je između 20 i 50 miliona osoba povređeno. Osmi je vodeći uzrok smrti za sve starosne grupe, nadmašujući HIV/AIDS, tuberkulozu i dijareju [1]. Veći deo povreda izazvanih saobraćajnim nesrećama obuhvata traume ekstremiteta, pri čemu su donji ekstremiteti najčešće povređeni kod pešaka i motociklista, koji su posebno eksponirani zbog odsustva zaštitnih struktura koje su prisutne kod vozača u vozilima [2].

Prema podacima Nacionalne uprave za bezbednost saobraćaja na putevima (NHTSA – National Highway Traffic Safety Administration), pešaci čine između 16 i 17% svih smrtnih slučajeva u saobraćaju u Sjedinjenim Američkim Državama, u petogodišnjem periodu praćenja od 2017. do 2021. godine [3].

Povrede stopala i donjih ekstremiteta prilikom gaženja vozilom spadaju među najozbiljnije povrede koje pešaci mogu zadobiti u odnosu na druge delove tela (Grafikon 1). Podaci pokazuju da je najveći broj povređenih pešaka (42,10%) bio starosne dobi od 41 do 69 godina, a 81,31% činili su muškarci [4]. U ovim slučajevima, terapije kao što su V.A.C. (vacuum-assisted closure) terapija i hiperbarična oksigenacija mogu značajno doprineti bržem oporavku i smanjenju komplikacija [5].

Cilj ovog rada je da prikaže neophodnost multidisciplinarnog u lečenju kompleksnih povreda, kao i da

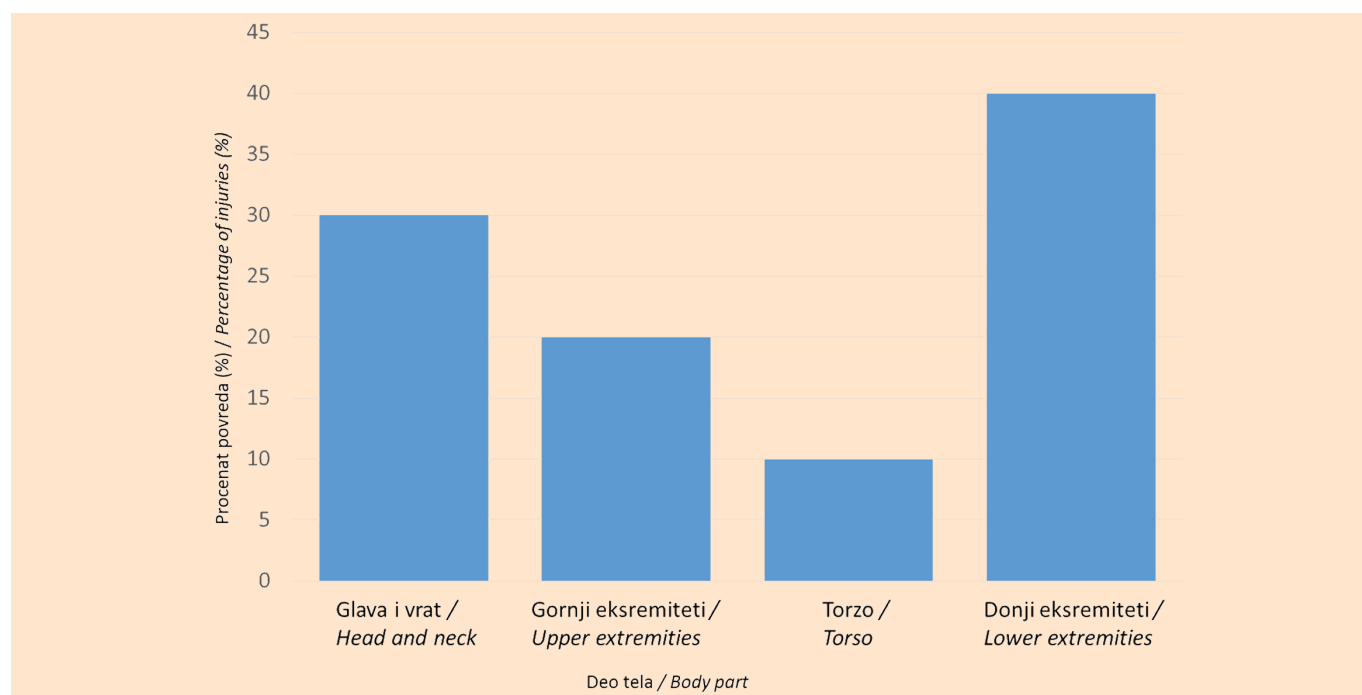
INTRODUCTION

Traffic-related trauma is one of the leading causes of death and injury worldwide. According to the World Health Organization (WHO), more than 1.3 million people die annually in road traffic accidents, while between 20 and 50 million are injured. It is the eighth leading cause of death across all age groups, surpassing HIV/AIDS, tuberculosis, and diarrheal diseases [1]. A large portion of traffic-related injuries involve limb trauma, with the lower extremities most commonly affected, particularly among pedestrians and motorcyclists who are more exposed due to the lack of protective structures present in vehicles [2].

According to data from the National Highway Traffic Safety Administration (NHTSA), pedestrians accounted for between 16% and 17% of all traffic-related fatalities in the United States during the five years from 2017 to 2021 [3].

Foot and lower limb injuries caused by vehicle run-over incidents are among the most severe injuries a pedestrian can sustain (Chart 1). Data shows that the majority of injured pedestrians (42.10%) were aged 41 to 69, and 81.31% were male [4]. In such cases, therapies such as vacuum-assisted closure (V.A.C.) and hyperbaric oxygen therapy (HBOT) can significantly contribute to faster recovery and reduced complications [5].

This case report aims to highlight the necessity of a multidisciplinary approach in treating complex injuries and to emphasize that the timely selection of appropriate therapeutic protocols can result in both functional-



Grafikon 1. Distribucija povreda po delovima tela - World Health Organization (WHO), Global Status Report on Road Safety, 2018

Figure 1. Distribution of body part injuries - World Health Organization (WHO), Global Status Report on Road Safety, 2018

istakne da pravovremeni odabir odgovarajućeg terapijskog protokola daje rezultate koji su i funkcionalno i estetski zadovoljavajući, s obzirom na obim povrede.

PRIKAZ SLUČAJA

Pacijentkinja, starosti 77 godina, povređena je kao pešak kada joj je autobus prešao preko levog stopala. Na pregledu su konstatovani otvoreni prelomi II i III metatarsalne kosti (Gustillo tip II), uz prisutno oštećenja kože i kompresiju tetiva ekstenzorne grupe na dorzalnoj strani stopala, uz uredan neurovaskularni nalaz (Slika 1, Slika 2). Na dan povrede, učinjeno je operativno lečenje koje je uključivalo obilno ispiranje rana, mekotkivni debridman i fiksaciju preloma II i III metatarsalne kosti (MT) Kirschner iglama (K iglama). Postavljena je potkolena gipsana imobilizacija, a ordinirana je trojna antibiotska terapija: Azaran 1 g intravenski, dva puta dnevno; Amikacin 500 mg intravenski, dva puta dnevno i solucija Orvagila, 500 ml intravenski, tri puta 500 ml dnevno. Pacijentkinja je primila antikoagulantnu profilaksu (Fraxiparin u dozi od

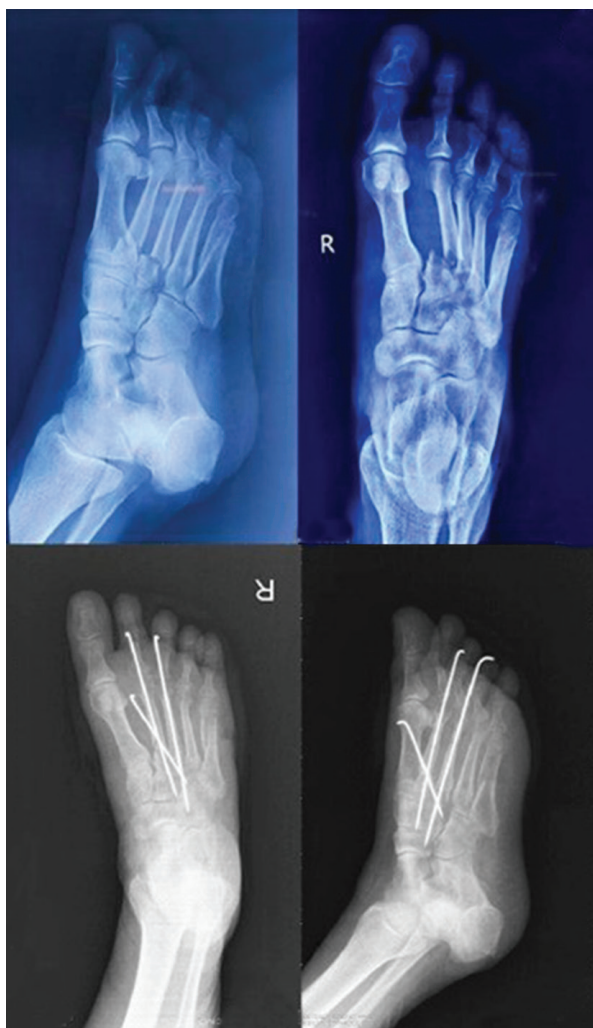
ly and aesthetically satisfactory outcomes, considering the extent of the injury.

CASE REPORT

A 77-year-old female patient was injured as a pedestrian when a bus ran over her left foot. Examination revealed open fractures of the II and III metatarsal bones (Gustilo type II), with skin damage and compression of the extensor tendons on the dorsal aspect of the foot, but with preserved neurovascular status (Figure 1, Figure 2). On the day of injury, surgical treatment was performed, which included extensive wound irrigation, soft tissue debridement, and fixation of the II and III metatarsal bones with Kirschner wires (K-wires). A below-knee plaster cast was applied, and triple antibiotic therapy was administered: Azaran 1 g IV twice daily, Amikacin 500 mg IV twice daily, and Orvagil solution 500 ml IV three times daily. The patient also received anticoagulant prophylaxis (Fraxiparin 0.6 ml subcutaneously once daily) and tetanus prophylaxis (Tetagam 250 IU/ml serum and Tetavaksal 40 IU/0.5 ml vaccine), in accordance with the immunization schedule [6].

Three days post-surgery, the patient began hyperbaric oxygen therapy (HBOT) to achieve hyperoxia and promote soft tissue healing. A total of 20 HBOT sessions were completed. The wounds were regularly dressed and managed with serial debridements. Despite treatment, skin necrosis developed on the dorsal aspect of the foot. Thirty-three days post-injury, a second surgical intervention was performed. This included repeated soft tissue debridement and excision of necrotic tissue from the dorsal foot, resulting in a skin defect that was managed with a V.A.C. device (V.A.C. Ulta®), applied under continuous pressure of 125 mmHg.

On day 36 post-injury, the skin defect was treated with platelet-rich fibrin (PRF), manufactured by Vivostat®. PRF is prepared in a closed system to concentrate fibrin and platelets 7–10 times above normal values from 120 ml of the patient's autologous blood, drawn 15 minutes before anesthesia. The blood is collected directly into specially designed, single-use, sterile bottles. The automated preparation process takes about 25 minutes and yields 5–6 ml of the final product. The automated process is carried out in the anteroom of the operating block, and upon completion of centrifugation, the final product cassette is brought into the operating room and inserted into the Vivostat® applicator, where the solution is buffered. A sterile system is directly connected to the applicator unit, which includes a spray option for solution application. The application process lasts 3–4 minutes. When the spray is applied to the donor site defect, immediate polymerization occurs, re-



Slika 1. Radiografija stopala nakon povrede i nakon operativnog lečenja

Figure 1. Radiography of the foot after injury and after operative



Slika 2. Klinički nalaz povrede

Figure 2. The foot after injury

0,6 ml subkutano, jednom dnevno), kao i antitetanusnu profilaksu (serum Tetagam 250 i.j./ml, i vakcina Tetavak-sal 40 i.j. / 0,5 ml) u skladu sa kalendarom vakcinacije [6].

Tri dana nakon operacije, pacijentkinja je započela terapiju u hiperbaričnoj komori (HBO) kako bi se dobili uslovi hiperoksije koji su doveli do poboljšanja zarastanja mekih tkiva. Ukupno je sprovedeno dvadeset terapija u HBO komori. Rane su redovno previjane i obrađivane u smislu sukcesivnih debridmana. Uprkos primenjenim merama lečenja dolazi do razvoja nekroze kože na dorzalnoj strani stopala. Trideset tri dana nakon povrede je obavljena druga hirurška intervencija. Tokom te procedure izvršen je ponovni debridman mekih tkiva i uklanjanje polja nekroze sa dorzuma stopala nakon čega je zaostao defekt kože, a na koji je postavljen V.A.C. aparat (vakumska terapija negativnim pritiskom za zarastanje rana), proizvođača V.A.C. Ulta[®], pod režimom kontinuiranog pritiska 125 mgHg.

U daljem toku lečenja, 36-og dana nakon povrede, defekt kože je pokriven PRF-om (fibrin bogat trombocitima), proizvođača Vivostat[®]. Priprema Vivostata[®] PRF se vrši u zatvorenom sistemu sa ciljem dobijanja koncentracije fibrina i trombocita 7–10 puta većih od normalnih vrednosti, dobijenih iz 120 ml autologe krvi pacijenta, koja se uzima 15 minuta pre uvođenja u anesteziju. Krv se direktno prikuplja u specijalno dizajnirane, jednokratne sterilne boce. Automatizovani proces pripreme traje do 25 minuta i rezultira sa 5–6 ml finalnog proizvoda. Sam automatizovani proces se vrši u predslu operacionog bloka, a po završetku centrifugiranja se unosi u operacionu salu i kaseta sa dobijenim finalnim proizvodom se aplikuje u Vivostat[®] aplikator gde se rastvor puferizuje. Direktno na jedinicu aplika-

sulting in the formation of a bioactive fibrin matrix. This procedure was repeated on day 43 to cover the remaining 2 cm diameter defect (**Figure 3**). Granula-



Slika 3. Stopalo nakon PRF tretmana

Figure 3. The foot after PRF treatment



Slika 4. Stopalo sa Tiersch-ovim transplantatom

tora se povezuje sterilan sistem koji poseduje opciju raspršivanja rastvora - sprej aplikator. Proces aplikacije traje 3–4 minuta i prilikom nanošenja spreja na defekt donornog mesta dolazi do momentalne polimerizacije i formiranja bioaktivnog fibrinskog matriksa. Ovaj postupak je ponovljen još jedanput, 43. dana, u drugom aktu, u cilju kompletnog pokrivanja zaostalog defekta, koji je iznosio 2 cm u prečniku (Slika 3). Na primenjene mere lečenja dolazi do formiranja granulacija nad dorzumom stopala, rana je bez znakova infekcije te je odlučeno da se pristupi pokrivanju defekta kože. Četrdeset sedmog dana od povrede, obavljena je nova

Figure 4. Foot with Thiersch transplant

tion tissue formed over the dorsal foot, and with no signs of infection, it was decided to proceed with skin defect coverage. On day 47, a new surgery was performed using a split-thickness autologous skin graft according to the Tiersch technique [7], with removal of K-wires (Figure 4). The donor site was on the anterior thigh of the contralateral leg, which was dressed aseptically. A skin graft mesh device is used to process the autologous skin graft, allowing for the creation of an adequate flap for application to the dorsal side of the foot.

Following the application of the Thiersch graft, the patient underwent regular dressing changes.



Slika 5. Stopalo sa Tiersch-ovim transplantatom

Figure 5. Foot with Thiersch transplant

operacija tokom koje je defekt kože dorzuma pokriven autotransplantatom kože prema Tiersch metodi [7], korišćenjem mesh graft- a prilikom čega su uklonjene K igle (Slika 4). Donorna regija anteriorne strane femoralne regije kontralateralne noge sa koje je uzet autotransplantat je sterilno previjen. Mesh graft uređajem se obradi kožni autotransplantat kako bi se dobio adekvatan flap za aplikovanje na dorzalnu stranu stopala.

Nakon primene Tiersch-ovog transplantata, pacijentkinja je redovno previjana. Na osnovu urednog lokalnog nalaza samog transplantata i donorne regije, odlučeno je da se lečenje pacijentkinje nastavi u kućnim uslovima, uz previjanje vazelinskim gazama i rivanolskim oblogama. Dve nedelje nakon otpusta iz bolnice, odnosno dva meseca od povrede, rane su zarasle, dozvoljen je oslonac na operisanu nogu (Slika 5), a pacijentkinja je upućena na dalju fizikalnu terapiju, koja je sprovedena u nadležnom rehabilitacionom centru narednih tri meseca. Šest meseci od inicijalne povrede, pacijentkinja je kompletno osposobljena za samostalni hod bez korišćenja pomagala.

DISKUSIJA

Lečenje otvorenih preloma stopala anatomskom repozicijom i fiksacijom K-iglama ostaju zlatni standard lečenja. Uobičajene hirurške komplikacije nakon ovakvih operacija uključuju odbacivanje implantanata ili iritaciju mekih tkiva, refrakturu, nesrastanje preloma, povredu senzitivnih grana nerva i hronični bol. Pacijenti treba da budu informisani o različitim opcijama lečenja i da budu deo procesa odlučivanja, posebno kada je vreme za oporavak i povratak prethodnim aktivnostima od suštinske važnosti [8].

Kod pedijatrijske populacije, otvorena repozicija i fiksacija K-iglama daje zadovoljavajuće rezultate bez pretećih komplikacija, prema postojećim podacima literature. Ranom hirurškom intervencijom, otvorenom repozicijom i blagovremenom rehabilitacijom kod mlađih osoba postiže se dobra redukcija preloma, a nakon rehabilitacije i pun opseg pokreta svih zglobova stopala i skočnog zgloba [9].

Otvoreni prelomi su povezani sa većom stopom infekcija i odloženim zarastanjem preloma, stoga su, pored fiksacije preloma važni i prevencija infekcije i praćenje lokalnog statusa mekih tkiva. Davanje antibiotika treba sprovesti što je ranije moguće i tokom 24–72 časa u zavisnosti od povrede. Inicijalni debridman i procena težine povrede određuju strategiju lečenja, naročito kod starijih osoba, kao u našem slučaju. Fiksacija preloma sledi opšte traumatološke principe. U slučajevima značajne kontaminacije, gubitka kosti ili velikog oštećenja mekog tkiva, vrši se privremena fiksacija i privremeno zatvaranje rane. Definitivni tretman

Based on the satisfactory local conditions of both the graft and the donor site, it was decided to continue the patient's treatment at home, using dressings with vaseline gauze and Rivanol compresses. Two weeks after hospital discharge and two months after the injury, the wounds had healed, and weight-bearing on the operated leg was permitted (Figure 5). The patient was then referred for continued physical therapy, which was carried out at the designated rehabilitation center over the following three months. Six months after the initial injury, the patient was able to walk independently without the use of assistive devices.

DISCUSSION

Open foot fractures treated with anatomical reduction and K-wire fixation remain the gold standard for treatment. Common complications include implant rejection or soft tissue irritation, refracture, nonunion, nerve injuries, and chronic pain. Patients should be informed about treatment options and included in decision-making, especially when return to function is a priority [8].

In pediatric cases, open reduction and K-wire fixation typically yield satisfactory results with minimal severe complications. Early surgical intervention and rehabilitation in younger patients usually result in sound fracture reduction and full joint mobility after therapy [9].

Open fractures are associated with a higher rate of infections and delayed fracture healing; therefore, in addition to fracture fixation, infection prevention and monitoring of the local soft tissue status are crucial. Antibiotic administration should be initiated as early as possible and continued for 24 to 72 hours, depending on the nature of the injury. Initial debridement and assessment of injury severity determine the treatment strategy, particularly in elderly patients, as in our case. Fracture fixation follows general traumatological principles. In cases of significant contamination, bone loss, or extensive soft tissue damage, temporary fixation and provisional wound closure are performed. Definitive soft tissue coverage should be achieved within 72 hours to reduce the risk of fracture-related infections. For segmental bone defects, various approaches are available to restore bone continuity, depending on the size of the defect and the local condition of surrounding structures such as tendons, nerves, and skin coverage defects [10].

Studies have shown that wound healing in elderly individuals is slower. Poor healing of chronic wounds in the elderly population is more often attributed to comorbidities rather than age alone [11]. Split-thickness

pokrivanjem mekog tkiva treba da se izvedu u roku od 72 h kako bi se smanjio rizik od infekcija povezanih sa prelomom. Za koštane segmentne defekte dostupni su različiti pristupi za obnavljanje kontinuiteta kosti, u zavisnosti od veličine i lokalnog nalaza okolnih struktura kao što su tetive, nervi, defekti kožnog pokrivača [10].

Istraživanja su pokazala da je zarastanje rana kod starijih osoba usporeno. Loše zarastanje hroničnih rana kod starije populacije češće se može pripisati komorbiditetu, a ne samo starosti. [11]. Kožni transplantati parcijalne debljine imaju prednost zato što sadrže manje tkiva koja zahtevaju revaskularizaciju nego kožni transplantati pune debljine kože. Stoga je veća verovatnoća da će biti uspešan na predhodno pripremljenom tkivu. Prednosti korišćenja kožnog transplantata parcijalne debljine kože su njihove veće šanse da prežive pod uslovima vaskularne kompromitacije, njihova relativno laka aplikacija, njihova sposobnost pokrivanja velikih kožnih defekata. Glavni nedostatak ovih graftova bio bi kozmetički u smislu boje kože, prisustvo granulacija na donorskim mestima koje zahteva posebnu negu. Graftovi su obično bez dlaka i znojenje je slabo zbog nedostataka adneksa kože [12].

Hiperbarična terapija (HBO) je primena 100% kiseonika na atmosferskim pritiscima, u cilju povećanja sadržaja kiseonika iznad fiziološkog nivoa, čime se stvaraju uslovi hiperoksije [9]. Hiperbarična terapija maksimizira prednosti kiseonika i povećava prirodne odbrambene mehanizme tela kako bi se poboljšalo zarastanje rana. To je odlična procedura za zarastanje rana, ali je treba koristiti samo kada je to opravdano. Da bi se koristila ova procedura na odgovarajući način, lekar mora da razume indikacije i kontraindikacije [13].

Vacuum assisted closure (V.A.C.) terapija koristi negativni pritisak kako bi se poboljšala cirkulacija u povređenom području i stimulisalo stvaranje granulationog tkiva, što značajno ubrzava proces zarastanja [14]. Uklanjanjem viška tečnosti i eksudata, V.A.C. terapija smanjuje otok i olakšava optimalne uslove za zarastanje rane. Kontinuirano uklanjanje eksudata pomaže u uklanjanju devitalizovanog tkiva, tako da se i rizik od pojave infekcije smanjuje [14]. Stvara se zatvoreno okruženje koje pomaže u smanjenju nakupljanja bakterija, čime se smanjuje rizik od infekcije. Ovo je posebno korisno kod otvorenih rana i povreda koje su podložne kontaminaciji [13]. Mehanička stimulacija koju pruža negativni pritisak pomaže u formiranju granulationog tkiva, ključnog za zarastanje rane, što pomaže u obnovi oštećenih struktura [15].

Proces zarastanja mišića i rana, kao i doprinos faktora rasta procesu zarastanja je oblast koja se intenzivno proučava. Koncentrisanjem ovih faktora rasta, PRF može poboljšati procese zarastanja. Neke od prvih

skin grafts have an advantage because they contain less tissue requiring revascularization compared to full-thickness skin grafts. Therefore, they are more likely to succeed on previously prepared tissue.

The advantages of using split-thickness skin grafts include a higher likelihood of survival under conditions of vascular compromise, relatively easy application, and their ability to cover significant skin defects. The main disadvantage of these grafts is cosmetic, including differences in skin color and the presence of granulation tissue at donor sites, which requires special care. The grafts are typically hairless and exhibit reduced sweating due to the absence of skin adnexa [12].

Hyperbaric oxygen therapy (HBO) involves administering 100% oxygen under increased atmospheric pressure to elevate oxygen levels above physiological norms, thereby creating conditions of hyperoxia [9]. HBO maximizes the benefits of oxygen and enhances the body's natural defense mechanisms to promote wound healing. It is an effective wound healing procedure, but should only be used when clinically justified. To apply this treatment appropriately, the physician must understand its indications and contraindications [13].

Vacuum-assisted closure (V.A.C.) therapy utilizes negative pressure to enhance circulation in the injured area and stimulate the formation of granulation tissue, thereby significantly accelerating the healing process [14]. By removing excess fluid and exudate, V.A.C. therapy reduces swelling and facilitates optimal wound healing conditions. Continuous exudate removal also helps eliminate devitalized tissue, thereby reducing the risk of infection [14]. It creates a closed environment that helps decrease bacterial accumulation, thereby lowering the risk of infection. This is especially beneficial for open wounds and injuries prone to contamination [13]. The mechanical stimulation provided by negative pressure supports the development of granulation tissue, which is essential for wound healing and the restoration of damaged structures [15].

The process of muscle and wound healing, as well as the role of growth factors in this process, is an area of intense research. By concentrating these growth factors, PRF can enhance healing processes. Some of the first studies to demonstrate this were conducted by Wright-Carpenter and colleagues, who evaluated the effects of PRF on muscle injuries in humans. The study showed that the recovery time of patients treated with PRF was reduced to 16.6 days, compared to 22.3 days for patients treated with conventional methods. This supported the use of PRF during patient treatment, confirming earlier observations from animal models and in vitro studies [16].

studija koje su ovo otkrile izveli su Rajt-Karpenter i saradnici koji su procenili efekte PRF-a na povrede mišića kod ljudi. Studija je pokazala da je vreme oporavka pacijenata tretiranih PRF smanjeno na 16,6 dana u poređenju sa 22,3 dana kod pacijenata lečenih konvencionalnim metodama. Ovo je podržalo upotrebu PRF-a tokom lečenja pacijenta, potvrđujući prethodna zapažanja na životinjskim modelima i *in vitro* studijama [16].

Prema eksperimentalnoj studiji koju su izveli M. Cianforlini i saradnici, proces zarastanja nakon direktne ili indirektna povrede mišića su složeni, ali jasno definisan i uključuje dobro koordinisane korake: degeneraciju, upalu, regeneraciju i fibrozu. Uprkos ovoj čestoj pojavi i prisustvu velikog broja podataka o patofiziologiji povreda mišića, nijedna od trenutnih strategija lečenja se nije pokazala stvarno efikasnom u strogo kontrolisanim ispitivanjima. Plazma bogata trombocitima (PRP) je obećavajući alternativni pristup zasnovan na sposobnosti autoloških faktora rasta (GF) da ubrzaju zarastanje tkiva, poboljšaju regeneraciju mišića, povećaju neovaskularizaciju i smanje fibrozu. Ova studija je fokusirana na upotrebu različitih koncentracija PRP-a kao izvora faktora rasta [17].

Fibrin bogat trombocitima (PRF) je bogat faktorima rasta koji stimulišu proliferaciju ćelija, što doprinosi bržem zarastanju kože i mekih tkiva. Ovi faktori rasta poboljšavaju regeneraciju tkiva i sintezu kolagena, što dovodi do čvrstog i elastičnog zarastanja. Primećeno je da PRF sadrži 23% više koncentracije leukocita od obične plazme, koji pomažu u kontroli mikroba u rani i smanjenju rizika od infekcije [18]. Kada se PRF koristi kao dodatak prilikom presađivanja tkiva, povećava se verovatnoća uspešne integracije grafta i smanjuje rizik od odbacivanja, što može značajno doprineti ishodu lečenja [19].

Terapija rana negativnim pritiskom je dramatično promenila negu složenih rana na stopalima. U poređenju sa standardnom negom rana, pacijenti sa ranama dijabetičkog stopala koji se leče terapijom negativnim pritiskom imaju 5,9 puta veću verovatnoću da će zarasti i 4,4 puta manje šanse da će zahtevati amputaciju. Terapija negativnim pritiskom povećava perfuziju rane, ubrzava formiranje granulacionog tkiva, smanjuje edem i smanjuje bioopterećenje [20].

Kishore Vellingiri i saradnici, su prikazali slučaj lečenja pacijenta sa povredom stopala i upotrebom V.A.C. terapije. Navedeni pacijent je povređen u saobraćajnom traumatizmu prignječenjem, zadobio je povredu kalkaneusa sa gubitkom dela koštanog tkiva i oštećenjem loknog tkiva. Autori su primetili da benefiti značajno nadmašuju troškove V.A.C. sistema, što ga čini osnovnom opcijom lečenja za pacijente sa ovakvim vrstama povrede [21].

According to an experimental study conducted by M. Cianforlini and colleagues, the healing process following direct or indirect muscle injury is complex yet clearly defined, comprising well-coordinated phases: degeneration, inflammation, regeneration, and fibrosis. Despite the frequent occurrence of such injuries and the abundance of data on the pathophysiology of muscle damage, none of the current treatment strategies has proven truly effective in strictly controlled trials. PRP is a promising alternative approach based on the ability of autologous growth factors (GFs) to accelerate tissue healing, enhance muscle regeneration, increase neovascularization, and reduce fibrosis. This study focused on the use of different concentrations of PRP as a source of growth factors [17].

Platelet-Rich Fibrin is rich in growth factors that stimulate cell proliferation, thereby contributing to faster healing of skin and soft tissues. These growth factors enhance tissue regeneration and collagen synthesis, leading to firm and elastic wound healing. It has been observed that PRF contains 23% higher leukocyte concentration compared to regular plasma, which helps control microbial presence in the wound and reduces the risk of infection [18]. When used as an adjunct during tissue grafting, PRF increases the likelihood of successful graft integration and reduces the risk of graft rejection, which can significantly contribute to treatment outcomes [19].

Negative pressure wound therapy (NPWT) has dramatically changed the management of complex foot wounds. Compared to standard wound care, patients with diabetic foot wounds treated with NPWT are 5.9 times more likely to achieve wound closure and 4.4 times less likely to require amputation. NPWT increases wound perfusion, accelerates granulation tissue formation, reduces edema, and lowers the bioburden [20].

Kishore Vellingiri and colleagues presented a case of foot trauma treated with V.A.C. therapy. The patient sustained a calcaneal injury with bone loss and local tissue damage due to a crush injury in a traffic accident. The authors noted that the benefits of the V.A.C. system significantly outweigh its costs, making it a primary treatment option for patients with such injuries [21].

The combination of V.A.C. therapy and PRF enables efficient wound healing, reduces the risk of infection, and provides optimal wound bed preparation for further reconstructive surgery, thereby improving treatment success in cases of complex soft tissue injuries and open fractures, as demonstrated in the treatment of the presented patient.

Kombinacija V.A.C. terapije i PRF-a omogućava efikasno zarastanje, smanjenje rizika od infekcija i optimalnu pripremu rane za dalju rekonstruktivnu hiruriju, čime se povećava uspešnost lečenja kod složenih povreda mekih tkiva i otvorenih preloma, što je i postignuto prilikom lečenja navedene pacijentkinje.

ZAKLJUČAK

Pravovremena primena inicijalnog operativnog lečenja na sam dan povrede, u kombinaciji sa specifičnim terapijskim metodama i multidisciplinarnim pristupom, bila je ključna za postizanje visokog kvaliteta nege i optimalnog ishoda kod pacijentkinje starije životne dobi. Prva operacija, koja je obuhvatala ispiranje, debridman i stabilizaciju preloma, stvorila je osnovu za uspešan oporavak, smanjujući rizik od infekcije i komplikacija koje bi mogle dodatno ugroziti stanje pacijentkinje.

Starija životna dob sa sobom nosi povećan rizik od usporenog zarastanja i komplikacija, što čini brzu intervenciju i stalno praćenje još važnijim. Multidisciplinarni pristup omogućio je precizno planiranje i pravovremeno sprovođenje dodatnih terapija, kao što su hiperbarična oksigenacija, V.A.C. terapija i PRF tretman. Ovakav integrisani model lečenja, prilagođen specifičnim potrebama pacijentkinje, predstavlja primer značaja sveobuhvatne nege koja obuhvata sve aspekte oporavka, čime su maksimalizovane šanse za potpuni funkcionalni oporavak čak i kod pacijenata sa složenim povredama u starijoj životnoj dobi.

Sukob interesa: Nije prijavljen.

CONCLUSION

The timely initiation of surgical treatment on the day of injury, combined with specific therapeutic methods and a multidisciplinary approach, was crucial in delivering high-quality care and achieving an optimal outcome in this elderly patient. The initial surgery, which included irrigation, debridement, and fracture stabilization, laid the groundwork for successful recovery by minimizing the risk of infection and other complications that could have further compromised the patient's condition.

Advanced age carries an increased risk of delayed healing and complications, making prompt intervention and continuous monitoring even more important. The multidisciplinary approach enabled precise planning and timely implementation of additional therapies, including hyperbaric oxygen therapy, V.A.C. therapy, and PRF treatment. This integrated treatment model, tailored to the patient's specific needs, exemplifies the importance of comprehensive care that addresses all aspects of recovery, maximizing the chances for complete functional restoration even in elderly patients with complex injuries.

Conflict of interest: None declared.

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UPOTREBA IMPLANTA SA DIZAJNOM ROTIRAJUĆE ŠARKE U REVIZIONOJ TOTALNOJ ARTROPLASTICI KOLENA

PRIKAZ SLUČAJA

CASE REPORT

THE USE OF ROTATING HINGE KNEE PROSTHESIS IN REVISION TOTAL KNEE ARTHROPLASTY

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SAŽETAK

Uvod: Broj totalnih artroplastika kolena pokazuje rastući trend u svim svetskim ortopedskim centrima. Iako totalna artroplastika kolena pokazuje odličnu stopu dugoročnog preživljavanja, ne iznenađuje činjenica da će, imajući u vidu produženje životnog veka i sve stariju populaciju sa većim brojem komorbiditeta, i učestalost revizionih artroplastika kolena takođe rasti. Česte indikacije za reviziju totalne artroplastike kolena predstavljaju aseptično razlabavljenje i periprotetski prelomi.

Prikazi slučajeva: Pacijentkinja starosti 60 godina javila se u našu ustanovu zbog tegoba u vidu bola i nestabilnosti desnog kolena. Primarna artroplastika urađena je u drugoj ustanovi pre 9 godina. Radiografska evaluacija pokazala je aseptično razlabavljenje komponenti totalne endoproteze kolena, sa utonućem tibijalne komponente u varusnoj poziciji. Pacijentkinja starosti 73 godine primljena je u našu ustanovu zbog povrede levog kolena nastale usled pada na ravnoj podlozi, 5 dana pre prijema. Primarna artroplastika urađena je pre 14 godina u našoj ustanovi. Trauma RTG snimci povređenog kolena ukazali su na Lewis tip IIB periprotetski prelom tibijalnog platoa. Kod obe pacijentkinje urađena je revizionna artroplastika koristeći implantat povećane stabilnosti sa dizajnom rotacione šarke. Postoperativni oporavak protekao je uspešno u oba slučaja. Radiografije kolena pokazale su adekvatnu poziciju implanta nakon perioda praćenja od 2 godine.

Zaključak: Upotreba implanta povećane stabilnosti sa dizajnom rotacione šarke u revizionoj artroplastici kolena pokazuje ohrabrujuće rezultate i ishode, naročito u slučajevima gde postoji značajan gubitak koštane mase, kao i ligamentarna nestabilnost.

Ključne reči: revizionna totalna artroplastika kolena, implant povećane stabilnosti sa dizajnom rotacione šarke, aseptično razlabavljenje, periprotetski prelomi kolena

ABSTRACT

Introduction: The number of total knee arthroplasty (TKA) procedures shows a growing trend in orthopedic hospitals worldwide. Although TKA has an excellent long-term survival rate, it is not surprising that, given the increased life expectancy and aging population with a more significant number of comorbidities, the frequency of revision TKA will also rise. Common indications for revision TKA represent aseptic loosening and periprosthetic fractures.

Case reports: A 60-year-old female patient presented to our hospital with complaints of pain and instability of her right knee, accompanied by decreased range of motion. Primary TKA was performed in another institution nine years ago. Radiographic evaluation demonstrated aseptic loosening of TKA components, with subsidence of the tibial component into varus malposition. A 73-year-old female patient was admitted to our Hospital because of an injury to her left knee resulting from a fall from a standing height that happened five days before the presentation. Primary TKA was performed 14 years ago in our Hospital. A trauma X-ray series of the injured knee revealed a Lewis type IIB periprosthetic fracture of the tibial plateau. In both patients, revision TKA was performed using a rotating hinge implant with augmentation of the tibial defect caused by loosening in the first case and fracture in the second case. Postoperative recovery was successful in both cases, with radiographic imaging showing adequate position of the implant at 2-year follow-up.

Conclusion: The use of rotating hinge knee prostheses in revision total knee arthroplasty demonstrates promising outcomes, particularly in cases involving significant bone loss and instability.

Keywords: revision total knee arthroplasty, rotating hinge knee, aseptic loosening, knee periprosthetic fracture

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UVOD

Broj totalnih artroplastika kolena (TKA) pokazuje trend rasta u ortopedskim bolnicama širom sveta. Očekuje se da će se u Sjedinjenim Američkim Državama broj pacijenata koji se podvrgavaju TKA povećati sedam puta u periodu od 2004. do 2030. godine [1]. Iako TKA ima odličnu dugoročnu stopu preživljavanja - neke studije pokazuju da ona iznosi 89–96% u intervalu od 15 godina - nije iznenađujuće što će, s obzirom na produženje životnog veka i starenje populacije sa sve većim brojem komorbiditeta, učestalost revizionih TKA takođe rasti [2,3]. Više studija je ispitivalo epidemiološke aspekte revizionih TKA i otkrilo da su najčešće indikacije aseptično labavljenje, periprotetska infekcija zgloba (PJI), nestabilnost, patelofemoralne komplikacije i periprotetske frakture kolena [4,5].

Pored PJI i nestabilnosti, aseptično labavljenje predstavlja jedan od najčešćih razloga za reviziju kolenskih proteza. Ono je multifaktorijalne etiologije, a pretpostavljeni faktori rizika koji imaju ključnu ulogu u patogenetskim mehanizmima labavljenja komponenti proteze uključuju neuspeh u fiksaciji cementa (posebno na interfejsu cement-kost), osteolizu usled reakcije histiocitnih ćelija na habanje polietilena, malpoziciju komponenti, upotrebu ograničenih dizajna proteza i neadekvatan napon mekih tkiva i ligamenata [6].

Za razliku od aseptičnog labavljenja, periprotetske frakture predstavljaju retku indikaciju za revizionu TKA. Njihova učestalost se kreće od 0,3% do 5,5%, pri čemu su frakture distalnog femura češće od fraktura proksimalne tibije [7]. Međutim, neke studije prikazuju jednaku učestalost fraktura i na femoralnoj i na tibijalnoj strani, sa stopama od 0,3% do 2,5% za femur i od 0,4% do 1,7% za tibiju [8]. Felix i saradnici razvili su najčešće korišćeni sistem klasifikacije periprotetskih fraktura proksimalne tibije, koji ima izuzetnu kliničku vrednost jer usmerava i olakšava izbor plana lečenja [9].

Revizionu TKA karakterišu veliki izazovi za ortopedске hirurge. Najvažnija pitanja koja treba rešiti tokom operacije uključuju poravnanje komponenti, nivo zglobne linije, neusaglašenost između ekstenzije i fleksije faze, kao i biomehaniku patelofemoralnog zgloba i aparata za ekstenziju. Obimni gubitak kosti i nestabilnost u frontalnoj i sagitalnoj ravni često zahtevaju upotrebu ograničenih, šarki dizajna implantata sa metalnim augmentima i stemovima koji se fiksiraju pod pritiskom ili cementiraju [10].

Ova serija slučajeva prikazuje dva primera u kojima je revizionu TKA bila indikovana zbog aseptičnog labavljenja i periprotetske frakture tibije, a u kojima je revizionu proceduru izvedena korišćenjem NexGen® Rotirajuće Šarke Kolena (Zimmer Biomet, Warsaw, Indiana, Sjedinjene Američke Države).

INTRODUCTION

The number of total knee arthroplasty (TKA) procedures shows a growing trend in orthopedic hospitals worldwide. It is expected that in the United States, the number of patients undergoing TKA will increase sevenfold from 2004 to 2030 [1]. Although TKA has a great to excellent long-term survival rate, with some studies demonstrating this rate to be 89–96% in 15-year interval, it is not surprising that, given the increased life expectancy and aging population with a more significant number of comorbidities, the frequency of revision TKA will also rise [2,3]. Several studies have examined the epidemiological aspects of revision TKA. They discovered that the most common indications are aseptic loosening, periprosthetic joint infection (PJI), instability, patellofemoral complications, and periprosthetic knee fractures [4,5].

Alongside PJI and instability, aseptic loosening is one of the most common reasons for revision of knee arthroplasties. It is multifactorial in origin, and presumed risk factors that have a crucial role in pathogenetic pathways of prosthesis component loosening include failure of cement fixation (at the cement-bone interface in particular), osteolysis due to the response of histiocytic cells to polyethylene wear, component malalignment, use of constrained prosthetic designs, and improper soft tissue and ligament tension [6].

Unlike aseptic loosening, periprosthetic fractures represent a rare indication for revision TKA. Their prevalence ranges from 0.3% to 5.5%, with distal femur fractures being more common than proximal tibia fractures [7]. However, some studies demonstrate an equal occurrence of fractures on the femoral and tibial sides, with rates ranging from 0.3% to 2.5% on the femoral side and from 0.4% to 1.7% on the tibial side, respectively [8]. Felix et al. developed the most frequently used classification system for proximal tibial periprosthetic fractures, which has excellent clinical value because it guides and facilitates the choice of treatment plan [9].

Revision TKA represents a great challenge for orthopedic surgeons. The most critical issues that should be addressed during surgery include component alignment, joint line level, extension-flexion gap mismatch, and the biomechanics of the patellofemoral joint and extensor apparatus. Extensive bone loss and instability in both the coronal and sagittal planes often necessitate the use of a constrained, hinged implant design with metal augments and press-fit or cemented stem extensions [10].

This case series demonstrates two cases in which revision TKA was indicated due to aseptic loosening and periprosthetic tibia fracture, in which the revision procedure was performed using NexGen® Rotating Hinge Knee (Zimmer Biomet, Warsaw, Indiana, United States).

PRIKAZI SLUČAJEVA

Slučaj 1

Pacijentkinja stara 60 godina javila se u našu ustanovu zbog bolova i nestabilnosti desnog kolena, praćenih smanjenim obimom pokreta i otežanim hoda. Primarna TKA urađena je u drugoj ustanovi pre devet godina zbog primarnog osteoartritisa kolena. Prvi simptomi su se pojavili tri godine pre dolaska, a značajno su se pogoršali tokom poslednjih nekoliko meseci, ozbiljno narušavajući sposobnost obavljanja svakodnevnih aktivnosti (ADL). Pacijentkinja nije imala značajnu medicinsku anamnezu povezanu sa trenutnim problemom kolena.

Tokom kliničkog pregleda uočili smo antalgijski i nestabilan obrazac hoda, karakterisan varusnim trzajem i deformitetom hiper-ekstenzije (recurvatum). Hodanje je bilo onemogućeno bez korišćenja pomoćnih sredstava (štake) u obe ruke. Pri inspekciji, dok je pacijentkinja bila udobno smeštena na pregledu, uočeno je blago oticanje desnog kolena, koje je bilo u varus položaju. Na prednjem delu desnog kolena nalazio se stari, zarastao hirurški ožiljak, bez znakova zapaljenja. Aktivni obim pokreta (ROM) iznosio je 0–90°, dok je pasivni ROM bio -10–100°, sa 10° hiperekstenzije. Prisustvo nestabilnosti kolena potvrđeno je varus stres testom, koji je pokazao značajno otvaranje sa lateralne strane. Vaskularni i neurološki status desne noge bio je očuvan. Na kraju fizičkog pregleda izmereni su klinički i funkcionalni skorovi Američkog društva za koleno (Knee Society Scores – KSS), koji su iznosili 35 i 27.

Radiološka procena obuhvatila je standardnu seriju rendgenskih snimaka desnog kolena (Slika 1). Ante-

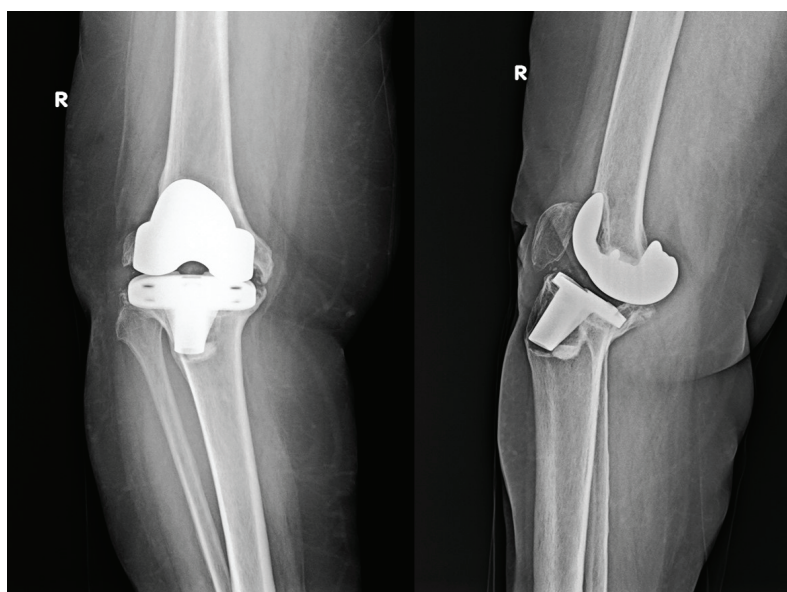
CASE REPORTS

Case 1

A 60-year-old female patient presented to our hospital with complaints of pain and instability of her right knee, accompanied by decreased range of motion and difficulty walking. Primary TKA was performed in another institution nine years ago because of primary knee osteoarthritis. The first symptoms appeared three years before presentation, and they worsened significantly throughout the last couple of months, interfering significantly with the performance of activities of daily living (ADL). The patient did not report any other notable medical history related to the current knee problem.

During the physical examination, we initially observed an antalgic and unstable gait pattern, characterized by varus thrust and recurvatum deformity. Ambulation was impossible without assistive devices (crutches) in both arms. Upon inspection, with the patient comfortably positioned on the examination bed, we found minor swelling in the right knee, which was in varus alignment. There was an old, healed surgical scar on the anterior aspect of the right knee, with no signs of inflammation. The active range of motion (ROM) was 0–90°, and the passive ROM was -10–100°, with 10° of hyperextension. The finding of knee instability was confirmed while performing a varus stress test, which demonstrated a significant opening on the lateral side. The vascular and neurologic status of the right leg was intact. We obtained clinical and functional American Knee Society Scores (KSS) at the end of the physical exam, which were 35 and 27, respectively.

The radiologic assessment included a standard X-ray series of the right knee (Figure 1). AP and lateral views



Slika 1. Preoperativni AP i profilni snimak desnog kolena pacijentkinje starosti 60 godina koji pokazuje aseptično razlabavljenje totalne endoproteze kolena, sa teškom malpozicijom tibijalne komponente u varusu i femoralne komponente u ekstenziju

Figure 1. Preoperative right knee AP and lateral view of 60-year old female patient suffering from aseptic loosening of total knee prosthesis, with severe malposition of tibial component into varus and femoral component into extension

roposteriorni (AP) i bočni prikazi pokazali su ozbiljno labavljenje komponenti, sa radiolucenim zonama širim od 5 mm oko i tibijalne i femoralne komponente. Tibijalna komponenta je potonula u varus položaj, a vrh tibijalnog nastavka gotovo da je probijao lateralni plato. Na bočnom snimku se uočavala femoralna komponenta u položaju ekstenzije i značajno povećanje zadnjeg nagiba tibije.

Uzimajući u obzir kliničke nalaze (teška, dvosmerna nestabilnost) i očekivani gubitak kosti vidljiv na radiografiji kolena, odlučili smo da izvedemo revizionu TKA sa implantatom u obliku rotirajuće šarke. Nakon razgovora sa pacijentkinjom o terapijskim opcijama, mogućim komplikacijama i postoperativnim funkcionalnim očekivanjima, dobijena je informisana saglasnost. Pacijentkinja je primljena u bolnicu dan pre planirane operacije. Profilaksa protiv tromboembolije (niskomolekularni heparin – LMWH) započeta je dan pre operacije i nastavljena tokom pet nedelja. Imajući u vidu višu učestalost periprotetskih infekcija nakon revizije TKA, antibiotska terapija (cefazolin) uvedena je preoperativno i nastavljena tokom pet dana posle operacije.

Nakon standardne preoperativne pripreme operativnog polja i u uslovima opšte anestezije, izveden je longitudinalni rez na prednjoj strani desnog kolena, prateći stari hirurški ožiljak. S obzirom na očekivano produženo trajanje operacije, odlučeno je da se revizionu TKA izvede bez naduvavanja pneumatske manžetne. Nakon disekcije mekih tkiva, urađena je standardna medijalna parapatelarna artrotomija i otvorena je zglobna šupljina. U početku su uklonjena fibrotična ožiljna tkiva i priraslice iz suprapatelarnog džepa, kao i iz medijalnih i lateralnih kanala. Zglobna tečnost i uzorci tkiva poslati su na mikrobiološku analizu za intraoperativnu (ekstemporalnu) biopsiju, kako bi se isključilo prisustvo patogenih bakterija.

Nakon oslobađanja mekih tkiva, Homan retraktori su postavljeni posteriorno, što je omogućilo luksaciju kolenske proteze. Zatim je započeto uklanjanje olabavljenih komponenti proteze. Polietilenski umetak uklonjen je pomoću specijalnog ekstraktora. Femoralna komponenta je razdvojena na spoju komponenta-cement upotrebom uskih osteotoma i recipročne testere, uz izuzetnu pažnju da se izbegne jatrogeno oštećenje kosti. Ekstrakcija femoralne komponente završena je korišćenjem tzv. „slap hammer” alata. Tibijalna komponenta je uklonjena na sličan način pomoću recipročne testere.

Nakon procene gubitka kosti i stabilnosti ligamentata, pristupilo se pripremi intramedularnog kanala tibije korišćenjem reamera sa postepenim povećanjem prečnika. Tibijalna površina je resecirana kako bi se izravnala i omogućilo postavljanje trabekularnog bloka pune veličine (10 mm) i augmenta polubloka (5 mm)

demonstrated severe component loosening, with more than 5 mm of radiolucent zones surrounding both the tibial and femoral components. The tibial component subsided into a varus position, with the tip of the tibial keel nearly protruding through the lateral plateau. The lateral view also showed a femoral component in the extended position and a significant increase in posterior tibial slope.

Given the clinical findings (severe, bidirectional instability) and the expected bone loss evident on knee radiographs, we decided to perform a revision TKA with a rotating hinge knee implant. We obtained informed consent after discussing treatment options, possible complications, and postoperative functional expectations with the patient. The patient was admitted to the Hospital one day before the planned surgery. Thromboembolic prophylactic therapy (low molecular weight heparin, LMWH) was started one day before the surgery and continued for five weeks. Given the higher incidence of periprosthetic joint infection after revision TKA, antibiotic treatment (cefazolin) was started preoperatively and continued for five days after surgery.

After standard preoperative preparation of the surgical field, under the conditions of general anesthesia, a longitudinal incision was made in the anterior aspect of the right knee following the old surgical scar. Given the expected prolonged surgical time, we decided to perform a revision TKA without inflating the tourniquet. After soft tissue dissection, standard medial parapatellar arthrotomy was done, and the joint space was revealed. Initially, we removed the fibrotic scar tissue and adhesions from the suprapatellar pouch and medial and lateral gutters. Joint aspiration fluid and tissue samples were sent to the microbiology department for extempore biopsy to check for the possible presence of pathogenic bacteria. After soft tissue release, Homan retractors were placed posteriorly, allowing for the luxation of the knee prosthesis. We then began by extracting the loosened prosthesis components. The polyethylene insert was removed using a special extractor. The femoral component was then detached at the component-cement interface using narrow osteotomes and a reciprocating saw, with extreme care being taken to avoid any iatrogenic bone loss. Extraction of the femoral component was completed with the use of a slap hammer. The tibial component was removed in a similar fashion using a reciprocating saw.

After assessing bone loss and ligamentous stability, we proceeded with preparing the medullary canal of the tibia using reamers of progressively increasing diameter. A tibial recut was made to flatten the surface of the tibial plateau and allow the accommodation of a trabecular whole block (size 10 mm) and a half block augment (size 5 mm), which was placed medially. After

koji je postavljen medijalno. Nakon izbora odgovarajuće veličine tibijalne platforme i određivanja njene pozicije, započeta je priprema distalnog femura. Intramedularni kanal femura reamiran je istom tehnikom kao kod tibije. Procena veličine i rotacije femoralne komponente izvršena je uzimajući u obzir mediolateralni prečnik izmeren između epikondila. Probna femoralna komponenta je postavljena i izvršeno je balansiranje fleksionog i ekstenzionog razmaka.

Zbog preoperativno prisutnog recurvatum deformiteta, jedan od imperativa bio je postavljanje femoralne komponente distalnije, što je zahtevalo upotrebu distalnih augmenata. Neusklađenost između fleksije i ekstenzije rešena je posteriornim augmentima na femuru. Pored pravilnog poravnanja i stabilnosti u ekstenziji i fleksiji, procenjen je i nivo zglobove linije korišćenjem dostupnih anatomske repera, kao što su medijalni i lateralni epikondil, kao i patela.

Nakon probnog postavljanja komponenti, verifikovani su kinematika kolena i stabilnost kroz puni obim pokreta. Potom je turniket naduvan, a koštane površine očišćene pulsirajućim ispiranjem. Cement je apliciran u intramedularne kanale tibije i femura, a konačne komponente su postavljene. Nakon očvršćavanja cementa, postavljen je završni polietilenski umetak i montiran je mehanizam šarke. Rana je potom temeljno isprana i zatvorena po anatomske slojevima.

Rehabilitacija je započeta prvog postoperativnog dana, u skladu sa protokolima bolnice. Rana mobilizacija uključivala je pasivne i aktivne vežbe obima pokreta radi poboljšanja fleksibilnosti i smanjenja ukočenosti zgloba. Puna težinska opterećenja bila su dozvoljena u skladu sa tolerancijom pacijenta, uz korišćenje pomoćnih sredstava poput štaka ili hodalice radi stabilnosti pri hodu. Postizanje adekvatnog obima fleksije kolena bilo je prioritet, što je podsticano korišćenjem uređaja za kontinuirani pasivni pokret (CPM), koji je bio podešen na unapred određenu brzinu i obim, uz postepeno prilagođavanje u skladu sa tolerancijom i napretkom pacijenta.

Postepeno su uključene vežbe za jačanje kvadricepsa, zadnje lože i okolne muskulature kako bi se podržala stabilnost i funkcija zgloba. Takođe, edukacija pacijenta je uključivala savete o svakodnevnim aktivnostima i strategijama za zaštitu zgloba radi optimizacije funkcionalnog oporavka. Rehabilitacioni plan bio je individualno prilagođen potrebama svakog pacijenta, uz blisko kliničko praćenje radi prepoznavanja eventualnih komplikacija i postizanja optimalnih rezultata.

Postoperativni tok bio je uredan, bez komplikacija, i pacijentkinja je otpuštena iz bolnice petog postoperativnog dana. Prva postoperativna kontrola zakazana je mesec dana nakon operacije, kada je pacijentkinja prikazala značajno poboljšan obrazac hoda i izraženo povećanje

selecting the appropriate size of the tibial platform and determining its position, we prepared the distal femur. We began by reaming the medullary canal, following the same procedure as for the tibia. We then assessed the size and rotation of the femoral component, taking into account the mediolateral diameter calculated from the trans-epicondylar distance. We then placed the trial femoral component and performed balancing of flexion and extension gaps.

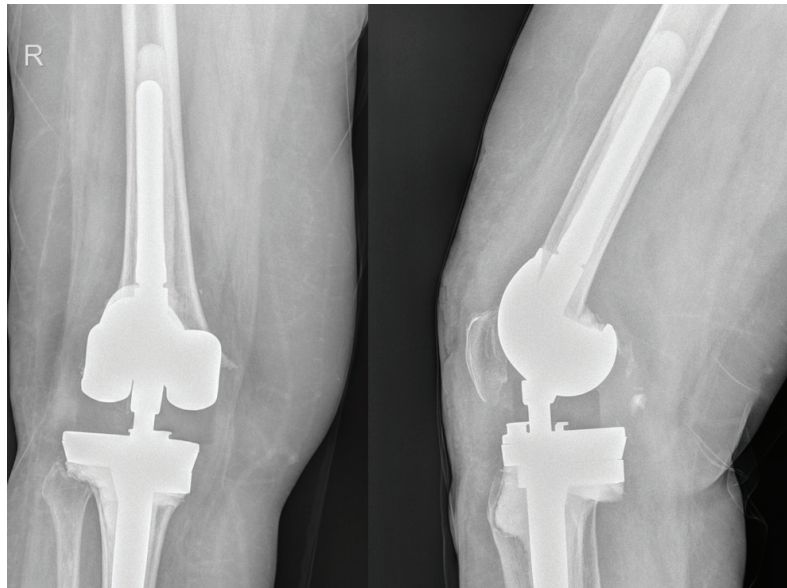
Given the preoperative recurvatum deformity, one of the imperatives was to put the femoral component more distally, which necessitated the use of distal augments. The resultant flexion-extension gap mismatch was solved with posterior femoral augments. Besides proper alignment and stability in extension and flexion, the joint line level was assessed using available anatomic landmarks, such as the medial and lateral epicondyles and the patella.

After trial reduction, knee kinematics and stability were verified through a full range of motion. The tourniquet was then inflated, and bone surfaces were cleaned with a pulsatile lavage system. Cement was applied into the medullary canals of the tibia and femur, and final components were placed. Once the cement was cured, the final polyethylene insert was inserted, and the hinge post mechanism was assembled. The wound was then thoroughly irrigated and sutured following the anatomic layers.

Rehabilitation began on the first postoperative day, following the hospital's protocols. Early mobilization included passive and active range-of-motion exercises to promote flexibility and reduce joint stiffness. Full weight-bearing was permitted as tolerated, with patients using assistive devices such as crutches or a walker to ensure stability during ambulation. Achieving an adequate range of knee flexion was a priority, reinforced through the use of a continuous passive motion (CPM) apparatus, typically set at a predetermined speed and range and adjusted gradually based on patient tolerance and progress.

Gradual progression of strengthening exercises targeting the quadriceps, hamstrings, and surrounding musculature was initiated to support joint stability and function. Additionally, patient education emphasized activities of daily living and joint protection strategies to optimize functional recovery. The rehabilitation plan was tailored to meet the individual needs of each patient, with close clinical monitoring to address any complications and facilitate optimal outcomes.

The postoperative course was uneventful, and the patient was discharged from the Hospital on the 5th postoperative day. The first postoperative control was scheduled one month after surgery, and the patient



Slika 2. Postoperativni AP i profilni snimak iste pacijentkinje učinjen na kontrolnom pregledu 2 godine nakon operacije, koji pokazuje urednu poziciju proteze, bez znakova razlabavljenja

Figure 2. Postoperative AP and lateral views of the same patient at 2-year follow-up, showing no signs of component malalignment or loosening

obima pokreta desnog kolena. Praćenje je nastavljeno dve godine, a pri poslednjoj kontroli pacijentkinja je u potpunosti povratila normalnu funkcionalnost bez ikakvih simptoma. Ovo poboljšanje je dodatno potvrđeno kliničkim i funkcionalnim KSS skorovima, koji su iznosili 88 i 95. Kontrolne radiografije su pokazale dobro postavljene komponente TKA bez znakova labavljenja (Slika 2).

Slučaj 2

Pacijentkinja stara 73 godine primljena je u našu bolnicu zbog povrede levog kolena nastale usled pada sa visine stajanja, koja se dogodila pet dana pre javljanja. Glavna tegoba bila je bol u levom kolenu prilikom pokušaja oslanjanja na nogu. Primarna TKA urađena je pre 14 godina u našoj ustanovi. Fokusiranim fizikalnim pregledom u urgentnoj jedinici utvrđeno je prisustvo izraženog otoka i deformiteta levog kolena, dok je pokretljivost kolena bila ograničena zbog bola. Na prednjoj strani levog kolena uočen je stari hirurški ožiljak. Nisu zapažene kožne promene niti poremećaji lokalnog vaskularnog i neurološkog statusa.

Urađena je trauma serija rendgenskih snimaka povređenog kolena. Prikazana je periprotetska fraktura tibijalne ploče, tip IIB, prema klasifikaciji koju su predložili Lewis i saradnici (fraktura koja zahvata celu proksimalnu tibiju uz labavljenje tibijalne komponente) (Slika 3). Tibijalna komponenta je propala u varus položaj, a njen vrh je probio kroz anterolateralnu korteksu proksimalne metafize tibije. Na bočnom snimku uočen je drastično povećan tibijalni nagib.

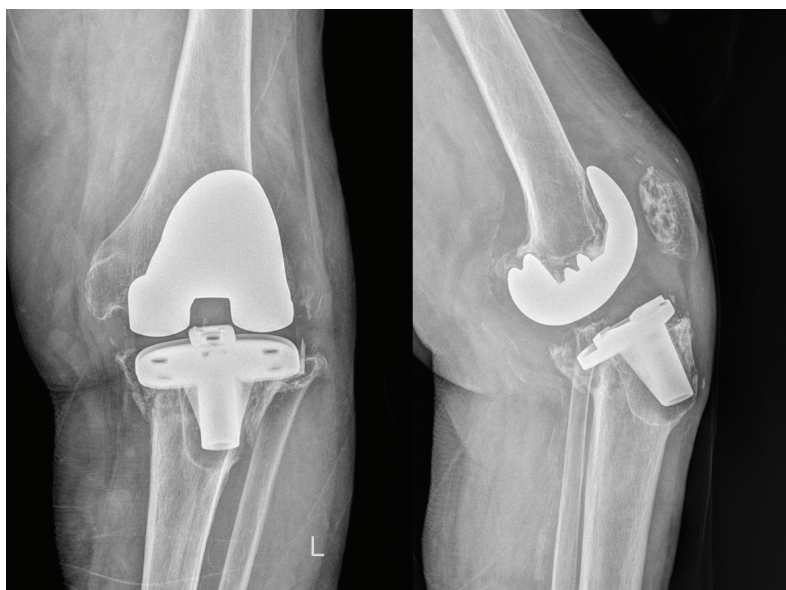
Zbog otkaza tibijalne komponente izazvanog periprotetskom frakturom, odlučeno je da se uradi revi-

presented with a significantly improved gait pattern and a notable increase in right knee range of motion. Follow-up continued for two years, and at the last visit, the patient returned entirely to normal functional status and was free of any symptoms. This improvement was further confirmed with clinical and functional KSS, which measured 88 and 95, respectively. Control radiographs confirmed well-positioned TKA components without signs of loosening (Figure 2).

Case 2

A 73-year-old female patient was admitted to our hospital because of an injury to her left knee that resulted from a fall from a standing height that happened five days before the presentation. Her chief complaint is pain in the left knee in an attempt to bear weight. Primary TKA was performed 14 years ago in our Hospital. A focused physical examination at the Emergency Unit revealed significant swelling and deformity of the left knee, with movement of the left knee inhibited by pain. An old surgical scar was inspected on the front aspect of the left knee. There were no skin lesions or disturbance of local vascular and neurologic status.

A trauma X-ray series of the injured knee was obtained. They demonstrated a periprosthetic fracture of the tibial plateau, type IIB, according to the classification system proposed by Lewis et al. (fracture spanning across the entire proximal tibia with tibial component loosening) (Figure 3). The tibial component subsided into a varus position, with its tip protruding through the anterolateral cortex of the proximal tibial metaphysis. The lateral view also demonstrated a drastically increased tibial slope.



Slika 3. Preoperativni AP i profilni snimak levog kolena pacijentkinje starosti 73 godine koji pokazuje periprotetski prelom proksimalne tibije nakon pada na ravnoj podlozi

Figure 3. Preoperative left knee AP and lateral view of 73-year old female patient who suffered from proximal tibia periprosthetic fracture following fall from standing height

ziona TKA uz primenu implantata sa rotirajućom šarkom (RHK). Nakon dobijanja informisanog pristanka pacijentkinje, sprovedena je preoperativna priprema. Primijenjen je isti protokol za tromboembolijsku i antibiotsku profilaksu, s obzirom na složenost operacije i visok rizik od komplikacija u ovoj starosnoj grupi.

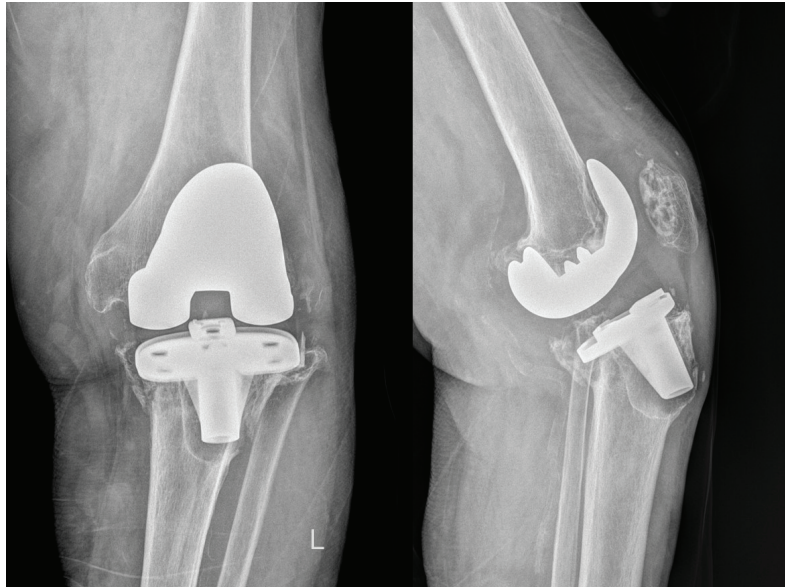
Hirurški zahvat izveden je u opštoj anesteziji. U dogovoru sa anesteziologom, odlučeno je da se koristi "Cell Saver" aparat za prikupljanje i obradu aspirirane krvi, koja se potom vraćala pacijentkinji, imajući u vidu očekivani gubitak krvi tokom intervencije. Hirurška tehnika se ni u jednom aspektu nije razlikovala od one primenjene u prvom slučaju. Posebna pažnja posvećena je ekstrakciji tibijalne komponente, kako bi se očuvalo što više kosti. Zbog obrasca preloma i lošeg kvaliteta kosti, bilo je neophodno resecirati deo proksimalne tibije kako bi se došlo do zdravog koštanog tkiva koje bi omogućilo pravilno postavljanje tibijalne komponente.

Radi rešavanja problema sa nivoom zglobove linije i očekivane labavosti u ekstenzionom i fleksionom razmaku, odlučeno je da se tibija augmentira trabekularnim blokom pune veličine od 10 mm. Takođe je bila neophodna i revizija femoralne komponente, kako bi se obezbedio prostor za veliki okvir potreban za smeštaj mehanizma šarke. Priprema femura zahtevala je upotrebu distalnih i posteriornih augmenata. Dugme patele je uklonjeno zbog znakova istrošenosti, a s obzirom na loš kvalitet preostale kosti, odlučeno je da se ne ugrađuje nova komponenta patele.

Primijenjen je identičan protokol rehabilitacije kao i u prethodnom slučaju, s tim što puna težinska opte-

Given the failure of the tibial component caused by a periprosthetic fracture, we decided to perform a revision TKA again using an RHK implant. We obtained informed consent and proceeded with the preoperative preparation. The same protocol for thromboembolic and antibiotic prophylactic therapy was followed, given the complexity of surgical treatment and the high risk of complications in this age group. The procedure was performed under general anesthesia. After consultation with the attending anesthesiologist, we decided to use a Cell Saver machine to collect and process the aspirated blood and then return it to the patient due to the expected blood loss during the surgery. The surgical technique did not differ in any aspect from the first case. Special care was taken during the extraction of the tibial component to preserve as much bone as possible. Given the fracture pattern and poor bone quality, we had to resect part of the proximal tibia to reach good-quality bone that would allow for proper seating of the tibial component. To resolve the problem with the joint line level and the expected loose extension and flexion gap, we again decided to augment the tibia with the 10 mm whole block trabecular augment. A revision of the femoral component was also required to accommodate the large box necessary to seat the hinge mechanism. Femoral preparation also necessitated the use of distal and posterior augments. The patellar button was removed due to evidence of wear, and we did not want to pursue implanting another button, given the poor quality of the remaining bone.

The identical rehabilitation protocol was followed in this case, except that full weight-bearing was not



Slika 4. Postoperativni AP i profilni snimak iste pacijentkinje učinjen na kontrolnom pregledu godine nakon operacije, koji pokazuje urednu poziciju proteze, bez znakova razlabavljenja

Figure 4. Postoperative AP and lateral views of the same patient at 2-year follow-up, showing no signs of component malalignment or loosening

rećenja nisu bila dozvoljena tokom prve tri postoperativne nedelje. Pacijentkinja je otpuštena iz bolnice sedmog postoperativnog dana i vraćena na redovnu kontrolu mesec dana nakon operacije, sa zadovoljavajućim rezultatima. Kontrolni rendgenski snimak levog kolena, urađen dve godine nakon operacije, pokazao je dobro postavljene komponente bez znakova otkaza implantata (Slika 4).

Informisani pristanak za objavljivanje ovih slučajeva dobijen je od pacijentkinja, u skladu sa etičkim standardima.

DISKUSIJA

Lečenje kompleksnih revizija TKA i dalje predstavlja veliki izazov u ortopedskoj hirurgiji, naročito kada se radi o slučajevima sa značajnim gubitkom kosti, ligamentarnom nestabilnošću ili prethodnim višestrukim operacijama. U takvim situacijama, tradicionalne proteze sa fiksnim ležištem ili polu-konzervativne proteze kolena možda neće obezbediti potrebnu funkcionalnu stabilnost i opseg pokreta. Ova serija slučajeva prikazuje primenu proteza sa rotirajućom šarkom kao održivo rešenje kod revizionih TKA intervencija kod pacijenata sa navedenim komplikacijama.

Proteze sa rotirajućom šarkom nude više prednosti u poređenju sa konvencionalnim dizajnima, prvenstveno zbog svoje urođene stabilnosti i prilagodljivosti kompromitovanim anatomskim uslovima. Ove proteze imaju mehanizam rotacije koji omogućava prošireni opseg pokreta, smanjuje mehanička uklještenja i poboljšava dinamiku fleksije i ekstenzije. Ovo može biti posebno korisno u revizionim slučajevima kod kojih je

allowed for the first three postoperative weeks. The patient was discharged from the Hospital after seven days and returned for regular control one month after the surgery with satisfactory results. The control X-ray of the left knee, taken 2 years after surgery, showed well-positioned components with no signs of implant failure (Figure 4). Informed consent was obtained from the patients for the publication of their cases, in accordance with ethical standards.

DISCUSSION

The management of complex revisions in TKA remains a formidable challenge in orthopedic surgery, particularly when addressing issues such as significant bone loss, ligamentous instability, or multiple prior surgeries. In these scenarios, traditional fixed-bearing or semi-constrained knee prostheses may not provide the necessary functional stability and range of motion. This case series highlights the application of rotating hinge knee prostheses as a viable solution in revision TKA for patients experiencing these complications.

Rotating hinge prostheses offer several advantages over conventional designs, primarily due to their inherent stability and adaptability to anatomical conditions that are compromised. The design features a rotating mechanism that allows for an enhanced range of motion, reduces impingement, and facilitates better flexion-extension dynamics. This can be particularly beneficial in revision cases where the integrity of the soft tissue envelope is compromised, allowing for more predictable outcomes and improved patient satisfaction [11,12]. Our findings are consistent with previous

narušena integritet mekih tkiva, jer omogućava predvidljivije ishode i povećano zadovoljstvo pacijenata [11,12]. Naši nalazi su u skladu sa prethodnom literaturom, koja takođe ukazuje na poboljšane funkcionalne rezultate i stabilnost implantata kod sličnih grupa pacijenata [13,14].

Naša serija slučajeva je pokazala zadovoljavajuće kliničke ishode, uključujući smanjenje bola i poboljšanje funkcionalnih rezultata, što se poklapa sa postojećom literaturom koja podržava primenu rotirajućih šarki u sličnim revizionim situacijama [15]. Posebno značajno jeste uključivanje procene pacijenata putem subjektivnih pokazatelja (PROMs), što je naglasilo važnost procene ne samo kliničkih parametara, već i percipiranog kvaliteta života nakon operacije. Upoređivanje naših rezultata sa prethodnim istraživanjima naglašava kliničku važnost rotirajućih šarki u postizanju balansa između stabilnosti i pokretljivosti u složenim revizionim slučajevima.

Međutim, upotreba rotirajućih šarki nije bez izazova. Potrebna je složenija hirurška tehnika, postoji povećan rizik od komplikacija kao što su infekcije i labavljenje komponenti, a neophodno je i pažljivo preoperativno planiranje i procena. Rizici uključuju mehanički otkaz (npr. dislokaciju šarke ili frakturu), aseptično labavljenje i infekciju – sve to može negativno uticati na ishod i zahtevati dodatne operacije. Strategije za smanjenje tih rizika uključuju pažljiv odabir kandidata, detaljnu procenu kvaliteta kostiju i interdisciplinarnu saradnju radi optimalnog perioperativnog vođenja [15]. Prepoznavanje ovih potencijalnih ograničenja u skladu je sa nalazima iz literature, koja ističe da dugoročna izdržljivost ovih proteza ostaje oblast za dalja istraživanja.

Na kraju, iako primena proteza sa rotirajućom šarkom u revizionoj TKA donosi specifične prednosti, ona zahteva sveobuhvatno razumevanje indikacija i kontraindikacija, kao i otvoren dijalog o očekivanjima pacijenata. Ova serija slučajeva podseća na važnost individualizovanog pristupa hirurškom lečenju u kontekstu revizije artroplastike, pomerajući granice onoga što je moguće postići u rekonstrukciji složenih povreda kolena. Potrebne su daljnje studije velikih razmera sa dužim praćenjem kako bi se ovi nalazi potvrdili i ustanovili dugoročni rezultati ovog pristupa [16].

ZAKLJUČAK

Upotreba proteza kolena sa rotirajućom šarkom u revizionim totalnim artroplastikama kolena pokazuje ohrabrujuće rezultate, naročito u slučajevima sa značajnim gubitkom kosti i nestabilnošću. Ova serija slučajeva naglašava značaj individualizovanog hirurškog planiranja i detaljne preoperativne procene u posti-

literature, which demonstrates improved functional outcomes and implant stability in similar patient populations [13,14].

Our case series demonstrated satisfactory clinical outcomes, including pain reduction and improved functional scores, aligning with the existing literature advocating for the use of rotating hinge prostheses in similar revision scenarios [15]. Notably, the incorporation of patient-reported outcome measures (PROMs) underscored the importance of assessing not only clinical metrics but also the perceived quality of life among patients post-operatively. Comparing our results with prior research emphasizes the clinical significance of rotating hinge designs in achieving a balance between stability and mobility in complex revision scenarios.

However, the use of rotating hinge knee prostheses is not without its challenges. The increased complexity of surgical technique, potential for higher rates of complications such as infections and component loosening, and the need for meticulous preoperative planning and assessment must be emphasized. Risks include mechanical failure (e.g., hinge dislocation or fracture), aseptic loosening, and infection – all of which can adversely impact outcomes and may require further surgical intervention. Strategies to mitigate these risks include the careful selection of candidates, thorough evaluation of host bone quality, and interdisciplinary collaboration for optimal perioperative management [15]. Recognizing these potential limitations align with findings from the literature, which note that long-term durability remains an area for ongoing investigation.

Ultimately, while the adoption of rotating hinge knee prostheses in revision TKA presents unique advantages, it necessitates a comprehensive understanding of the specific indications and contraindications, as well as an open dialogue about patient expectations. This case series serves as a reminder of the importance of tailored surgical solutions in the context of revision arthroplasty, pushing forward the boundaries of what can be achieved in complex knee reconstructions. Further large-scale studies with extended follow-up are warranted to validate these findings and establish long-term outcomes associated with this approach [16].

CONCLUSION

The use of rotating hinge knee prostheses in revision total knee arthroplasty demonstrates promising outcomes, particularly in cases involving significant bone loss and instability. This case series underscores the importance of individualized surgical planning and thor-

zanju optimalnih rezultata kod pacijenata. Potrebna su dodatna istraživanja kako bi se ovi nalazi potvrdili i ustanovila dugoročna efikasnost ove metode.

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ough preoperative assessment in achieving optimal patient outcomes. Further research is necessary to validate these findings and establish long-term efficacy.

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COLLES FRACTURE – HISTORICAL RETROSPECTION

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SAŽETAK

U kraćem istorijskom osvrtu, autor hronološkim redom iznosi najznačajnije ličnosti u hirurgiji koje su proučavale “prelom radijusa na tipičnom mestu” (lat. *fractura radii loco typico*). Navode se i eponimi koji se uobičajeno koriste u svakodnevnoj praksi, uz ličnosti za koje se vezuju.

Ključne reči: fraktura, istorija

ABSTRACT

The author presents a short historical retrospection of the most important surgeons who studied Colles fracture, in chronological order. The author also describes the eponyms most commonly used in daily surgical practice, along with the historical figures that they are linked to.

Keywords: fracture, history

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Prelom distalnog okrajka radijusa, u praksi često nazivan *fractura radii in loco typico* – mada je ispravniji termin *fractura radii in zona typica* – jedan je od najčešćih preloma sa kojima se hirurzi ili traumatolozi susreću u svom svakodnevnom radu. Njegova učestalost dovoljan je izazov za jedan kraći istorijski pregled, koji omogućava bolje razumevanje ove frakture [1,2].

Mada pisanih dokumenata nema, jedan istraživač je na ekshumiranoj egipatskoj mumiji otkrio frakturu sa intaktnom imobilizacijom daščicama, kakvu i danas susrećemo širom sveta u nedostatku modernih oblika imobilizacije [3].

Od vremena Hipokrata pa do početka XIX veka, prelomi distalnog okrajka radijusa su često pogrešno tumačeni kao iščašenje ručnog zgloba. U Hipokratovim radovima (V vek pre nove ere) nalazimo samo nejasne opise preloma podlaktice, mada je poznato da je on razlikovao luksacije zglobova i prelome nekih kostiju [4,5].

Ambroaz Pare (*Ambroise Paré*, 1510–1590) je prvi spomenuo mogućnost preloma radijusa i ulne [6].

Žan Luj Peti (*Jean Louis Petit*, 1674–1750) opisuje pomak fragmenata ustranu i po dužini, smatrajući da je za to odgovoran *musculus pronator teres* [7].

Do kraja XVIII veka, ovaj tip preloma nije bio dovoljno poznat, pa su se do tog vremena mešali pojmovi uganuće, iščašenje i prelom.

Klod Puto (*Claude Pouteau*, 1725–1775) bio je briljantni šef hirurgije u bolnici *Hôtel-Dieu de Paris* [1,7]. U delu štampanom posthumno (1783. godine) u Parizu, Puto je opisao prelome distalnog okrajka radijusa [8]. Opazio je da u ovom prelomu često nedostaju tipični klinički znaci – patološka pomicnost i krepitacije, pa se zbog toga mogu zameniti distorzija i luksacija, te diastaza radijusa i ulne. Puto opisuje prelome distalnog okrajka radijusa sa dorzalnim izbočenjem ili pomakom distalnog fragmenta. Prepoznavao je nekoliko vrsta frakture, čak i impaktirane, kod kojih nije mogao da izazove krepitacije [8]. Navedeni rad Kloda Putoa nije bio zapažen izvan Francuske tako da za njega nije znao Ejbram Koles kada je, 1814. godine, u Edinburgu publikovao svoj rad: „O prelomu distalnog okrajka radijusa“ [9].

Ejbram Koles (*Abraham Colles*, 1773–1843) bio je znameniti irski hirurzi i profesor anatomije na Irskom kraljevskom koledžu hirurgije (engl. *Royal College of Surgeons in Ireland*) [9–13]. Jasno i kratko je opisao najčešće konstatovanu frakturu distalnog okrajka radijusa. Ono što pomalo iznenađuje je da, mada odličan anatom i crtač, Koles ovaj svoj rad nije propratio ilustracijama i analizom ozleđivanja. Možda je to dovelo do toga da je Koles ovu frakturu locirao nešto proksimalnije [6,13–16]. Prema njegovom shvatanju prelom se nalazi otprilike inč i po (oko 4 cm) udaljen od radiokarpalnog zgloba, sa deformitetom zglobne površine, tako

Fracture of the distal end of the radius, in clinical practice commonly referred to as *fractura radii in loco typico* – although the more correct term is *fractura radii in zona typica* – is one of the most frequent fractures encountered by surgeons or traumatologists in their daily work. Its high incidence presents a sufficient reason for a brief historical overview, enabling a better understanding of this fracture [1,2].

Although there are no written records, a researcher discovered a fracture with intact immobilization with wooden splints on an exhumed Egyptian mummy, similar to the type of immobilization that can still be found worldwide in the absence of modern forms of immobilization [3].

From the time of Hippocrates until the beginning of the 19th century, fractures of the distal end of the radius were often mistakenly interpreted as dislocations of the wrist joint. In Hippocrates' writings (5th century BCE), only vague descriptions of forearm fractures can be found, although it is known that he distinguished between joint dislocations and fractures of certain bones [4,5].

Ambroise Paré (1510–1590) was the first author to mention the possibility of fracture of the radius and ulna [6].

Jean Louis Petit (1674–1750) described the displacement of fragments laterally and along the length of the bone, attributing this to the action of the *pronator teres* muscle [7].

This type of fracture was not well understood until the end of the 18th century, and the terms sprain, dislocation, and fracture were often confused.

Claude Pouteau (1725–1775) was the brilliant chief surgeon of the *Hôtel-Dieu de Paris* [1,7]. In an article published posthumously in 1783, in Paris, Pouteau described fractures of the distal end of the radius [8]. He observed that in this type of fracture, the typical clinical signs – abnormal mobility and crepitus – are often absent, which can lead to sprains, dislocations, or diastasis of the radius and ulna being confused with one another. Pouteau described fractures of the distal end of the radius with dorsal protrusion or displacement of the distal fragment. He recognized several types of fractures, including impacted ones, wherein crepitus could not be elicited [8]. Pouteau's article went largely unnoticed outside of France, and as a result, Abraham Colles was unaware of it when he published his paper *On the fracture of the carpal extremity of the radius*, in Edinburgh, in 1814 [9].

Abraham Colles (1773–1843) was a renowned Irish surgeon and Professor of anatomy at the Royal College of Surgeons in Ireland [9–13]. He described clearly and concisely the most commonly observed fracture of the distal end of the radius. What is somewhat surprising is that,

da odnos pri inspekciji podseća na luksaciju. Glavica ulne prominira prema napred i ka unutra. Edem u zoni loma nastaje zbog krvarenja među tetivama fleksora podlaktice. To je njegovo objašnjenje zašto pacijent ima bolove prilikom pronacije, supinacije i provokacije fleksije. Nema krepitacije, kao ni patološke mobilnosti. Ukoliko se pacijent povuče za šaku, nastali deformitet se ispravlja, ali odmah nakon otpuštanja ekstremiteta, deformitet se ponovo manifestuje. Značajno je da je Koles opisao pomak uzdužne osovine ruke u radijalnu stranu. I ovaj rad je objavljen u lokalnom medicinskom časopisu, pa je ostao nezapažen [9].

Baron Gijom Dipitren (*Gulliam Dupuytren*, 1777–1835) je još studentima ukazivao na ovaj prelom radijusa na svojim predavanjima. On kaže, u jednom svom radu, objavljenom posthumno, 1847. godine, „da je uočio činjenicu da su mnogi pogrešno dijagnostikovali prelome distalnog okrajka radijusa kao luksacije ručnog zgloba“ [18,19]. Nadalje, on ističe da je fraktura karpalnog kraja radijusa česta, i da je uvek u tom prelomu video pretpostavljenu dislokaciju ručnog zgloba, mada se nije radilo o iščašenju [20].

Žan Gaspar Blez Guaran (*Jean-Gaspard Blaise Goyrand*, 1803–1886) je bio izvanredan hirurg u Eksu (nedaleko Marselja) [1]. Razlikovao je epifizeolize i prelome distalnog okrajka radijusa od radio-karpalnih iščašenja. Zapazio je prominiranje distalnog kraja ulne udružene sa avulzijom stiloidnog nastavka ulne. Uočio je i to da je, kod najvećeg broja fraktura, distalni fragment pomeren dorzalno, mada u nekim slučajevima opisuje i pomeranje ulomaka prema dlanu. Oba tipa ovih preloma ilustrovao je u svojim radovima 1832. godine, odnosno 1836. godine [21,22].

Ogist Nelaton (*Auguste Nelaton*, 1807–1873) je proširio anatomske studije preloma opisujući različite varijacije ozleda i stepene kominucije. Intenzivno je eksperimentisao sa mehanizmima povređivanja na kadaverima. Podlaktice umrlih dezartikulisao je u laktu i uklanjao olekranon. Sa fiksiranom šakom – u dorzalnoj ili volarnoj fleksiji, i vertikalno uspravljenom podlakticom – lomio je čekićem gornji kraj podlaktice. Tako nastale prelome radijusa je disecirao i upoređivao sa mehanizmom povrede. Nelaton upozorava na značaj malih kostiju u području korena šake, pošto se u času pada čovek po pravilu dočekuje na ispruženu ruku u dorzalnoj fleksiji šake. Pri tom, udarac primaju na sebe karpalne kosti, te se čunkasta kost utiskuje u distalni kraj radijusa. Iz ovoga je vidljivo da je Nelaton pristalica Dipitrenove teorije udara i protivudara (fr. *coup et contrecoup*) [23,24].

Alfred Arman Lui Mari Velpo (*Alfred-Armand-Louis-Marie Velpeau*, 1795–1866) je posebno zanimljiva ličnost u istoriji medicine. On je eklatantan primer za to kako čovek neumornim radom i snagom volje može

despite being an excellent anatomist and illustrator, Colles did not accompany this publication with illustrations or an analysis of the injury mechanism. This may have led him to define the location of the fracture slightly more proximally than it actually occurs [6,13–16]. According to his understanding, the fracture is situated approximately an inch and a half (around 4 cm) from the radiocarpal joint, with a deformity of the articular surface, which makes it appear, on inspection, as a dislocation. The head of the ulna protrudes forward and inward. Swelling at the fracture site arises due to bleeding between the forearm flexor tendons. This, he explained, is why the patient experiences pain during pronation, supination, and elicited flexion. There is no crepitus nor pathological mobility. If the patient's hand is pulled, the deformity is corrected; however, once the limb is released, the deformity reappears. Notably, Colles described a shift of the longitudinal axis of the hand toward the radial side. This article was also published in a local medical journal and thus remained largely unnoticed [9].

Baron Guillaume Dupuytren (1777–1835) had already been pointing out this type of radial fracture to his students during his lectures. In one of his studies, published posthumously in 1847, he stated that “he had observed many cases of mistakenly diagnosed fractures of the distal end of the radius as dislocations of the wrist joint” [18,19]. Furthermore, he emphasized that fractures of the carpal end of the radius were common and that he always observed what appeared to be a dislocation of the wrist in such fractures. However, it was not actually a dislocation [20].

Jean-Gaspard Blaise Goyrand (1803–1886) was an exceptional surgeon from Aix (near Marseille) [1]. He made a distinction between epiphysiolysis and fractures of the distal end of the radius, on the one hand, and radiocarpal dislocations, on the other. He noted the prominence of the distal end of the ulna, often accompanied by an avulsion of the ulnar styloid process. He also observed that in the majority of fractures, the distal fragment was displaced dorsally, although in some cases he described displacement of the fragments toward the palm. He illustrated both types of these fractures in his works published in 1832 and 1836 [21,22].

Auguste Nélaton (1807–1873) expanded anatomical studies of fractures by describing various injury patterns and degrees of comminution. He conducted extensive experiments regarding injury mechanisms using cadavers. He disarticulated the forearms of the deceased at the elbow and removed the olecranon. With the hand fixed, in either dorsal or volar flexion, and the forearm positioned vertically, he struck the upper part of the forearm with a hammer to induce frac-

da napreduje od neukog pastira do jednog od najvećih autoriteta operativne hirurgije. Bio je manuelno spretni operater, vešt govornik, pronicljiv dijagnostičar, te marljivi stručan pisac. Krasile su ga savršena jasnoća i preciznost izražavanja. Prvi je koji je deformitet koji se javlja u prelomu distalnog okrajka radijusa nazvao *talon de fourchette*, što su anglosaksonski autori, 1859. godine, preveli kao deformitet u obliku srebrne viljuške (engl. *silver fork deformity*) [1,11,25,26].

Godine 1838, Džon Rija Barton (*John Rhea Barton*, 1794–1871) je opisao dislokacionu frakturu radio-karpalnog zgloba, koja je kasnije eponimski povezana sa njim [1,13,27,28]. Barton opisuje dva tipa preloma: prvi, sa dorzalnim pomakom fragmenata, i drugi, ređi tip, sa palmarnim pomakom. Kao i Robert Viljem Smit, devet godina kasnije, Barton je kao dorzalni pomak verovatno opisao Kolesovu frakturu. Opazio je da se prelom obično završava nepovoljno po bolesnika. Barton jasno opisuje subluksaciju ručnog zgloba kao posledicu preloma koji zahvata artikulacionu površinu karpalnog kraja radijusa i naglašava da su – pri ovom nesrećnom padu – često slomljeni radijus i ulna, ali da zglob nije luksiran [27,28].

U svojoj „Studiji o prelomima u blizini zglobova i nekim oblicima traumatskih i kongenitalnih luksacija“, Robert Viljem Smit (*Robert William Smith*, 1807–1873) je, 1847. godine, objavio poglavlje o prelomima kostiju podlaktice u blizini ručnog zgloba [30]. Ono sadrži: anatomske opis Kolesove frakture, opis separacije distalne epifize radijusa, kao i opis preloma distalnog okrajka radijusa sa pomakom donjeg ulomka prema napred i sa dorzalnom angulacijom – Smitov prelom. Kao i Guaran, i Smit je analizirao postmortalne patoanatomske supstrate sraslih preloma, s tim što im se opisi odnose na klinička stanja i kliničku sliku, što svakako doprinosi nejasnoći pojma opisanog kao dorzalna prominencija distalnog okrajka radijusa. Smit to i ističe kad kaže da ne može sa sigurnošću da govori o anatomskom svojstvu preloma jer nije imao prilike da analizira sveži prelom već, postmortalno, skelet podlaktice nakon već sraslog preloma koji je pacijent tokom svog života nekada pretrpeo. On opisuje palmarni pomak distalnog ulomka radijusa i dislokaciju donjeg radio-ulnarnog zgloba. Moguće je da je prelom koji opisuje Smit ono što je danas poznato kao Bartonov prelom, ali je sam eponim – već poodavno povezan za Smitom – poznat i kao obrnuti Kolesov prelom uzrokovan padom na dorzum flektirane šake [30,31].

Narednih nekoliko decenija napori istraživača bili su usmereni na anatomske sekcije i eksperimente na leševima, u pokušajima da se razjasne tipovi preloma i njihov odnos sa mehanizmima povrede. Tako, M. Didej (*M. Diday*) uočava neke zakonitosti u frakturnoj pukotini. On smatra da je lom posledica rezultante dveju sila koje bi se mogle matematički izračunati [32].

He then dissected these resulting radial fractures and compared them to the injury mechanisms. Nélaton emphasized the importance of the small bones in the wrist region, noting that during a fall, a person typically lands on an outstretched hand in dorsiflexion. In such cases, the carpal bones absorb the impact, and the scaphoid is driven into the distal end of the radius. From this, it is clear that Nélaton supported Dupuytren's theory of impact and counter-impact (Fr. *coup et contrecoup*) [23,24].

Alfred-Armand-Louis-Marie Velpeau (1795–1866) is a particularly fascinating figure in the history of medicine. He is a striking example of how a person, through tireless work and great willpower, can rise from an uneducated shepherd to one of the greatest authorities in operative surgery. He was a manually skillful surgeon, an eloquent speaker, a perceptive diagnostician, and a diligent and knowledgeable writer, known for his perfect clarity and precision of expression. He was the first to describe the deformity that appears in fractures of the distal end of the radius as *talon de fourchette*, a term that English-speaking authors referred to, in 1859, as the *silver fork deformity* [1,11,25,26].

In 1838, John Rhea Barton (1794–1871) described a dislocation fracture of the radiocarpal joint, which was later associated with him through an eponym [1,13,27,28]. Barton described two types of fractures: the first with dorsal displacement of the fragments, and the second, a rarer type, with palmar displacement. Like Robert William Smith, nine years later, Barton most likely described a Colles fracture as one with dorsal displacement. He observed that the fracture usually ended unfavorably for the patient. Barton clearly described subluxation of the wrist joint as a consequence of a fracture involving the articular surface of the carpal end of the radius and emphasized that in such unfortunate falls, the radius and ulna are often fractured. However, the joint itself is not dislocated [27,28].

In his *Treatise on Fractures in the Vicinity of Joints, and on Certain Forms of Accidental and Congenital Dislocations*, Robert William Smith (1807–1873) published, in 1847, a chapter on the fractures of the bones of the forearm, in proximity to the wrist joint [30]. It includes an anatomical description of Colles fracture, a description of distal radial epiphyseal separation, as well as a description of the fracture of the distal end of the radius with palmar displacement of the distal fragment and dorsal angulation – now known as a Smith fracture. Like Goyrand, Smith analyzed postmortem pathological specimens of healed fractures. However, their descriptions relate to clinical conditions and presentations, definitely contributing to the ambiguity of the term – dorsal prominence of the distal radius.

Tek otkrićem iks zraka Vilhelma Konrada Rendgena počinje egzaktno razjašnjavanje patoanatomskog supstrata preloma distalnog okrajka radijusa [33].

U oktobru 1897. godine, organizovan je sastanak lekara Nemačke poliklinike u Njujorku. Tada je Karl Bek (*Carl Beck*, 1865–1911), američki hirur, obavestio skup o tome da je počeo da koristi rendgenske zrake tri meseca nakon Rendgenovog objavljenog otkrića, 1896. godine, te da je do tada analizirao 44 bolesnika sa Kolesovim prelomom. Pri tome je zaključio: „Što se mene tiče moram da zapazim da niko pre mene nije to opisao, tako da nisam video primer u kome je dijagnoza potvrđena pre rendgenskog snimka – jer, svi autori opisuju postojanje deformiteta, otoka i bolne osetljivosti u tom predelu“ [34].

Drugi entuzijasta koji je koristio rendgenske zrake je bio Frederik Koton (*Frederick Cotton*) iz Bostona. On je objavio sličan rad o 140 bolesnika sa prelomima distalnog okrajka radijusa, te opisao eksperimentalne i anatomske korelacije koje je uočio na rendgenskim snimcima [35–37].

U prvom kvartalu prošlog veka (1900–1925), za vreme nagle ekspanzije automobilizma, u literaturi se pojavio termin šoferska fraktura, koju je opisao Emil Kude (*Emile Coude*). Naime, prilikom mehaničkog paljenja automobila ručnim pokretačem (kurblo), vozači su često povređivali ruku. U anglosaksonskoj literaturi, ekvivalentno značenje imao je pojam *backfire fracture*, što je, 1926. godine, razjasnio Edvards (*H. C. Edwards*) [1,38].

Nadalje su se problematikom preloma distalnog okrajka radijusa zanimali, između ostalih: Desto (*Destot*), Pilčer (*Pilcher*), Majer (*Mayer*), Morton (*Morton*), Klajnsmit (*Kleinschmidt*), Olerud (*Olerud*), Lidstrom (*Lidström*), Ehalt (*Ehalt*), Frikman (*Frykman*), de Bron (*de Bruijn*), Hančević i mnogi drugi. Svi oni uočavaju veliku šarolikost preloma distalnog okrajka radijusa kao i varijante u pomaku fragmenta, pa misao Spida (*K. Speed*) kako nema dve jednake Kolesove frakture – izražena još davne 1935. godine – najbolje ukazuje na svu komplikovanost preloma distalnog okrajka radijusa, kojeg u svakodnevnoj praksi najčešće nazivamo *fractura radii in loco typico* [7,39].

Zaključujući ovaj kratki istorijski pregled poimanja frakture radijusa u tipičnoj zoni, treba uvažiti činjenicu da su se do danas u literaturi održali samo eponimi koji jasno definišu tipove preloma, i to:

1. Kolesov prelom (u anglosaksonskoj literaturi), odnosno Puto-Kolesov prelom (u francuskoj literaturi)
2. Bartonov – volarni i dorzalni prelom
3. Smitov ili inverzni (obrnuti) Kolesov prelom [1,40,41].

Sukob interesa: Nije prijavljen.

Smith himself acknowledged this, stating that he could not speak with certainty about the anatomical nature of the fracture because he did not have the opportunity to examine a fresh fracture, only the skeletal forearm of a patient who had suffered the injury in his lifetime and whose fracture had already healed by the time of analysis. He described palmar displacement of the distal fragment of the radius and dislocation of the distal radioulnar joint. The fracture Smith described may correspond to what is known today as a Barton fracture, but the eponym – long since associated with Smith – also refers to what is called a *reverse Colles fracture*, caused by a fall onto the dorsum of the flexed hand [30,31].

In the ensuing decades, researchers focused their efforts on anatomical dissections and experiments on cadavers in attempts to clarify the types of fractures and their relationship to injury mechanisms. Thus, M. Diday observed certain patterns in fracture lines. He believed a fracture to be the consequence of the resultant force of two separate forces, which can be mathematically calculated [32].

It was only with the discovery of X-rays, by Wilhelm Conrad Röntgen, that the precise elucidation of the pathoanatomical substrate of distal radius fractures began [33].

In October 1897, a meeting of doctors from the German Polyclinic in New York was organized. At that time, Carl Beck (1865–1911), an American surgeon, reported that he had begun using X-rays three months after Röntgen's discovery was published in 1896, and that by the time of the meeting, he had analyzed 44 patients with Colles' fracture. He concluded: "As far as I am concerned, I must note that no one before me had described this, so I had not seen a case in which the diagnosis was confirmed before the X-ray image – because all authors describe the presence of deformity, swelling, and tenderness in that region" [34].

Another enthusiast who used X-rays was Frederick Cotton from Boston. He published a similar study on 140 patients with fractures of the distal end of the radius and also described experimental and anatomical correlations he observed on the X-ray images [35–37].

In the first quarter of the last century (1900–1925), during the rapid expansion of motor vehicle use, the term *chauffeur fracture* appeared in the literature, described by Emile Coude. Namely, while manually starting a car with a hand crank, drivers often injured their hands. In literature published in the English language, the equivalent term was *backfire fracture*, more precisely described by H. C. Edwards in 1926 [1,38].

The issue of distal radius fractures was further addressed by a number of researchers, including Destot,

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Concluding this brief historical overview of the understanding of radial fractures in the typical zone, it is important to acknowledge the fact that, to this day, only those eponyms that clearly define fracture types have remained in the literature, namely:

1. Colles fracture (in the literature published in English), or Pouteau-Colles fracture (in French literature)
2. Barton fracture – volar type and dorsal type
3. Smith fracture or the reverse (inverted) Colles fracture [1,40,41].

Conflict of interest: None declared.

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COVER PAGE (first page) should include the title of the paper, without acronyms, a suggested short title of the paper, the full names of the authors (without titles) indexed using numbers, the official name of the institutions where the authors work, place and country (in the order corresponding to the indexed numbers of the authors). At the bottom of the page, provide the name, contact address, phone number, fax number and email address of the corresponding author. The cover page should be in Serbian and English language (second page).

ABSTRACT should be up to 250 words, including acronyms (third page). For original papers, preliminary and short communications, meta-analyses and review papers, the abstract should have the following structure: Introduction, Aim, Methods, Results, Conclusion. Each of these segments should be written as a separate paragraph. For case report, the summary should have the following sections: Introduction, Case Report, Conclusion; each part should be written as a separate paragraph. For other types of papers, the abstract does not have a special structure. List three to six key words or phrases below the abstract. Words from the

ba da se ponavljaju reči iz naslova, a ključne reči treba da budu relevantne i opisne. U izboru ključnih reči koristiti *Medical Subject Headings* – MeSH (<http://www.nlm.nih.gov/mesh>). Sažetak treba da bude napisan na srpskom i engleskom jeziku.

Na **četvrtoj strani** treba da se nalazi prevod teksta koji je na trećoj strani (sažetak). Ova strana mora da ima identičnu strukturu trećoj strani. Od pete strane broji se broj strana predviđen za odgovarajuću strukturu rada.

STRUKTURA RADA. Svi podnaslovi se pišu velikim masnim slovima (**bold**). Originalni rad, meta-analiza, prethodno i kratko saopštenje obavezno treba da imaju sledeće podnaslove: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Metode rada, Rezultati, Diskusija (koncizna, jasna, predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi), Zaključak (mora proisteći isključivo iz rezultata istraživanja rada, Spisak skraćenica (ukoliko su korišćene u tekstu), Zahvalnica, Literatura (navodi se arapskim brojevima redosledom kojim je u tekstu navedena u uglastim zagradama, vidi dalje). Struktura rada kod pregleda literature sastoji se od Uvoda, Većeg broja podnaslova, Zaključka, Literature. Autori preglednog rada treba da navedu bar tri rada (kao autori ili koautori) publikovanih u časopisima s recenzijom. Struktura rada kod prikaza jednog ili više slučajeva čine: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Prikaz bolesnika, Diskusija, Literatura. Ne treba koristiti imena bolesnika, inicijale, niti brojeve istorija bolesti, naročito u ilustracijama. Prikazi slučajeva ne smeju imati više od pet autora.

STATISTIČKE METODE, PRIKAZ I INTERPRETACIJA REZULTATA

Ukoliko je moguće, sve numeričke vrednosti zaokružiti na jedno decimalno mesto. Ne duplirati prikaz rezultata u tabelama i grafikonima. Za prikaz rezultata u tabelama i tekstu preporuka je da se: numerički podaci sa normalnom raspodelom i bez ekstremnih vrednosti prikazuju kao aritmetička sredina $\pm$ standardna devijacija; numerički podaci čija raspodela odstupa od normalnosti ili kada postoje ekstremne vrednosti, i ordinalni podaci prikazuju kao medijana i opseg (minimalna – maksimalna vrednost); nominalni podaci i ordinalni podaci sa malim brojem kategorija prikazuju kao n (%).

Prilikom opisa primenjenih statističkih metoda, prikaza i interpretacije rezultata u radu pridržavati se *SAMPL Guidelines* (Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines*. *Int J Nurs Stud* 2015;52(1):5-9.). Primenjene statističke metode treba opisati dovoljno detaljno da ih čitalac može ponoviti na svojim podacima. Navesti korišćeni statistički test i nivo značajnosti. Saopštiti tačnu *p*-vrednost na 3 decimalna mesta.

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DECIMALNI BROJEVI. U tekstu rada na engleskom jeziku, u tabelama, na grafikonima i drugim prilogima decimalne brojeve pisati sa tačkom (npr. 12.5 ± 3.8), a u tekstu na srpskom jeziku sa zareзом (npr. $12,5 \pm 3,8$). Kad god je to moguće, broj zaokružiti na jednu decimalu.

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title should not be repeated, and the key words should be relevant and descriptive. The Medical Subject Headings – MeSH thesaurus (<http://www.nlm.nih.gov/mesh>) should be used for selecting the key word. The abstract should be submitted in both Serbian and English language.

The **fourth page** should contain the translation of the text from the third page (abstract). This page must have the identical structure as the third page.

The number of pages provided for the appropriate structure of the paper is counted from the fifth page.

STRUCTURE OF THE PAPER. Capital bold letters should be used for all subheadings. Original papers, meta-analyses, preliminary and short communications must have the following subheadings: Introduction (the objective of the paper should be stated in the last paragraph of the Introduction), Methodologies, Results, Discussion (concise and clear, it represents the interpretation and comparison of study results with relevant studies published in domestic and international literature), Conclusion (it must derived solely from the results of the research), List of acronyms (if used in the text), Acknowledgment, and Literature (listed using Arabic numerals, in the order in which they appear in the text, in square brackets, see below). The structure of literature review papers should be: Introduction, a number of subheadings, Conclusion, and Literature. The authors of the reviews should list at least three papers (as authors or co-authors) published in peer-reviewed journals. The structure of the paper presenting one or more cases should consists of: Introduction (the objective of the paper should be given as the last paragraph of the Introduction), Case Report, Discussion, and Literature. Patient names, initials, and medical history numbers should not be used, especially in illustrations. Case reviews should not have more than five authors.

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If possible, all numbers should be rounded to one decimal place. The display of results in tables and graphs should not be repeated. When presenting results in tables and text, it is recommended that numerical data with normal distribution and without extreme values be presented as arithmetic mean $\pm$ standard deviation; that numerical data whose distribution deviates from normal distribution or when there are extreme values, and ordinal data, be presented as the median and range (minimum–maximum value); that nominal data and ordinal data with a small number of categories be displayed as n (%).

When describing the applied statistical methods, presentation and interpretation of results in the paper, follow the *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.). The applied statistical methods should be described in sufficient detail so that the reader may repeat them using own data. Indicate the statistical test used and the level of significance. Report the correct *p*-value to the third decimal place.

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ACRONYMS should be used only when necessary, i.e. for very long names of chemical compounds and names that are already commonly used as acronyms (standard acronyms, such as DNA, AIDS, HIV). For each acronym, the full term should be given at the first appearance in the text, unless it is a standard unit of measure. Acronym should not be used in the title. Avoid using acronyms in the abstract, but if necessary, explain each acronym at the first appearance in the text.

DECIMAL NUMBERS. In the English text of the paper, in tables, graphs and other appendices decimal numbers are written with a point (e.g. 12.5 ± 3.8), and in the text in Serbian with a comma (e.g. $12,5 \pm 3,8$). Whenever possible, round the number to one decimal place.

(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).

PRILOZI su tabele, slike (fotografije, crteži, sheme, grafikoni), do šest po radu. Svaki prilog se dostavlja kao poseban dokument, obeležen na isti način kao u tekstu. Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje

TABELE. Svaka tabela treba da bude sama po sebi lako razumljiva. Naslov treba otkucati iznad tabele, a objašnjenja ispod nje. Tabele se označavaju arapskim brojevima prema redosledu navođenja u tekstu. Tabele crtati isključivo u programu *Word*, kroz meni *Table–Insert–Table*, uz definisanje tačnog broja kolona i redova koji će činiti mrežu tabele. Desnim klikom na mišu – pomoću opcija *Merge Cells* i *Split Cells* – spajati, odnosno deliti ćelije. Kucati fontom *Times New Roman*, veličinom slova 12 pt, s jednostrukim proredom i bez uvlačenja teksta. Korišćene skraćenice u tabeli treba objasniti u legendi ispod tabele. Ukoliko je rukopis na srpskom jeziku, priložiti nazive tabela i legendu na oba jezika. Takođe, u jednu tabelu, u okviru iste ćelije, uneti i tekst na srpskom i tekst na engleskom jeziku (nikako ne praviti dve tabele na dva jezika!).

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ali još nisu objavljeni, treba označiti sa *in press* i priložiti dokaz o prihvatanju rada za objavljivanje.

Podaci o korišćenju literaturi u tekstu označavaju se arapskim brojevima u uglastim zagrada – npr. [1,2], i to redosledom kojim se pojavljuju u tekstu. Reference se citiraju prema **Vankuverskom stilu** (uniformisanim zahtevima za rukopise koji se predaju biomedicinskim časopisima), koji je uspostavio Međunarodni komitet urednika medicinskih časopisa (<http://www.icmje.org>), čiji format koriste U.S. National Library of Medicine i baze naučnih publikacija. Primeri navođenja publikacija (članaka, knjiga i drugih monografija, elektronskog, neobjavljenog i drugog objavljenog materijala) mogu se pronaći na internet-stranici http://www.nlm.nih.gov/bsd/uniform_requirements.html. Prilikom navođenja literature veoma je važno pridržavati se pomenutog standarda, jer je to jedan od najbitnijih faktora za indeksiranje prilikom klasifikacije naučnih časopisa. Podaci sa interneta citiraju se uz navođenje datuma pristupa tim podacima.

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Original papers must account for at least 80% of the total number of references, i.e. the number of cited books, book chapters, and reviews must be less than 20%. Citing abstracts is not permitted. If it is important to comment on results that have been published only in the form of an abstract, it is necessary to cite this in the text of the paper. References to articles that have been accepted for publication but have not yet been published should be marked "in press" and proof of acceptance of the paper for publication should be attached.

Information about the literature used in the paper is indicated in the text by Arabic numerals in square brackets, e.g. [1,2], in the order in which they appear in the text. References are cited according to the **Vancouver style** (Uniform Requirements for Manuscripts Submitted to Biomedical Journals), established by the International Committee of Medical Journal Editors (<http://www.icmje.org>), whose format is used by the U.S. National Library of Medicine and scientific publication databases. Examples of citations of publications (articles, books and other monographs, electronic, unpublished and other published material) are available at http://www.nlm.nih.gov/bsd/uniform_requirements.html. When citing literature, it is very important to abide by the mentioned standard, because it is one of the most important indexing factors when classifying scientific journals. Online data is cited with the date of access to that data.

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U postupku prijave neophodno je da se naglasi kojoj kategoriji rad pripada: uvodnik, stručni rad, originalni rad, prethodna ili kratka saopštenja, pregledni članak, prikaz slučaja, prikaz serije slučajeva, članak iz istorije medicine i drugo.

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- 3) a declaration on absence of conflict of interest.

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