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EDITORIJAL



„Koreni učenja su gorki, ali su plodovi slatki.“

Aristotel

I tako, u praskozorje nastupajuće 2026. godine smogosmo snage i znanja da se, po ko zna koji put, otrgnemo od teške svakodnevice i učmalosti i da se radovima koji su pred vama još više približimo naučnoj istini. Baviti se danas naukom, sakupljati informacije, obrađivati ih i publikovati nije nimalo lak zadatak. Pa ipak, ima i takvih. I dok god je tako nada postoji. Nismo se predali. Težak je put i zadatak ali su i plodovi rada slatki i dugo traju. U ovom broju „Srpskog medicinskog časopisa Lekarske komore“ svi publikovani radovi imaju svoju specifičnost i bave se problematikom iz različitih grana medicine. Prikazujemo vam ih redom.

Rad autorke Margo Tonelije bavi se uticajem klimatskih promena na čovekovo zdravlje sa posebnim osvrtom na rad epidemiologa i probleme prilikom sakupljanja validnih informacija, kao i značajem zdravstvenih informacionih sistema u prikupljanju podataka.

Milivojević i saradnici u svom radu ističu karakteristike i razlike između primarnog i sekundarnog membranoznog glomerulonefritisa, kao i patohistološke specifičnosti ovih entiteta.

Tema osteoporoze je uvek interesantna. U svom preglednom radu Tomašević-Todorović i saradnici ukazuju na pojavu osteoporoze tokom lečenja autoimunskih bolesti. Naime, i pored napretka u prevenciji, dijagnostici i lečenju, učestalost osteoporoze kod obolelih od autoimunskih bolesti je i dalje visoka i zahteva adekvatan pristup i lečenje.

Pojava hipertenzije kod onkoloških bolesnika je sve češća. Petrović i saradnici, u svom radu, upravo rasvetljavaju ovaj neželjeni klinički entitet koji se razvija tokom lečenja različitih malignih bolesti. Uzimajući u obzir činjenicu da broj obolelih od malignih bolesti raste u svetu i da je onkohipertenzija sve češća u ovoj populaciji bolesnika, autori ističu značaj ranog prepoznavanja i lečenja ove komplikacije.

U eri produženog životnog veka i sve većeg broja obolelih od srčane insuficijencije, Stoičkov i saradnici ističu značaj kontrolisanog fizičkog treninga kod ove populacije bolesnika. Adekvatna fizička aktivnost predstavlja još jednu od mera koja povećava mišićnu masu i izdržljivost i na taj način, indirektnim putem, utiče na smanjenje intenziteta simptoma u srčanoj insuficijenciji, naravno, uz popravljanje kvaliteta života.

Sve češća primena oralnih antikoagulanasa povezana je i sa sve češćim i pomalo neobičnim neželjenim događajima. U svom radu, Hadži-Nikolić ističe pojavu intersticijske bolesti pluća i buloznog pemfigoida, koji su povezani sa primenom ovih lekova.

EDITORIAL

"The roots of education are bitter, but the fruit is sweet."

Aristotle

And thus, on the eve of the approaching year 2026, we have once again found the strength and knowledge to break away from the weight of arduous everyday reality and intellectual inertia, and through the articles presented here, draw even closer to scientific truth. Engaging in science today – gathering information, processing it, and publishing results – is by no means an easy task. Yet there are still those who persevere. As long as this remains so, hope endures. We have not surrendered. The road and the task are demanding, but the fruits of such labor are lasting and deeply rewarding. In this issue of the Serbian Journal of the Medical Chamber, each article is distinctive and addresses topics from diverse branches of medicine. We hereby present them to you, individually.

The article by Margo Tonnelier examines the impact of climate change on human health, with particular emphasis on the role of epidemiologists and the challenges involved in collecting valid data, as well as the importance of health information systems in data collection.

In their article, Milivojević et al. highlight the characteristics and differences between primary and secondary membranous glomerulonephritis, as well as the pathohistological specificities of these entities.

The topic of osteoporosis is always of interest. In their review article, Tomašević-Todorović et al. draw attention to the occurrence of osteoporosis during the treatment of autoimmune diseases. Despite advances in prevention, diagnosis, and therapy, the prevalence of osteoporosis among patients with autoimmune diseases remains high and requires an appropriate clinical approach and treatment.

Hypertension in oncology patients is becoming increasingly common. In their article, Petrović et al. shed light on this adverse clinical entity that develops during the treatment of various malignant diseases. Given the global increase in the number of patients with malignancies and the rising prevalence of oncohypertension in this population, the authors emphasize the importance of early recognition and management of this complication.

In an era of increased life expectancy and a growing number of patients with heart failure, Stoičkov et al. emphasize the importance of supervised physical training in this patient population. Adequate physical activity represents an additional measure that increases muscle mass and endurance, and thus indirectly contributes to a reduction in the intensity of heart failure symptoms, while indeed improving quality of life.

Iako predstavlja retko stanje, hifema u neonatalnom dobu zahteva brzu i preciznu oftalmološku procenu. Etiologija ove pojave je različita. Autori, Vasović i saradnici ističu da pojava obostrane hifeme u ovom periodu zahteva ozbiljan klinički pregled radi isključivanja drugih bolesti.

U prikazu slučaja, Aleksić opisuje pacijenta koji istovremeno boluje od jedne mijeloproliferativne i jedne limfoproliferativne bolesti. Udruženost dve hematološke maligne bolesti nije tako retka pojava u kliničkoj praksi i zahteva uvek poseban klinički tretman koji zavisi od prirode i agresivnosti bolesti, komorbiditeta, starosti, i drugih faktora.

Na koncu, još jedan apel da izdržimo i istrajemo na ovom putu nauke i struke i to baš onako kako dolikuje trenutku o kome živimo.

Živeli, i srećna vam Nova 2026. godina!

S poštovanjem,
Prof. dr Predrag Đurđević
Pomoćnik glavnog i odgovornog urednika

The increasing use of oral anticoagulants is also associated with more frequent and somewhat unusual adverse events. The article written by Hadži-Nikolić draws attention to the occurrence of interstitial lung disease and bullous pemphigoid, both linked to the use of these medications.

Although a rare condition, neonatal hyphema requires prompt and precise ophthalmological evaluation. Its etiology is diverse. Vasović et al. emphasize that the occurrence of bilateral hyphema during this period necessitates a thorough clinical examination to rule out other diseases.

The case report presented by Aleksić describes a patient simultaneously suffering from a myeloproliferative disorder and a lymphoproliferative disorder. The concomitance of two hematological malignancies is not uncommon in clinical practice. It always requires a specialized clinical approach, depending on the nature and aggressiveness of the diseases, comorbidities, age, and other factors.

In conclusion, once again, an appeal to everyone to persevere and remain steadfast on the path of science and professionalism, in a manner befitting the times we are living in.

Happy New Year 2026!

Sincerely,
Prof. Predrag Đurđević, MD, PhD
Assistant-Editor-in-Chief

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TOPLITNI TALASI I ZDRAVSTVENA ZAŠTITA: POVEZIVANJE PODATAKA I PRAKSE

RAD PO POZIVU

INVITED PAPER

HEATWAVES AND HEALTHCARE: BRIDGING DATA AND FRONTLINE PRACTICE

Margo Tonnelier¹

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SAŽETAK

Toplotni talasi i srodni ekološki događaji otkrivaju ključne ranjivosti preopterećenih zdravstvenih sistema i ukazuju na potrebu integrisanja kliničkih i ekoloških podataka radi podrške blagovremenim javnozdravstvenim intervencijama. Međutim, učešće zdravstvenih radnika u prikupljanju podataka često je ograničeno velikim obimom posla i fragmentiranom, restriktivnom strukturom zdravstvenih informacionih sistema. Ovaj rad razmatra strategije za jačanje veze između produkcije javnozdravstvenih podataka i kliničkog odgovora u cilju smanjenja zdravstvenih rizika povezanih sa toplotnim talasima. Programi direktnog uključivanja epidemiologa u rad na terenu unapređuju razumevanje operativnih ograničenja i podstiču osmišljavanje pragmatičnih intervencija. Međutim, nedostatak standardizovanih zdravstvenih mera i široko prihvaćenog konceptualnog okvira ograničava delotvornost epidemiologije toplotnih talasa. Smatramo da takvi pristupi mogu sistematski poboljšati validnost, primenljivost i pravičnost javnozdravstvenih istraživanja i prakse, te predlažemo okvir za standardizovano zdravstveno praćenje tokom toplotnih talasa.

Ključne reči: toplotni talasi, epidemiologija, javno zdravlje, zdravstveni rizici

ABSTRACT

Heatwaves and related environmental events expose critical vulnerabilities in overburdened health systems and underscore the need to integrate clinical and environmental data to support timely public health interventions. However, healthcare professionals' participation in data collection is often limited by high workloads and fragmented, restrictive health information system architectures. This article explores strategies to strengthen the link between public health data production and clinical response to mitigate the health risks associated with heatwave events. Field immersion programs for epidemiologists enhance understanding of operational constraints and promote the design of pragmatic interventions. However, the lack of standardized health measures and a widely accepted conceptual framework limits the effectiveness of heatwave epidemiology. We argue that such approaches can systematically improve the validity, applicability, and equity of public health research and practice, and propose a framework for standardized health monitoring during heatwaves.

Keywords: heatwaves, epidemiology, public health, health risks

RESUME

Les vagues de chaleur et les événements environnementaux associés révèlent les vulnérabilités des systèmes de santé surchargés et soulignent la nécessité d'intégrer les données cliniques et environnementales afin de soutenir la mise en place d'actions rapides de santé publique. Cependant, la participation des professionnels de santé à la collecte de données reste limitée en raison de charges de travail élevées et d'une architecture des systèmes d'information sanitaire souvent fragmentée et restrictive. Dans cet article, nous examinons les moyens de renforcer le lien entre la production de données de santé publique et la réponse clinique afin de mieux atténuer les risques sanitaires liés aux vagues de chaleur. Les programmes d'immersion sur le terrain pour les épidémiologistes permettent de mieux comprendre les contraintes opérationnelles et de concevoir des interventions plus pragmatiques. Toutefois, l'absence de mesures sanitaires standardisées et d'un cadre conceptuel largement accepté continue de limiter l'efficacité de l'épidémiologie des vagues de chaleur.

Mots clés: Chaleur extrême, Épidémiologie, Santé Publique, Évaluation de l'impact sur la santé

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KONTEKST KOJI SE BRZO MENJA

Zdravstveni sistemi širom sveta suočavaju se sa sve ozbiljnijim izazovima. Klimatske promene, vidljive kroz sve učestalije i intenzivnije toplotne talase [1], dodatno se pogoršavaju ponovnom pojavom epidemija [2], starenjem stanovništva [3] i strukturnim ekonomskim pritiscima [4]. Zajedno, ovi faktori opterećuju zdravstvene ustanove, produbljuju postojeće nejednakosti u domenu zdravstvene zaštite, te povećavaju zahteve u odnosu na zdravstvene radnike u pogledu njihovog kapaciteta da adekvatno odgovore na potrebe [5].

Toplotni talasi postaju sve veći prioritet u domenu javnog zdravlja [6,7]. Oni su direktno povezani sa pojavom toplotnih udara i poremećajima sna, a indirektno sa lošijim mentalnim zdravljem, porastom međuljudskog nasilja i pogoršanjima postojećih kardiovaskularnih i respiratornih bolesti [8–11]. Iako je svest o toplotnim talasima kao javnozdravstvenom problemu porasla, njihovi posredni zdravstveni efekti i dalje su nedovoljno istraženi. Šumski i periurbani požari, koji su sve češći tokom ekstremnih vrućina, ne samo da izazivaju povrede i raseljavanje stanovništva [12], već i povećavaju izloženost finim česticama, čime doprinose respiratornom morbiditetu, uz fiziološke posledice toplotnog stresa [12]. Ove krize prožimaju više disciplina i zahtevaju trajnu integraciju ekoloških i zdravstvenih podataka – uključujući temperaturu, kvalitet vazduha, zdravstvene pokazatelje pacijenata i parametre primarne zdravstvene zaštite – kako bi se omogućili efikasni odgovori. Zdravstveni radnici su zaduženi za sprovođenje preventivnih i edukativnih mera radi umanjenja zdravstvenih posledica, uz istovremeno pružanje zdravstvene nege pogođenim pacijentima. Istovremeno, ovi rizici zahtevaju ozbiljne populacione analize i sisteme ranog upozoravanja u cilju praćenja trendova, informisanja javnosti i zdravstvenih radnika, kao i usmeravanja javne politike i raspodele resursa. Ovaj rad ima za cilj da razmotri strategije za jačanje veze između produkcije javnozdravstvenih podataka i kliničkog odgovora na potrebe, kako bi se smanjili zdravstveni rizici povezani sa pojavom toplotnih talasa.

ZAJEDNIČKI SISTEM PRAĆENJA ZA EPIDEMIOLOGE I ZDRAVSTVENE RADNIKE

Zdravstveni radnici predstavljaju prvu liniju nadzora nad funkcionisanjem zdravstvenog sistema. Oni uočavaju, u *realnom vremenu*, porast broja pacijenata primljenih zbog toplotnog udara, dehidracije, kardio-respiratornih komplikacija ili akutnih psihijatrijskih stanja. Požari povezani sa toplotnim talasima dodatno otežavaju situaciju, dovodeći do opekotina, trauma tokom evakuacije i pogoršanja respiratornih oboljenja usled izloženosti finim česticama.

A RAPIDLY CHANGING CONTEXT

Healthcare systems worldwide face increasing challenges. Climate changes, reflected in the rising frequency and severity of heatwaves [1], is further compounded by the resurgence of epidemics [2], population ageing [3], and structural economic pressures [4]. Together, these factors strain healthcare organizations, exacerbate health inequalities, and heighten demands on professionals' capacity to respond [5].

Heatwaves are gradually becoming a public health priority [6,7]. They are directly linked to heatstroke and disrupted sleep patterns and indirectly associated with poorer mental health, increased interpersonal violence, and exacerbations of underlying cardiovascular and respiratory diseases [8–11]. Although awareness of heatwaves as a public health issue has grown, their indirect health consequences remain insufficiently explored. Forest and peri-urban fires, which occur more frequently during periods of extreme heat, not only cause injuries and population displacement [12] but also increase exposure to fine particulate matter, contributing to respiratory morbidity, in addition to the physiological effects of heat stress [12]. These crises span multiple disciplines and require sustained integration of environmental and health data – including temperature, air quality, patient health indicators, and frontline care metrics – to inform effective responses. Healthcare professionals are responsible for implementing preventive and educational measures to reduce health impacts while also providing care to affected patients. At the same time, these hazards demand robust population-level analyses and early warning systems to monitor trends, alert the public and healthcare workers, and guide public policy and resource allocation. This article aims to explore strategies to strengthen the connection between public health data production and clinical response in order to mitigate the health risks associated with heatwave events.

A SHARED MONITORING SYSTEM BETWEEN EPIDEMIOLOGISTS AND HEALTHCARE PROFESSIONALS

Healthcare professionals act as the frontline monitors of their health systems. They observe, in *real time*, increases in admissions for heatstroke, dehydration, cardiorespiratory complications, or psychiatric crises. Heatwave-associated fires further exacerbate the situation, causing burns, trauma from evacuations, and respiratory exacerbations from fine particulate exposure.

Epidemiologists operate both retrospectively and in near-real time: they analyze historical data to better understand determinants of population health and

Epidemiolozi deluju i retrospektivno i u približno realnom vremenu: analiziraju istorijske podatke kako bi bolje razumeli determinante zdravlja populacije, te koriste najnovije i prognozirane podatke za izdavanje upozorenja – iako se u slučaju toplotnih talasa ta upozorenja najčešće izdaju prvenstveno putem meteoroloških službi i službi civilne zaštite. Oni funkcionišu kao svojevrsni „zdravstveni radar“, prikupljajući, analizirajući i distribuirajući informacije koje potom usmeravaju dalje delovanje. Identifikovanjem najugroženijih grupa – stara lica, deca, ljudi sa višestrukim komorbiditetima, radnici na otvorenom i socijalno ugrožene populacije – epidemiolozi omogućavaju adekvatnu prevenciju i ciljano delovanje [13].

Leto 2003. godine jasna je ilustracija ranjivosti Zapadne Evrope kada su u pitanju toplotni talasi i njihov uticaj na zdravlje stanovništva. U Francuskoj su Emon i Žugla procenili višak smrtnosti upoređujući zabeležene smrti tokom prvih 20 dana avgusta 2003. godine sa prosečnim brojem smrti u istom periodu između 2000. i 2002. godine [14]. U Portugalu je između prvog i 31. avgusta 2003. godine zabeleženo 2.099 smrtnih slučajeva više nego što se očekivalo prema referentnom periodu 1997-2001 [15]. Potonji toplotni talasi nastavili su da izazivaju značajan višak mortaliteta širom regiona. Na primer, toplotni talas u Češkoj, 2015. godine, izazvao je veći porast viška smrtnosti nego takav događaj iz 1994. godine (265% naspram 240% iznad osnovne vrednosti) [16]. U Belgiji je Sciensano zabeležio 4,3% viška smrtnosti u svim starosnim grupama tokom leta 2020. godine, kada je Kraljevski meteorološki institut Belgije registrovao dva toplotna talasa (23-26. jun i 2-17. avgust 2020). Drugi toplotni talas poklopio se sa najvećim brojem dnevnih smrtnih slučajeva tokom letnjeg perioda u Belgiji, sa 492 smrti zabeležene 13. avgusta 2020. godine [17].

Kada se sistematski organizuju i distribuiraju, gore navedena zapažanja služe kao pokazatelji za unapređivanje epidemioloških modela i identifikovanje ranih znakova upozorenja. Primer Belgije, gde se podaci o smrtnosti u realnom vremenu integrišu sa klimatskim indikatorima, ilustruje dodatnu vrednost ovakve međusektorske saradnje. Ipak, u mnogim evropskim zemljama ovakvo praćenje i dalje nije prisutno.

RAZLIKE U STEPENU RAZVIJENOSTI RAZLIČITIH EPIDEMIOLOŠKIH DISCIPLINA

Epidemiologija infektivnih bolesti oslanja se na dobro uspostavljene sisteme nadzora sa rutinskim protokolima koji omogućavaju brzo izdavanje upozorenja o izbijanju epidemija [18]. Nasuprot tome, ekološka epidemiologija – koja se bavi toplotnim talasima, šumskim požarima i zagađenjem vazduha – i dalje je manje sistematizovana i često je ograničena fragmentisanim podacima i sporijim izveštavanjem [19]. Iako inovacije kao

use recent and forecast data to raise alerts – although for heatwaves, such alerts are often issued primarily by meteorological services and civil protection agencies. They act as a health radar, collecting, analyzing, and disseminating information that guides responses. By identifying the most vulnerable groups – the elderly, children, people with multiple morbidities, outdoor workers, and socially disadvantaged populations – they enable tailored prevention and targeted action [13].

The summer of 2003 remains emblematic of Western Europe's vulnerability to heatwaves and their impact on population health. In France, Hémon and Jougla estimated excess mortality by comparing observed deaths during the first 20 days of August 2003 with the 2000-2002 average number of deaths for the same period [14]. In Portugal, between August 1 and August 31, 2003, there were 2,099 excess deaths relative to the expected baseline for the 1997-2001 period [15]. Subsequent heatwaves continued to cause substantial mortality across the region. For example, the 2015 heatwave in the Czech Republic caused a larger increase in excess mortality than the 1994 event (265% versus 240% above the baseline) [16]. In Belgium, Sciensano recorded a 4.3% excess mortality rate across all ages during the summer of 2020, when the Royal Meteorological Institute of Belgium reported two heatwaves (23-26 June and 2-17 August, 2020). The second heatwave coincided with the highest number of daily deaths for the summer period in Belgium, with 492 deaths on 13 August 2020 [17].

When systematically structured and shared, the above-described observations serve as indicators for refining epidemiological models and identifying early warning signs. Belgium's integration of real-time mortality data with climate indicators demonstrates the added value of such cross-sector collaboration. However, such monitoring remains absent in many European countries.

DIFFERENT LEVELS OF DEVELOPMENT ACROSS EPIDEMIOLOGICAL DISCIPLINES

Infectious disease epidemiology relies on well-established surveillance systems, with routine protocols that enable rapid outbreak alerts [18]. By contrast, environmental epidemiology – focused on heatwaves, wildfires, and air pollution – remains less systematized and is often constrained by fragmented data and slower reporting [19]. Although advances such as high-resolution sensors and exposome approaches are expanding the capacities of environmental epidemiologists, the field continues to face challenges in translating environmental data into timely public health alerts [19,20]. Ethical frameworks are only re-

što su senzori visoke rezolucije i pristupi zasnovani na ekspozomu, proširuju kapacitete ekološke epidemiologije, ova oblast je i dalje suočena sa izazovima prilikom pretvaranja ekoloških podataka u blagovremena javnozdravstvena upozorenja [19,20]. Etički okviri se tek poslednjih godina konsoliduju kako bi se obezbedila temeljitost studija koje ispituju zdravstvene efekte višestrukih, interagujućih ili vremenski promenljivih izlaganja datim elementima [21]. Zbog toga je od ključnog značaja jačanje saradnje sa meteorološkim službama i hitnim službama u bolnicama, jer upozorenja na toplotne talase i šumske požare često potiču od službi izvan zdravstvenog sektora i moraju biti integrisana kako bi efikasno usmeravala javnozdravstvene intervencije.

SPREMNOST ZDRAVSTVENIH RADNIKA DA UČESTVOJU U PRIKUPLJANJU EPIDEMIOLOŠKIH PODATAKA

Glavna prepreka učešću zdravstvenih radnika u prikupljanju epidemioloških podataka jeste obim njihovog posla, naročito tokom vanrednih situacija. Oni već rade pod hroničnim pritiskom – nedostatak osoblja, starenje populacije pacijenata i rast broja prijema [22,23]. Ekstremni vremenski događaji povezani sa klimatskim promenama dodatno povećavaju ovaj teret [5]. Na primer, poklapanje toplotnih talasa sa pandemijom KOVID-19 oboljenja 2020. godine, jasno je pokazalo koliko je veliko opterećenje i iscrpljenost zdravstvenih radnika [24,25]. Takvo preopterećenje ne samo da ograničava učešće u inicijativama nadzora i razmene podataka, već služi i kao upozorenje: potrebno je preispitati raspodelu kompetencija i organizaciju zdravstvene zaštite [26].

Još jedna prepreka leži u fragmentiranoj i često restriktivnoj strukturi zdravstvenih informacionih sistema. Preterana ograničenja pristupu podacima i slaba interoperabilnost mogu značajno da ometaju epidemiološka istraživanja [27]. Kada su skupovi podataka nepotpuni ili ograničeni na određene dijagnostičke kategorije, mnoge potencijalne studije postaju neizvodljive. Nedostatak standardizacije podataka, logističke poteškoće u prikupljanju i upravljanju podacima, kao i izostanak sistematskih lokalnih etičkih odbora dodatno otežavaju sprovođenje studija koje bi bile uporedive i ponovljive [28].

Upotreba standardizovane sestrinske terminologije i dosledno vođenje dokumentacije pokazalo se kao način da se poboljša kvalitet nege, obezbedi kontinuitet i poveća upotrebljivost prikupljenih podataka [29]. Ipak, ovi alati se i dalje nedovoljno koriste, često zbog preopterećenosti poslom i ograničene digitalne pismenosti. Uključivanje ovih veština u početnu obuku zdravstvenih radnika moglo bi da pomogne u prevazilaženju jaza između kliničke dokumentacije, istraživanja i praćenja na nivou populacije.

cently being consolidated to ensure rigor in studies examining the health effects of multiple, interacting, or time-varying exposures [21]. Strengthening collaboration with meteorological services and hospital emergency units is therefore essential, as alerts for heatwaves and wildfires often originate outside the health sector and must be integrated before they can effectively inform public health action.

HEALTHCARE PROFESSIONALS' READINESS TO PARTICIPATE IN EPIDEMIOLOGICAL DATA COLLECTION

The main barrier to healthcare professionals' participation in epidemiological data collection is their workload, particularly during emergency events. Professionals already operate under chronic pressure – staff shortages, ageing patient populations, rising admissions [22,23]. Climate-related extreme events further intensify this strain [5]. For instance, the convergence of heatwaves with the COVID-19 pandemic in 2020 highlighted the strain being placed on healthcare workers' resilience [24,25]. Such an overload not only restricts participation in surveillance and data-sharing initiatives but also serves as a warning: the distribution of skills and the organization of care need to be reexamined [26].

Another obstacle lies in the fragmented and often restrictive architecture of health information systems. Excessive data restrictions and limited interoperability can significantly hinder epidemiological research [27]. When data sets are incomplete or confined to specific diagnostic categories, many potential studies become unfeasible. The lack of data standardization, logistical challenges in data collection and management, and the absence of systematic local ethics committees further complicate the implementation of comparable and reproducible studies [28].

The use of standardized nursing terminologies and consistent documentation practices has been shown to improve care quality, ensure continuity, and increase the utility of collected data [29]. However, these tools remain underused, often due to workload constraints and limited digital literacy. Incorporating these skills into the initial training of professionals could help bridge the gap between clinical documentation, research, and population-level monitoring.

Finally, another barrier to healthcare professionals' participation in epidemiological data collection is the level of their motivation to engage in research. A recent systematic review has highlighted that limited time for research, organizational constraints, lack of funding, and insufficient institutional support all reduce healthcare professionals' willingness to invest their efforts in research [30]. Without addressing

Konačno, još jedna prepreka učešću zdravstvenih radnika u prikupljanju epidemioloških podataka jeste njihov nivo motivacije za uključivanje u istraživanja. Nedavna sistematska analiza pokazala je da ograničeno vreme za istraživanje, organizaciona ograničenja, nedostatak finansiranja i nedovoljna institucionalna podrška umanjuju spremnost zdravstvenih radnika da ulože trud u učešće u naučnim studijama [30]. Ako se po pitanju ovih faktora ne nađu adekvatna rešenja, manja je verovatnoća da će zdravstveni radnici integrisati epidemiološko rezonovanje u svoju praksu.

PREISPITIVANJE OBRAZOVANJA I OBUKE ZDRAVSTVENIH RADNIKA

Ograničena zastupljenost epidemiologije i statistike u ranim fazama obrazovanja lekara i medicinskih sestara može imati za posledicu da zdravstveni radnici budu slabije upoznati sa načinima svakodnevne primene zdravstvenih podataka u praksi. Nasuprot tome, dobro osmišljeni obrazovni programi koji povezuju istraživanje i praksu u javnom zdravlju – poput onih koji se primenjuju u Kvebeku, Kanadi – podstiču aktivno uključivanje u rad sa populacionim zdravstvenim podacima, sistemima nadzora i primenjenim istraživačkim projektima. Time se unapređuju sposobnosti zdravstvenih radnika da tumače podatke, procenjuju zdravstvene rizike i uvode preventivne mere u svoju praksu [31,32]. Ovakva iskustva pokazuju da je od ključnog značaja da se kultura javnog zdravlja i pripremljenost na ekstremne događaje povezane sa klimatskim promenama integrišu u prvi nivo obuke odnosno obrazovanja zdravstvenih kadrova [33,34]. Štaviše, ovakva reforma mogla bi da doprinese rešavanju aktuelne krize dobrobiti zdravstvenih radnika i valorizacije njihovog rada. Dokazi ukazuju da sveže obučeni kadrovi često ulaze u radno okruženje nedovoljno pripremljeni za psihološke i organizacione zahteve koje to okruženje nosi, što značajno utiče na njihovo mentalno zdravlje i ostanak u profesiji [35].

Sistem zdravstvene zaštite kao takav prolazi kroz značajnu transformaciju. Upis na programe master studija javnog zdravlja (engl. *Master of Public Health, MPH*) i visoke studije sestrinstva (engl. *Advanced Practice Nursing, APN*) je u porastu, što odražava kako rastuću potrebu za interdisciplinarnim i analitičkim veštinama, tako i hitnu potrebu za rešavanjem globalnog nedostatka medicinskih sestara [36,37]. Uloge koje na sebe preuzimaju zdravstveni radnici APN obrazovnog profila redefinišu tradicionalne hijerarhije u zdravstvenoj zaštiti proširivanjem kliničke autonomije, podsticanjem međusektorske saradnje i jačanjem veza između brige o pacijentima i istraživačke delatnosti [38]. Na isti način, sve veća prisutnost stručnjaka sa master diplomom u oblasti javnog zdravlja u bolnicama i drugim in-

these factors, healthcare professionals are less likely to integrate epidemiological reasoning into their practice.

REEXAMINING HEALTHCARE TRAINING

The limited role of epidemiology and statistics in the early stages of medical and nursing education may contribute to healthcare professionals' limited familiarity with and use of health data in practice. Conversely, structured training programs that integrate public health research and practice – such as those implemented in Quebec, Canada – strengthen direct engagement with population health data, surveillance systems, and applied research projects, thereby enhancing healthcare workers' ability to interpret data, anticipate health risks, and adopt preventive measures in their practice [31,32]. Building on such approaches, integrating a culture of public health and preparedness for climate-related extreme events in initial training has become essential [33,34]. Importantly, such reform could also help address the current crisis of wellbeing and recognition among healthcare professionals. Evidence shows that new graduates often enter the workforce underprepared for its psychological and organizational demands, which has a considerable impact on their mental health and retention [35].

The healthcare landscape is undergoing a significant transformation. Enrolment in Master of Public Health (MPH) and Advanced Practice Nursing (APN) programs has increased, reflecting both the growing demand for interdisciplinary and analytical skills and the urgent need to address the global nursing shortage [36,37]. APN roles are redefining traditional care hierarchies by expanding clinical autonomy, promoting cross-sector collaboration, and strengthening links between patient care and research [38]. Similarly, the increasing presence of MPH graduates within hospital and community settings signals a convergence between clinical expertise and population health competencies [39] – a positive development for bridging the persistent gap between frontline practice and epidemiological insight.

This paradigm shift reflects the dedication of healthcare professionals to participating in an educational reform that is both integrative and forward-thinking. Training in health surveillance, modeling, risk communication, and the responsible use of digital technologies enables professionals to interpret complex data ecosystems, understand the structural determinants of health, and actively contribute to public health intelligence [38,39]. By rethinking education to better align with day-to-day practical experience

stitucijama ukazuje na približavanje kliničkog stručnog znanja i kompetencija iz oblasti populacionog zdravlja [39] – što predstavlja pozitivan pomak ka premošćavanju dugotrajnog jaza između prakse na prvoj liniji zdravstvene zaštite i epidemioloških saznanja.

Ova promena paradigme odražava posvećenost zdravstvenih radnika učešću u obrazovnoj reformi koja je istovremeno integrativna i usmerena ka budućnosti. Obuka iz oblasti zdravstvenog nadzora, modelovanja, komunikacije rizika i odgovorne upotrebe digitalnih tehnologija omogućava stručnjacima da tumače složene ekosisteme podataka, razumeju strukturne determinante zdravlja i aktivno doprinose javnozdravstvenoj inteligenciji [38,39]. Preispitivanjem obrazovanja kako bi se ono bolje uskladilo sa svakodnevnim praktičnim iskustvom i novonastalim potrebama javnog zdravlja, Evropa ima priliku ne samo da unapredi otpornost, već i cenjenost, privlačnost i održivost profesija koje su pod sve većim opterećenjem.

PONOVNO POVEZIVANJE EPIDEMIOLOGA SA KONTEKSTOM PODATAKA

Epidemiolozi bi imali značajnu korist od povremenog boravka u kliničkim okruženjima, gde bi mogli neposredno da sagledaju praktična ograničenja, kao što su opterećenje poslom, raznolikost pacijenata i istovremeno prisustvo, često suprotstavljenih prioriteta. Skorašnja studija, čiji je cilj bio izrada vodiča za osmišljavanje nastavnih programa iz epidemiologije, pokazala je delotvornost pristupa učenju zasnovanog na praktičnom radu i promišljanju [40]. U tom smislu, programi poput *Epidemic Intelligence Service (EIS)* pri Centru za kontrolu i prevenciju bolesti (engl. *Centers for Disease Control and Prevention – CDC*) predstavljaju dobar primer ovakvog praktičnog pristupa: polaznici stižu neposredno terensko iskustvo uz blisko mentorstvo, učeći kako da epidemiološke podatke pretoče u konkretna javnozdravstvena rešenja i kako da obezbede da sistemi nadzora i preduzete mere ostanu čvrsto utemeljeni u realnom, svakodnevnom kontekstu prve linije zdravstvene zaštite [41]. Takvo iskustvo iz prve ruke pomaže da se razjasni zašto je pojedine podatke teško prikupiti ili zašto se smernice ne mogu uvek dosledno i delotvorno primeniti u praksi, a istovremeno podstiče realističnije i pragmatičnije osmišljavanje intervencija [41].

Ovaj pristup dodatno je potkrepljen dokazima dobijenim kroz druge programe obuke iz terenske epidemiologije. Programi obuke iz terenske epidemiologije (engl. *Field Epidemiology Training Programs, FETP*) jesu dvogodišnje inicijative zasnovane na principu „učenja kroz rad“, osmišljene da ojačaju kako kadrovske kapacitete, tako i sisteme javnozdravstvenog nadzora. Slično tome, Evropski program za obuku iz interventne epi-

and emerging public health needs, Europe has the opportunity not only to strengthen resilience but also to enhance recognition, attractiveness, and sustainability of the professions that are under strain.

RECONNECTING EPIDEMIOLOGISTS WITH THE CONTEXT BEHIND THE DATA

Epidemiologists would benefit from periodic immersion in clinical environments to directly observe practical constraints such as workload pressures, patient diversity, and competing priorities. A recent study aimed at developing a guide for designing epidemiology courses demonstrates the effectiveness of an immersive and reflective learning environment [40]. In concrete terms, programs such as the Centers for Disease Control and Prevention's Epidemic Intelligence Service (EIS) illustrate this practical approach: officers gain real-world field experience under close mentorship, learning to translate data into practical public health solutions and ensuring that surveillance systems and response efforts remain grounded in the frontline context of healthcare [41]. Such first-hand exposure clarifies why certain data remain difficult to capture or why guidelines may not always translate effectively into practice, while fostering more grounded, pragmatic modelling and intervention design [41].

This approach is also supported by evidence from other field epidemiology training programs. Field Epidemiology Training Programs (FETPs) are two-year, 'learning by doing' initiatives designed to strengthen both the workforce and the public health surveillance systems. Similarly, the European Programme for Intervention Epidemiology Training (EPIET) trains field epidemiologists – often in collaboration with national programs – highlighting the importance of structured mentoring, field assignment rotation, and iterative reflection on operational challenges in strengthening epidemiological capacity and data literacy [42].

Treadwell et al. [43] call for a reform of data collection practices to include more disaggregated information, enabling a clearer understanding of – and response to – health inequalities. They argue that this requires a fundamental transformation of data collection methods and structures.

Collectively, these perspectives suggest that combining field immersion, well-designed collaborative networks, and targeted training can help reconnect epidemiologists with the operational context underpinning the data, thereby enhancing the validity, applicability, and equity of public health research and practice.

miologije (engl. *European Programme for Intervention Epidemiology Training – EPIET*) obučava terenske epidemiologe – često u saradnji sa nacionalnim programima – ističući značaj strukturisanog mentorstva, rotacije terenskih zadataka i iterativnog promišljanja o operativnim izazovima u jačanju epidemioloških kapaciteta i pismenosti u radu sa podacima [42].

Tredvel i saradnici [43] pozivaju na reformu praksi prikupljanja podataka kako bi se obuhvatili detaljnije razloženi podaci, što bi omogućilo jasnije razumevanje zdravstvenih nejednakosti i adekvatnije reagovanje na njih. Oni ističu da ovo zahteva temeljni preobražaj metoda i struktura prikupljanja podataka.

U celini, ovi stavovi ukazuju na to da kombinovanje terenskog rada, dobro osmišljenih mreža saradnje i ciljane obuke može doprineti ponovnom povezivanju epidemiologa sa operativnim kontekstom koji stoji u osnovi podataka, čime se unapređuju validnost, primenljivost i pravičnost javnozdravstvenih istraživanja i prakse.

IZGRADNJA ZAJEDNIČKOG OKVIRA ZA ZDRAVSTVENI NADZOR TOPLOTNIH TALASA

Primer toplotnih talasa posebno jasno ilustruje jaz između epidemiologa i zdravstvenih radnika u tumačenju i korišćenju podataka, budući da trenutno ne postoji široko prihvaćen konceptualni okvir niti standardizovan skup zdravstvenih pokazatelja za merenje njihovog uticaja. Iako brojne studije kvantifikuju višak smrtnosti [44,45] ili višak hospitalizacija [46], ti napori se često zasnivaju na različitim metodologijama, što otežava poređenje rezultata i uspostavljanje zajedničkog stručnog jezika među disciplinama.

U akutnim kliničkim uslovima, pokazatelji kao što su višak smrtnosti, popunjenost bolničkih kapaciteta i prijem u jedinice intenzivne nege (JIN) obezbeđuju primenljive signale u realnom vremenu, kako kliničarima tako i javnozdravstvenim institucijama. Pored ovih neposrednih mera, pokazatelji populacionog zdravlja – uključujući prevalenciju, incidenciju, prevremenu smrtnost, morbiditet i invaliditet, kakvi se koriste u Studiji globalnog opterećenja bolešću (engl. *Global Burden of Disease – GBD*) [47] – nude standardizovan metod za kvantifikovanje i mortaliteta i morbiditeta u populacijama, kao i za poređenje relativnog uticaja različitih uzroka bolesti i povreda. Zbirne mere, kao što su godine života prilagođene invaliditetu (engl. *disability-adjusted life years – DALYs*), razvijene u okviru GBD studije, objedinjuju ove pokazatelje u jedinstvenu meru ukupnog opterećenja bolešću, dok godine života prilagođene kvalitetu (engl. *quality-adjusted life years – QALYs*) obuhvataju uticaj zdravstvenih stanja na kvalitet života pacijenata, povezujući kliničke ishode sa proživljenim iskustvom.

BUILDING A COMMON FRAMEWORK FOR HEATWAVE HEALTH MONITORING

The example of heatwaves is particularly illustrative of the gap between epidemiologists and healthcare professionals in interpreting and using data, as no widely accepted conceptual framework or standardized set of health metrics currently exists to measure their impact. While numerous studies quantify excess mortality [44,45] or excess hospitalizations [46], these efforts often rely on different methodologies, making it difficult to compare results or establish a shared language across disciplines.

In acute clinical settings, indicators such as excess mortality, hospital bed occupancy, and intensive care unit (ICU) admissions provide actionable, real-time signals for both clinicians and public health authorities. Beyond these immediate measures, population health indicators – including prevalence, incidence, premature mortality, morbidity, and disability, as used in the Global Burden of Disease (GBD) Study [47] – offer a standardized method for quantifying both mortality and morbidity across populations and comparing the relative impact of different causes of disease and injury. Summary measures such as disability-adjusted life years (DALYs), developed as part of the GBD Study, integrate these indicators into a single metric of overall disease burden, while quality-adjusted life years (QALYs) capture the impact of health conditions on patients' quality of life, linking clinical outcomes to lived experience.

Establishing a common set of such indicators at the European level could facilitate clearer communication between epidemiologists, healthcare professionals, and policymakers by providing a shared reference for measuring health impact, setting public health targets, and prioritizing interventions. These measures are particularly valuable for anticipating health risks, planning preventive strategies, evaluating progress over time, and comparing burden across different causes of disease, rather than serving solely as tools for immediate crisis response [48,49].

CONCLUSION

In a world where heatwaves, fires, epidemics, and socio-economic crises are intensifying, it is essential to raise awareness among both epidemiologists and healthcare professionals about the benefits of closer collaboration. Reconciling these two complementary and interdependent fields requires the development of a clear conceptual framework and a shared language. Rethinking training programs in both domains could represent a long-term strategy to strengthen the resilience of health systems.

Uspostavljanje zajedničkog skupa ovakvih pokazatelja na evropskom nivou moglo bi da olakša jasnu komunikaciju između epidemiologa, zdravstvenih radnika i donosilaca odluka, pružajući zajedničku referentnu osnovu za merenje zdravstvenog uticaja, postavljanje javnozdravstvenih ciljeva i određivanje prioriteta intervencija. Ove mere su naročito dragocene za predviđanje zdravstvenih rizika, planiranje preventivnih strategija, praćenje napretka tokom vremena i poređenje opterećenja među različitim uzrocima bolesti, a ne samo kao alati za neposredan odgovor na krizne situacije [48,49].

ZAKLJUČAK

U svetu u kojem se toplotni talasi, požari, epidemije i socioekonomske krize sve više intenziviraju, od ključnog je značaja da se unapredi svest, kako među epidemiolozima tako i među zdravstvenim radnicima, o koristima bliskije saradnje. Usklađivanje ove dve komplementarne i međusobno zavisne oblasti zahteva uspostavljanje jasnog konceptualnog okvira i zajedničkog stručnog jezika. Preispitivanje i unapređivanje programa obrazovanja/obuke u oba domena moglo bi predstavljati dugoročnu strategiju za jačanje zdravstvenih sistema.

SPISAK SKRAĆENICA

APN – *Advanced Practice Nursing*; visoke studije sestrinstva
DALYs – *disability-adjusted life years*; godine života prilagođene invaliditetu
EIS – *Epidemic Intelligence Service*; Epidemiološka obaveštajna služba
EPIET – *European Programme for Intervention Epidemiology Training*; Evropski program za obuku iz interventne epidemiologije
FETPs – *Field Epidemiology Training Programs*; programi obuke iz terenske epidemiologije
GBD Study – *The Global Burden of Disease Study*; Studija globalnog opterećenja bolešću
JIN – jedinica intenzivne nege
MPH – *Master of Public Health*; master studije javnog zdravlja
QALYs – *quality-adjusted life years*, godine života prilagođene kvalitetu

Sukob interesa: Nije prijavljen.

LIST OF ACRONYMS

APN – *Advanced Practice Nursing*
DALYs – *disability-adjusted life years*
EIS – *Epidemic Intelligence Service*
EPIET – *European Programme for Intervention Epidemiology Training*
FETPs – *Field Epidemiology Training Programs*
GBD Study – *The Global Burden of Disease Study*
ICU – *intensive care unit*
MPH – *Master of Public Health*
QALYs – *quality-adjusted life years*

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CURRICULUM VITAE



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MORFOLOŠKE PROMENE U BUBREZIMA I KLINIČKA SLIKA PACIJENATA SA MEMBRANOZNIM GLOMERULONEFRITISOM PRIMARNE I SEKUNDARNE ETIOLOGIJE

ORIGINALNI RAD

ORIGINAL ARTICLE

MORPHOLOGICAL CHANGES IN KIDNEYS AND CLINICAL PRESENTATION IN PATIENTS WITH PRIMARY AND SECONDARY MEMBRANOUS NEPHROPATHY

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SAŽETAK

Uvod/Cilj: Membranozni glomerulonefritis (MGN) klinički se najčešće manifestuje nefrotskim sindromom, a etiološki može biti idiopatski – primarni MGN (pMGN), ili u sklopu drugih bolesti – sekundarni MGN (sMGN). Uzimajući u obzir različite terapijske pristupe, cilj rada bio je uporediti kliničke i patohistološke parametre među pacijentima sa pMGN i sMGN.

Metode: Retrospektivnom analizom biopsijskih uzoraka tkiva bubrega dijagnostikovanih na Institutu za patologiju Medicinskog fakulteta u Beogradu u periodu 2011 - 2023. godine, izdvojeno je 99 pacijenata dijagnostikovanih kao MGN, podeljenih u odnosu na etiologiju u dve grupe: pacijente sa pMGN ($n = 44$) i pacijente sa sMGN ($n = 55$). Klinički, kao i patohistološki parametri (na optičkoj i imunofluorescentnoj mikroskopiji) upoređeni su u ispitivanim grupama.

Rezultati: Dok su muškarci češće obolevali od MGN, žene su češće imale sMGN ($p = 0,036$). Hematurija je češće uočena kod ispitanika sa sMGN ($p = 0,009$). Vrednosti proteinurije su bile značajno više među pacijentima sa pMGN ($p = 0,018$), što je u vezi sa znatno većim sniženjem koncentracije serumskih ukupnih proteina kod njih ($p = 0,011$). Endokapilarna proliferacija je znatno češće bila prisutna kod obolelih od sMGN ($p = 0,032$). Izrazita pozitivnost nekoliko imunofluorescentnih markera je bila statistički značajno češća kod ispitanika sa sMGN: IgA, IgM, C1q, κ -lanci i λ -lanci ($p < 0,05$).

Zaključak: Osobe ženskog pola češće boluju od sMGN. Karakteristike sMGN su prisustvo hematurije, endokapilarne hiper celularnosti i pozitivnosti imunofluorescence na markere koji se ne viđaju u pMGN (IgA, IgM, C1q), dok su karakteristike pMGN značajno više vrednosti proteinurije, praćene sniženjem koncentracije proteina u serumu.

Ključne reči: membranozni glomerulonefritis, primarni, sekundarni

ABSTRACT

Introduction/Aim: Membranous nephropathy (MN) typically presents as nephrotic syndrome and may be idiopathic (primary MN, pMN) or occur secondary to other diseases (secondary MN, sMN). Given the differing therapeutic approaches, this study aimed to compare clinical and pathohistological parameters between patients with pMN and sMN.

Methods: Through a retrospective analysis of kidney biopsy samples diagnosed at the Institute of Pathology, Faculty of Medicine, Belgrade, between 2011 and 2023, 99 patients with membranous nephropathy were identified. These patients were divided into two groups: patients with pMN ($n = 44$) and patients with sMN ($n = 55$). Clinical and pathohistological parameters (by optical and immunofluorescence microscopy) were compared among study participants.

Results: While males more frequently suffered from MN, females more frequently had sMN ($p = 0.036$). Haematuria was more common in subjects with sMN ($p = 0.009$). Proteinuria values were significantly higher among patients with pMN ($p = 0.018$), related to a significantly greater decrease in serum total protein values in them ($p = 0.011$). Endocapillary proliferation was significantly more frequent among those with sMN ($p = 0.032$). Marked positivity of several immunofluorescent markers was significantly more common in subjects with sMN: IgA, IgM, C1q, κ -chains, and λ -chains ($p < 0.05$).

Conclusion: Females are more commonly affected by sMN. Characteristics of sMN include presence of haematuria, endocapillary hypercellularity and immunofluorescence positivity for markers not seen in pMN (IgA, IgM, C1q), while characteristics of pMN include significantly higher levels of proteinuria, accompanied by significantly reduced serum protein values.

Keywords: membranous nephropathy, primary, secondary

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UVOD

Membranozni glomerulonefritis (MGN) predstavlja hronično bubrežno oboljenje koje karakteriše subepitelno taloženje depozita imunoglobulina i komponenata komplementa u glomerulima, te se najčešće klinički manifestuje nefrotskim sindromom [1]. Oboljenje se najčešće javlja u uzrastu 50 - 60 godina, i to oko dva puta češće kod muškaraca, dok deca retko obolevaju [2,3]. U odnosu na etiologiju deli se na primarni i sekundarni MGN [4]. Primarni MGN odlikuje autoimuni odgovor na podocitne antigene u odsustvu sekundarnog uzroka; neki od do sada detektovanih antigena su: *PLA₂R*, *THSD7A* [5,6]. U osnovi sekundarnog MGN mogu biti: autoimunske bolesti (sistemski eritemski lupus, Šegrenov sindrom, autoimuni tireoiditis), infekcije (hepatitis B i C virusne infekcije, HIV, sifilis, malarija), lekovi i toksini (nesteroidni antiinflamatorni lekovi, penicilamin, soli zlata, živa), kao i maligne bolesti (karcinomi pluća, prostate, kolona i uterusa, hematološka maligna oboljenja), kod kojih je detektovan *NELL-1* antigen [7,8].

Zlatni standard u dijagnostici MGN predstavlja patohistološka evaluacija biopsijskih uzoraka tkiva bubrega. Kod pacijenata sa nefrotskim sindromom u kliničkoj slici, serumskom pozitivnošću antitela na *PLA₂R* i očuvanom ekskretornom bubrežnom funkcijom, biopsija bubrega nije neophodna [9]. Na optičkoj mikroskopiji se uočava difuzno uniformno zadebljanje glomerularne bazalne membrane; vremenom njen matriks formira strukture nalik „šiljcima“ između deponovanih imunskih kompleksa [10]. Karakterističan nalaz imunofluorescentne mikroskopije predstavlja prisustvo sitnozrnastih, granularnih depozita IgG i C3 komponente komplementa duž glomerularne bazalne membrane [10].

Terapija za MGN zavisi od njegove etiologije. Pacijenti sa primarnom bolešću se leče imunosupresivnom terapijom (kortikosteroidima, ciklofosfamidom, inhibitorima kalcineurina), ali i rituksimabom, monoklonskim antitelom usmerenim ka CD20 antigenu B-limfocita [11,12]. Kod pacijenata sa sekundarnim MGN terapija je usmerena ka oboljenju koje je u njegovoj osnovi. Kod svih pacijenata se, kao suportivna terapija, primenjuju diuretici, ACE inhibitori, blokatori angiotenzinskih receptora i statini, a u cilju kontrole arterijskog pritiska, edema, proteinurije i lipidnog statusa [11].

Uzimajući u obzir značaj etiologije MGN u terapijskom pristupu, cilj ove studije je bio uporediti kliničke (distribucija prema polu, starosti, vrednosti proteinurije, prisustvo hematurije, koncentracije ukupnih proteina i albumina u serumu, pokazatelji ekskretorne bubrežne funkcije i prisustvo najčešćih komorbiditeta) i patohistološke parametre (promene na glomerulima, tubulointersticijumu i krvnim sudovima na optičkoj mikroskopiji, kao i intenzitet depozita imunoglobulina,

INTRODUCTION

Membranous glomerulonephritis (MGN) is a chronic kidney disease characterized by subepithelial deposition of immunoglobulins and complement components within the glomeruli, most commonly presenting clinically as nephrotic syndrome [1]. The disease most commonly occurs between 50 and 60 years of age and is approximately twice as prevalent in men, while it is rarely observed in children [2,3]. Based on etiology, it is classified into primary and secondary MGN [4]. Primary MGN is characterized by an autoimmune response against podocyte antigens in the absence of an identifiable secondary cause; antigens identified to date include *PLA₂R* and *THSD7A* [5,6]. Secondary MGN may be associated with autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroiditis), infections (hepatitis B and C, HIV, syphilis, malaria), drugs and toxins (non-steroidal anti-inflammatory drugs, penicillamine, gold salts, mercury), as well as malignant diseases (lung, prostate, colon, and uterine cancers, and hematological malignancies), in which the *NELL-1* antigen has been identified [7,8].

The gold standard for diagnosing MGN is the histopathological evaluation of kidney biopsy samples. In patients presenting with nephrotic syndrome who are serum-positive for *PLA₂R* antibodies and have preserved renal excretory function, a kidney biopsy is not required [9]. On light microscopy, a diffuse and uniform thickening of the glomerular basement membrane is observed, with the matrix gradually forming "spike"-like projections between the deposited immune complexes [10]. A hallmark of immunofluorescence microscopy is the presence of fine, granular deposits of IgG and the complement component C3 along the glomerular basement membrane [10].

Treatment of MGN depends on its underlying etiology. Patients with primary MGN receive immunosuppressive therapy, including corticosteroids, cyclophosphamide, and calcineurin inhibitors, as well as rituximab, a monoclonal antibody targeting the CD20 antigen on B lymphocytes [11,12]. In patients with secondary MGN, treatment is focused on the underlying condition. Supportive therapy, including diuretics, ACE inhibitors, angiotensin receptor blockers, and statins, is used in all patients to manage blood pressure, edema, proteinuria, and lipid levels [11].

Considering the significance of MGN etiology for therapeutic strategy, this study aimed to compare clinical parameters, such as gender and age distribution, proteinuria levels, presence of hematuria, serum total protein and albumin concentrations, markers of renal excretory function, and the most common comorbidities, with pathohistological features, including

njihovih lakih lanaca i komponenata komplemenata na imunofluorescentnoj mikroskopiji) među pacijentima sa primarnom i sekundarnom bolešću.

METODE RADA

U retrospektivnoj studiji obuhvaćeno je 99 biopsijskih uzoraka tkiva bubrega dijagnostikovanih kao MGN u periodu 2011 - 2023. godine na Institutu za patologiju „Dr Đorđe Joannović“ Medicinskog fakulteta u Beogradu. Od pomenutih 99 uzoraka, 64 su pripadala pacijentima lečenim na Klinici za nefrologiju Univerzitetskog kliničkog centra Srbije, 27 pacijentima lečenim u Kliničko-bolničkom centru „Zvezdara“, 4 pacijentima lečenim u Kliničko-bolničkom centru „Zemun“, 2 pacijentima lečenim na Univerzitetској dečjoj klinici i 2 pacijentima lečenim u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“. Pacijenti su podeljeni u dve grupe u odnosu na etiologiju bolesti: pacijente sa primarnim MGN ($n = 44$) i pacijente sa sekundarnim MGN ($n = 55$).

Klinički i laboratorijski podaci, zabeleženi u vreme biopsije, prikupljeni su pregledom medicinske dokumentacije pacijenata. Vrednosti proteinurije $< 3,5$ g/24 h označene su kao subnephrotske, dok su vrednosti $\geq 3,5$ g/24 h označene kao nephrotske [11]. Fiziološke vrednosti ukupnih proteina u serumu iznose 62 - 82 g/L, a albumina 35-52 g/L [13]. Brzina glomerularne filtracije procenjena je primenom CKD-EPI 2021 jednačine. Gradus hronične bubrežne bolesti određen je prema vrednostima procenjene brzine glomerularne filtracije [11]. Patohistološki podaci su prikupljeni iz izveštaja prethodno evaluiranih biopsijskih uzoraka tkiva bubrega.

Za statističku analizu korišćen je program IBM SPSS Statistics 22 (SPSS Inc., Čikago, Illinois, SAD). Za proveru normalnosti podataka korišćene su računске metode: koeficijent varijacije, *skewness* i *kurtosis* vrednosti. Procena statističke značajnosti razlike u vrednostima numeričkih varijabli među pacijentima sa primarnim i sekundarnim MGN vršena je primenom Studentovog t-testa za dva nezavisna uzorka, za podatke koji su pratili normalnu raspodelu. Za podatke čija raspodela nije bila normalna ili su bili ordinalni primenjen je Mann-Whitney U test. Procena statističke značajnosti razlike u učestalostima nominalnih varijabli između dveju grupa pacijenata vršena je primenom χ^2 testa za r x k tabele i Fišerovog testa tačne verovatnoće. Hipoteze su testirane sa nivoom značajnosti od 0,05.

REZULTATI

Klinički parametri

Detaljan prikaz kliničkih parametara kod pacijenata sa primarnim i sekundarnim MGN prikazan je u **Tabeli 1**. Od ukupno 99 pacijenata, 63,6% ($n = 63$) bile su

glomerular, tubulointerstitial, and vascular changes on light microscopy, as well as the intensity of immunoglobulin, light chain, and complement component deposits on immunofluorescence microscopy, between patients with primary and secondary MGN.

METHODS

The retrospective study included 99 kidney biopsy samples diagnosed as MGN between 2011 and 2023 at the Institute of Pathology “Dr. Đorđe Joannović,” Faculty of Medicine, Belgrade. Of these 99 samples, 64 were from patients treated at the Clinic for Nephrology, University Clinical Center of Serbia, 27 from the Clinical Hospital Center “Zvezdara”, 4 from the Clinical Hospital Center “Zemun”, 2 from the University Children’s Clinic; and 2 from the Institute for Mother and Child Health Protection of Serbia “Dr. Vukan Čupić”. Patients were divided into two groups based on disease etiology: those with primary MGN ($n = 44$) and those with secondary MGN ($n = 55$).

Clinical and laboratory data recorded at the time of biopsy were collected through review of patients’ medical records. Proteinuria values $< 3,5$ g/24 h were classified as subnephrotic, while values of $\geq 3,5$ g/24 h were classified as nephrotic [11]. Normal serum total protein levels range from 62 to 82 g/L, and albumin from 35 to 52 g/L [13]. Glomerular filtration rate was estimated using the CKD-EPI 2021 equation, and the stage of chronic kidney disease was determined based on the estimated glomerular filtration rate values [11]. Pathohistological data were obtained from the reports of previously analyzed kidney biopsy samples.

Statistical analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA). Data normality was assessed using the coefficient of variation, skewness, and kurtosis. For numerical variables with a normal distribution, differences between patients with primary and secondary MGN were evaluated using the Student’s t-test for two independent samples. For data with a non-normal distribution or ordinal scale, the Mann-Whitney U test was applied. Differences in the frequencies of nominal variables between the two patient groups were assessed using the χ^2 test for r x k tables and Fisher’s exact test. Hypotheses were tested at a significance level of 0.05.

RESULTS

Clinical parameters

A detailed overview of the clinical parameters in patients with primary and secondary MGN is presented in **Table 1**. Among the 99 patients, 63.6% ($n = 63$) were male and 36.4% ($n = 36$) were female. The secondary

Tabela 1. Klinički parametri ispitanika sa membranoznim glomerulonefritisom

Table 1. Clinical parameters of subjects with membranous nephropathy

Klinički parametri / Clinical parameters		Primarni MGN / Primary MN	Sekundarni MGN / Secondary MN	p
Pol / Sex [n (%)]	Muški / Male	33 (75.0%)	30 (45.5%)	0.036
	Ženski / Female	11 (25.0%)	25 (54.5%)	
Starost (godine) / Age (years)		52.8 ± 14.74	51.7 ± 15.9	0.704
Rang proteinurije / Proteinuria range [n (%)]	Subnephrotska / Subnephrotic	2 (4.5%)	7 (12.7%)	0.159
	Nephrotska / Nephrotic	42 (95.5%)	48 (87.3%)	
Proteinurija / Proteinuria (g/24 h)		8.8 (2.9-55.0)	6.9 (1.9-45.1)	0.018
Hematurija / Haematuria [n (%)]	Odsutna / Absent	35 (79.5%)	30 (54.5%)	0.009
	Prisutna / Present	9 (20.5%)	25 (45.5%)	
Ukupni proteini u serumu / Serum total protein (g/L)		44.8 ± 7.87	50.1 ± 7.67	0.011
Albumin u serumu / Serum albumin (g/L)		22.6 ± 6.60	25.3 ± 6.40	0.085
Kreatinin u serumu / Serum creatinine (μmol/L)		88.5 (41-575)	87.5 (21-419)	0.938
Urea u serumu / Serum urea (mmol/L)		8.2 ± 4.2	8.0 ± 5.1	0.874
Procenjena brzina glomerularne filtracije / eGFR (mL/min)		89.1 ± 45.9	72.2 ± 43.3	0.125
Gradus hronične bubrežne bolesti / Chronic kidney disease grade [n (%)]	G1	14 (46.7%)	13 (35.1%)	0.110
	G2	9 (30.0%)	6 (16.2%)	
	G3	4 (13.3%)	12 (32.4%)	
	G4	3 (10.0%)	4 (10.8%)	
	G5	0 (0.0%)	2 (5.4%)	
Hipertenzija / Hypertension [n (%)]	Odsutna / Absent	12 (27.3%)	19 (34.5%)	0.438
	Prisutna / Present	32 (72.7%)	36 (65.5%)	
Dijabetes melitus / Diabetes mellitus [n (%)]	Odsutna / Absent	42 (95.5%)	49 (89.1%)	0.248
	Prisutna / Present	2 (4.5%)	6 (10.9%)	

Legenda: MGN – membranozni glomerulonefritis

Legend: MN – membranous nephropathy; eGFR – estimated glomerular filtration rate

osobe muškog pola, dok su osobe ženskog pola činile preostalih 36,4% ($n = 36$). Sekundarnu formu bolesti imalo je 69,4% ($n = 25$) osoba ženskog pola naspram 47,6% ($n = 30$) osoba muškog pola, pri čemu je ova razlika u distribuciji prema polu bila statistički značajna ($p = 0,036$). Prosečna starost pacijenata sa primarnim MGN iznosila je $52,8 \pm 14,7$ godine, a kod onih sa sekundarnim MGN $51,7 \pm 15,9$ godina ($p = 0,704$).

Većina pacijenata je u vreme uzimanja biopsije imala proteinuriju nefrotskog ranga. Kod 9,1% ($n = 9$) ispitanika proteinurija je bila subnephrotska, a većina njih ($n = 7$) imala je MGN sekundarne etiologije. Medijana vrednosti proteina u 24-časovnom urinu kod pacijenata sa primarnim oblikom bolesti (medijana 8,8 g/24 h; opseg 2,9 - 55,0 g/24 h) bila je znatno viša nego kod onih sa sekundarnim MGN (medijana 6,9 g/24 h; opseg 1,9 - 45,1 g/24 h), $p = 0,018$. Hematuriju, najčešće mikroskopsku, imalo je 34,3% ($n = 34$) ispitanika, među kojima je 73,5% ($n = 25$) pacijenata bilo sa sekundarnom bolešću ($p = 0,009$).

form of the disease was observed in 69.4% ($n = 25$) of female patients compared to 47.6% ($n = 30$) of male patients, a difference that was statistically significant ($p = 0.036$). The mean age of patients with primary MGN was 52.8 ± 14.7 years, while that of patients with secondary MGN was 51.7 ± 15.9 years ($p = 0.704$).

Most patients exhibited nephrotic-range proteinuria at the time of biopsy. Proteinuria was subnephrotic in 9.1% ($n = 9$) of cases, the majority of whom ($n = 7$) had secondary MGN. The median 24-hour urine protein level in patients with primary MGN (median 8.8 g/24 h; range 2.9-55.0 g/24 h) was significantly higher than in those with secondary MGN (median 6.9 g/24 h; range 1.9-45.1 g/24 h; $p = 0.018$). Hematuria, mostly microscopic, was observed in 34.3% ($n = 34$) of patients, with 73.5% ($n = 25$) of these cases occurring in patients with secondary MGN ($p = 0.009$).

The mean total protein level in patients with primary MGN was 44.8 ± 7.9 g/L, representing a significantly greater reduction ($p = 0.011$) compared to patients

Izmerena vrednost ukupnih proteina kod pacijenata sa primarnim MGN bila je $44,8 \pm 7,9$ g/L, dakle sa znatno većim sniženjem vrednosti ($p = 0,011$) nego kod ispitanika sa sekundarnim MGN ($50,1 \pm 7,7$ g/L). Koncentracije serumskog albumina, iako snižene, nisu se znatno razlikovale između dveju grupa ispitanika (Tabela 1).

Pokazatelji ekskretorne bubrežne funkcije (serumske koncentracije uree i kreatinina, procenjena brzina glomerularne filtracije i gradus hronične bubrežne bolesti) nisu pokazali statistički značajnu razliku kod pacijenata sa primarnim i sekundarnim MGN, iako su pacijenti sa gradusom G3, G4 i G5 hronične bubrežne bolesti češće imali sekundarnu formu bolesti (Tabela 1).

Najčešći komorbiditeti u ispitivanoj populaciji bili su hipertenzija i dijabetes melitus. Među pacijentima sa hipertenzijom raspodela je bila približno jednaka – 47,1% ($n = 32$) njih je imalo primarni MGN, a 52,9% ($n = 36$) sekundarni ($p = 0,438$). Sa druge strane, iako je dijabetes melitus zabeležen kod svega 8,1% ($n = 8$) ispitanika, njih 75,0% ($n = 6$) imalo je sekundarnu formu bolesti ($p = 0,248$).

Patohistološki parametri

Na optičkoj mikroskopiji kod svih pacijenata uočeno je jednolično zadebljanje glomerularne bazalne membrane, karakteristično za pacijente obolele od MGN, kako primarne, tako i sekundarne etiologije (Slika 1). Pokazatelji hroničnih lezija glomerula (udeo globalno

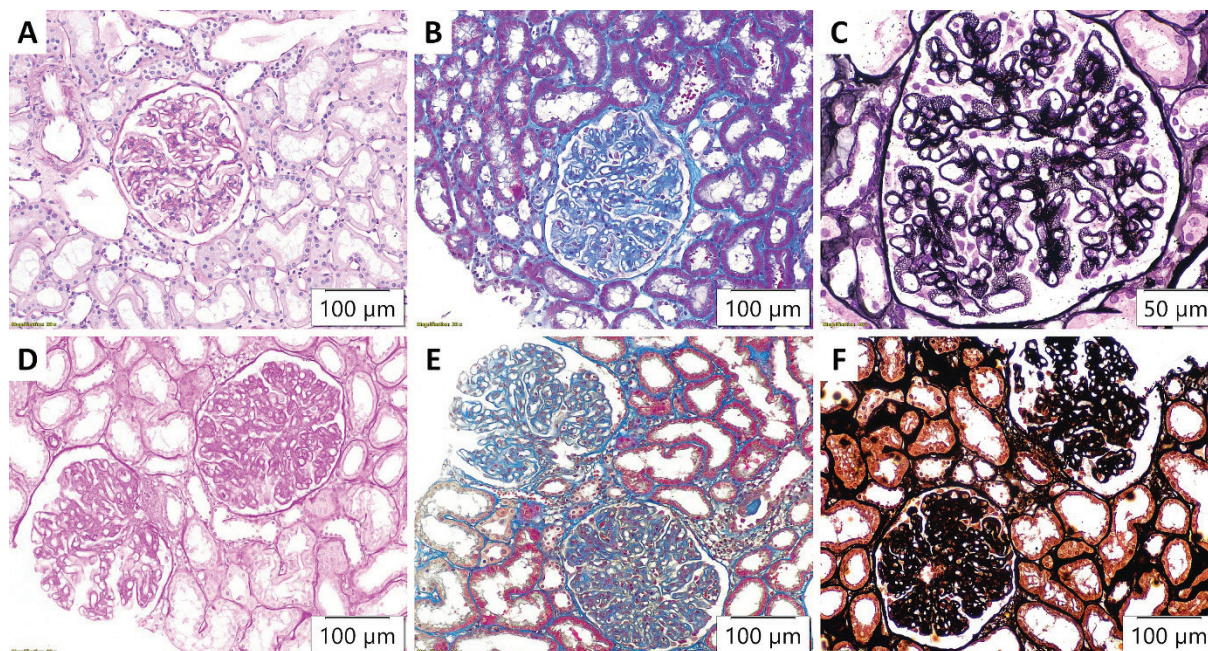
with secondary MGN (50.1 ± 7.7 g/L). Although serum albumin levels were also reduced, no significant difference was observed between the two groups (Table 1).

Indicators of excretory renal function, including serum urea and creatinine levels, estimated glomerular filtration rate, and chronic kidney disease stage, did not differ significantly between patients with primary and secondary MGN, although higher stages of chronic kidney disease (G3, G4, and G5) were more frequently observed in patients with secondary MGN (Table 1).

The most frequent comorbidities in the study population were hypertension and diabetes mellitus. Among patients with hypertension, the distribution was nearly even, with 47.1% ($n = 32$) having primary MGN and 52.9% ($n = 36$) having secondary MGN ($p = 0.438$). Diabetes mellitus was present in only 8.1% ($n = 8$) of patients, yet 75.0% ($n = 6$) of these cases were associated with secondary MGN ($p = 0.248$).

Histopathological parameters

On light microscopy, all patients exhibited uniform thickening of the glomerular basement membrane, a hallmark of MGN regardless of etiology (Figure 1). Indicators of chronic glomerular damage, such as the proportion of globally and segmentally sclerotic glomeruli, did not differ significantly between primary and secondary MGN (Table 2). Crescentic glomerular formations were more common in patients with secondary MGN, although this difference was not statistically



Slika 1. Promene u glomerulima na optičkoj mikroskopiji u primarnom (A) Periodic acid-Schiff (PAS), x200, (B) Masson's trichrome stain (MTS), x200, (C) Jones methenamine silver (JMS), x400; i sekundarnom membranoznom glomerulonefritisu, sa uočenom endokapilarnom hipercelularnošću (D) PAS, x200, (E) MTS, x200, (F) JMS, x200.

Figure 1. Changes in glomeruli on light microscopy in primary (A) Periodic acid-Schiff (PAS), x200, (B) Masson's trichrome (MTS), x200, (C) Jones methenamine silver (JMS), x400; and secondary membranous nephropathy, with evident endocapillary hypercellularity (D) PAS, x200, (E) MTS, x200, (F) JMS, x200

Tabela 2. Patohistološki parametri ispitanika s membranoznim glomerulonefritisom na optičkoj mikroskopiji

Patohistološki parametri / Pathohistological parameters		Primarni MGN / Primary MN	Sekundarni MGN / Secondary MN	p
Udeo globalno sklerotičnih glomerula / Global sclerotic glomeruli percentage (%)		0.0 (0.0-66.7)	0.0 (0.0-61.5)	0.412
Udeo glomerula sa segmentnom glomerulosklerozom / Segmental sclerotic glomeruli percentage (%)		0.0 (0.0-20.0)	0.0 (0.0-42.9)	0.814
Udeo glomerula sa polumesecima / Percentage of glomeruli with crescents (%)		0.0 (0.0-14.3)	0.0 (0.0-40.0)	0.091
Endokapilarna proliferacija / Endocapillary hypercellularity [n (%)]	Odsutna / Absent	43 (97.7%)	46 (85.2%)	0.032
	Prisutna / Present	1 (2.3%)	8 (14.8%)	
Karioreksa / Karyorrhexis [n (%)]	Odsutna / Absent	44 (100.0%)	52 (96.3%)	0.500
	Prisutna / Present	0 (0.0%)	2 (3.7%)	
Intersticijska fibroza / Interstitial fibrosis [n (%)]	Odsutna / Absent	15 (34.1%)	8 (14.8%)	0.008
	Blaga / Mild	24 (54.5%)	31 (57.4%)	
	Umerena / Moderate	4 (9.1%)	11 (20.4%)	
	Teška / Severe	1 (2.3%)	4 (7.4%)	
Tubulska atrofija / Tubular atrophy [n (%)]	Odsutna / Absent	22 (50.0%)	14 (25.9%)	0.031
	Blaga / Mild	16 (36.4%)	30 (55.6%)	
	Umerena / Moderate	5 (11.4%)	8 (14.8%)	
	Teška / Severe	1 (2.3%)	2 (3.7%)	
Hijalinizacija krvnih sudova / Blood vessels hyalinosis [n (%)]	Odsutna / Absent	30 (68.2%)	43 (78.2%)	0.261
	Prisutna / Present	14 (31.8%)	12 (21.8%)	
Fibrointimalna hiperplazija / Fibrointimal hyperplasia [n (%)]	Odsutna / Absent	20 (45.5%)	25 (45.5%)	1.000
	Prisutna / Present	24 (54.5%)	30 (54.5%)	

Legenda: MGN – membranozni glomerulonefritis

Table 2. Pathohistological parameters of patients with membranous nephropathy by light microscopy

Legend: MN – membranous nephropathy

i segmentno sklerotičnih glomerula) nisu pokazali značajne razlike među ispitanicima sa primarnim i sekundarnim MGN (Tabela 2). Glomeruli sa polumesečastim formacijama su bili češći kod obolelih od sekundarnog MGN, ali bez statističke značajnosti ($p = 0,091$). Endokapilarna proliferacija uočena je kod 9,1% ($n = 9$) ispitanih uzoraka tkiva, među kojima je 88,9% ($n = 8$) odgovaralo pacijentima sa sekundarnom bolešću ($p = 0,032$), (Tabela 2, Slika 1D). Karioreksa je uočena kod svega dva pacijenta sa sekundarnim MGN ($p = 0,500$).

Za razliku od hroničnih lezija krvnih sudova (hipertrofija medije, fibroelastoza intime i hijalinizacija krvnih sudova), pokazatelji hroničnih lezija tubulointersticijuma (intersticijska fibroza i tubulska atrofija) pokazali su statistički značajnu razliku između ispitivanih grupa, pri čemu su češće bile udružene sa sekundarnim MGN (Tabela 2).

Na imunofluorescentnoj mikroskopiji, pored IgG i C3 komponente komplementa, čiji sitnozrnasti depoziti duž glomerularne bazalne membrane predstavljaju tipičan nalaz u MGN (Slika 2), izrazita pozitivnost ostalih markera (IgA, IgM, C1q, κ -lanci i λ -lanci) znatno češće je bila udružena sa sekundarnim MGN (Tabela 3).

significant ($p = 0.091$). Endocapillary proliferation was noted in 9.1% ($n = 9$) of the examined tissue samples, of which 88.9% ($n = 8$) were from patients with secondary MGN ($p = 0.032$) (Table 2, Figure 1D). Karyorrhexis was observed in only two patients with secondary MGN ($p = 0.500$).

Unlike chronic vascular lesions (including medial hypertrophy, intimal fibroelastosis, and vascular hyalinization), indicators of chronic tubulointerstitial damage, such as interstitial fibrosis and tubular atrophy, differed significantly between the groups, occurring more frequently in patients with secondary MGN (Table 2).

On immunofluorescence microscopy, in addition to IgG and the complement component C3, whose fine granular deposits along the glomerular basement membrane represent a characteristic finding in MGN (Figure 2), pronounced positivity for other markers (IgA, IgM, C1q, κ chains, and λ chains) was significantly more frequently observed in secondary MGN (Table 3).

DISCUSSION

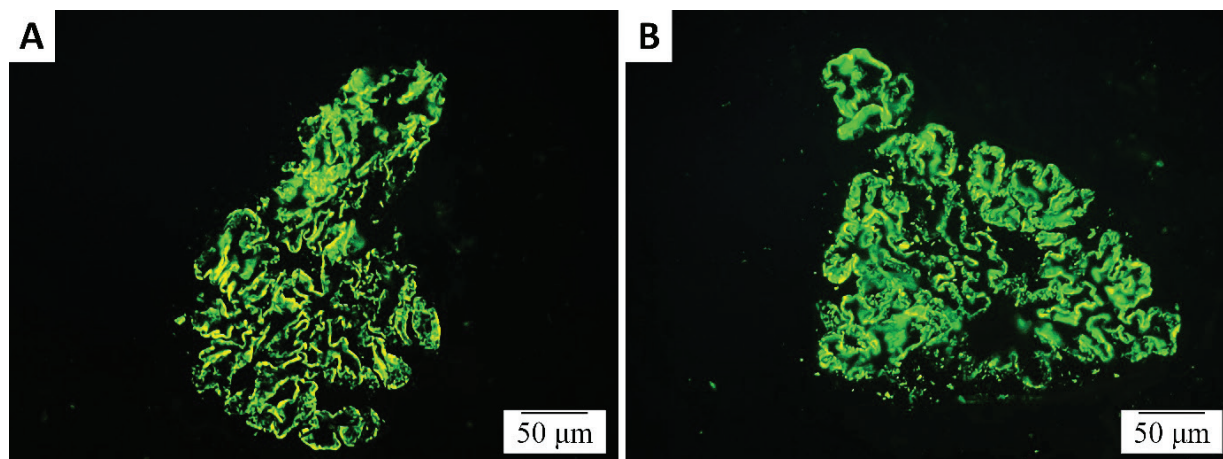
Tabela 3. Patohistološki parametri pacijenata s membranosnim glomerulonefritisom na imunofluorescentnoj mikroskopiji

Table 3. Pathohistological parameters of patients with membranous nephropathy by immunofluorescence

Patohistološki parametri / Pathohistological parameters		Primarni MGN / Primary MN	Sekundarni MGN / Secondary MN	p
IgA [n (%)]	-	32 (74.4%)	28 (50.9%)	0.002
	+	10 (23.3%)	7 (12.7%)	
	++	1 (2.3%)	13 (23.6%)	
	+++	0 (0.0%)	7 (12.7%)	
IgG [n (%)]	-	0 (0.0%)	0 (0.0%)	0.045
	+	1 (2.3%)	0 (0.0%)	
	++	4 (9.3%)	1 (1.8%)	
	+++	38 (88.4%)	54 (98.2%)	
IgM [n (%)]	-	22 (51.2%)	14 (25.5%)	0.001
	+	19 (44.2%)	25 (45.5%)	
	++	2 (4.7%)	15 (27.3%)	
	+++	0 (0.0%)	1 (1.8%)	
C1q [n (%)]	-	22 (51.2%)	9 (16.4%)	<0.001
	+	19 (44.2%)	21 (38.2%)	
	++	2 (4.7%)	19 (34.5%)	
	+++	0 (0.0%)	6 (10.9%)	
C3 [n (%)]	-	6 (14.0%)	6 (10.9%)	0.046
	+	13 (30.2%)	12 (21.8%)	
	++	17 (39.5%)	15 (27.3%)	
	+++	7 (16.3%)	22 (40.0%)	
κ-lanci [n (%)]	-	41 (95.3%)	38 (69.1%)	0.001
	+	1 (2.3%)	7 (12.7%)	
	++	0 (0.0%)	7 (12.7%)	
	+++	1 (2.3%)	3 (5.5%)	
λ-lanci [n (%)]	-	33 (76.7%)	32 (58.2%)	0.023
	+	3 (7.0%)	4 (7.3%)	
	++	6 (14.0%)	7 (12.7%)	
	+++	1 (2.3%)	12 (21.8%)	

Legenda: MGN – membranosni glomerulonefritis

Legend: MN – membranous nephropathy



Slika 2. Nalaz na imunofluorescentnoj mikroskopiji: sitnozrnasti depoziti (A) IgG i (B) C3 duž glomerularne bazalne membrane, x400

Figure 2. Immunofluorescence microscopy findings: fine granular deposits of (A) IgG and (B) C3 along the glomerular basement membrane, x400

DISKUSIJA

U ovoj retrospektivnoj studiji poređeni su klinički i patohistološki parametri između pacijenata sa primarnim i sekundarnim MGN. Osobe muškog pola su činile 63,6% ispitanika, što je u skladu sa podacima iz literature, koji navode da je odnos muškog prema ženskom polu u obolevanju od MGN 1,5 - 2 : 1 [14,15]. Takođe, čak 69,4% ispitanika ženskog pola imalo je sekundarni oblik bolesti. Ovakva distribucija prema polu se može objasniti značajnim udelom autoimunskih bolesti u etiologiji sekundarnog MGN. Naime, osobe ženskog pola znatno češće obolevaju od autoimunskih bolesti, koje mogu biti u osnovi sekundarnog oblika MGN [7,16]. Takva bolest sa najvećom učestalošću jeste sistemski eritemski lupus, kod kojeg bubreg može pokazivati promene po tipu membranoznog glomerulonefritisa, lupus nefritis klase V [17]. Osobe ženskog pola obolevaju 2 – 15 puta češće od sistemskog eritemskog lupusa [18,19].

Membranozni glomerulonefritis se najčešće prezentuje nefrotskim sindromom: izraženom proteinurijom, hipoalbuminemijom, perifernim edemima ili anasarkom, hiperlipidemijom i lipidurijom [20]. Jedna trećina pacijenata sa primarnim MGN ulazi u spontanu remisiju nakon više meseci ili godina [21]. Vrednosti proteinurije su važan faktor progresije bolesti – vrednosti < 4 g/24 h su udružene sa niskim rizikom, a vrednosti > 8 g/24 h sa visokim rizikom od progresije [22]. Naši rezultati su pokazali statistički značajno više vrednosti proteina u 24-časovnom urinu kod ispitanika sa primarnim MGN. Posledično, zbog većeg gubitka proteina urinom, ispitanici sa primarnim oblikom bolesti su imali znatno niže vrednosti ukupnih proteina u serumu od fizioloških.

Podaci iz literature ukazuju na to da prisustvo mikroskopske hematurije, arterijske hipertenzije i promena u bubrežnoj funkciji povećavaju verovatnoću sekundarne etiologije MGN [23,24]. Rezultati naše studije ukazali su na statistički značajno češće javljanje mikroskopske hematurije kod obolelih od sekundarnog MGN (73,5%) u poređenju sa obolelima od primarnog. Takođe, pacijenti sa sekundarnom formom bolesti su imali niže vrednosti procenjene brzine glomerularne filtracije nego ispitanici sa primarnim MGN, kao i češće javljanje viših gradusa (G3, G4 i G5) hronične bubrežne bolesti, ali ove razlike nisu dostigle statističku značajnost. Nasuprot ovome, raspodela u prisustvu arterijske hipertenzije nije pokazala razlike.

Pored toga što predstavlja zlatni standard u postavljanju dijagnoze MGN, patohistološka evaluacija biopsijskih uzoraka tkiva bubrega može ukazati i na moguću etiologiju, primarnu odnosno sekundarnu. Tako prisustvo mezangijalne i endokapilarne hiper celular-

In this retrospective study, clinical and pathohistological parameters were compared between patients with primary and secondary MGN. Male patients accounted for 63.6% of the study population, which is consistent with published data indicating a male-to-female ratio of approximately 1.5-2:1 in the incidence of MGN [14, 15]. Moreover, as many as 69.4% of female patients had a secondary form of the disease. This gender-based distribution may be explained by the substantial contribution of autoimmune diseases to the etiology of secondary MGN, as women are considerably more likely to develop autoimmune disorders, which can underlie the secondary form of MGN [7,16]. The autoimmune disease most frequently associated with this pattern is systemic lupus erythematosus, in which renal involvement may manifest as membranous glomerulonephritis, corresponding to class V lupus nephritis [17]. Systemic lupus erythematosus occurs 2 to 15 times more frequently in females [18,19].

Membranous glomerulonephritis most commonly presents with nephrotic syndrome, characterized by marked proteinuria, hypoalbuminemia, peripheral edema or anasarca, hyperlipidemia, and lipiduria [20]. Approximately one third of patients with primary MGN achieve spontaneous remission after several months or years. [21]. Proteinuria levels are an important factor in disease progression – values < 4 g/24 h are associated with a low risk, whereas values > 8 g/24 h are associated with a high risk of progression [22]. Our results demonstrated significantly higher 24-hour urinary protein levels in patients with primary MGN. Consequently, owing to greater urinary protein loss, patients with the primary form of the disease exhibited significantly reduced serum total protein levels compared with physiological values.

Literature data indicate that the presence of microscopic hematuria, arterial hypertension, and impaired renal function increases the likelihood of a secondary etiology of MGN [23,24]. The results of our study showed that microscopic hematuria was significantly more common in patients with secondary MGN (73.5%) compared to those with primary MGN. Additionally, patients with secondary MGN had lower estimated glomerular filtration rates and a higher frequency of advanced chronic kidney disease stages (G3, G4, and G5) than those with primary MGN, although these differences were not statistically significant. In contrast, the prevalence of arterial hypertension did not differ between the groups.

In addition to serving as the gold standard for diagnosing MGN, histopathological evaluation of kidney biopsy samples can also suggest a possible etiology, whether primary or secondary. Specifically, the pres-

nosti na optičkoj mikroskopiji sa većom verovatnoćom ukazuje na sekundarnu etiologiju MGN [23]. Rezultati naše studije upućuju na isti zaključak – od 9 uzoraka tkiva sa uočenom endokapilarnom proliferacijom, 88,9% njih je odgovaralo pacijentima sa sekundarnim MGN. Pozitivnost na *PLA₂R* i *THSD7A* antigene upućuje na primarnu etiologiju bolesti [25,26]. Sa druge strane, pozitivnost na *EXT1* i *EXT2* antigene udružena je sa autoimunskim bolestima kao etiološkim činiocem sekundarnog MGN (pre svega sistemskim eritemskim lupusom), dok je *NELL-1* u trećini slučajeva udružen sa malignim oboljenjem [27,28].

„Full house“ nalaz imunofluorescentne mikroskopije predstavlja izrazitu pozitivnost na svih 5 markera, IgG, C3, ali i IgA, IgM i C1q, i odlika je pre svega sekundarnog MGN u okviru sistemskog eritemskog lupusa [29]. Depoziti IgG i C3 komponente komplementa duž glomerularne bazalne membrane predstavljaju karakterističan nalaz u membranoznom glomerulonefritisu, bez obzira na etiologiju bolesti, ali je ipak primećeno da je njihova izrazita pozitivnost bila češće udružena sa sekundarnom bolešću. Marker IgA, IgM i C1q pokazali su statistički značajnu razliku u distribuciji u odnosu na etiologiju MGN i znatno češće su bile prisutne umere- na i izražena pozitivnost na ove markere kod obolelih od sekundarnog MGN. Razlike u distribuciji pozitivno- sti na κ -lance i λ -lance ne mogu se adekvatno tumačiti iz razloga što se ova dva markera do 2018. godine nisu rutinski određivala na Institutu za patologiju Medicin- skog fakulteta u Beogradu.

ZAKLJUČAK

Osobe ženskog pola češće boluju od sekundarnog MGN. Karakteristike MGN sekundarne etiologije su prisustvo hematurije, endokapilarne hipercelularnosti i pozitivnosti imunofluorescence na markere koji se ne viđaju u primarnom MGN (IgA, IgM, C1q), dok su karakteristike MGN primarne etiologije značajno više vrednosti proteinurije, praćene značajno sniženom koncentracijom proteina u serumu.

SPISAK SKRAĆENICA

MGN – membranozni glomerulonefritis
pMGN – primarni membranozni glomerulonefritis
sMGN – sekundarni membranozni glomerulonefritis

Sukob interesa: Nije prijavljen.

ence of mesangial and endocapillary hypercellularity on light microscopy is more indicative of a secondary etiology [23]. The results of our study support this conclusion—of the nine tissue samples exhibiting endo- capillary proliferation, 88.9% were from patients with secondary MGN. Conversely, positivity for *PLA₂R* and *THSD7A* antigens indicates a primary etiology [25,26]. On the other hand, positivity for *EXT1* and *EXT2* anti- gens is linked to autoimmune diseases as the underly- ing cause of secondary MGN, primarily systemic lupus erythematosus, whereas *NELL-1* positivity is associated with malignancy in approximately one-third of cases [27,28].

The “full house” pattern on immunofluorescence microscopy, characterized by positivity for all five markers, i.e., IgG, C3, as well as IgA, IgM, and C1q, is primarily indicative of secondary MGN in the context of systemic lupus erythematosus [29]. Deposits of IgG and the complement component C3 along the glo- merular basement membrane are a characteristic fea- ture of membranous glomerulonephritis, regardless of disease etiology; however, marked positivity for these markers was more frequently observed in secondary MGN. The distribution of IgA, IgM, and C1q positivity differed significantly according to MGN etiology, with moderate to strong positivity for these markers being significantly more common in secondary MGN. Differences in κ -chain and λ -chain positivity could not be adequately interpreted, as these markers were not rou- tinely assessed at the Institute of Pathology, Faculty of Medicine in Belgrade, until 2018.

CONCLUSION

Females are more likely to develop secondary MGN. Features of secondary MGN include hematuria, endo- capillary hypercellularity, and immunofluorescence positivity for markers not typically seen in primary MGN (IgA, IgM, C1q). In contrast, primary MGN is char- acterized by significantly higher levels of proteinuria, accompanied by markedly reduced serum protein con- centrations.

ABBREVIATION LIST

MGN – membranous glomerulonephritis
pMGN – primary membranous glomerulonephritis
sMGN – secondary membranous glomerulonephritis

Conflict of interest: None declared.

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OSTEOPOROSIS IN AUTOIMMUNE DISEASES

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SAŽETAK

Uvod: Osteoporoza je jedna od najčešćih ekstraartikularnih komplikacija u mnogim hroničnim inflamatornim reumatskim bolestima, kao što su: reumatoidni artritis, psorijazni artritis, ankilozirajući spondilitis, sistemski eritemski lupus, i dr.

Metode: Istraživali smo PubMed, Scopus i Web of Science baze podataka kako bismo pronašli studije objavljene u poslednjih 10 godina. Rad je napisan u vidu preglednog članka.

Rezultati: Većina studija kod postmenopausalnih žena pronalazi povezanost između visokog nivoa proinflammatory markeri i povećanog gubitka koštanog tkiva. Literaturni podaci ukazuju na povezanost niskog rizika od velikih osteoporotičnih preloma, preloma kuka i nevertebralnih preloma kod pacijenata sa psorijaznim artritisom koji su na terapiji lekovima koji modifikuju tok bolesti. Procena pacijenta sa autoimunskim reumatskim bolestima obuhvata anamnezu, klinički pregled, procenu rizika od preloma, laboratorijske analize, kao i osteodenzitometriju. Nепрепознавање i netretiranje osteoporoze je uslovljeno sledećim faktorima: nedovoljno znanje o osteoporozi i koristi od terapije, zabrinutost zbog mogućih neželjenih efekata terapije, slaba motivisanost i loša edukacija pacijenata. Razvijeno je nekoliko različitih metoda za smanjenje propusta u prepisivanju terapije, a među njima se *Fracture Liaison Service* pokazao kao najefikasniji. Strategije za upravljanje osteoporozom obuhvataju edukaciju pacijenata, promene životnog stila, prevenciju padova, adekvatnu ishranu, kontrolu aktivnosti bolesti, kao i uvođenje lekova za osteoporoze.

Zaključak: Uprkos značajnim naprecima u prevenciji, dijagnostici i tretmanu, prevalencija osteoporoze je visoka i zahteva pravovremeno prepoznavanje i sveobuhvatni pristup. Procena faktora rizika od padova i preloma kostiju, kao i potencijala za oporavak, od velikog je značaja kod pacijenata sa autoimunskim reumatskim bolestima.

Ključne reči: osteoporoza, prevalencija, faktori rizika, prelomi, terapija

ABSTRACT

Introduction: Osteoporosis is one of the most common extra-articular complications in many chronic inflammatory rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and systemic lupus erythematosus etc..

Methods: We searched the PubMed, Scopus, and Web of Science databases for studies published within the last 10 years. This is a review article.

Results: Most studies on postmenopausal women have found a correlation between high levels of pro-inflammatory markers and increased bone loss. Literature data indicate a link between a low risk of major osteoporotic fractures, hip fractures, and non-vertebral fractures in patients with PsA who are on disease-modifying therapies. Patient assessment in autoimmune rheumatic inflammatory diseases includes medical history, clinical examination, fracture risk assessment, laboratory tests, and bone densitometry. The lack of adequate diagnosis and treatment of osteoporosis is influenced by factors such as insufficient knowledge about osteoporosis and its therapeutic benefits, concerns about potential side effects of treatment, low motivation, and inadequate patient education on the subject. Several methods have been developed to reduce prescribing errors and oversights, with the *Fracture Liaison Service* proving to be the most effective. Strategies for managing osteoporosis include patient education, lifestyle modifications, fall prevention, proper nutrition, disease activity control, and the introduction of osteoporosis medication.

Conclusion: Despite significant advances in prevention, diagnosis, and treatment, the prevalence of osteoporosis remains high and requires timely recognition and a more comprehensive approach. Assessing risk factors for falls and fractures, as well as recovery potential, is crucial in patients with autoimmune rheumatic inflammatory diseases.

Keywords: osteoporosis, prevalence, risk factors, fractures, therapy

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UVOD

Prema definiciji Svetske zdravstvene organizacije (SZO), osteoporoza je sistemska, progresivna bolest skeleta, koju karakteriše smanjena koštana masa, te mikroarhitektonsko propadanje koštanog tkiva sa posledičnim povećanjem krhkosti kostiju i podložnosti prelomima. Snaga kostiju odražava integraciju dve glavne karakteristike: gustinu i kvalitet kostiju. Osteoporoza je široko rasprostranjeno oboljenje od koje oboleva jedna od tri žene, kao i jedan od pet muškaraca starosti preko 50 godina [1]. Najugroženija populacija su žene u postmenopauzi [2]. Prema rezultatima meta-analize iz 2022. godine, prevalencija osteoporoze i osteopenije se kreće od 19,7%-40,4% [3]. Među najčešćim faktorima rizika od osteoporoze izdvajaju se: godine starosti, ženski pol, genetska predispozicija, pušenje, česta konzumacija alkohola, neadekvatna ishrana i smanjen unos kalcijuma i vitamina D, hronična upotreba sistemskih kortikosteroida, kao i komorbiditeti među kojima su i autoimunska oboljenja, najčešće reumatoidni artritis (RA) [4]. Osteoporoza predstavlja značajnu i često nedovoljno prepoznatu komplikaciju u autoimunskim bolestima. Prevalencija autoimunskih reumatskih bolesti (AIRB) procenjena je na 3.225/100.000 [5]. Rano prepoznavanje ovih bolesti je ključno za sprečavanje njihovih komplikacija i za započinjanje odgovarajućeg lečenja [6].

Prevalencija osteoporoze je značajno veća kod pacijenata obolelih od reumatoidnog artritisa u odnosu na opštu populaciju, i do 27,6%, što se objašnjava patofiziološkim mehanizmima razvoja ovog oboljenja, kao i terapijskim opcijama kod obolelih od reumatoidnog artritisa, koje vrlo često uključuju hroničnu upotrebu sistemske kortikosteroidne terapije [7]. Rezultati analize 21 objavljene studije pokazuju da se prevalencija osteoporoze kod obolelih od psorijaznog artritisa (PsA) kreće od 1,4% do 68,8% [8]. Prema podacima retrospektivne studije iz 2024. godine, incidencija osteoporoze i osteopenije kod obolelih od psorijaznog artritisa kreće se između 11,7% i 33,1% [9]. Kod osoba muškog pola mlađih od 50 godina, PsA može da doprinese ranijem gubitku koštane mase u odnosu na tradicionalne faktore rizika [9]. Pacijenti sa psorijaznim artritisom imaju i povišeni rizik od preloma kostiju u odnosu na opštu populaciju [10].

Osteoporoza je česta pojava kod obolelih od ankilozirajućeg spondilitisa (AS), ali se nedovoljno prepoznaje u kliničkoj praksi [11]. Kombinovana analiza u vidu dvoenergetske rendgenske apsorptiometrije (engl. *dual-energy X-ray absorptiometry* – DXA) i kvantitativne kompjuterizovane tomografije kod pacijenata sa ranim i dugotrajnim AS pokazala je smanjenu mineralnu koštanu gustinu (engl. *bone mineral density* – BMD) i gubitak koštane mase u kičmi i kukovima [12]. Prevalencija osteoporoze kod obolelih od aksijalnog

INTRODUCTION

According to the World Health Organization (WHO) definition, osteoporosis is a systemic, progressive skeletal disease characterized by reduced bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and susceptibility to fractures. Bone strength reflects the integration of two main characteristics: bone density and bone quality. Osteoporosis is a widespread condition, affecting one in three women and one in five men over the age of 50 years [1]. The population that is at greatest risk comprises postmenopausal women [2]. According to the results of a 2022 meta-analysis, the prevalence of osteoporosis and osteopenia ranges from 19.7% to 40.4% [3]. Among the most common risk factors for osteoporosis are advanced age, female sex, genetic predisposition, smoking, frequent alcohol consumption, inadequate nutrition, reduced intake of calcium and vitamin D, chronic use of systemic corticosteroids, as well as comorbidities, including autoimmune diseases, most commonly rheumatoid arthritis (RA) [4]. Osteoporosis represents a significant and often underrecognized complication in autoimmune diseases. The prevalence of autoimmune rheumatic diseases (ARDs) is estimated at 3,225 per 100,000 population [5]. Early recognition of these diseases is crucial for preventing complications and for initiating appropriate treatment [6].

The prevalence of osteoporosis is significantly higher in patients with rheumatoid arthritis than in the general population, as much as by 27.6%, which can be explained by the pathophysiological mechanisms of the disease as well as by therapeutic approaches in rheumatoid arthritis, which very often include the chronic use of systemic corticosteroid therapy [7]. The results of an analysis of 21 published studies indicate that the prevalence of osteoporosis in patients with psoriatic arthritis (PsA) ranges from 1.4% to 68.8% [8]. According to data from a retrospective study published in 2024, the incidence of osteoporosis and osteopenia in patients with psoriatic arthritis ranges between 11.7% and 33.1% [9]. In males younger than 50 years, PsA may contribute to earlier bone mass loss compared with traditional risk factors [9]. Patients with psoriatic arthritis also have an increased fracture risk, as compared with the general population [10].

Osteoporosis is a common condition in patients with ankylosing spondylitis (AS) but remains underrecognized in clinical practice [11]. A combined assessment using dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography revealed reduced bone mineral density (BMD) and bone loss in the spine and hips of patients with early and long-standing AS [12]. The prevalence of osteoporosis in patients

Tabela 1. Prevalencija osteoporoze u različitim populacijama i autoimunskim reumatskim bolestima (AIRB)

Bolest/Populacija	Prevalencija osteoporoze/osteopenije	Faktori rizika/Napomene	Referenca
Opšta populacija >50 godina	1 od 3 žene, 1 od 5 muškaraca	Starost, ženski pol, genetika, pušenje, alkohol, neadekvatan unos kalcijuma i vitamina D, kortikosteroidi	1-3
Reumatoidni artritis (RA)	Do 27,6%	Patofiziološki mehanizmi + hronična upotreba kortikosteroida	4, 7
Psorijazni artritis (PsA)	1,4%-68,8%	Kod muškaraca <50 godina može uzrokovati raniji gubitak koštane mase; povišeni rizik od preloma	8-10
Ankilozirajući spondilitis (AS)	13%-25%	Nedovoljno prepoznat; smanjena BMD u kičmi i kukovima	11, 12
Aksijalni spondiloartritis (axSpA)	11,7%-34,4%	Deficit vitamina D, smanjena mobilnost/rizik od preloma 11% – 24,6%	13
Sistemske eritemski lupus (SEL)	Osteoporoza: ~13%; Osteopenija: ~38%	Hronična upotreba glukokortikoida, trajanje bolesti, rana menopauza, hipovitaminoza vitamina D/ 1,8× veći rizik od preloma, 4× veći rizik od preloma kičme	14, 15

Table 1. Prevalence of osteoporosis in different populations and autoimmune rheumatic diseases (AIRDs)

Disease/Population	Prevalence of osteoporosis/osteopenia	Risk factors/Annotations	Reference
General population >50 years	1 in 3 women; 1 in 5 men	Age, female sex, genetics, smoking, alcohol, inadequate calcium and vitamin D intake, corticosteroids	1-3
Rheumatoid arthritis (RA)	Up to 27.6%	Pathophysiological mechanisms + chronic corticosteroid use	4, 7
Psoriatic arthritis (PsA)	1.4%-68.8%	In men <50 years of age, it may cause earlier loss of bone mass; increased risk of fractures	8-10
Ankylosing spondylitis (AS)	13%-25%	Insufficiently recognized; reduced BMD in the spine and hips	11, 12
Axial spondyloarthritis (axSpA)	11.7%-34.4%	Vitamin D deficiency, reduced mobility/fracture risk 11%–24.6%	13
Systemic lupus erythematosus (SLE)	Osteoporosis: ~13%; Osteopenia: ~38%	Chronic glucocorticoid use, disease duration, early menopause, vitamin D hypovitaminosis/1.8 x increased fracture risk, 4 x increased risk of vertebral fractures	14, 15

spondiloartritisa (engl. *axial spondyloarthritis* – *axSpA*) se kreće između 11,7% i 34,4%, dok je rizik od preloma kostiju između 11% i 24,6%, uz značajne faktore rizika, kao što su deficit vitamina D i smanjena mobilnost pacijenata zbog osnovnog oboljenja [13].

Prevalencija osteoporoze kod pacijenata obolelih od sistemskog eritemskog lupusa (SEL) je oko 13%, a osteopenije oko 38% [14]. Glavni faktori rizika kod ove populacije su hronična upotreba glukokortikoida, dužina trajanja bolesti i rana menopauza sa sniženom koštanom mineralnom gustinom (engl. *bone mineral density* – *BMD*) i hipovitaminozom vitamina D [15]. Pacijenti sa sistemskim eritemskim lupusom imaju 1,8 puta veći opšti rizik od nastanka preloma i četiri puta veći rizik od nastanka preloma kičmenih pršljenova [14]. Rezultati navedenih studija prikazani su u Tabeli 1. Tabela prikazuje prevalenciju osteoporoze i osteopenije u opštoj populaciji i kod pacijenata sa različitim inflamatornim reumatskim bolestima, uz navođenje glavnih faktora rizika i specifičnih napomena za svaku grupu.

MATERIJALI I METODE

Metodologija ovog rada zasnovana je na pregledu literature iz baza: *PubMed*, *Scopus* i *Web of Science*, ko-

with axial spondyloarthritis (axSpA) ranges from 11.7% to 34.4%, while the fracture risk ranges from 11% to 24.6%, with significant risk factors including vitamin D deficiency and reduced patient mobility due to the underlying disease [13].

The prevalence of osteoporosis in patients with systemic lupus erythematosus (SLE) is approximately 13%, while the prevalence of osteopenia is approximately 38% [14]. The main risk factors in this population include chronic glucocorticoid use, disease duration, and early menopause associated with reduced bone mineral density (BMD) and vitamin D hypovitaminosis [15]. Patients with SLE are at a 1.8 times higher overall fracture risk and at a four times higher risk of vertebral fractures [14]. The results of the above-described studies are presented in Table 1. The table summarizes the prevalence of osteoporosis and osteopenia in the general population and among patients with various inflammatory rheumatic diseases, highlighting key risk factors and specific annotations for each group.

MATERIALS AND METHODS

The methodology of this study is based on a literature review of the PubMed, Scopus, and Web of Science da-

risteći ključne reči povezane sa reumatskim bolestima i osteoporozom (osteoporoza, prevalencija, faktori rizika, prelomi, terapija). Uključeni su članci objavljeni na engleskom jeziku u poslednjih deset godina, koji se odnose na odrasle pacijente i pružaju podatke o prevalenciji, faktorima rizika i terapijskim pristupima. Isključeni su radovi koji nisu relevantni, studije sa pedijatrijskom populacijom i prikazi slučajeva. Prikupljeni podaci analizirani su deskriptivno i tematski, sa fokusom na kliničke karakteristike, mehanizme gubitka koštane mase i strategije lečenja. Rad je napisan u vidu preglednog članka.

Faktori koji utiču na koštanu mineralnu gustinu kod autoimunskih reumatskih bolesti

Hronični inflamatorni odgovori kod autoimunskih reumatskih bolesti (AIRB), kao što su reumatoidni artritis i sistemski eritemski lupus, aktiviraju osteoklaste, čime ubrzavaju resorpciju kostiju i dovode do smanjenja koštane gustine [16]. Citokini koje oslobađaju imunске ćelije tokom inflamatornog odgovora utiču na metabolizam kostiju, podstičući razvoj osteoporoze. Formiranje sindezmofta i ankiloze dodatno povećavaju opterećenje u kortikalnim zonama i paravertebralnim ligamentima, a gubitak trabekularne kosti u vertebralnim telima može dovesti do smanjenja koštane mineralne gustine [17]. Bol i ograničena pokretljivost uzrokovani ovim bolestima smanjuju fizičku aktivnost pacijenata, što dalje utiče na zdravlje kostiju [18].

Moguća veza između psorijaznog artritisa (PsA) i osteoporoze može se naći u izraženijoj demineralizaciji uočenoj kod pacijenata sa PsA, koja se intenzivira starenjem, nedostatkom estrogena i pogoršanim indeksima kvaliteta života [19]. Istraživanja su pokazala da pacijenti sa PsA imaju veću verovatnoću za razvoj fraktura u poređenju sa zdravom kontrolnom grupom bez psorijaze, ali nije sa sigurnošću potvrđena povezanost visokog rizika od fraktura sa sniženom mineralnom koštanom gustinom. Dalja istraživanja su neophodna radi utvrđivanja PsA kao faktora rizika od osteoporoze [20]. Noviji literaturni podaci su pokazali da kod pacijenata sa PsA, muškarci imaju povećan rizik od osteoporoze, kao i od osteoporotičnih fraktura, čak i ako su mlađi od 50 godina [21]. PsA je opisan kao nezavisni faktor rizika za smanjenu gustinu kostiju i padove, a samim time i za povezane frakture [22].

Pacijenti oboleli od ankilozirajućeg spondilitisa (AS) imaju snižen BMD i povećan rizik od preloma. Dodatni rizik od osteoporoze i fraktura imaju mlađi pacijenti i pacijenti u ranim fazama ove bolesti [23]. Vertebralne frakture kod AS su često nestabilne zbog okoštavanja potpornih i elastičnih ligamenata. Inflamatorni citokini, uključujući faktor tumorske nekroze (engl. *tumor necro-*

tabases, using keywords related to rheumatic diseases and osteoporosis (osteoporosis, prevalence, risk factors, fractures, therapy). Articles published in English within the last ten years focusing on adult patients and reporting data on prevalence, risk factors, and therapeutic approaches were included. Studies that were not relevant, those involving pediatric populations, and case reports were excluded. The collected data were analyzed descriptively and thematically, with a focus on clinical characteristics, mechanisms of bone loss, and treatment strategies. This is a review article.

Factors affecting bone mineral density in autoimmune rheumatic diseases

Chronic inflammatory responses in autoimmune rheumatic diseases (ARDs), such as rheumatoid arthritis and systemic lupus erythematosus, activate osteoclasts, thereby accelerating bone resorption and leading to reduced bone density [16]. Cytokines released by immune cells during the inflammatory response affect bone metabolism, promoting the development of osteoporosis. The formation of syndesmophytes and ankylosis further increases mechanical load in cortical bone regions and paravertebral ligaments, while the loss of trabecular bone in vertebral bodies can result in decreased bone mineral density [17]. Pain and reduced mobility caused by these diseases limit patients' physical activity, which further adversely affects bone health [18].

A possible link between psoriatic arthritis (PsA) and osteoporosis may be found in the more pronounced demineralization observed in patients with PsA, which is intensified by aging, estrogen deficiency, and impaired quality-of-life indexes [19]. Studies have shown that patients with PsA are more likely to develop fractures compared with a healthy control group without psoriasis; however, a definite association between a high fracture risk and reduced bone mineral density has not been conclusively established. Further research is needed to confirm PsA as a risk factor for osteoporosis [20]. More recent literature data have shown that in patients with PsA, men have an increased risk of osteoporosis as well as of osteoporotic fractures, even when they are younger than 50 years [21]. PsA has been described as an independent risk factor for reduced bone density and falls, and consequently for associated fractures [22].

Patients with ankylosing spondylitis (AS) have reduced bone mineral density (BMD) and an increased fracture risk. Younger patients and those in the early stages of the disease are at additional risk of osteoporosis and fractures [23]. Vertebral fractures in AS are often unstable due to ossification of supporting and elastic ligaments. Inflammatory cytokines, including

sis factor – TNF)-alfa i interleukini (IL): IL-1, IL-6 i IL-17, povećavaju aktivnost osteoklasta i razgradnju kostiju [24]. Istraživanja pokazuju da su gubitak koštane mase i prelomi povezani sa sistemskim eritemskim lupusom (SEL), što nije u vezi samo sa samom bolešću, već i sa niskim nivoom vitamina D i neželjenim efektima terapije [25].

Uticaj lekova za lečenje autoimunskih reumatskih bolesti na koštanu mineralnu gustinu

Lekovi koji se primenjuju kod autoimunskih reumatskih bolesti su neophodni za lečenje osnovnog oboljenja, ali imaju brojna neželjena dejstva na mišićno-skeletni sistem i gustinu kostiju. Zbog svog antiinflamatornog efekta, glukokortikoidna terapija se često primenjuje kod obolelih od AIRB. Razumevanje mehanizama delovanja glukokortikoida na kost, imunoloških veza i vitamina D, kao i prepoznavanje uticaja hronične inflamacije na koštani metabolizam omogućava bolje razumevanje neželjenih efekata na skelet [26]. Glukokortikoidi umanjuju apsorpciju kalcijuma u digestivnom traktu, povećavaju ekskreciju kalcijuma putem bubrega i suprimiraju funkciju osteoblasta što sve dovodi do smanjene sinteze koštanog tkiva. Takođe doprinose apoptozi osteocita i osteoblasta, što dovodi do povećane resorpcije kostiju. Ovi efekti zajedno doprinose smanjenju BMD-a i povećanju rizika od preloma kostiju [27]. Rizik od preloma kostiju, posebno od preloma kičmenih pršljenova, značajno se povećava nakon kontinuirane upotrebe glukokortikoida tokom tri meseca i nastavlja da se povećava sa njihovom sve dužom upotrebom [28]. Doze kortikosteroida koje su na dnevnom nivou veće od 7,5 mg povećavaju rizik od velikih osteoporotičnih fraktura za 15%, a od preloma kuka za 20% [29]. Kako bi se ovi neželjeni efekti ublažili preporučuje se da se koriste najniže delotvorne terapijske doze glukokortikoida i to tokom najkraćeg mogućeg vremenskog perioda. Uz kortikosteroide je neophodna primena vitamina D i kalcijuma, kako bi se smanjili štetni efekti na koštano tkivo [29].

Klasični lekovi koji modifikuju tok bolesti (engl. *disease-modifying therapies/drugs*), uključujući metotreksat i sulfasalazin, koji se rutinski upotrebljavaju kod obolelih od AIRB, imaju manji uticaj na BMD u odnosu na glukokortikoide. Metotreksat je u nekim studijama povezan sa redukcijom sinteze koštanog matriksa, međutim razlozi za ovo još uvek nisu u potpunosti razjašnjeni. Pacijenti koji se nalaze na terapiji metotreksatom mogu imati povišen rizik od preloma kostiju, što se ne povezuje sa upotrebom terapije nego sa osnovnom bolešću i drugim faktorima rizika [30].

Biološka terapija (inhibitori *TNF* i inhibitori IL) usmerena je na specifične komponente imunskog

tumor necrosis factor (TNF)-alpha and interleukins (IL) such as IL-1, IL-6, and IL-17, increase osteoclast activity and bone resorption [24]. Studies indicate that bone loss and fractures are associated with systemic lupus erythematosus (SLE), which is associated not only with the disease itself but also with low vitamin D levels and adverse effects of therapy [25].

The effect of medications used in the treatment of autoimmune rheumatic diseases on bone mineral density

Medications used in the treatment of autoimmune rheumatic diseases are essential for managing the underlying condition but have numerous adverse effects on the musculoskeletal system and bone density. Owing to its anti-inflammatory effects, glucocorticoid therapy is frequently used in patients with autoimmune rheumatic diseases (ARDs). Understanding the mechanisms of action of glucocorticoids on bone, the immunological interactions, and the role of vitamin D, as well as recognizing the impact of chronic inflammation on bone metabolism, enables a better understanding of their adverse skeletal effects [26]. Glucocorticoids reduce calcium absorption in the gastrointestinal tract, increase renal calcium excretion, and suppress osteoblast function, all of which lead to decreased bone tissue synthesis. They also promote apoptosis of osteocytes and osteoblasts, resulting in increased bone resorption. Together, these effects contribute to a reduction in BMD and an increased fracture risk [27]. The fracture risk, particularly for vertebral fractures, increases significantly after continuous glucocorticoid use for three months and continues to rise with longer duration of therapy [28]. Daily corticosteroid doses exceeding 7.5 mg increase the risk of major osteoporotic fractures by 15% and the risk of hip fractures by 20% [29]. To mitigate these adverse effects, it is recommended to use the lowest effective therapeutic doses of glucocorticoids for the shortest possible duration. Concomitant administration of vitamin D and calcium is necessary to reduce the harmful effects of glucocorticoids on bone tissue [29].

Conventional disease-modifying drugs (disease-modifying antirheumatic drugs, DMARDs), including methotrexate and sulfasalazine, which are routinely used in patients with ARDs, have a lesser impact on BMD compared with glucocorticoids. In some studies, methotrexate has been associated with reduced bone matrix synthesis; however, the reasons for this association have not yet been fully clarified. Patients receiving methotrexate therapy may have an increased fracture risk, which is attributed not to the medication itself but to the underlying disease and other risk factors [30].

odgovora, kako bi se suzbili inflamatorni procesi u organizmu. Time što umanjuju sistemsku inflamaciju, ovi lekovi imaju pozitivan efekat na *BMD* i umanjuju resorpciju kostiju kod pacijenata sa RA i drugim AIRB [31]. Inhibitori Janus kinaze (JK), kao što su tofacitinib i baricitinib, predstavljaju noviju grupu lekova koji modifikuju tok bolesti primenjivanih u lečenju AIRB. Njihov uticaj na *BMD* je još uvek nepoznat. Prema do sada prikupljenim podacima, smatra se da bi oni mogli da imaju neutralan ili čak pozitivan efekat na koštani metabolizam [32]. Hormonska supstitucijska terapija (HST) ima značajnu ulogu u autoimunskim bolestima. Kod hipotireoze indukovane autoimunskim tireoiditisom nadoknada hormona štitaste žlezde održava eutiroidni status, smanjuje simptome hipotireoze i doprinosi očuvanju koštane mase. Time se smanjuje rizik od osteoporoze i preloma, što je čest problem kod pacijenata sa hroničnim autoimunskim poremećajima [33].

DIJAGNOSTIKA

Zlatni standard za postavljanje dijagnoze osteoporoze je *DXA* dijagnostika, koja meri koštanu mineralnu gustinu. Dijagnostički proces započinje kliničkom procenom faktora rizika, koja obuhvata podatke o godinama, polu, prethodnim prelomima, porodičnoj anamnezi osteoporoze, upotrebi glukokortikoida i načinu života [34,35]. Nakon identifikovanja rizičnih pacijenata, sledi izvođenje *DXA* pregleda u predelu lumbalne kičme i vrata femura. Glavni kriterijum neophodan za postavljanje dijagnoze osteoporoze je T-skor $< -2,5$ [36]. Međutim, dijagnostički kriterijumi se ne zasnivaju samo na T-skoru, već je potrebno uzeti u obzir i rizik od preloma, koji se procenjuje na osnovu prethodnih preloma, komorbiditeta i drugih faktora rizika [37]. Z-skor se koristi kod mlađih osoba i žena u perimenopauzi; vrednosti ≤ -2 ukazuju na *BMD* niži od očekivanog za starosno doba pacijenta [38]. Kliničke smernice preporučuju da se *DXA* uradi kod svih žena starijih od 65 godina, kao i kod mlađih žena u postmenopauzi i muškaraca starijih od 50 godina sa dodatnim faktorima rizika [38].

Dopunska laboratorijska dijagnostika uključuje procenu parametara koštanog metabolizma (parathormon, N - terminalni propeptid prokolagena tipa 1, koštana alkalna fosfataza, beta-kroslaps, fosfor, vitamin D i kalcijum), kao i funkcije tireoidne i paratiroidne žlezde. *Fracture Risk Assessment Tool (FRAX)* predstavlja koristan internetski alat koji izračunava desetogodišnju verovatnoću preloma kuka ili drugih značajnih preloma [39]. Unapređena verzija, *FRAX plus*, uključuje dodatne faktore, kao što su: lokalizacija prethodnih preloma, broj padova u prethodnoj

Biological therapy (TNF inhibitors and IL inhibitors) targets specific components of the immune response to suppress inflammatory processes in the body. By reducing systemic inflammation, these agents have a positive effect on *BMD* and decrease bone resorption in patients with RA and other ARDs [31]. Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, represent a newer group of disease-modifying agents used in the treatment of ARDs. Their impact on *BMD* is not yet fully known. Based on currently available data, they are considered to have a neutral or even potentially positive effect on bone metabolism [32]. Hormone replacement therapy (HRT) plays an important role in autoimmune diseases. In hypothyroidism induced by autoimmune thyroiditis, thyroid hormone replacement maintains a euthyroid state, reduces hypothyroid symptoms, and contributes to the preservation of bone mass. This reduces the risk of osteoporosis and fractures, which are common problems in patients with chronic autoimmune disorders [33].

DIAGNOSTICS

The gold standard for diagnosing osteoporosis is dual-energy X-ray absorptiometry (DXA), which measures bone mineral density (BMD). The diagnostic process begins with a clinical assessment of risk factors, including age, sex, previous fractures, family history of osteoporosis, glucocorticoid use, and lifestyle factors [34,35]. After identifying patients at risk, DXA examination of the lumbar spine and femoral neck is performed. The main criterion required for establishing a diagnosis of osteoporosis is a T-score < -2.5 [36]. However, diagnostic criteria are not based solely on the T-score. The fracture risk must also be taken into account, as assessed on the basis of previous fractures, comorbidities, and other risk factors [37]. The Z-score is used in younger individuals and perimenopausal women; values ≤ -2 indicate BMD lower than expected for the patient's age [38]. Clinical guidelines recommend performing DXA in all women older than 65 years, as well as in younger postmenopausal women and men older than 50 years with additional risk factors [38].

Additional laboratory diagnostics include assessment of bone metabolism parameters (parathyroid hormone, N-terminal propeptide of type I procollagen, bone alkaline phosphatase, beta-CrossLaps, phosphorus, vitamin D, and calcium), as well as evaluation of thyroid and parathyroid gland function. The Fracture Risk Assessment Tool (FRAX) is a useful online tool that calculates the 10-year probability of hip fracture or other major osteoporotic fractures [39]. An enhanced version, FRAX Plus, incorporates additional factors such as

Tabela 2. Tumačenje vrednosti skora trabekularne kosti (engl. *trabecular bone score – TBS*)

Aspekt	Opis	Ref.
Definicija	Indirektni parametar kvaliteta trabekularne mikroarhitekture, izveden iz DXA pregleda lumbalne kičme.	41
Način merenja	Računarski algoritam analizira varijacije u sivoj skali DXA slike L1–L4 regiona, nezavisno od BMD.	41
Vrednosti (granice)	TBS $\geq 1,350$ → normalna mikroarhitektura TBS 1,200–1,350 → degradirana mikroarhitektura TBS $\leq 1,200$ → značajno degradirana mikroarhitektura	49
Klinički značaj	Pružila dodatnu procenu rizika od preloma, nezavisno od BMD – Može razlikovati pacijente sa sličnim T-skorom ali različitim rizikom od preloma	41
Prednosti	Jednostavno: koristi postojeće DXA preglede – Nema dodatno zračenje – Korisno kod pacijenata sa sekundarnom osteoporozom (RA, SEL, DM tip 2)	43
Ograničenja	Manja pouzdanost kod ekstremnog indeksa telesne mase – BMI (< 15 ili > 37 kg/m ²) – Samo lumbalni region (L1–L4) – Nije zamena za BMD, već dopuna	41
Preporuke za primenu	U kombinaciji sa BMD i FRAX skorom – za precizniju procenu rizika od preloma, posebno kod pacijenata sa „graničnim“ BMD vrednostima ili sekundarnim faktorima rizika.	49

Table 2. Interpretation of trabecular bone score values (TBS)

Aspect	Description	Ref.
Definition	An indirect parameter of trabecular microarchitecture quality, derived from DXA assessment of the lumbar spine.	41
Measurement method	A computer algorithm analyzes variations in the grayscale DXA image of the L1–L4 region, independent of BMD.	41
Values (cut-off values)	TBS ≥ 1.350 → normal microarchitecture TBS 1.200–1.350 → degraded microarchitecture TBS ≤ 1.200 → significantly degraded microarchitecture	49
Clinical significance	Provides additional assessment of fracture risk, independent of BMD – Can differentiate between patients with similar T-score but different fracture risk	41
Advantages	Simple: uses existing DXA scans – No additional radiation – Useful in patients with secondary osteoporosis (RA, SLE, Type 2 DM)	43
Limitations	Less reliable in extreme body mass index – BMI (< 15 or > 37 kg/m ²) – Lumbar region only (L1–L4) – Not a substitute for BMD, but a supplementary method	41
Recommendations for application	Used in combination with BMD and the FRAX score – for a more accurate assessment of fracture risk, especially in patients with “borderline” BMD values or secondary risk factors.	49

godini, doze kortikosteroida i skor trabekularne kosti (engl. *trabecular bone score – TBS*), čime se poboljšava preciznost procene rizika [40]. Tumačenje vrednosti TBS-a prikazano je u Tabeli 2. Tabela prikazuje osnovne informacije o skoru trabekularne kosti – TBS: šta meri (mikroarhitektura kosti), kako se meri (analizom DXA snimka lumbalne kičme), klinički značaj (dopuna BMD u proceni rizika od preloma), prednosti, ograničenja i preporuke za primenu.

Pojedini dijagnostički kriterijumi koji se rutinski koriste kod zdrave populacije mogu biti nepouzdana kod obolelih od autoimunskih reumatskih bolesti. Kod pacijenata sa AIRB (RA, axSpA, PsA, SEL) neophodno je prilagoditi dijagnostički pristup jer bolest i terapija mogu da utiču na rezultate DXA merenja. Lokalizovana razređenja kostiju kod RA i novoformirana kost kod axSpA mogu dovesti do lažno sniženih ili lažno povišenih vrednosti BMD, pa je tumačenje nalaza otežano [41].

the location of previous fractures, the number of falls in the preceding year, corticosteroid doses, and the trabecular bone score (TBS), thereby improving the accuracy of risk assessment [40]. Interpretation of TBS values is presented in Table 2. The table summarizes key aspects of TBS: what it measures (bone microarchitecture), how it is measured (analysis of lumbar spine DXA images), clinical significance (complement to BMD in fracture risk assessment), advantages, limitations, and recommended use.

Certain diagnostic criteria routinely used in the general population may be unreliable in patients with autoimmune rheumatic diseases. In patients with ARDs (RA, axSpA, PsA, SLE), it is necessary to adapt the diagnostic approach because both the disease itself and its treatment may affect DXA measurement results. Localized bone loss in RA and new bone formation in axSpA may lead to falsely low or falsely elevated BMD values, making interpretation more challenging [41].

U ovim slučajevima može biti korisno dodatno merenje periferne koštane gustine, kao što je *BMD* distalne podlaktice, kao i upotreba *TBS*-a za precizniju procenu rizika od preloma. Kod pacijenata sa *axSpA* i visokim rizikom od preloma preporučuje se kombinovanje *DXA* i *TBS* metoda radi bolje identifikacije onih kojima je potrebna rana intervencija [42]. Pravovremena procena i kontinuirano praćenje su od ključnog značaja, naročito kod pacijenata na dugotrajnoj terapiji glukokortikoidima, kod kojih se preporučuje češća kontrola *BMD*-a i reevaluacija rizika od preloma [43].

Primena *FRAX* algoritma kod pacijenata sa autoimunskim reumatskim bolestima ima poseban klinički značaj jer omogućava ranu identifikaciju osoba sa povišenim rizikom od preloma i olakšava odluku o započinjanju specifične terapije. Uključivanje podataka o upotrebi glukokortikoida u *FRAX* indeks značajno doprinosi preciznijoj proceni rizika od preloma, imajući u vidu da hronična glukokortikoidna terapija predstavlja jedan od vodećih uzroka sekundarne osteoporoze [41]. Kada se u *FRAX* unese i izmerena vrednost *BMD* na vratu femura, procena rizika postaje još pouzdanija, što je od posebnog značaja kod pacijenata sa RA ili *axSpA*, kod kojih se osteoporoza može javiti u mlađem životnom dobu [44].

Ipak, važno je naglasiti da *FRAX* ne uzima u obzir aktivnost bolesti, stepen inflamacije, funkcionalnu onesposobljenost ili učestalost padova, zbog čega može da potceni rizik kod pacijenata sa visoko aktivnom bolešću ili kod onih sa značajnim strukturnim oštećenjem. Takođe, standardni *FRAX* model ne pravi razliku između niskih i visokih doza glukokortikoida, pa se kod pacijenata na dugotrajnoj terapiji dozama većim od 7,5 mg prednizona preporučuje korekcija izračunatog rizika za dodatnih 15-20% [45].

Zbog ovih ograničenja preporučuje se kombinovanje *FRAX* alata sa dodatnim metodama procene, kao što su *TBS* i vertebralna morfometrija, kako bi se unapredilo identifikovanje pacijenata sa visokim rizikom od preloma i optimizovalo donošenje terapijskih odluka. Vertebromorfometrija (engl. *lateral vertebral assessment – LVA*) predstavlja slikovnu metodu kojom se, korišćenjem *DXA* metode, vrši detekcija i analiza vertebralnih fraktura. Za razliku od klasične radiografije, *LVA* omogućava nižu dozu zračenja i bržu procenu deformiteta kičmenih pršljenova. U kontekstu osteoporoze i autoimunskih bolesti, *LVA* je posebno korisna jer otkrivanjem fraktura omogućava blagovremenu korekciju terapije i precizniju procenu rizika od novih preloma [46]. **Table 3 and Figure 1** prikazuje *FRAX* upitnik na srpskom jeziku. Na slici je prikazan algoritam prevencije i lečenja pacijenata sa osteoporozom, prema literaturnim podacima.

In such cases, additional assessment of peripheral bone density, such as *BMD* of the distal forearm, as well as the use of *TBS*, may be useful for a more accurate evaluation of fracture risk. In patients with *axSpA* and a high fracture risk, combining *DXA* and *TBS* methods is recommended to better identify those who require early intervention [42]. Timely assessment and continuous monitoring are of crucial importance, particularly in patients receiving long-term glucocorticoid therapy, in whom more frequent *BMD* monitoring and reassessment of fracture risk are recommended [43].

The application of the *FRAX* algorithm in patients with autoimmune rheumatic diseases has particular clinical significance, as it enables early identification of individuals at increased fracture risk and facilitates decisions regarding the initiation of specific therapy. Inclusion of data on glucocorticoid use in the *FRAX* index significantly contributes to a more accurate fracture risk assessment, given that chronic glucocorticoid therapy is one of the leading causes of secondary osteoporosis [41]. When the measured *BMD* value at the femoral neck is also entered into *FRAX*, risk estimation becomes even more reliable, which is particularly important in patients with RA or *axSpA*, in whom osteoporosis may occur at a younger age [44].

However, it is important to emphasize that *FRAX* does not take into account disease activity, the degree of inflammation, functional disability, or the frequency of falls, and therefore may underestimate risk in patients with highly active disease or those with significant structural damage. In addition, the standard *FRAX* model does not differentiate between low and high doses of glucocorticoids. Thus, in patients receiving long-term therapy with doses exceeding 7.5 mg of prednisone, adjustment of the calculated risk by an additional 15-20% is recommended [45].

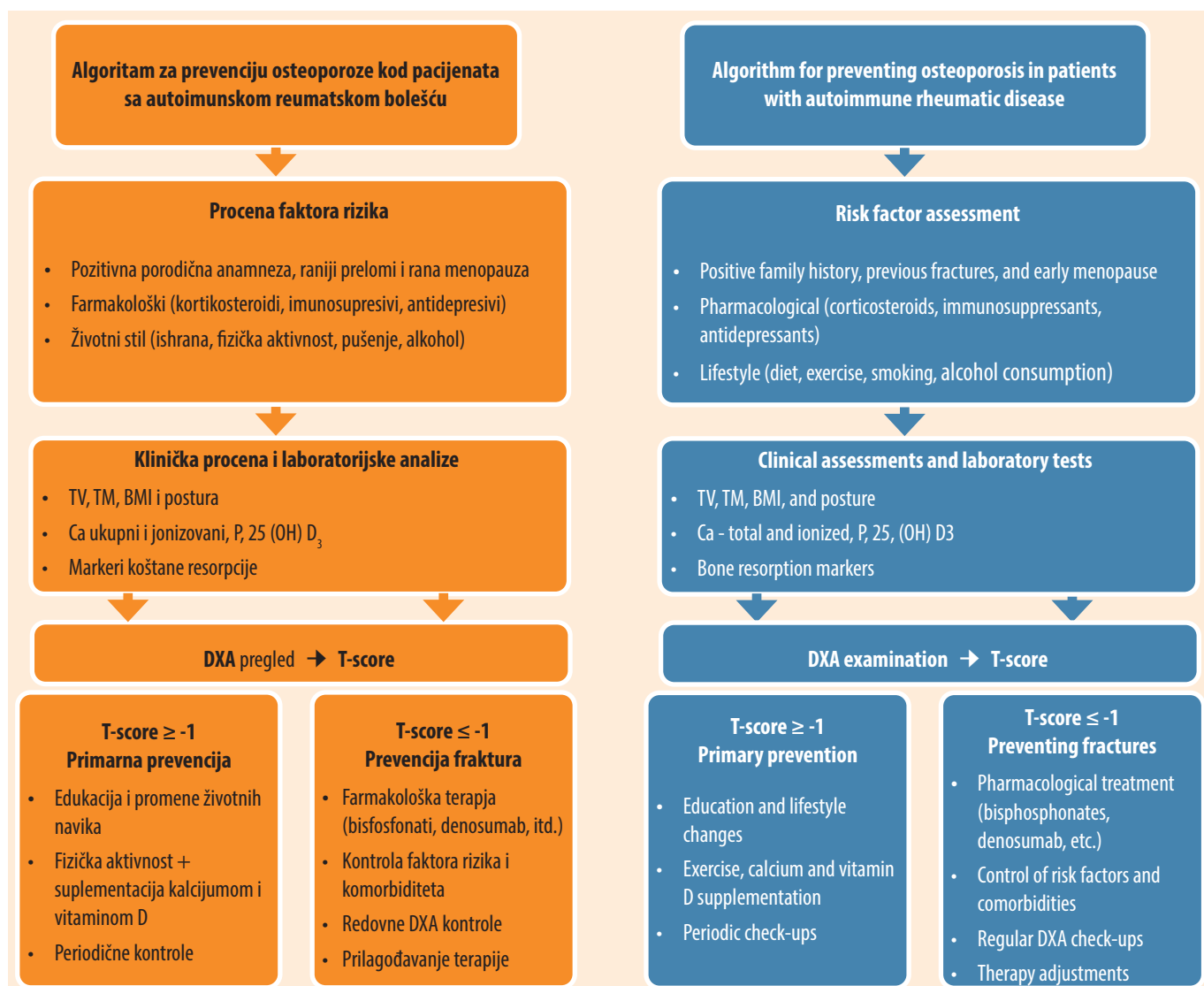
Because of these limitations, combining the *FRAX* tool with additional assessment methods, such as *TBS* and vertebral morphometry, is recommended in order to improve identification of patients at high fracture risk and optimize therapeutic decision-making. Vertebral morphometry (*lateral vertebral assessment – LVA*) is an imaging method that uses *DXA* to detect and analyze vertebral fractures. Unlike conventional radiography, *LVA* allows for lower radiation exposure and faster assessment of vertebral deformities. In the context of osteoporosis and autoimmune diseases, *LVA* is particularly useful because detecting fractures enables timely adjustment of therapy and a more accurate assessment of the risk of subsequent fractures [46]. **Table 3 and Figure 1** presents the *FRAX* questionnaire. Figure 1 presents the algorithm designed to assist in the prevention and treatment of osteoporosis, according to the literature.

Tabela 3. TFRAX upitnik

Pitanje	Odgovor
1. Životno doba (između 40 i 90 godina)	_____
2. Pol	☐ Ženski ☐ Muški
3. Težina (kg)	_____
4. Visina (cm)	_____
5. Prethodni prelom	☐ Da ☐ Ne
6. Roditelj sa prelomom kuka	☐ Da ☐ Ne
7. Trenutno pušim	☐ Da ☐ Ne
8. Glukokortikoidi	☐ Da ☐ Ne
9. Reumatoidni artritis	☐ Da ☐ Ne
10. Sekundarna osteoporoza	☐ Da ☐ Ne
11. Alkohol ≥ 3 jedinice/dan	☐ Da ☐ Ne
12. BMD vrata bedrene kosti	_____

Table 3. The FRAX questionnaire

Question	Answer
1. Age (between 40 and 90 years)	_____
2. Sex	☐ Female ☐ Male
3. Weight (kg)	_____
4. Height (cm)	_____
5. Previous fracture	☐ Yes ☐ No
6. Parent with a hip fracture	☐ Yes ☐ No
7. I currently smoke	☐ Yes ☐ No
8. Glucocorticoids	☐ Yes ☐ No
9. Rheumatoid arthritis	☐ Yes ☐ No
10. Secondary osteoporosis	☐ Yes ☐ No
11. Alcohol ≥ 3 units/day	☐ Yes ☐ No
12. Femoral neck BMD	_____



Slika 1. Algoritam za pristup pacijentu sa povišenim rizikom od nastanka osteoporoze [33,34,36]

Figure 1. Algorithm for the management of patients at increased risk of developing osteoporosis [33,34,36]

SMERNICE ZA KLINIČKU PRAKSU

Pravovremeno prepoznavanje faktora rizika, edukacija pacijenata, i započinjanje odgovarajuće terapije mogu značajno da smanje rizik od preloma i poboljšaju kvalitet života. Prevencija obuhvata modifikaciju faktora rizika, suplementaciju kalcijuma i vitamina D, prilagođenu fizičku aktivnost, redovno praćenje gustine kostiju i prevenciju padova [33].

Terapija prvog izbora za lečenje osteoporoze kod većine pacijenata zasniva se na primeni lekova sa anti-resorptivnim efektom, pre svega oralnih bisfosfonata, u skladu sa preporukama Američkog udruženja endokrinologa (engl. *American Association of Endocrinologists – AACE*) [47]. Kod pacijenata koji imaju intoleranciju ili kontraindikacije za oralne bisfosfonate, primena intravenskih bisfosfonata ili denosumaba predstavlja alternativu. Obe kategorije medikamenata spadaju u grupu anti-resorptivnih lekova. Bisfosfonati, bez obzira na način primene (oralni ili intravenski), direktno inhibiraju osteoklastnu aktivnost, dok denosumab, koji predstavlja monoklonoalno antitelo koje se vezuje za ligand aktivatora receptora nuklearnog faktora Kappa-B (engl. *Receptor Activator of Nuclear factor Kappa-B Ligand-RANKL*), svoje anti-resorptivno delovanje ostvaruje indirektno [48]. Selektivni modulatori estrogenskih receptora (engl. *selective estrogen receptor modulators – SERMs*) mogu se razmotriti kao dodatna opcija, naročito kod žena u postmenopauzi sa umerenim rizikom. Za pacijente sa visokim rizikom od preloma koji ne mogu da koriste oralnu terapiju, preporučuje se primena denosumaba ili teriparatida (rekombinantnog oblika parathormona), koji se primenjuju subkutano. Kod pacijenata sa veoma visokim rizikom od fraktura ili onih koje su već imali višestruke prelome, preporučuje se uvođenje anaboličkih lekova (teriparatid) ili lekova sa dvostrukim mehanizmom dejstva, kao što je romosozumab. Lek romosozumab je monoklonoalno antitelo koje inhibira sklerostin i time utiče na formiranje nove kosti i umanjuje aktivnost osteoklasta. Aplikuje se jednom godišnje subkutanim putem. Važno je naglasiti da se rizik od preloma procenjuje nakon svake nove fraktуре, bez obzira na vreme njenog nastanka, i da se rizik povećava nakon prekida terapije [49].

Kod pacijenata sa RA dodatnu ulogu u zaštiti kostiju ima adekvatno lečenje osnovne bolesti. Konvencionalni lekovi koji modifikuju tok bolesti (npr. metotreksat) i biološki lekovi (TNF inhibitori, IL-6 inhibitori, rituksimab, abatacept) smanjuju aktivnost bolesti i time redukuju inflamaciju, što može pozitivno da utiče na metabolizam kostiju, iako je njihov efekat na BMD ograničen [50].

Kod odraslih osoba, koje započinju ili nastavljaju glukokortikoidnu terapiju duže od tri meseca, pre-

CLINICAL PRACTICE GUIDELINES

Timely identification of risk factors, patient education, and initiation of appropriate therapy can significantly reduce fracture risk and improve quality of life. Prevention includes modification of risk factors, calcium and vitamin D supplementation, appropriately tailored physical activity, regular monitoring of bone density, and fall prevention strategies [33].

First-line therapy for the treatment of osteoporosis in most patients is based on the use of anti-resorptive agents, primarily oral bisphosphonates, in accordance with the recommendations of the American Association of Clinical Endocrinology (AACE) [47]. In patients who are intolerant of or have contraindications to oral bisphosphonates, intravenous bisphosphonates or denosumab are alternative options. Both categories of medications belong to the group of anti-resorptive drugs. Bisphosphonates, regardless of the route of administration (oral or intravenous), directly inhibit osteoclast activity, whereas denosumab, a monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand (RANKL), exerts its anti-resorptive effect indirectly [48]. Selective estrogen receptor modulators (SERMs) may be considered as an additional option, particularly in postmenopausal women who are at moderate risk. For patients at high risk of fracture who are unable to use oral therapy, treatment with denosumab or teriparatide (a recombinant form of parathyroid hormone), administered subcutaneously, is recommended. In patients at very high risk of fracture or those who have already sustained multiple fractures, initiation of anabolic agents (teriparatide) or agents with a dual mechanism of action, such as romosozumab, is recommended. Romosozumab is a monoclonal antibody that inhibits sclerostin, thereby promoting new bone formation and reducing osteoclast activity. It is administered subcutaneously once a year. It is important to emphasize that fracture risk should be reassessed after each new fracture, regardless of the time of occurrence, and that fracture risk increases after discontinuation of therapy [49].

In patients with rheumatoid arthritis (RA), adequate treatment of the underlying disease plays an additional role in bone protection. Conventional disease-modifying antirheumatic drugs (e.g., methotrexate) and biological agents (TNF inhibitors, IL-6 inhibitors, rituximab, abatacept) reduce disease activity and thereby decrease inflammation, which may have a beneficial effect on bone metabolism, although their direct impact on BMD is limited [50].

In adults who are beginning or continuing glucocorticoid therapy for longer than three months, the recommendations of the American College of Rheu-

ma preporukama Američkog reumatološkog koledža (engl. *American College of Rheumatology – ACR*) neophodno je sprovesti inicijalnu procenu rizika od fraktura odmah nakon početka terapije. Kod osoba starijih od 40 godina procena obuhvata kliničku evaluaciju prethodnih fraktura, DXA merenje sa vertebralnom procenom fraktura (LVA) ili rendgenski pregled kičmenog stuba, kao i izračunavanje FRAX rizika kod osoba starijih od 40 godina. Kod pacijenata sa umerenim, visokim ili veoma visokim rizikom od fraktura, snažno se preporučuje započinjanje farmakološke terapije – oralnim ili intravenskim bisfosfonatima, denosumabom ili teriparatidom. Kod pacijenata sa deficitom hormona, supstituciona terapija takođe može da doprinese modulaciji imunskog odgovora i smanjenju rizika od komplikacija povezanim sa autoimunskim bolestima. [50]. Navedene preporuke predstavljene su u Tabeli 4. sa odgovarajućim referencama. Tabela prikazuje različite vrste terapije za osteoporozu, uključujući primere lekova, njihov mehanizam delovanja i indikacije. Obu-

matology (ACR) emphasize the need for an initial fracture risk assessment immediately after beginning treatment. In individuals older than 40 years, this assessment includes clinical evaluation of prior fractures, DXA measurement with lateral vertebral assessment (LVA) or spinal radiography, as well as calculation of the FRAX risk. In patients with moderate, high, or very high fracture risk, initiation of pharmacological therapy – oral or intravenous bisphosphonates, denosumab, or teriparatide – is strongly recommended. In patients with hormone deficiencies, substitution therapy may also contribute to the modulation of the immune response and the reduction of the risk of complications associated with autoimmune diseases [50]. These recommendations are presented in Table 4 with the corresponding references. This table presents different treatments for osteoporosis, including examples of drugs, their mechanisms of action, and indications. It covers oral and intravenous bisphosphonates, RANKL monoclonal antibodies, selective estrogen receptor

Tabela 4. Pregled terapije osteoporoze: mehanizmi i indikacije

Vrsta terapije	Primeri lekova/metoda	Mehanizam delovanja	Indikacije/napomene	Reference
Oralni bisfosfonati	Alendronat, Ibandronat	Direktna inhibicija osteoklasta → smanjenje resorpcije kostiju	Terapija prvog izbora kod većine pacijenata	49
Intravenozni bisfosfonati	Zoledronat	Direktna inhibicija osteoklasta → smanjenje resorpcije kostiju	Alternativa kod intolerancije ili kontraindikacija na oralne bisfosfonate	49, 52
Monoklonoalno antitelo protiv RANKL	Denosumab	Indirektno antiresorptivno dejstvo: inhibicija aktivacije osteoklasta	Pacijenti sa visokim rizikom od preloma, intolerancija na bisfosfonate	52
Selektivni modulatori estrogenih receptora (SERM)	Raloksifen	Modulacija estrogenih receptora u kostima → smanjenje resorpcije	Žene u postmenopauzi sa umerenim rizikom od preloma	49
Anabolički lekovi	Teriparatid (PTH 1–34)	Stimulacija osteoblasta → povećanje stvaranja nove koštane mase	Visok rizik od preloma, višestruke frakture, neefikasna antiresorptivna terapija	49
Lekovi sa dvostrukim mehanizmom	Romosozumab	Anaboličko dejstvo + smanjenje resorpcije	Veoma visok rizik od preloma	49

Table 4. Overview of osteoporosis therapy: mechanisms and indications

Type of therapy	Examples of drugs/methods	Mechanism of action	Indications/annotations	Reference
Oral bisphosphonates	Alendronate, Ibandronate	Direct inhibition of osteoclasts → reduction of bone resorption	First-line therapy in most patients	49
Intravenous bisphosphonates	Zoledronate	Direct inhibition of osteoclasts → reduction of bone resorption	Alternative in case of intolerance or contraindication to oral bisphosphonates	49, 52
Anti-RANKL monoclonal antibody	Denosumab	Indirect antiresorptive effect: inhibition of osteoclast activation	Patients with a high fracture risk, intolerance to bisphosphonates	52
Selective estrogen receptor modulators (SERMs)	Raloxifene	Modulation of estrogen receptors in bones → reduction of resorption	Postmenopausal women with a moderate risk of fracture	49
Anabolic drugs	Teriparatide (PTH 1–34)	Stimulation of osteoblasts → increased formation of new bone mass	High fracture risk, multiple fractures, ineffective antiresorptive therapy	49
Drugs action drugs	Romosozumab	Anabolic effect + reduction of resorption	Very high fracture risk	49

hvata oralne i intravenske bisfosfonate, monoklonalna antitela protiv RANKL, selektivne modulatora estrogennih receptora (SERM) i anaboličke lekove poput teriparatida i romosozumaba, uz napomenu kada se koja terapija primenjuje.

Fracture Liaison Services (FLS) predstavlja organizovani model čiji je glavni cilj smanjenje rizika od preloma kod osoba starijih od 50 godina, kroz pravovremeno postavljanje dijagnoze i započinjanje adekvatnog lečenja osteoporoze. Najnovija istraživanja pokazuju da je implementacija *FLS* protokola dovela do značajnog smanjenja rizika od preloma kod oba pola (za 13% kod žena i za 10% kod muškaraca), kao i do smanjenja stope mortaliteta za 18% kod žena i za 15% kod muškaraca [51]. Uvođenje *FLS* pristupa kod pacijenata sa AIRB ima poseban značaj jer omogućava pravovremenu dijagnostiku, rano započinjanje terapije i multidisciplinarni pristup koji uključuje reumatologa, endokrinologa i fizijatra [52].

ZAKLJUČAK

Osteoporoza je česta i ozbiljna komplikacija autoimunskih reumatskih bolesti koja značajno utiče na kvalitet života i funkcionalni status obolelih. Njeno nastajanje je multifaktorijsko: hronična inflamacija i imunološka disregulacija pospešuju aktivaciju osteoklasta i ubrzano resorptivno propadanje kosti, dok farmakološki tretmani, posebno dugotrajna terapija glukokortikoidima, dodatno inhibiraju osteoblastnu funkciju i smanjuju mineralnu gustinu kostiju. Osim toga, ograničena pokretljivost i smanjena fizička aktivnost kod pacijenata sa bolom i deformitetima doprinose progresiji osteoporoze.

Prevenција osteoporoze predstavlja osnovu očuvanja koštane mase i smanjenja rizika od preloma kod pacijenata sa autoimunskim reumatskim bolestima. Ključni preventivni pristupi uključuju prilagođenu fizičku aktivnost, obezbeđivanje adekvatnog unosa kalcijuma i vitamina D, kao i smanjenje faktora rizika povezanih sa medikamentoznom terapijom i životnim stilom. Pravovremeno identifikovanje pacijenata sa povećanim rizikom putem kliničke procene faktora rizika, *DXA* pregleda, *FRAX* indeksa i dodatnih metoda, kao što je *TBS*, omogućava rano uvođenje preventivnih mera i personalizovanog praćenja. Ukoliko prevencija nije dovoljna i dolazi do progresije osteoporoze, ciljano farmakološko lečenje, uzimajući u obzir tip i aktivnost osnovne bolesti, može značajno da smanji rizik od preloma i očuva funkcionalni kapacitet pacijenata. Farmakološke strategije, uključujući antiresorptivne i anaboličke lekove, trebalo bi da budu individualizovane, uzimajući u obzir tip i aktivnost osnovne bolesti, starost pacijenta i prisustvo komorbiditeta. Integraci-

modulators (SERMs), and anabolic drugs such as teriparatide and romosozumab, along with guidelines on when each treatment is used.

Fracture Liaison Services (FLS) represent an organized care model whose primary goal is to reduce fracture risk in individuals older than 50 years through timely diagnosis and initiation of appropriate osteoporosis treatment. Recent studies show that implementation of FLS protocols has led to a significant reduction in fracture risk in both sexes (by 13% in women and by 10% in men), as well as a reduction in mortality rates by 18% in women and by 15% in men [51]. The introduction of the FLS approach in patients with autoimmune rheumatic diseases is of particular importance, as it enables timely diagnosis, early initiation of therapy, and a multidisciplinary approach involving a rheumatologist, endocrinologist, and physiatrist [52].

CONCLUSION

Osteoporosis is a common and serious complication of autoimmune rheumatic diseases that significantly affects patients' quality of life and functional status. Its development is multifactorial: chronic inflammation and immune dysregulation promote osteoclast activation and accelerated bone resorption, while pharmacological treatments, particularly long-term glucocorticoid therapy, further inhibit osteoblast function and reduce bone mineral density. In addition, limited mobility and reduced physical activity in patients with pain and deformities contribute to the progression of osteoporosis.

Prevention of osteoporosis represents the cornerstone of preserving bone mass and reducing fracture risk in patients with autoimmune rheumatic diseases. Key preventive approaches include appropriately tailored physical activity, ensuring adequate intake of calcium and vitamin D, and reducing risk factors related to pharmacological therapy and lifestyle. Timely identification of patients at increased risk through clinical assessment of risk factors, *DXA* scanning, the *FRAX* index, and additional methods, such as *TBS*, enables early implementation of preventive measures and personalized follow-up. When prevention is insufficient, and osteoporosis progresses, targeted pharmacological treatment – taking into account the type and activity of the underlying disease – can significantly reduce the fracture risk and preserve patients' functional capacity. Pharmacological strategies, including antiresorptive and anabolic agents, should be individualized, taking into account the type and activity of the underlying disease, patient age, and the presence of comorbidities. Integration of therapy for the underlying disease with specific osteoporosis treatment significantly re-

ja terapije osnovne bolesti sa specifičnim tretmanom osteoporoze značajno smanjuje rizik od preloma i doprinosi očuvanju funkcionalnog kapaciteta pacijenata.

Multidisciplinarni pristup je ključan za optimizaciju strategija prevencije, praćenja i lečenja. Buduća istraživanja trebalo bi da se usmere ka ciljanim terapijama koje umanjuju gubitak koštane mase bez ugrožavanja imunske kontrole, kao i na unapređenje alata za procenu rizika kako bi se identifikovali pacijenti sa visokim rizikom od razvoja osteoporoze. Tretirajući osteoporozu kao sastavni deo lečenja autoimunskih bolesti, kliničari mogu da smanje rizik od preloma i da poboljšaju dugoročni kvalitet života obolelih.

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ONCO-HYPERTENSION – A NEW CLINICAL ENTITY IN MODERN MEDICINE

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SAŽETAK

Kardiovaskularna i onkološka oboljenja u savremenom dobu predstavljaju neizostavni deo svakodnevne medicinske prakse na svim nivoima zdravstvene zaštite. Osim zajedničkih faktora rizika, ova oboljenja povezana su i na druge načine, a posebno je značajna potencijalna kardiotskičnost antineoplastičnih lekova. Jedan od čestih oblika kardiotskičnosti antineoplastične terapije je hipertenzija. S obzirom na to da se može manifestovati bilo kada tokom primene antineoplastične terapije, ali i po završetku specifičnog onkološkog lečenja, onkohipertenzija je klinički entitet o kojem uvek treba razmišljati pri susretu sa onkološkim pacijentima. Redovna kontrola arterijskog krvnog pritiska u ovoj populaciji neophodna je kako bi se obezbedilo blagovremeno prepoznavanje i lečenje onkohipertenzije, u cilju bezbednog sprovođenja onkološkog tretmana. Iako smernice za lečenje onkohipertenzije ne odstupaju značajno od opštih preporuka za lečenje hipertenzije, postoje određene specifičnosti koje se najpre odnose na izbor antihipertenziva i odstupanja u smislu ciljnih vrednosti arterijskog krvnog pritiska, u zavisnosti od stadijuma onkološkog oboljenja i prognoze. Veoma je važno prepoznati i momenat kada je neophodno obustaviti kardiotskičnu antineoplastičnu terapiju ili redukovati dozu antineoplastičnog leka, kako bi se izbegle životno ugrožavajuće kardiovaskularne posledice. Složenosti problema onkohipertenzije značajno doprinose i brojni faktori koji se susreću kod onkoloških pacijenata, poput komorbiditeta, prisustva bola ili drugih primenjenih lekova. S obzirom na to da se radi o veoma osetljivoj populaciji izloženoj posebnoj vrsti psihološkog stresa, posebno treba imati u vidu i mogućnost „efekta belog mantila“, kao i maskiranu hipertenziju.

Ključne reči: hipertenzija, maligna oboljenja, kardiotskičnost

ABSTRACT

Cardiovascular and oncological diseases represent an inevitable part of everyday medical practice at all levels of health care. Apart from common risk factors, these diseases are associated in other ways, and the potential cardiotoxicity of antineoplastic drugs is particularly significant. One of the frequent forms of cardiotoxicity is hypertension. Considering that it can manifest at any time during antineoplastic therapy and also after the completion of specific oncological treatment, onco-hypertension is a clinical entity that should always be kept in mind when caring for oncology patients. Regular arterial blood pressure checks in this population are necessary to ensure timely recognition and treatment of onco-hypertension and to carry out oncological treatment safely. Although the guidelines for the treatment of onco-hypertension are similar to the general recommendations for hypertension, some specificities primarily concern the choice of antihypertensive drugs and exceptions to target arterial blood pressure values depending on the stage of the oncological disease and its prognosis. It is crucial to recognize the time to stop cardiotoxic antineoplastic therapy or reduce the dose of the antineoplastic drug to avoid life-threatening cardiovascular complications. Numerous additional factors encountered in oncology patients, such as comorbidities, the presence of pain or other administered drugs, significantly contribute to the complexity of onco-hypertension. Given that this is a very sensitive population exposed to a specific type of psychological stress, the possibility of the “white coat effect” as well as masked hypertension should also be considered.

Keywords: hypertension, malignant diseases, cardiotoxicity

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UVOD

Pojam kardiotoksičnosti u sklopu lečenja onkoloških oboljenja pomenut je još početkom 70-ih godina prošlog veka [1]. Tokom 2020. godine širom sveta je dijagnostikovano skoro 20 miliona novih slučajeva malignih oboljenja, a iste godine je oko 10 miliona onkoloških pacijenata preminulo [2]. U proteklih 30 godina broj pacijenata sa hipertenzijom se udvostručio, tako da ih je 2019. godine bilo 1,3 milijardi u celom svetu [3]. Od približno 20 miliona kardiovaskularnih smrtnih ishoda godišnje, oko 50% slučajeva povezuje se upravo sa hipertenzijom [4,5]. Zbog svega gore navedenog, 2022. godine objavljen je prvi evropski vodič posvećen oblasti kardioonkologije [6]. Ipak, od svih kardiovaskularnih oboljenja, hipertenzija je najčešći komorbiditet onkoloških pacijenata [7]. Učestalost hipertenzije u populaciji onkoloških bolesnika je oko 40%, što je značajno više nego u opštoj populaciji. Shodno tome, u literaturi se tokom proteklih nekoliko godina pojavio novi pojam, onkohipertenzija [8].

Cilj rada je sagledavanje povezanosti hipertenzije, onkoloških oboljenja i antineoplastične terapije. Dodatni cilj je isticanje preporuka za lečenje onkohipertenzije i specifičnosti ovog terapijskog pristupa koje je potrebno imati u vidu na svim nivoima zdravstvene zaštite kako bi se obezbedilo blagovremeno i adekvatno zbrinjavanje pacijenata.

Hipertenzija i maligna bolest

Onkohipertenzija ima četiri osnovna aspekta. Hipertenzija može biti uzrok malignog oboljenja [9–15], ali i posledica malignog oboljenja [16–18] ili primenjene antineoplastične terapije [19]. Ponekad se maligno oboljenje može dovesti u vezu i sa prethodnom antihipertenzivnom terapijom [20,21]. Poznato je da pacijenti sa hipertenzijom imaju oko dva puta veći rizik za nastajanje karcinoma bubrega, posebno ukoliko su vrednosti arterijskog krvnog pritiska preko 160/100 mmHg [9]. Kod muškaraca je ustanovljena povezanost hipertenzije sa kolorektalnim karcinomom i karcinomom prostate [13,14], dok kod žena postoji povezanost hipertenzije sa pojavom karcinoma dojke u postmenopauzalnom periodu [15]. Antihipertenzivna terapija kao uzrok malignih oboljenja je polje koje zahteva dodatna istraživanja. Iz etičkih razloga, nijedna randomizovana klinička studija nije dizajnirana da pruži odgovor na ovo pitanje. Za sada je dodatna pažnja usmerena na diuretike – zbog eventualnog rizika od razvoja karcinoma bubrega, tiazidne diuretike – zbog povećanja rizika za nastajanje skvamocelularnog karcinoma kože, kao i na inhibitore angiotenzin-konvertujućeg enzima – zbog izvesnog povećanja rizika od karcinoma pluća [20–22]. Hipertenzija može biti i po-

INTRODUCTION

The concept of cardiotoxicity in the context of cancer treatment was first mentioned in the early 1970s [1]. In 2020, nearly 20 million new cancer cases were diagnosed worldwide, while approximately 10 million oncology patients died during the same year [2]. Over the past 30 years, the number of patients with hypertension has doubled, reaching 1.3 billion globally in 2019 [3]. Of the approximately 20 million annual cardiovascular deaths, around 50% are directly associated with hypertension [4,5]. Given the facts mentioned above, the first European guideline dedicated to cardio-oncology was published in 2022 [6]. Nevertheless, among all cardiovascular diseases, hypertension remains the most common comorbidity in oncology patients [7]. The prevalence of hypertension among oncology patients is about 40%, which is significantly higher than in the general population. Consequently, in recent years, the term onco-hypertension has emerged in the literature [8].

This paper examines the relationship among hypertension, malignancy, and antineoplastic therapy. An additional goal is to highlight the recommendations for the management of onco-hypertension and the specific therapeutic considerations that must be taken into account at all levels of healthcare to ensure timely and adequate patient management.

Hypertension and Malignancy

Onco-hypertension has four main aspects. Hypertension may be the cause of malignant disease [9–15], a consequence of malignancy [16–18], or the result of antineoplastic therapy [19]. Sometimes malignancy can also be linked to prior antihypertensive treatment [20,21]. It is known that patients with hypertension have approximately twice the risk of developing renal cancer, especially when blood pressure values exceed 160/100 mmHg [9]. Among men, hypertension has been associated with colorectal and prostate cancer [13,14], while in women it has been linked to postmenopausal breast cancer [15]. Antihypertensive therapy as a potential cause of malignancy is an area that requires further investigation. For ethical reasons, no randomized clinical trial has been designed to address this question. Currently, attention is focused on diuretics—due to a possible risk of renal cancer; thiazide diuretics—because of the increased risk of cutaneous squamous cell carcinoma; and angiotensin-converting enzyme inhibitors—due to a potential increase in lung cancer risk [20–22]. Hypertension may also occur as a consequence of malignancy itself, representing a component of paraneoplastic syndromes, such as those associated with renal cell

sledica maligne bolesti, odnosno deo paraneoplastičnog sindroma, što je slučaj kod karcinoma bubrega, hepatocelularnog karcinoma, mekotkivnog sarkoma i karcinoidnog sindroma [16–18]. Ipak, najveću oblast onkohipertenzije predstavlja hipertenzija kao posledica kardiotoksičnosti antineoplastične terapije [19,23]

carcinoma, hepatocellular carcinoma, soft-tissue sarcoma, and carcinoid syndrome [16–18]. However, the most prominent aspect of onco-hypertension is hypertension as a manifestation of cardiotoxicity induced by antineoplastic therapy [19,23] (Table 1). According to literature data, 99% of children treated for

Tabela 1. Grupe antineoplastičnih lekova koji mogu prouzrokovati hipertenziju

ANTINEOPLASTIČNA TERAPIJA	PRIMENA U ONKOLOGIJI	UČESTALOST ONKOHIPERTENZIJE
Inhibitori signalnog puta vaskularnog endotelog faktora rasta (VEGF-Spi)	Metastatski tumori (renalni, hepatocelularni, tiroidni, gastro-intestinalni, stromalni)	20%–90% *U zavisnosti od jačine i doze leka
Derivati platine	Karcinom testisa (najčešći malignitet kod mladih muškaraca), tumori ovarijuma, kolona, mokraćne bešike, pluća i pleure	50%
Inhibitori proteazoma	Multipli mijelom	10%–32% *Ređe kod novijih generacija lekova
Inhibitori Bruton tirozin kinaze (BTK)	Hronična limfocitna leukemija i „mantle cell“ limfom	70%
PARP inhibitori (niraparib)	Tumori ovarijuma i dojke	20%
(B)RAF/MEK inhibitori	Melanom i kolorektalni karcinom sa BRAF mutacijom	15%–20%
Inhibitori RET kinaze	Nesitnoćelijski karcinom pluća, tiroidni karcinom	20%–40%
Alkilirajući agensi	Veliki broj solidnih i hematoloških maligniteta	36%, a kod dece 15%–58%
mTOR inhibitori	Renalni karcinom, karcinom dojke i pankreasni neuroendokrini tumori	13%
Inhibitori kalcineurina	Nakon transplantacije matičnih ćelija hematopoeze	30%–60%
Androgen deprivaciona terapija	Karcinom prostate (40% pacijenata)	5%–25%
Inhibitori aromataze	Karcinom dojke (65%–70% pacijentkinja)	8%–13% *Još uvek tema polemike

Table 1. The groups of antineoplastic drugs that may cause hypertension

ANTINEOPLASTIC TREATMENT	TARGET CANCERS	ONCO-HYPERTENSION FREQUENCY
Vascular endothelial growth factor signaling pathway inhibitors (VEGF-Spi)	Metastatic cancers (renal, hepatocellular, thyroid, gastrointestinal, stromal)	20%–90% *Depending on the drug strength and dose
Platinum derivatives	Testicular cancer (the most frequent cancer in young males), ovarian, colorectal, bladder, lung, and pleural cancer	50%
Proteasome inhibitors	Multiple myeloma	10%–32% *Less often with newer generation drugs
Bruton tyrosine kinase (BTK) inhibitors	Chronic lymphocytic leukemia and “mantle cell” lymphoma	70%
PARP inhibitors (niraparib)	Ovarian and breast cancer	20%
(B)RAF/MEK inhibitors	Melanoma and colorectal cancer with BRAF mutation	15%–20%
RET kinase inhibitors	Non-small cell lung and thyroid cancer	20%–40%
Alkylating agents	A large number of solid and hematological cancers	36%, but 15%–58% in children
mTOR inhibitors	Renal, breast and pancreatic neuroendocrine cancer	13%
Calcineurin inhibitors	After stem cell transplantation	30%–60%
Androgen deprivation therapy	Prostate cancer (40% of patients)	5%–25%
Aromatase inhibitors	Breast cancer (65%–70% of patients)	8%–13% *Still a controversial issue

(Tabela 1). Prema literaturnim podacima, 99% dece lečene zbog malignog oboljenja tokom života će razviti neko od hroničnih oboljenja usled prethodno primenjene antineoplastične terapije [19]. Takođe, ustanovljeno je da osobe iz ove populacije do 50. godine života ispolje prosečno oko 17 neželjenih efekata antineoplastične terapije primenjene u detinjstvu, od kojih su 3–5 neželjenih efekata veoma ozbiljni, a potencijalno i životno ugrožavajući [19]. Učestalost hipertenzije kao posledice primene antineoplastične terapije u detinjstvu iznosi 70% do 50. godine života [19].

Onkohipertenzija kao posledica kardiotsičnosti antineoplastične terapije

Onkohipertenzija kao posledica kardiotsičnosti antineoplastične terapije javlja se sa učestalošću većom od 10% za većinu klasa antineoplastičnih lekova, što je svrstava u veoma često neželjeno dejstvo [24]. Mehanizmi onkohipertenzije usled kardiotsičnosti antineoplastične terapije su brojni, različiti i za sada samo delimično poznati. U najčešće mehanizme onkohipertenzije ubrajaju se inhibicija angiogeneze, redukcija kapilarne mreže, poremećaj ravnoteže vazoaktivnih činilaca (najpre snižavanje nivoa azotnog oksida i povećanje nivoa endotelina-1), oksidativni stres, nefrotoksičnost, kao i poremećaji na nivou autonomnog nervnog sistema [24].

Vreme ispoljavanja onkohipertenzije kao kardiotsičnosti može biti različito [6]. Kod većine antineoplastičnih lekova, hipertenzija može nastati bilo kada tokom primene terapije. Zbog toga se preporučuje merenje krvnog pritiska na svakoj kontroli. Takođe, preporučuje se i merenje krvnog pritiska u kućnim uslovima jednom nedeljno tokom prva tri meseca terapije, a potom jednom mesečno tokom celokupnog trajanja terapije. Ovo je posebno značajno kod hematoloških pacijenata koji su na terapiji inhibitorima Bruton tirozin kinaze jer pacijenti godinama ostaju na ovoj terapiji. Ipak, hipertenzija kao posledica kardiotsičnosti antineoplastične terapije može nastati i akutno, nakon nekoliko dana od početka primene terapije, što je tipično za inhibitore signalnog puta vaskularnog endotelnog faktora rasta (VEGF-Spi). Kod primene ovih lekova preporučuje se svakodnevno merenje krvnog pritiska tokom prvog ciklusa terapije i pri svakom povećanju doze, a potom na 2–3 nedelje. Iako ima akutni početak, onkohipertenzija prouzrokovana lekovima iz grupe VEGF-Spi je reverzibilna. Takođe, hipertenzija kao posledica kardiotsičnosti antineoplastične terapije može nastati i odloženo, nakon nekoliko godina od početka terapije, što je karakteristično za derivate platine. Platina se inkorporira u DNK, a cisplatin se u krvi može detektovati i 13 godina nakon primene. Zato

malignant diseases develop at least one chronic condition during their lifetime due to prior antineoplastic therapy [19]. Moreover, individuals from this population experience, on average, 17 adverse effects of childhood antineoplastic treatment by the age of 50, of which 3–5 are severe or potentially life-threatening [19]. The prevalence of hypertension secondary to childhood antineoplastic therapy is as high as 70% by the age of 50 [19].

Onco-hypertension as a Consequence of Antineoplastic Therapy Cardiotoxicity

Onco-hypertension resulting from cardiotoxicity of antineoplastic therapy occurs with a frequency greater than 10% for most classes of antineoplastic drugs, categorizing it as a frequent adverse effect [24]. The mechanisms of onco-hypertension associated with antineoplastic cardiotoxicity are numerous, diverse, and only partially known. The most common mechanisms include inhibition of angiogenesis, reduction of capillary density, imbalance of vasoactive mediators (primarily decreased nitric oxide and increased endothelin-1 levels), oxidative stress, nephrotoxicity, and disturbances of the autonomic nervous system [24].

The timing of onco-hypertension as cardiotoxicity onset varies [6]. For most antineoplastic drugs, hypertension can develop at any time during therapy. Therefore, blood pressure should be measured at each clinical visit. In addition, home blood pressure monitoring is advised once weekly during the first three months of therapy, and monthly thereafter throughout treatment. This is particularly relevant for hematologic patients receiving Bruton tyrosine kinase inhibitors, as these therapies are often continued for years. However, hypertension as a consequence of antineoplastic treatment cardiotoxicity may also develop acutely, within days of treatment initiation, as is typical with vascular endothelial growth factor signaling pathway inhibitors (VEGF-Spi). For these agents, daily blood pressure monitoring is recommended during the first treatment cycle and after each dose escalation, and every 2–3 weeks thereafter. Although it has an acute onset, VEGF-Spi-induced hypertension is reversible. Also, hypertension as a consequence of cardiotoxicity of antineoplastic therapy can occur delayed, years after the initiation of treatment, as seen with platinum-based agents. Platinum becomes incorporated into DNA, and cisplatin can be detected in the bloodstream up to 13 years after exposure. Therefore, these patients require long-term follow-up and sustained blood pressure control [6].

je kod ovih pacijenata potrebno dugoročno praćenje i dugotrajna kontrola arterijskog krvnog pritiska [6].

Ciljne vrednosti arterijskog krvnog pritiska kod lečenja onkohipertenzije

Kod pacijenata sa malignim oboljenjem, antihipertenzivna terapija se uvodi kada su vrednosti arterijskog krvnog pritiska $\geq 140/90$ mmHg, odnosno kada su u opsegu hipertenzije I stepena ukoliko je maligno oboljenje izlečeno, ukoliko lečenje malignog oboljenja još uvek traje i očekuje se izlečenje, ali i kada postoji diseminacija bolesti uz očekivano preživljavanje duže od tri godine (klasa preporuka I) [6]. Kod pacijenata sa metastatskim promenama i očekivanim preživljavanjem između jedne i tri godine vrednosti arterijskog krvnog pritiska u opsegu hipertenzije I stepena treba razmotriti kao prihvatljive (klasa preporuka IIa), a iste vrednosti arterijskog krvnog pritiska se mogu razmotriti i kod pacijenata sa lošom prognozom i očekivanim preživljavanjem kraćim od godinu dana (klasa preporuka IIb). Ciljne vrednosti arterijskog krvnog pritiska kod većine pacijenata sa onkohipertenzijom su $< 140/90$ mmHg (klasa preporuka I). Sa druge strane, mogu se razmotriti i vrednosti $< 130/80$ mmHg ukoliko pacijenti dobro tolerišu niže vrednosti pritiska, a posebno ako se radi o pacijentima sa visokim ili veoma visokim kardiovaskularnim rizikom (klasa preporuka IIb). Apsolutna indikacija za prekid antineoplastične terapije je hipertenzija III stepena ($\geq 180/100$ mmHg). Terapija se može nastaviti kada se vrednosti arterijskog krvnog pritiska snize ispod $160/100$ mmHg, ali tada obavezno treba razmotriti smanjenje doze antineoplastičnih lekova [6].

Izbor antihipertenzivne terapije kod lečenja onkohipertenzije

Kod pacijenata sa hipertenzijom I stepena ($< 160/100$ mmHg) savetuje se antihipertenzivna monoterapija [6]. Prvu liniju terapije predstavljaju inhibitori angiotenzin-konvertujućeg enzima ili blokatori angiotenzinskih receptora, dok drugu liniju terapije čine dihidropiridinski kalcijumski antagonisti. Ukoliko su vrednosti arterijskog krvnog pritiska u opsegu hipertenzije II stepena, indicovana je kombinovana antihipertenzivna terapija. Primenuje se kombinacija inhibitora sistema renin-angiotenzin-aldosteron i kalcijumskih antagonista u cilju ostvarivanja brze i efikasne kontrole hipertenzije. U slučaju rezistentne hipertenzije, treba razmotriti beta-blokatore (najpre vazodilatatorne, kao što su nebivolol i karvedilol), potom spironolakton, nitrate i hidralazin. Klasa lekova koju treba izbegavati kod onkoloških pacijenata su nedihidropiridinski kalcijumski antagonisti (verapamil i diltiazem). Iako nisu apsolutno kontraindikovani, istovremena primena sa lekovima

Target Blood Pressure Values in Onco-hypertension Management

In cancer patients, antihypertensive therapy is indicated when blood pressure values are $\geq 140/90$ mmHg, that is, within grade 1 hypertension, if the malignancy is cured, if active cancer treatment is ongoing with curative intent, or in disseminated disease with an expected survival longer than three years (Class I recommendation) [6]. In patients with metastatic disease and expected survival between one and three years, grade 1 hypertension values may be considered acceptable (Class II recommendation). The same applies to patients with a poor prognosis and a life expectancy of less than 1 year (Class IIb recommendation). For most patients with onco-hypertension, target blood pressure values are $< 140/90$ mmHg (Class I recommendation). On the other side, lower targets ($< 130/80$ mmHg) may be considered if well tolerated, particularly in those with high or very high cardiovascular risk (Class IIb recommendation). Absolute indication for discontinuation of antineoplastic therapy is grade III hypertension ($\geq 180/100$ mmHg). Therapy may be resumed once blood pressure is reduced below $160/100$ mmHg, with mandatory consideration of antineoplastic dose reduction [6].

Choice of Antihypertensive Therapy in Onco-hypertension

For patients with grade I hypertension ($< 160/100$ mmHg), antihypertensive monotherapy is recommended [6]. First-line agents include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, while dihydropyridine calcium channel blockers are considered second-line therapy. In grade II hypertension, combination therapy is indicated, typically involving a renin-angiotensin-aldosterone system inhibitor and a calcium channel blocker, to achieve rapid and effective blood pressure control. In resistant hypertension, beta-blockers (particularly vasodilating agents such as nebivolol and carvedilol), then spironolactone, nitrates, and hydralazine should be considered. The class of drugs to be avoided in oncology patients includes non-dihydropyridine calcium channel blockers (verapamil and diltiazem). Although not absolutely contraindicated, their concomitant use with VEGF-SPI agents carries the risk of worsening hypertension due to CYP3A4-mediated pharmacokinetic interactions and increased plasma concentrations of the antineoplastic drug [6].

Additional Factors Contributing to Onco-hypertension

In oncology patients, besides antineoplastic therapy, it's necessary to be aware that numerous associated

iz grupe VEGF-Spi nosi rizik od pogoršanja postojeće hipertenzije zbog interakcije na nivou metaboličkog sistema CYP3A4 u jetri i povećanja koncentracije anti-neoplastičnog leka u plazmi [6].

Pridruženi faktori koji doprinose onkohipertenziji

Pored antineoplastične terapije, kod onkoloških pacijenata je neophodno imati u vidu da postoje brojni pridruženi faktori koji mogu uticati na vrednosti arterijskog krvnog pritiska [23,24]. Tu spadaju komorbiditeti (npr. sekundarni depoziti u endokranijumu), konkomitantna terapija (kortikosteroidi koji se često primenjuju kao adjuvantna terapija ili nesteroidni antiinflamatorni lekovi primenjeni kao analgetici), bol, stres, anksioznost, poremećaj bubrežne funkcije (radijaciona nefropatija ili nefrotoksičnost antineoplastičnih lekova) i insuficijencija baroreceptora nakon radijacije u predelu vrata i grudnog koša. Takođe, i kod ovih pacijenata mogu postojati „efekat belog mantila“ i maskirana hipertenzija [23,24].

ZAKLJUČAK

Onkohipertenzija predstavlja novi oblik hipertenzije čija učestalost je u porastu, shodno porastu učestalosti onkoloških oboljenja, ali i razvoju novih antineoplastičnih lekova koji imaju svoje neželjene efekte na kardiovaskularni sistem. Za blagovremeno i adekvatno zbrinjavanje pacijenata sa onkohipertenzijom važno je dobro poznavanje kardiotoksičnih efekata antineoplastične terapije, ali je potrebno uzeti u obzir i stadijum onkološke bolesti i očekivano preživljavanje pacijenta kako bi se kod svakog pacijenta definisale ciljne vrednosti arterijskog krvnog pritiska. Otežavajuća okolnost u zbrinjavanju onkohipertenzije može biti istovremeno postojanje drugih kardiovaskularnih oboljenja koja povećavaju kardiovaskularni rizik, ali i drugih hroničnih oboljenja i pridruženih faktora koji mogu kompromitovati efekte primenjene antihipertenzivne terapije. Zbog svega navedenog, hipertenzija kod onkoloških pacijenata zahteva individualan i sveobuhvatan pristup koji je neophodno realizovati na svim nivoima zdravstvene zaštite, od ambulantne nadležnog lekara opšte prakse do specijalizovanih tercijarnih zdravstvenih ustanova.

Sukob interesa: Nije prijavljen.

factors can affect arterial blood pressure [23,24]. These include comorbidities (e.g., intracranial metastases), concomitant medications (such as corticosteroids used as adjuvant therapy or nonsteroidal anti-inflammatory drugs used for pain management), pain, stress, anxiety, renal dysfunction (radiation nephropathy or drug-induced nephrotoxicity), and baroreceptor insufficiency following neck or thoracic irradiation. Additionally, both “white coat effect” and masked hypertension may occur in these patients [23,24].

CONCLUSION

Onco-hypertension represents a novel and increasingly prevalent form of hypertension, reflecting the rising incidence of cancer and the development of new antineoplastic drugs, which have cardiotoxic potential. Timely and adequate management of patients with onco-hypertension requires a thorough understanding of the cardiotoxic effects of antineoplastic therapy, along with consideration of oncological disease stage and the patient's expected survival, to define individualized blood pressure targets. Management may be further complicated by concurrent cardiovascular diseases, additional chronic conditions, and factors that can compromise the efficacy of antihypertensive therapy. For all these reasons, hypertension in oncology patients demands an individualized and comprehensive approach that must be implemented at all levels of healthcare from primary care to specialized tertiary institutions.

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EFEKTI KONTROLISANOG FIZIČKOG TRENINGA KOD BOLESNIKA SA SRČANOM INSUFICIJENCIJOM

STRUČNI ČLANCI

PROFESSIONAL ARTICLES

EFFECTS OF CONTROLLED PHYSICAL TRAINING IN PATIENTS WITH HEART FAILURE

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SAŽETAK

Srčana insuficijencija (engl. heart failure – HF) je klinički sindrom koji se sastoji od kardijalnih simptoma (npr. nedostatak vazduha, otok potkolenica i umor), koje mogu pratiti znaci (npr. povišen jugularni venski pritisak, pukoti nad plućima i periferni edemi). Bolesnici sa HF imaju česte hospitalizacije, narušen im je kvalitet života i skraćen životni vek. Bolesnici sa HF imaju smanjen fizički radni kapacitet, koji je u velikoj meri izazvan narušenom hemodinamikom protoka krvi u aktivnoj skeletnoj muskulaturi. Bolesnicima sa HF potrebno je uraditi kardiopulmonalni test fizičkim opterećenjem, radi procene nivoa i vrsta fizičke aktivnosti koji će se nakon toga sprovesti i neophodno je izvršiti stratifikaciju rizika. Treba početi procenom trenutnih mogućnosti i potreba pacijenta za vežbanjem i sastaviti početni program vežbanja sa određenom vrstom vežbi, njihovim intenzitetom, brojem ponavljanja i trajanjem u minutima tokom jednog dana, kao i brojem dana u kojima treba vežbati tokom nedelje. Preporučuje se vožnja bicikle (statičke ili obične) i pešačenje, što predstavlja aerobni, dinamički tip vežbanja. Aerobni tip treninga se preporučuje 3–5 puta nedeljno (30–60 minuta po treningu), a prioritet ima intervalni tip treninga. Ovaj vid treninga poboljšava snagu i izdržljivost skeletnih mišića i dovodi do povećanja mišićne mase. Kod bolesnika sa srčanom insuficijencijom i kaheksijom preporučuje se rezistentni tip treninga, koji je kombinacija izotoničkog i izometrijskog opterećenja. Ovu vrstu treninga treba sprovesti dva puta nedeljno u trajanju 12–20 minuta. Ovaj vid treninga poboljšava snagu i izdržljivost skeletnih mišića i dovodi do povećanja mišićne mase. Fizički trening povećava mišićnu masu skeletnih mišića, promer mišićnog vlakna, snagu, izdržljivost i fizički radni kapacitet.

Ključne reči: srčana slabost, aerobni trening, fizičke vežbe, fizički radni kapacitet

ABSTRACT

Heart failure (HF) is a clinical syndrome characterized by cardiac symptoms (e.g., breathlessness, ankle swelling, and fatigue), which may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema). Patients with HF often experience frequent hospitalizations, impaired quality of life, and shortened life expectancy. They also have decreased exercise capacity, primarily due to impaired hemodynamics within the active skeletal muscles. Patients with HF should undergo a cardiopulmonary exercise test to assess their activity level and type, as well as to perform risk stratification. The initial step should include evaluating the patient's current exercise capacity and needs, then creating a personalized exercise program that details the types of exercises, their intensity, repetitions, duration in minutes per session, and the number of days per week allocated for training. Cycling (either on a stationary or regular bicycle) and walking are recommended because they are aerobic, dynamic forms of exercise. Aerobic training should be performed 3–5 times a week (30–60 minutes per session), with emphasis on interval training. This type of training enhances skeletal muscle strength and endurance, leading to increased muscle mass. In patients with heart failure and cachexia, resistance training is advised, combining both isotonic and isometric exercises. This type of training should be performed twice a week for 12 to 20 minutes per session. Resistance training also enhances skeletal muscle strength and endurance and encourages muscle growth. Physical training enhances skeletal muscle mass, fiber diameter, strength, endurance, and exercise capacity.

Keywords: heart failure, aerobic training, physical exercises, physical work capacity

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UVOD

Srčana insuficijencija (engl. *heart failure* – HF) je klinički sindrom koji se sastoji od kardijalnih simptoma (npr. nedostatak vazduha, otok potkolenica i umor) koje mogu pratiti znaci (npr. povišen jugularni venski pritisak, pukoti nad plućima i periferni edemi). HF nastaje usled strukturne i/ili funkcionalne abnormalnosti srca koje rezultira povećanim intrakardijalnim pritiscima i/ili neadekvatnim srčanim minutnim volumenom srca u miru i/ili naporu. Identifikacija etiologije srčane disfunkcije je obavezna u dijagnostici HF radi odluke o daljem lečenju. Najčešće, HF nastaje usled miokardne disfunkcije: sistolne, dijasolne ili obe [1].

HF ostaje vodeći globalni uzrok smrtnosti, morbiditeta i lošeg kvaliteta života uz visoku upotrebu resursa i troškove zdravstvene zaštite. Iako je incidencija HF vremenom blago opala, njena prevalenca raste zbog poboljšanih tretmana HF i dužeg životnog veka u populaciji [2]. U evropskim zemljama, srednja incidenca HF je 3,20 slučajeva na 1000 osoba, a srednja prevalenca HF je 17,20 slučajeva na 1000 ljudi [1,3].

Iako ishemijska bolest srca ostaje jedan od najčešćih uzroka HF, poboljšanja u lečenju akutnog infarkta miokarda (AIM) i sekundarne prevencije smanjili su rizik od HF hospitalizacije nakon prvog AIM-a. Prevalenca srčane insuficijencije se povećava sa godinama starosti, a najčešći uzrok u bolesnika mlađih od 75 godina je koronarna bolest [1,4–6].

Pacijenti osim HF, često imaju i nekoliko drugih bolesti. Komorbiditeti se grubo dele na kardiovaskularne i nekardiovaskularne bolesti. Od kardiovaskularnih komorbiditeta najčešći su arterijska hipertenzija, koronarna bolest i atrijalna fibrilacija [7,8]. Od nekardiovaskularnih komorbiditeta najčešći su dijabetes melitus, bubrežna insuficijencija, hronična opstruktivna bolest pluća i anemija [9,10].

Prema vrednostima ejeckione frakcije leve komore (engl. *left ventricular ejection fraction* – LVEF) srčana slabost se deli na onu sa očuvanom, blago redukovanom i redukovanom ejeckionom frakcijom leve komore. Redukovana LVEF je definisana kao $\leq 40\%$, npr. kod onih za značajnom redukcijom sistolne funkcije leve komore i ovo se označava kao (engl. *heart failure with reduced ejection fraction* – HFrEF). Pacijenti sa LVEF opsega 41% do 49% imaju blago redukovanu sistolnu funkciju leve komore, tj. „srčana insuficijencija blago redukovane ejeckione frakcije” (engl. *heart failure with mildly reduced ejection fraction* – HFmrEF). HF sa očuvanom ejeckionom frakcijom (engl. *heart failure with preserved ejection fraction* – HFpEF) podrazumeva LVEF $\geq 50\%$. Za postavljanje dijagnoze srčane insuficijencije sa očuvanom ili umereno smanjenom LVEF osim prisustva simptoma i znaka potrebno je prisustvo povećane vrednosti natri-

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by cardiac symptoms (e.g., shortness of breath, leg swelling, and fatigue), which may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema). HF occurs due to structural and/or functional abnormalities of the heart, leading to increased intracardiac pressures and/or inadequate cardiac output at rest and during exertion. Identifying the etiology of cardiac dysfunction is essential for diagnosing HF and guiding further treatment. Most often, HF results from myocardial dysfunction, which can be systolic, diastolic, or both [1].

HF remains a leading global cause of mortality, morbidity, and poor quality of life, with high resource utilization and healthcare costs. Although the incidence of HF has slightly decreased over time, its prevalence continues to increase due to improved HF treatments and increased life expectancy in the general population [2]. In European countries, the median incidence of HF is 3.20 cases per 1000 people, while the median prevalence is 17.20 cases per 1000 individuals [1,3].

Although ischemic heart disease remains one of the most common causes of HF, advances in treating acute myocardial infarction (AMI) and secondary prevention have lowered the risk of HF hospitalization after a first AMI. The prevalence of heart failure increases with age, and among patients under 75 years old, the most common cause is coronary artery disease [1,4–6].

Patients with HF often have multiple other comorbidities. Comorbidities are generally classified into cardiovascular and non-cardiovascular conditions. Among cardiovascular comorbidities, the most common are arterial hypertension, coronary artery disease, and atrial fibrillation [7,8]. For non-cardiovascular comorbidities, the most frequent include diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, and anemia [9,10].

According to left ventricular ejection fraction (LVEF), heart failure is classified into preserved, mildly reduced, and reduced ejection fraction. Reduced LVEF is defined as $\leq 40\%$, indicating a significant decrease in left ventricular systolic function, known as heart failure with reduced ejection fraction (HFrEF). Patients with LVEF between 41% and 49% have mildly reduced systolic function, called heart failure with mildly reduced ejection fraction (HFmrEF). Heart failure with preserved ejection fraction (HFpEF) refers to an LVEF of 50% or higher. To diagnose HF with preserved or mildly reduced LVEF, symptoms and signs must be present along with elevated natriuretic peptide levels and at least one of the following: relevant structural heart disease (such as left ventricular hypertrophy or left atrial

uretskog peptida uz prisustvo minimum još jednog od sledećih kriterijuma: relevantno strukturno oštećenje srca (hipertrofija leve komore ili uvećana leva pretkomora) i/ili dijasolna disfunkcija leve komore [1,11–13].

Srčana insuficijencija može biti i rezultat disfunkcije desne komore. Mehanika i funkcija desne komore su izmenjene u sklopu opterećenjem pritiskom, ili volumenom. Osnovna etiologija hronične srčane slabosti desne komore je plućna hipertenzija nastala usled disfunkcije leve komore, ali postoje brojni drugi uzroci [1,14].

U kliničkoj praksi, za težinu srčane insuficijencije najčešće su korišćene klasifikacije Njujorškog kardiološkog društva (NYHA klasifikacija) i klasifikacija Američkog Udruženja kardiologa (ACC/AHA) [1].

NYHA funkcionalna klasifikacija zasnovana je na težini simptoma i fizičkoj aktivnosti:

- Klasa I: Bolesnik nema ograničenja fizičke aktivnosti, uobičajeno fizičko opterećenje ne dovodi do zamora, gušenja ili palpitacija.
- Klasa II: Postoji manje ograničenje fizičke aktivnosti, bolesnik se oseća dobro kada miruje ali uobičajene aktivnosti izazivaju zamor, gušenje ili palpitacije.
- Klasa III: Bolesnik ima značajno ograničenje fizičke aktivnosti, oseća se dobro u mirovanju, ali male uobičajene aktivnosti dovode do simptoma.
- Klasa IV: Pri najmanjoj fizičkoj aktivnosti javljaju se tegobe ili su simptomi SI prisutni u mirovanju a pogoršavaju se pri najmanjem fizičkom naporu.

ACC/AHA klasifikacija težine srčane insuficijencije:

- Stadijum A: Veliki rizik za razvoj srčane insuficijencije ali bez prisustva strukturnog oboljenja srca ili simptoma srčane insuficijencije.
- Stadijum B: Prisustvo strukturnog oboljenja srca bez simptoma i znakova srčane insuficijencije.
- Stadijum C: Prisustvo strukturnog oboljenja srca sa simptomima srčane insuficijencije.
- Stadijum D: Refrakтерна srčane insuficijencije koja zahteva primenu specijalnih intervencija.

HEMODINAMSKE PROMENE U SRČANOJ INSUFICIJENCIJI

Kod bolesnika sa HF smanjen je fizički radni kapacitet. Ovo smanjenje u velikoj meri izazvano je hemodinamikom protoka krvi u aktivnoj skeletnoj muskulaturi (sekundarno usled smanjenja minutnog volumena srca), tako da ovi bolesnici mogu postići manji maksimalni minutni volumen u odnosu na zdrave osobe. Neadekvatna hemodinamika protoka krvi u aktivnoj skeletnoj muskulaturi nastaje i usled disfunkcije endotela, tako da se pri fizičkom naporu krvni sudovi neadekvatno prošire. Udarni volumen u miru, koji je značajno smanjen u sistolnoj HF, slabo se povećava tokom vežbanja zbog smanjene sposobnost da se poveća

enlargement) and/or left ventricular diastolic dysfunction [1,11–13].

Heart failure can also result from right ventricular dysfunction. Right ventricular mechanics and function may be affected by pressure or volume overload. The primary cause of chronic right ventricular failure is pulmonary hypertension due to left ventricular dysfunction, although many other causes exist [1,14].

In clinical practice, the severity of HF is usually assessed using the New York Heart Association (NYHA) classification and the American College of Cardiology/American Heart Association (ACC/AHA) classification [1].

The NYHA functional classification is based on symptom severity and physical activity:

- Class I: No restrictions on physical activity; regular physical activity does not lead to fatigue, dyspnea, or palpitations.
- Class II: Slight restriction in physical activity; comfortable at rest, but normal activity causes fatigue, dyspnea, or palpitations.
- Class III: Significant restriction of physical activity; comfortable at rest, but less-than-normal activity causes symptoms.
- Class IV: Symptoms of heart failure are present at rest; any physical activity leads to increased discomfort.

ACC/AHA Classification of Heart Failure Severity:

- Stage A: High risk of developing heart failure but without structural heart disease or heart failure symptoms.
- Stage B: Structural heart disease present but without signs or symptoms of HF.
- Stage C: Structural heart disease presenting with symptoms of heart failure.
- Stage D: Refractory heart failure requiring specialized interventions.

HEMODYNAMIC CHANGES IN HEART FAILURE

In patients with HF, physical exercise capacity is limited. This limitation mainly results from hemodynamic changes in active skeletal muscle (secondary to reduced cardiac output), so these patients can achieve a lower maximal cardiac output than healthy individuals. Inadequate blood flow hemodynamics in active skeletal muscle also stem from endothelial dysfunction, leading to insufficient vasodilation during physical activity. Stroke volume at rest, which is significantly reduced in systolic HF, increases only slightly during exercise due to impaired ability to enhance left ventricular preload and LVEF [15]. The reduced capacity to increase left ventricular end-diastolic volume results from the dilated left ventricle already operating near its maximum volume, exhausting its preload reserve [4,16].

prethodno opterećenje (*preload*) leve komore i LVEF [15]. Smanjena sposobnost da se poveća enddiastolni volumen leve komore objašnjava se činjenicom da dilatirana leva komora radi sa već maksimalnim volumenom, tako da su iscrpljene njene rezervne mogućnosti za povećanje *preloada* [4,16].

Kod bolesnika sa HF, vršna potrošnja kiseonika (*peak VO₂*) i *VO₂* na ventilatornom anaerobnom pragu su tipično redukovani u odnosu na zdrave osobe, proporcionalno težini simptoma srčane insuficijencije. Ventilatorni anaerobni prag se temelji na konceptu da pri određenom radu snabdevanje mišića kiseonikom ne ispunjava njegove zahteve, a ova neravnoteža povećava zavisnost od anaerobne glikolize za proizvodnju energije, sa laktatima kao konačnim metaboličkim proizvodom. Mlečna kiselina se tada puferuje bikarbonatima, oslobađa se višak *CO₂*. Rezultat porasta nivoa *CO₂* jeste povećanje ventilacije zbog aktivacije hemoreceptora u karotidnim sinusima sa ciljem eliminisanja viška *CO₂*.

Kada je izražen u odnosu na izmereni *peak VO₂*, ventilatorni anaerobni prag se javlja na približno 40%–60% od *peak VO₂* u većini srčanih bolesnika, s trendom prema većem procentu od *peak VO₂* u bolesnika s hroničnom srčanom insuficijencijom [16].

FIZIČKI TRENING / VEŽBANJE – OPŠTA RAZMATRANJA

Termin „vežbanje” se definiše kao „aktivnost koja zah-teva fizički napor i koja se sprovodi radi održavanja ili poboljšanja zdravlja i pripremljenosti” ili kao „telesni napor radi razvoja i održavanja fizičke pripremljenosti”. Postoji čitav niz sličnih definicija, a u svima je uočljivo da je vežba opisana kao aktivan proces, tokom kojeg pojedinac svesno preduzima dodatne napore (u odnosu na stanje mirovanja) koji uključuju određeni stepen fizičkog opterećenja. Kada bi proučavali istoriju medicine uvideli bi da je vežbanje od samih početaka preporučivano za očuvanje zdravlja i kao oblik lečenja. Verovatno jedan od najčešće navođenih citata koji se pripisuje Hipokratu glasi: „Kada bismo svakom pojedincu dali pravu količinu ishrane i vežbanja, ne premalo i ne previše, pronašli bismo najsigurniji put do zdravlja”. Međutim, tokom poslednje decenije koncept „Vežbanje je lek” postao je globalna zdravstvena inicijativa, s ciljem da procena fizičke aktivnosti i promocija vežbanja postane standard u kliničkoj praksi, povezujući zdravstvenu zaštitu sa fizičkom aktivnošću i vežbanjem zasnovanom na dokazima. Osnov za takav pristup je teza da fizička aktivnost i vežbanje promovišu optimalno zdravlje i da trebaju biti sastavni deo prevencije i lečenja mnogih zdravstvenih stanja. Ovakvim pristupom ohrabruju se lekari i drugi pružaoci zdravstvenih usluga da uključe vežbanje prilikom kreiranja planova lečenja

In patients with HF, peak oxygen consumption (*peak VO₂*) and *VO₂* at the ventilatory anaerobic threshold are usually diminished compared to healthy individuals, in proportion to the severity of HF symptoms. The ventilatory anaerobic threshold is based on the idea that, at a certain workload, oxygen delivery to the muscles no longer meets their metabolic needs. This imbalance increases reliance on anaerobic glycolysis for energy production, with lactate as the end product. Lactic acid is then buffered by bicarbonate, releasing excess *CO₂*. The rise in *CO₂* levels stimulates increased ventilation by activating chemoreceptors in the carotid sinuses, aiming to eliminate excess *CO₂*.

When expressed relative to measured *peak VO₂*, the ventilatory anaerobic threshold generally occurs at about 40%–60% of *peak VO₂* in most cardiac patients, with a tendency toward a higher proportion of *peak VO₂* in patients with chronic HF [16].

PHYSICAL TRAINING / EXERCISE – GENERAL CONSIDERATIONS

The term “exercise” is defined as “activity that requires physical effort and is performed to maintain or improve health and fitness” or as “physical exertion undertaken to develop and maintain physical fitness.” Numerous similar definitions exist, all emphasizing that exercise is an active process during which an individual consciously exerts extra effort (compared with rest), involving a certain degree of physical load. A review of medical history shows that exercise has been recommended for health maintenance and therapeutic purposes since ancient times. One of the most frequently cited quotes attributed to Hippocrates states: “If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.” However, in the past decade, the concept “Exercise is Medicine” has become a global health initiative, aiming to make physical activity assessment and the promotion of exercise a standard part of clinical practice, connecting healthcare with evidence-based physical activity and exercise. This approach is based on the idea that physical activity and exercise promote optimal health and should be essential for preventing and treating many medical conditions. This strategy encourages physicians and other healthcare providers to include exercise in treatment plans and refer patients to evidence-based exercise programs and qualified exercise professionals. The role of exercise in preventing and managing chronic diseases is relatively well understood [17]. It is believed that, alongside exercise, proper dietary modification can

i da upućuju pacijente na programe vežbanja zasnovane na dokazima i kvalifikovane stručnjake za vežbanje. Značaj vežbanja u prevenciji i lečenju hroničnih bolesti su relativno dobro opisane [17]. Smatra se da uz vežbanje, jedino pravilna modifikacija ishrane, deluje na smanjenje rizika od skoro svih hroničnih bolesti istovremeno [18]. Sistematski pregledni članci i meta-analize pokazuju da je vežbanje slično delotvorno kao i lekovi za lečenje nekoliko hroničnih stanja, što pruža naučnu potporu konceptu „Vežbanje je lek” [19,20].

Pacijenti mogu dobiti sveobuhvatnu procenu i svojevrstni recept u vidu smernica i uputstava za vežbanje u kliničkom modulu. U skladu sa tim, vežbanje treba sprovoditi u modulu zajednice. Razvoj aktivne zdravstvene tehnologije omogućava pacijentima da efikasnije vežbaju. Razvoj opreme za vežbanje, omogućava ljudima da steknu dobro iskustvo vežbanja i u izvesnoj meri smanje verovatnoću povreda pri vežbanju. Najnoviji napredak u tehnologiji, uključujući rehabilitacionu robotiku, uređaje za nošenje, virtuelnu stvarnost, veštačku inteligenciju i pametnu telemedicinu, pružaju pacijentima povratne informacije u realnom vremenu i kontinuirano im pomažu da ispune planirane ciljeve tokom vežbanja [21].

Individualizacija znači da treba izabrati intenzitet i vreme vežbanja u skladu sa ličnim mogućnostima. Ne preporučuje se potpuno praćenje iskustava drugih ljudi sa vežbanjem. Postepenost znači da intenzitet i vreme vežbanja treba povećavati korak po korak. Iznenadni visoki intenzitet i produženo vežbanje mogu naneti štetu, a ne potencirati zdravstvene koristi. Princip upornosti se odnosi na to da pacijent treba da shvati vežbu kao deo života i da razvija redovne navike za vežbanje. Nepridržavanje ovih principa otežava postizanje očekivanih rezultata. Izbor vrste, intenziteta, trajanja i ponavljanja vežbanja je složen zadatak [22,23].

FIZIČKI TRENING KOD KARDIOVASKULARNIH BOLESNIKA

Aktuelne smernice Svetske zdravstvene organizacije o fizičkoj aktivnosti i sedentarnom ponašanju naglašavaju da sve odrasle osobe treba da imaju 150–300 minuta fizičke aktivnosti umerenog intenziteta nedeljno [24]. Navedeno se može zameniti sa fizičkom aktivnosti visokog intenziteta ili nekom ekvivalentnom kombinacijom aerobne aktivnosti umerenog i visokog intenziteta u trajanju od 75–150 minuta nedeljno. Fizička neaktivnost ima velike efekte na globalno zdravlje i važan je faktor rizika za kardiovaskularne bolesti i ukupnu smrtnost, dok redovna fizička aktivnost ima suprotne efekte [25]. Jedna od studija sa najvećim obuhvatom ispitanika, ukupno njih 116.221, je pokazala da se faktori rizika za kardiovaskularne bolesti i ukupnu smrt-

also reduce the risk of nearly all chronic diseases [18]. Systematic reviews and meta-analyses show that exercise is as effective as pharmacological treatments for several chronic conditions, providing scientific support for the “Exercise is Medicine” concept [19,20].

Patients may receive a comprehensive assessment and a personalized exercise “prescription” in the clinical module. Based on this, exercise should be implemented within the community module. Advances in active health technology enable patients to exercise more effectively. Developments in exercise equipment allow individuals to gain a better exercise experience and reduce the likelihood of injuries. Recent progress in technology, including rehabilitation robotics, wearable devices, virtual reality, artificial intelligence, and innovative telemedicine, provides patients with real-time feedback and continuous support in meeting their exercise goals [21].

Individualization involves choosing the intensity and duration of exercise based on personal abilities. It is not advisable to completely follow other people’s exercise routines. Progressiveness means gradually increasing the intensity and duration. Sudden high-intensity or long-duration exercise can cause harm rather than health benefits. The principle of persistence emphasizes that individuals should see exercise as part of daily life and develop consistent habits. Not following these principles decreases the chances of reaching desired results. Selecting the type, intensity, duration, and frequency of exercise is a complex task [22,23].

PHYSICAL TRAINING IN CARDIOVASCULAR PATIENTS

Current World Health Organization guidelines on physical activity and sedentary behavior stress that all adults should accumulate 150–300 minutes of moderate-intensity physical activity each week [24]. This can be replaced with high-intensity exercise or a combination of moderate- and high-intensity aerobic activities totaling 75–150 minutes weekly. Physical inactivity has serious consequences for global health and is a key risk factor for cardiovascular disease and all-cause mortality, while regular physical activity has the opposite effect [25]. One of the most extensive studies, involving 116,221 participants, showed that cardiovascular risk factors and all-cause mortality decrease by 19%–25% when the minimum weekly physical activity guidelines are followed, and by 15%–31% when both duration and high-intensity criteria are met [26].

Cardiovascular diseases are, at least in part, caused by poor or unhealthy diets and other lifestyle habits, which can be summarized as maladaptive dietary and lifestyle factors. A key aspect of lifestyle is physical ac-

nost smanjuju 19%–25% ukoliko se ispune smernice o minimalnoj fizičkoj aktivnosti na nedeljnom nivou, odnosno 15%–31% ukoliko se ispune kriterijumi trajanja aktivnosti i njen intenzitet bude visok [26]. Kardiovaskularna oboljenja su, barem delimično, posledica neodgovarajuće ili loše ishrane i drugih životnih navika, koje se mogu sažeti kao neprilagođeni faktori ishrane i načina života. Kritični sastavni element životnog stila su fizička aktivnost i vežbanje [27]. Dostizanje i održavanje preporučenih nivoa fizičke aktivnosti je u korelaciji sa smanjenim rizicima od infarkta miokarda i moždanog udara, kao i ukupne smrtnosti od kardiovaskularnih bolesti [28,29]. Vežbanje vrlo verovatno štiti od koronarne bolesti srca smanjenjem faktora rizika kao što su: povišen krvni pritisak, gojaznost, hiperlipidemija i insulinska rezistencija. Pored toga, vežbanje pruža pozitivne efekte na remodelovanje miokarda [5]. Vežbanje umerenog intenziteta koje se često praktikuje (prosečno 60–75minuta dnevno) smanjuje rizik od smrti povezan sa dugim periodima sedenja [30]. Viši intenziteti vežbanja i smanjenje vremena sedentarnih aktivnosti smanjuju sveukupni rizik smrtnosti [31]. Nalazi meta analiza pokazuju da postizanje preporučenih nivoa fizičke aktivnosti smanjuje rizik od nepovoljnih kardiovaskularnih događaja za 17%, smrtnost od kardiovaskularnih bolesti za 23%, a učestalost obolevanja od dijabetes melitusa tip 2 za 26% [32]. Ove rezultate su takođe potvrdili Kivimäki i saradnici [33] zaključujući da je odsustvo fizičke aktivnosti bilo povezano sa 24% većim rizikom od koronarne bolesti srca, 16% povećanim rizikom od moždanog udara i 42% većim rizikom od dijabetes melitusa tip 2.

Podaci iz skorašnje meta analize pokazuju 17% manji rizik od smrtnosti od kardiovaskularnih oboljenja ukoliko se ovakva vrsta aktivnosti upražnjava 40–60 minuta nedeljno [34]. Kombinacija fizičke aktivnosti umerenog ili visokog intenziteta daje najizraženije efekte na poboljšanje zdravlja kardiovaskularnog sistema i smanjenje rizika smrtnosti [35–37]. Sekundarna prevencija kardiovaskularnih oboljenja optimalno obuhvata individualno planirane programe vežbanja, zajedno sa promenama u načinu života (skraćenje sedentarnih aktivnosti, prestanak pušenja, planiranje ishrane) [38,39]. Studija koja je trajala pet godina pokazala je 32% manji rizik od smrtnosti kod pacijenata sa kardiovaskularnim oboljenjima (prethodni infarkt miokarda, kardiorakalne operacije, angina pectoris) koji su učestvovali u programima rehabilitacije srca u poređenju sa onima koji nisu učestvovali [40]. Autori istraživanja koje je obuhvatilo 23.430 pacijenata sa kardiovaskularnim oboljenjima su zaključili da rehabilitacija srca zasnovana na vežbanju rezultira smanjenim rizikom od smrtnosti i poboljšanim kvalitetom života

tivity and exercise [27]. Achieving and maintaining the recommended levels of physical activity is associated with lower risks of myocardial infarction, stroke, and cardiovascular death [28,29]. Exercise likely protects against coronary heart disease by lowering risk factors such as hypertension, obesity, hyperlipidemia, and insulin resistance. Additionally, exercise has positive effects on myocardial remodeling [5]. Regular moderate-intensity exercise (about 60–75 minutes daily) reduces the risk of mortality linked to prolonged sitting [30]. Engaging in higher-intensity exercise and reducing sedentary time further decreases overall mortality risk [31]. Meta-analytic findings indicate that meeting recommended physical activity levels lowers the risk of adverse cardiovascular events by 17%, cardiovascular mortality by 23%, and the incidence of type 2 diabetes mellitus by 26% [32]. These findings were supported by Kivimäki et al. [33], who reported that physical inactivity was linked to a 24% higher risk of coronary heart disease, a 16% increased risk of stroke, and a 42% higher risk of type 2 diabetes mellitus. Recent meta-analytic data show a 17% lower risk of cardiovascular mortality when this type of activity is performed for 40–60 minutes weekly [34]. A combination of moderate- and high-intensity physical activity produces the most significant improvements in cardiovascular health and mortality reduction [35–37]. Secondary prevention of cardiovascular diseases ideally includes personalized exercise programs along with lifestyle changes (reducing sedentary behavior, quitting smoking, dietary planning) [38,39]. A five-year study showed a 32% reduction in mortality among patients with cardiovascular disease (previous myocardial infarction, cardiothoracic surgery, angina pectoris) who participated in cardiac rehabilitation programs compared to those who did not [40]. Authors of a study involving 23,430 cardiovascular patients concluded that exercise-based cardiac rehabilitation leads to decreased mortality and better quality of life [41].

Exercise should be regarded as an intervention that must be tailored and continuously adjusted to match the characteristics and preferences of the individuals it's prescribed for. Ideally, a maximal exercise test with direct measurement of maximal oxygen consumption (VO₂ max) should be conducted for accurate risk assessment and to determine exercise zones before developing a program [42]. Exercise, especially high-intensity exercise, is contraindicated in certain situations, such as the first two days after acute coronary syndrome or in conditions like uncontrolled arrhythmia, active endocarditis, myocarditis, or pericarditis, severe symptomatic aortic stenosis, decompensated

[41]. Vežbanje treba shvatiti kao intervenciju koja treba da bude individualizovana i kontinuirano prilagođena karakteristikama i sklonostima osoba kojima je sa terapijskim ciljem namenjena. U idealnom slučaju treba uraditi maksimalni test opterećenja sa direktnim merenjem maksimalne zapremine kiseonika koju telo može da iskoristi tokom vežbanja (VO₂ max) za pravilnu stratifikaciju rizika i određivanje zona vežbanja pre sastavljanja plana i programa [42]. Vežbanje, posebno ono većeg intenziteta, je kontraindikovano u nekim slučajevima kao što su prva dva dana nakon akutnog koronarnog sindroma ili u stanjima kao što su nekontrolisana aritmija, aktivni endokarditis, miokarditis ili perikarditis, simptomatska teška stenoza aorte, dekompenzovana srčana mana, akutna plućna embolija, duboka venska tromboza ili akutna disekcija aorte [42,43].

Iznenadna srčana smrt čini oko 50% od ukupnog mortaliteta u prvoj godini nakon preležanog infarkta miokarda. Bolesnici nakon preležanog infarkta miokarda često i dalje imaju faktore rizika za ishemijsku bolest srca. Potrebna je stroga kontrola ovih faktora rizika radi smanjenja rizika od daljih komplikacija i mortaliteta. Uz medikamentnu terapiju, vežbanje ima značajnu ulogu u kontroli faktora rizika [44]. Neadekvatna ishrana i fizička neaktivnost favorizuju ateroskleroza [45].

Pacijenti nakon hirurške revaskularizacije miokarda (engl. *Coronary Artery Bypass Graft* – CABG) su u riziku od novih neželjenih kardiovaskularnih događaja, aritmija i iznenadne srčane smrti [46]. Pored toga, period nakon hirurške intervencije karakteriše produženo smanjenje fizičke aktivnosti zbog dominantnog ležećeg položaja sa pratećom hipotrofijom skeletnih mišića, pogoršanja periferne cirkulacije i disfunkcije autonomnog nervnog sistema. Klinički se navedeno manifestuje izraženim smanjenjem tolerancije na fizički napor, prisustvom posturalne hipotenzije, tahikardije u mirovanju i psihološkim poremećajima, najčešće u vidu depresije ili anksioznosti. Stepenn smanjenja tolerancije na napor najviše zavisi od dužine boravka u krevetu i stepena oštećenja funkcije leve komore [47]. Zbog toga je neophodna dobra kontrola faktora rizika u cilju sekundarne prevencije koronarne bolesti. Podaci pokazuju da je kod pacijenata koji nisu imali fizičku aktivnost, za godinu dana zabeleženo je oko 15% restenoze, a 88% pacijenata imalo je neželjene kardiovaskularne događaje: infarkt miokarda, moždani udar, revaskularizacione procedure ili hospitalizaciju zbog angine pectoris [48].

Nova saznanja mogu otvoriti mogućnosti za poboljšanje efekata vežbanja korišćenjem efikasnijih ili ciljanih strategija. Iako ovaj cilj može izgledati futuristički, njegove pozitivne koristi bi trebalo da budu snažna motivacija za dalja istraživanja u ovoj oblasti. U među-

heart failure, acute pulmonary embolism, deep vein thrombosis, or acute aortic dissection [42,43].

Sudden cardiac death accounts for about 50% of mortality within the first year after myocardial infarction. Patients recovering from myocardial infarction often retain risk factors for ischemic heart disease, necessitating strict management to lower the risk of further complications and death. In addition to medication, exercise plays a crucial role in managing risk factors [44]. Poor diet and physical inactivity contribute to atherosclerosis [45].

Patients after coronary artery bypass grafting (CABG) remain at risk for new cardiovascular events, arrhythmias, and sudden cardiac death [46]. Additionally, the postoperative period is characterized by prolonged physical inactivity due to mostly lying in bed, which leads to skeletal muscle hypotrophy, impaired peripheral circulation, and autonomic dysfunction. Clinically, this manifests as significantly reduced exercise tolerance, postural hypotension, resting tachycardia, and psychological issues, most commonly depression or anxiety. The degree of reduced exercise tolerance mainly depends on the duration of bed rest and the severity of left ventricular dysfunction [47]. Therefore, strict management of risk factors is essential for secondary prevention of coronary disease. Data show that among patients who do not engage in physical activity, approximately 15% experience restenosis within one year, and 88% face adverse cardiovascular events, including myocardial infarction, stroke, revascularization procedures, or hospitalization for angina pectoris [48].

New findings could create opportunities to improve exercise outcomes through more efficient or targeted methods. Although this goal may seem futuristic, its potential advantages should encourage further research in this area. Meanwhile, the benefits that are already well-supported by evidence should be prioritized and implemented as critical initiatives [27,49].

It must always be emphasized that exercise programs should be safe and free from harmful effects, and that health benefits partly depend on the proper dose. The best approach is to view exercise as a therapeutic tool for cardiovascular disease. Healthcare professionals, primarily physicians, should play a role in encouraging, guiding, and promoting appropriate exercise habits in patients. The phrase "Exercise is Medicine" should go beyond simply telling patients to "exercise" or "exercise a few times per week," and instead mean that "exercise be prescribed to patients similarly to medication" [50,51]. This process begins with assessing the patient's current abilities and exercise needs,

vremenu, dokaze o prednostima koje su već očigledne treba primeniti i usvojiti kao kritične prioritete [27,49].

Stalno treba naglašavati da programi vežbanja treba da prvo budu bezbedni i bez štetnih efekata, kao i da su zdravstvene koristi, u izvesnoj meri, zavisne od doze. Kao optimalni pristup smatramo posmatranje vežbanja kao sredstva za lečenje kardiovaskularnih bolesti. Zdravstveni radnici, u prvom redu doktori medicine, treba da imaju ulogu u podsticanje, nekoj vrsti mentorskog vođenja i negovanja pravilnih navika pacijenata da vežbaju. Koncept „Vežbanje je lek” treba da ide dalje od jednostavnog govorenja pacijentima da „vežbaju” ili „vežbaju nekoliko dana u nedelji” i zahteva da se „vežbanje pacijentima propisuje na način analogan receptu za lekove” [50,51]. Umesto toga, treba početi procenom trenutnih mogućnosti i potreba pacijenta za vežbanjem i sastaviti početni program vežbanja sa određenom vrstom vežbi, njihovim intenzitetom, brojem ponavljanja i trajanjem u minutima tokom jednog dana, kao i brojem dana u kojima treba vežbati tokom nedelje. Uz to, treba iznaći načine za dodatnu motivaciju i ohrabrivanje pacijenta tokom sprovođenja programa vežbanja. Angažovanje kvalifikovanih profesionalaca je optimalni pristup za adekvatno sprovođenje programa i nadgledanje vežbanja. Sistematski pristup je moguće ostvariti kroz izmene nastavnih planova u obrazovanju lekara, na nivoima osnovnih i specijalističkih studija, uvrštavanjem nastavnih predmeta u kojima će se proučavati značaj i primena vežbanja u cilju prevencije i lečenja bolesti.

FIZIČKI TRENING U SRČANOJ INSUFICIJENCIJI

Stavovi i preporuke vodećih svetskih strukovnih organizacija kardiologa značajno su se menjali tokom prethodnih pola veka. Kao primer mogu poslužiti značajne promene u pristupu lečenju bolesnika sa insuficijencijom srca. Do osamdesetih godina dvadesetog veka obustava fizičke aktivnosti bila je jedna od terapijskih mera koja je primenjivana kod bolesnika sa ovim oboljenjem [52]. Preovladavalo je mišljenje da je fizičko vežbanje za ove bolesnike štetno, te da može dovesti do dilatacije leve komore, dekompenzacije, malignih aritmija, naprasne srčane smrti i, uopšte, do povećanja smrtnosti. Međutim, dvadesetak godina kasnije istraživanja ne samo da su negirala štetnost fizičke aktivnosti kod ovih bolesnika, već su ukazala na niz korisnih efekata [53,54]. Danas lečenje bolesnika sa insuficijencijom srca obuhvata nekoliko mogućnosti, a vežbanje je jedna od važnijih. Kod bolesnika sa srčanom insuficijencijom težak fizički rad nije preporučljiv, međutim kontrolisani fizički trening se pokazao koristan kod bolesnika sa NYHA klasom I-III (HF-ACTION) [55]. Bolesnicima sa HF potrebno je uraditi kardiopulmonalni test

then developing an initial program that specifies the type of exercise, intensity, repetitions, daily duration in minutes, and weekly sessions. Additional strategies should be employed to motivate and support the patient throughout the program. Involving qualified professionals is the most effective way to ensure proper implementation and monitoring. A structured approach can be developed by updating medical education curricula at both undergraduate and specialty-training levels, incorporating courses focused on the importance and application of exercise in disease prevention and treatment.

PHYSICAL TRAINING IN HEART FAILURE

The positions and recommendations of leading international cardiology societies have changed significantly over the past fifty years. A clear example is the major shift in how patients with heart failure are treated. Before the 1980s, stopping physical activity was considered a key treatment strategy for these patients [52]. The common belief was that exercise could be harmful and might lead to left ventricular dilatation, decompensation, dangerous arrhythmias, sudden cardiac death, and increased overall mortality. However, about twenty years later, studies not only challenged the idea that exercise was harmful but also demonstrated many health benefits [53,54]. Today, treating patients with heart failure involves multiple options, with exercise being one of the main components. Although intense physical activity is not recommended for heart failure patients, controlled physical training is beneficial for those with NYHA class I-III (HF-ACTION) [55]. Patients with heart failure should undergo a cardiopulmonary exercise test to assess their level and type of physical activity that will be prescribed, and risk stratification is essential. In patients with heart failure, physical training does not cause significant ischemia or arrhythmias; instead, it improves exercise capacity and alleviates symptoms. Cycling (stationary or regular) and walking are recommended as aerobic, dynamic forms of exercise. For patients with NYHA class II, an exercise intensity of 70%–80% of peak VO_2 is advised, while for NYHA class III patients, the recommended intensity is 50%–65% of peak VO_2 , with interval training being preferred. Aerobic exercise should be performed 3–5 times per week (30–60 minutes per session), prioritizing interval training [56].

In patients with heart failure, interval training shows significantly greater improvements in left ventricular ejection fraction, along with reductions in left ventricular end-diastolic diameter and pressure, compared to continuous training. Interval training also lowers pro-B-type natriuretic peptide (pro-BNP)

fizičkim opterećenjem, radi procene nivoa i vrsta fizičke aktivnosti koji će se nakon toga sprovoditi i neophodno je izvršiti stratifikaciju rizika. Kod bolesnika sa srčanom insuficijencijom, nakon fizičkog treninga ne dolazi do značajne ishemije i aritmija, a povećava se fizički radni kapacitet i smanjuju simptomi. Preporučuje se vožnja bicikle (statičke ili obične) i pešačenje, što predstavlja aerobni, dinamički tip vežbanja. Za bolesnike NYHA II klase preporučuje se intenzitet vežbanja 70%–80% *peak* VO₂, a za bolesnike NYHA III klase 50%–65% *peak* VO₂, a prednost ima intervalni trening. Aerobni tip treninga se preporučuje 3–5 puta nedeljno (30–60 minuta po treningu), a prioritet ima intervalni tip treninga [56]. Kod bolesnika sa srčanom insuficijencijom intervalni trening je pokazao značajno bolje efekte na povećanje ejekcije frakcije leve komore i na smanjenje enddiastolnog dijametra i pritiska leve komore u odnosu na kontinuirani trening. Takođe intervalni trening značajnije smanjuje pro-B-tip natriuretskog peptida (pro-BNP) kod bolesnika sa srčanom insuficijencijom [57]. U HF-ACTION studiji, kod bolesnika sa srčanom insuficijencijom, fizički trening je smanjio ukupnu smrtnost i broj hospitalizacija za 11%, dok su kardiovaskularna smrtnost i hospitalizacije smanjene za 15% [48,56].

Kod bolesnika sa srčanom insuficijencijom i kaheksijom preporučuje se rezistentni tip treninga, koji je kombinacija izotoničkog i izometrijskog opterećenja. Ovu vrstu treninga treba sprovoditi dva puta nedeljno u trajanju 12–20 minuta. Ovaj vid treninga poboljšava snagu i izdržljivost skeletnih mišića i dovodi do povećanja mišićne mase [48]. Istraživanja su pokazala da u hroničnoj srčanoj insuficijenciji vežbanje inhibiše neuro-hormonalnu stimulaciju i produkciju proinflammatory citokina [58]. Takođe, aerobni intervalni trening kod bolesnika sa HF smanjuje nivo natriuretskog peptida, sistemsku vaskularnu rezistenciju i oksidativni stres [59]. Kontrolisano vežbanje može da uspori patofiziologiju progresije srčane insuficijencije. Ovi povoljni efekti ujedno dovode do poboljšanja simptoma, fizičkog kapaciteta i kvaliteta života. Bolesnici kod kojih vežbanje ne dovodi do poboljšanja fizičkog kapaciteta imaju lošu prognozu. Intenzitet fizičkog vežbanja je izuzetno značajan. Nagle intenzivne vežbe dovode do povećanja produkcije proinflammatory citokina i markera oštećenja endotela u bolesnika sa srčanom insuficijencijom, dok se ove promene ne vide kada se izvode umerene vežbe [58,59].

Abnormalnosti endotela su karakteristike srčane insuficijencije. Narušeni su mnogi aspekti endotelne funkcije: vazomotorna, hemo-statična, antioksidantna i inflamatorna aktivnost. Suštinske razlike u endotelnoj disfunkciji zavise od etiologije, težine i stabilnosti bolesnika sa srčanom insuficijencijom. Pokazano je da

more effectively in patients with heart failure [57]. In the HF-ACTION study, exercise training in heart failure patients decreased all-cause mortality and hospitalizations by 11%, while cardiovascular mortality and hospitalizations were reduced by 15% [48,56].

In patients with heart failure and cachexia, resistance training, including isotonic and isometric exercises, is recommended. This type of training should be performed twice weekly for 12 to 20 minutes. It enhances skeletal muscle strength and endurance and promotes muscle mass gain [48]. Research indicates that in chronic heart failure, exercise reduces neuro-hormonal activation and the production of pro-inflammatory cytokines [58]. Aerobic interval training in heart failure patients also lowers levels of natriuretic peptides, systemic vascular resistance, and oxidative stress [59]. Controlled exercise may slow the progression of heart failure by influencing its underlying mechanisms. These benefits improve symptoms, physical capacity, and quality of life. Patients who do not experience improvements in exercise capacity tend to have a poorer prognosis. Exercise intensity plays a crucial role. Sudden high-intensity exercise can increase the production of pro-inflammatory cytokines and markers of endothelial injury in heart failure patients, whereas such changes are not observed during moderate exercise [58,59].

Endothelial abnormalities are a key feature of heart failure. Many aspects of endothelial function are impaired, including vasomotor, hemostatic, antioxidant, and inflammatory activities. The specifics of endothelial dysfunction vary depending on the cause, severity, and stability of the heart failure. It has been shown that even in healthy individuals, moderate exercise enhances acetylcholine-induced vasodilation. Improvements in flow-mediated dilation (FMD) after exercise are associated with reverse left ventricular remodeling, significant increases in LVEF, and decreases in NT-proBNP levels [59].

Exercise intensity is crucial. Sudden high-intensity activity raises the production of pro-inflammatory cytokines and markers of endothelial injury in heart failure patients, while moderate activity does not cause such changes. Besides improving vasodilation, controlled exercise encourages reverse left ventricular remodeling, significantly enhances left ventricular ejection fraction, and reduces levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [38,60]. Coronary endothelial dysfunction is independently linked to impaired left ventricular relaxation in patients with preserved LVEF who lack coronary artery disease. Additionally, based on the text, coronary endothelial dysfunction in coronary artery disease is connected

i kod zdravih osoba, umereni fizički trening povećava vazodilataciju indukovanu acetilholinom. Poboljšanje dilatacije brahijalne arterije, izazvana protokom (engl. *flow-mediated dilation* – FMD) nakon fizičkog treninga pratilo je reverzno remodeliranje leve komore, značajna poboljšanja LVEF i smanjenje nivoa NT-proBNP-a [59].

Intenzitet fizičkog vežbanja je izuzetno značajan. Nagle intenzivne vežbe dovode do povećanja produkcije proinflammatory citokina i markera oštećenja endotela u bolesnika sa srčanom insuficijencijom, dok se ove promene ne vide kada se izvode umerene vežbe. Pored povećanja vazodilatacije, kontrolisane fizičke vežbe dovode do reverzije remodelovanja leve komore, značajno povećavaju ejekcionu frakciju leve komore i redukuju nivo N-terminalnog pro-B-tip natriuretskog peptida (NT-pro-BNP) [38,60]. Koronarna endotelna disfunkcija je nezavisno udružena sa narušenom relaksacijom leve komore u pacijenata sa očuvanom LVEF u odsustvu koronarne bolesti. Takođe, koronarna endotelna disfunkcija u koronarnoj bolesti udružena je sa daljim pogoršanjem dijasolne disfunkcije leve komore. Ovi nalazi su podržani time da izmenjeni balans NO doprinosi miokardnoj ishemiji izazvanoj hipertrofijom miokarda i vodi do srčane insuficijencije. Tako, oštećenje koronarnog endotela možda ima centralno mesto u srčanoj insuficijenciji [38].

ZAKLJUČAK

Kontrolisani fizički trening je izuzetno koristan kod bolesnike sa srčanom insuficijencijom. Mnoge randomizovane, kontrolisane studije su pokazale da fizički trening može usporiti patofiziološku progresiju srčane insuficijencije. U hroničnoj srčanoj insuficijenciji fizički trening inhibiše neuro-hormonalnu stimulaciju i produkciju proinflammatory citokina, smanjuje nivo natriuretskog peptida i sistemsku vaskularnu rezistenciju i smanjuje oksidativni stres. Ovi povoljni efekti takođe povoljno utiču na simptome, fizički radni kapacitet i kvalitet života. Pacijenti od kojih fizički trening nije imao povoljne efekte na fizički radni kapacitet imaju lošu prognozu.

Intenzitet i vrsta fizičkog treninga su izuzetno bitni. Stalno treba naglašavati da programi vežbanja treba da prvo budu bezbedni i bez štetnih efekata, kao i da su zdravstvene koristi, u izvesnoj meri, zavisne od doze. Kod bolesnika sa srčanom insuficijencijom, aerobni intervalni trening je mnogo efikasniji od moderiranog kontinuiranog treninga. Pokazano je da i kod zdravih osoba, umereni fizički trening povećava vazodilataciju indukovanu acetilholinom. Poboljšanje FMD nakon fizičkog treninga izaziva reverziju remodelovanja leve komore, povećava ejekcionu frakciju leve komore i smanjuje nivo NT-pro-BNP.

with further deterioration of left ventricular diastolic dysfunction. These findings are supported by evidence that changes in nitric oxide balance contribute to myocardial ischemia caused by myocardial hypertrophy and lead to heart failure. Therefore, coronary endothelial injury may play a central role in the pathophysiology of heart failure [38].

CONCLUSION

Controlled physical training is highly beneficial for patients with heart failure. Numerous randomized, controlled trials have shown that exercise can slow the progression of heart failure's underlying causes. In chronic heart failure, physical training reduces neuro-hormonal activation and pro-inflammatory cytokine production, lowers levels of natriuretic peptides and systemic vascular resistance, and decreases oxidative stress. These positive effects also enhance symptoms, exercise capacity, and quality of life. Patients who do not see improvements in exercise capacity from physical training tend to have a poorer prognosis.

The intensity and type of exercise are critically important. Exercise programs must always be safe and free of harmful effects, and the health benefits depend, to some extent, on dose. In patients with heart failure, aerobic interval training is significantly more effective than moderate continuous training. Even in healthy individuals, moderate exercise increases acetylcholine-induced vasodilation. Improved FMD after exercise leads to reverse left ventricular remodeling, increases left ventricular ejection fraction, and reduces NT-proBNP levels.

Healthcare professionals, especially physicians, should play a crucial role in encouraging, guiding, and promoting proper exercise habits in patients. The process should start with an assessment of the patient's current exercise capacity and needs, followed by the development of an initial training program that specifies the type of exercise, intensity, repetitions, duration in minutes per day, and the number of exercise days per week. Additional strategies should be used to motivate and support patients throughout the program. Involving qualified professionals is the best way to ensure proper implementation and monitoring of the exercise program.

Conflict of interest: None declared.

Zdravstveni radnici, u prvom redu doktori medicine, treba da imaju ulogu u podsticanju, nekoj vrsti mentorskog vođenja i negovanja pravilnih navika pacijenata da vežbaju. Treba početi procenom trenutnih mogućnosti i potreba pacijenta za vežbanjem i sastaviti početni program vežbanja sa određenom vrstom vežbi, njihovim intenzitetom, brojem ponavljanja i trajanjem u minutima tokom jednog dana, kao i brojem dana u kojima treba vežbati tokom nedelje. Uz to, treba iznaći načine za dodatnu motivaciju i ohrabrivanje pacijenta tokom sprovođenja programa vežbanja. Angažovanje kvalifikovanih profesionalaca je optimalni pristup za adekvatno sprovođenje programa i nadgledanje vežbanja.

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INTERSTICIJUMSKA BOLEST PLUĆA I BULOZNI PEMFIGOID POVEZANI SA PRIMENOM DIREKTNIH ORALNIH ANTIKOAGULANASA: PRIKAZ SLUČAJA DETEKCIJE SIGNALA ZASNOVANIH NA LITERATURI U FARMAKOVIGILANCI

SERIJA SLUČAJEVA

CASE SERIES

INTERSTITIAL LUNG DISEASE AND BULLOUS PEMPHIGOID ASSOCIATED WITH DIRECT ORAL ANTICOAGULANT USE: A CASE REPORT OF LITERATURE-BASED PHARMACOVIGILANCE SIGNAL DETECTION

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SAŽETAK

Uvod/Cilj: Direktni oralni antikoagulansi (engl. *direct oral anticoagulants* – DOAC) značajno su unapredili prevenciju i lečenje tromboembolijskih poremećaja zahvaljujući predvidivoj farmakokinetici, pojednostavljenom doziranju i smanjenoj potrebi za monitoringom u poređenju sa antagonistima vitamina K. Međutim, sa sve većom kliničkom primenom, noviji dokazi ukazuju da DOAC lekovi mogu izazvati retke, ali klinički značajne nehemoragijske neželjene reakcije, kao što su intersticijska bolest pluća (engl. *interstitial lung disease* – ILD) i bulozni pemfigoid (BP). Cilj ove studije je da predstavi i kontekstualizuje ove slučajeve kako bi se povećala svest kliničara o retkim plućnim i dermatološkim neželjenim reakcijama povezanim sa DOAC terapijom.

Prikaz slučaja: Ova serija slučajeva prikazuje jedanaest starijih muškaraca kod kojih se razvila intersticijska bolest pluća (ILD) nakon primene apiksabana, dabigatrana ili edoksabana, pri čemu je vreme do pojave simptoma variralo od nekoliko dana do četiri godine. Kod većine pacijenata došlo je do poboljšanja nakon prekida leka i primene kortikosteroida, dok su dva slučaja imala fatalan ishod. Takođe je opisan detaljan slučaj buloznog pemfigoida povezanog sa primenom rivaroksabana kod 86-godišnjeg muškarca sa više pridruženih bolesti, koji se u potpunosti oporavio nakon prekida terapije rivaroksabanom i lečenja kortikosteroidima, bez ponovne pojave bolesti tokom jednogodišnjeg praćenja na apiksabanu.

Zaključak: Blagovremeno prepoznavanje i odgovarajuće zbrinjavanje ovih reakcija od presudnog su značaja za dobar ishod lečenja. Ova serija slučajeva posebno ističe važnost farmakovigilance i potrebu za daljim istraživanjima kako bi se razjasnili mehanizmi nastanka i faktori rizika koji doprinose razvoju ovakvih neželjenih reakcija.

Ključne reči: intersticijska bolest pluća, bulozni pemfigoid, direktni oralni antikoagulansi, novi oralni antikoagulansi, neželjene reakcije na lekove

ABSTRACT

Introduction/Objective: Direct oral anticoagulants (DOACs) have significantly improved the prevention and management of thromboembolic disorders owing to predictable pharmacokinetics, simplified dosing, and reduced monitoring compared to vitamin K antagonists. However, as clinical use increases, emerging evidence suggests that DOACs may also cause rare but clinically important non-hemorrhagic adverse events, such as interstitial lung disease (ILD) and bullous pemphigoid (BP). The aim of this study is to present and evaluate drug safety signal cases reported in the existing literature and to contextualize them in order to enhance clinician awareness of rare pulmonary and dermatologic adverse events associated with DOAC therapy.

Case report: This report describes signal detection of ILD in 11 elderly male patients following exposure to apixaban, dabigatran, or edoxaban, with latency periods ranging from several days to four years. Most patients showed clinical improvement following drug discontinuation and corticosteroid therapy; however, two experienced fatal outcomes. We additionally report a signal detection case of rivaroxaban-associated bullous pemphigoid in an 86-year-old male with multiple comorbidities, who fully recovered following rivaroxaban withdrawal and corticosteroid therapy, with no recurrence after one year of treatment with apixaban.

Conclusion: Prompt recognition and management are crucial for favorable outcomes. These cases underscore the importance of pharmacovigilance and the need for continued investigation to elucidate mechanisms and risk factors for such reactions.

Keywords: interstitial lung disease, bullous pemphigoid, direct oral anticoagulants, novel oral anticoagulants, adverse drug reactions

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UVOD

Tromboembolijski poremećaji kao što su moždani udar izazvan atrijskom fibrilacijom, venska tromboembolija i plućna embolija i dalje predstavljaju glavne uzročnike globalnog morbiditeta i mortaliteta, zbog čega je antikoagulantna terapija neophodna u savremenoj kliničkoj praksi [1–3]. Iako su ovi agensi veoma efikasni, njihovu terapijsku korist uvek moramo sagledavati u skladu sa bezbednosnim rizicima, posebno rizikom od krvarenja, koje može biti blago do opasno po život [3].

Uvođenje direktnih oralnih antikoagulanasa (DOAC), kao što su apiksaban, dabigatran, edoksaban i rivaroksaban, promenilo je paradigmu upravljanja antikoagulantnom terapijom, omogućavajući predvidivu farmakokinetiku, fiksno doziranje, manje interakcija sa lekovima i hranom, kao i smanjenu potrebu za rutinskim laboratorijskim praćenjem [1,2]. Međutim, uprkos prednostima ističe se važnost kontinuiranog praćenja bezbednosti leka nakon njegovog stavljanja u promet, kako bi se uočile retke ili neočekivane neželjene reakcije [3–5].

Farmakovigilanca je posebno važna, jer klinička ispitivanja često ne traju dovoljno dugo, ne uključuju dovoljno raznovrsnu populaciju ili dovoljno veliki uzorak da bi se otkrili retki ili odloženi događaji [4,5]. Spontano prijavljivanje i opservacione studije omogućili su identifikovanje ranije nepoznatih neželjenih reakcija na DOAC, koje se javljaju i van okvira hemoragijskih reakcija. Kada je reč o ovakvim reakcijama, sve češće se izveštava o dva retka, ali klinički značajna neželjena efekta - intersticijskoj bolesti pluća (ILD) i buloznom pemfigoidu (BP) [4–7].

U vezi sa ovim bolestima, nedavno su posebnu pažnju privukla dva stanja: intersticijska bolest pluća (IBP) povezana sa upotrebom direktnih oralnih antikoagulanasa i bulozni pemfigoid izazvan upotrebom rivaroksabana [4–7]. Iako retke, ove neželjene reakcije predstavljaju dijagnostičke izazove i mogu biti nedovoljno prepoznate u kliničkoj praksi [4–7]. Njihovo uočavanje podvlači važnost kontinuirane farmakovigilance, postojanja svesti kod lekara i stalnog istraživanja šireg bezbednosnog profila DOAC lekova [4–7].

Za potrebe ovog pregleda sprovedena je pomoćna pretraga literature koristeći baze podataka PubMed, Web of Science i Google Scholar do marta 2025. godine. Uključeni su samo članci koji su prošli postupak recenziranja, studije slučaja, serije slučajeva, pregledi i analize iz oblasti farmakovigilance objavljene na engleskom jeziku. Dodatni izvori izdvojeni su manuelnim pregledom referentnih listi relevantnih članaka. Duplikati su uklonjeni, a studije su ocenjivane na osnovu njihovog fokusa na retke, nehemoragijske neželjene

INTRODUCTION

Thromboembolic disorders such as atrial fibrillation-related stroke, venous thromboembolism, and pulmonary embolism remain major contributors to global morbidity and mortality, making anticoagulant therapy essential in modern clinical practice [1–3]. While these agents are highly effective, their therapeutic benefits must always be balanced against safety concerns, particularly the risk of bleeding events that can range from minor to life-threatening [3].

The introduction of direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, has changed anticoagulation management paradigms by providing predictable pharmacokinetics, fixed dosing, fewer drug and food interactions, and reduced need for routine laboratory monitoring [1,2]. However, these advantages have also highlighted the importance of continuous post-marketing safety monitoring to identify rare or unexpected adverse reactions [3–5].

Pharmacovigilance is particularly important, as clinical trials often lack sufficient duration, population diversity, or sample size to detect infrequent or delayed events [4,5]. Spontaneous reporting systems and observational studies have consequently revealed previously unrecognized adverse reactions to DOACs, extending beyond hemorrhagic events. Among these, two rare but clinically significant toxicities, i.e., interstitial lung disease (ILD) and bullous pemphigoid (BP), have been increasingly reported [4–7].

Among these, two conditions have recently gained attention: interstitial lung disease (ILD) associated with direct oral anticoagulants and rivaroxaban-induced bullous pemphigoid [4–7]. Though uncommon, these adverse events pose diagnostic challenges and may be underrecognized in clinical practice [4–7]. Their identification underscores the importance of ongoing pharmacovigilance, clinician awareness, and continued investigation into the broader safety profile of DOACs [4–7].

To inform this review, a supportive literature search was conducted using PubMed, Web of Science, and Google Scholar up to March 2025. Only peer-reviewed articles, case reports, case series, reviews, and pharmacovigilance analyses published in English were included. Additional sources were identified by manually screening the reference lists of relevant articles. Duplicate records were removed, and studies were evaluated for relevance based on their focus on rare, non-hemorrhagic adverse events associated with novel oral anticoagulants (NOACs).

This report aims to assess drug safety signal cases from the existing medical literature, present pharma-

reakcije povezane sa upotrebom novih oralnih antikoagulanasa (engl. *novel oral anticoagulants* - NOAC).

Ovaj izveštaj ima za cilj da proceni bezbednosne signale u vezi sa lekovima iz postojeće medicinske literature, predstavi rezultate medicinskog pregleda farmakovigilance pacijenata koji su oboleli od intersticijske bolesti pluća i buloznog pemfigoida, i sintetiše dostupne dokaze o ovim neželjenim reakcijama, sa fokusom na njihove kliničke karakteristike, potencijalne mehanizme i implikacije za lečenje pacijenata i praćenje bezbednosti lekova.

PRIKAZ SLUČAJA

Kao deo procesa otkrivanja bezbednosnih signala u farmakovigilanci, izveštavamo o objedinjenoj seriji koju čini 11 slučajeva starijih muškaraca kod kojih se nakon izlaganja apiksabanu, dabigatranu ili edoksabanu razvila intersticijska bolest pluća (ILD). Pored toga, dajemo detaljan prikaz slučaja 86-godišnjeg muškarca kod koga se nakon započinjanja terapije rivaroksabanom razvio bulozni pemfigoid (BP).

Intersticijska bolest pluća (ILD) povezana sa DOAC lekovima

Bezbednosni signal u vezi sa intersticijskom bolesti pluća (ILD) povezanom sa NOAC, odnosno DOAC lekovima, prvi put se javlja u izveštaju iz baze podataka o bezbednosti sa datumom zaključavanja podataka od 28. februara 2025. godine. Ovaj signal obuhvatio je objedinjenu seriju od 11 starijih muških pacijenata, objavljen u preglednom radu Hana i saradnika [8], u kojem su procenjeni dokazi dostupni do marta 2023. godine. Objedinjena serija slučajeva od 11 starijih muških pacijenata, starosti 65–91 godine (prosečna starost $79,6 \pm 7,1$ godina), kod kojih se tokom primene apiksabana, dabigatrana ili edoksabana javila intersticijska bolest pluća (ILD), evidentirana je kao signal farmakovigilance. Latentni period je značajno varirao, od tri dana do čak četiri godine po započinjanju terapije. Svi pacijenti su imali dispneju, a difuzno alveolarno krvarenje je bilo često prisutno. Klinički ishodi bili su neujednačeni: kod devet pacijenata došlo je do poboljšanja nakon obustave primene leka, često u kombinaciji sa pulsnom terapijom metilprednizolonom, dok su dva pacijenta preminula usled respiratorne insuficijencije. Zaključak ove serije jeste da se ILD može javiti prilikom upotrebe više različitih NOAC lekova, te da su rano snimanje, u kombinaciji sa momentalnom obustavom primene leka i primenom kortikosteroidne terapije, od ključnog značaja za poboljšanje ishoda [8]. Tokom procene farmakovigilance procenjeno je da kod primenjenih NOAC lekova postoji moguća uzročna povezanost sa uočenim reakcijama. Detaljni nalazi dobijeni u ovoj seriji prikazani su u Tabeli 1.

covigilance medical review results of patients experiencing ILD and BP, and synthesize the available evidence on these adverse events, with a focus on their clinical characteristics, potential mechanisms, and implications for patient management and drug safety monitoring.

CASE REPORT

As a part of a pharmacovigilance signal detection process, we report a collated series of 11 cases of elderly males who developed interstitial lung disease (ILD) following exposure to apixaban, dabigatran, or edoxaban. Additionally, we present a detailed case of an 86-year-old male who developed bullous pemphigoid (BP) following the initiation of rivaroxaban.

Interstitial Lung Disease (ILD) Associated with DOACs

A pharmacovigilance signal of ILD associated with NOACs or DOACs was first identified in the safety database report with a data lock point of 28 February 2025. This signal comprised a collated series of 11 elderly male patients, published in a literature review by Han et al. [8], which evaluated the evidence available up to March 2023. A collated case series of 11 elderly male patients, aged 65–91 years (mean age 79.6 ± 7.1), who developed ILD in association with apixaban, dabigatran, or edoxaban, was received as a pharmacovigilance signal. The latency period varied widely, ranging from three days to as long as four years following treatment initiation. All patients presented with dyspnea, and diffuse alveolar hemorrhage was a common feature. Clinical outcomes were mixed: nine patients improved following drug withdrawal, often in combination with methylprednisolone pulse therapy, while two patients died due to respiratory failure. The conclusion drawn from this series was that ILD can occur in association with several NOACs and that early imaging, combined with immediate drug discontinuation and corticosteroid therapy, is essential for improving outcomes [8]. Throughout the pharmacovigilance review process, the administered NOACs were assessed as having a possible causal relationship with the observed events. The detailed findings of this series are summarized in Table 1.

This signal remained under monitoring, with re-evaluation planned for the next safety database review to incorporate additional non-Asian data and refine risk factor assessment.

Rivaroxaban-Associated Bullous Pemphigoid (BP)

As part of our routine pharmacovigilance activities, a particularly well-documented Individual Case Safety Report (ICSR) of rivaroxaban-associated bullous pem-

Tabela 1. Ključni nalazi u okviru slučajeva ILD povezanih sa NOAC

Parametar	Nalaz
Pacijenti	11 odraslih muškaraca (65–91 godina; prosečna starost 79.6 ± 7.1)
NOAC koji je povezan sa događajem	apiksaban, dabigatran, edoksaban
Latentni period	3 dana – 4 godine po započinjanju terapije
Klinička slika	Dispneja kod svih; uobičajeno difuzno alveolarno krvarenje
Ishodi	9 pacijenata se oporavilo nakon isključivanja leka ± pulsna terapija metilprednizolonom; 2 preminulo (respiratorna insuficijencija)
Zaključak	ILD moguća usled primene više različitih NOAC lekova; preporučuju se rano snimanje i brzo povlačenje leka + steroidi

Table 1. Core findings of ILD cases associated with NOACs

Parameter	Findings
Patients	11 elderly males (65–91 y; mean 79.6 ± 7.1)
Implicated NOACs	Apixaban, Dabigatran, Edoxaban
Latency	3 days – 4 years post-start
Clinical picture	Dyspnea in all; diffuse alveolar hemorrhage common
Outcomes	9 recovered after withdrawal ± methylprednisolone pulse; 2 died (respiratory failure)
Conclusion	ILD possible with several NOACs; early imaging and prompt withdrawal + steroids recommended

Ovaj bezbednosni signal se i dalje prati, a za naredni pregled baze podataka o bezbednosti planirana je ponovna evaluacija kako bi se uključili dodatni podaci izvan Azije i unapredila procena faktora rizika.

Bulozni pemfigoid (BP) povezan sa upotrebom rivaroksabana

Zahvaljujući našim rutinskim aktivnosima na polju farmakovigilance, u našoj globalnoj bazi podataka otkriven je jedan posebno dobro dokumentovan izveštaj o bezbednosti pojedinačnog slučaja (engl. *Individual Case Safety Report – ICSR*) buloznog pemfigoida povezanog sa primenom rivaroksabana. Zahvaljujući ovom objavljenom slučaju otkrili smo poseban, dobro dokumentovan bezbednosni signal zasnovan na literaturi, koji se odnosi na pojedinačni slučaj buloznog pemfigoida povezanog sa upotrebom rivaroksabana. 86-godišnji muškarac sa složenom anamnezom, koja uključuje hipertenziju, dijabetes tipa 2, hroničnu bubrežnu bolest (engl. *chronic kidney disease – CKD*; eGFR 45–50 mL/min), dislipidemiju i paroksizmalnu atrijsku fibrilaciju (CHA₂DS₂-VASc skor = 4), započeo je terapiju rivaroksabanom u dozi od 15 mg dnevno i bisoprololom u julu 2019. godine, nakon postavljene dijagnoze atrijske fibrilacije. Do decembra 2019. godine kod pacijenta se javio opšti svrab, koji je u početku pripisan upotrebi rivaroksabana, što je dovelo do zamene terapije apiksabanom u januaru 2020. godine. Međutim, usled lošeg pridržavanja propisanog režima koji je podrazumevao uzimanje leka dva puta dnevno, rivaroksaban je ponovo uveden početkom februara, u dozi od 20 mg dnevno [6].

Istovremeno je primenjivana terapija koja je uključivala ramipril, metformin, atorvastatin, gliklazid, diltiazem i digoksin, dok upotreba lekova koji se izdaju bez recepta nije prijavljena. U roku od nedelju dana od

phigoid was identified in our global safety database. With this published case, we identified a distinct, well-documented literature-based signal of a single case of rivaroxaban-associated bullous pemphigoid. An 86-year-old male with a complex medical history, including hypertension, type 2 diabetes mellitus, chronic kidney disease (CKD; eGFR 45–50 mL/min), dyslipidemia, and paroxysmal atrial fibrillation (CHA₂DS₂-VASc score = 4) was initiated on rivaroxaban 15 mg daily and bisoprolol in July 2019 following the diagnosis of atrial fibrillation. By December 2019, he developed generalized pruritus, which was initially attributed to rivaroxaban, prompting a switch to apixaban in January 2020. However, due to poor adherence to the twice-daily regimen, rivaroxaban was reintroduced at a dose of 20 mg daily in early February [6].

Concomitant medications included ramipril, metformin, atorvastatin, gliclazide, diltiazem, and digoxin, with no reported use of over-the-counter products. Within one week of rivaroxaban re-initiation, the patient developed tense bullae on the abdomen, which subsequently progressed to crusted erosions and bullous eruptions on the limbs. He was admitted to hospital on March 2, 2020.

On examination, violaceous plaques with hemorrhagic crusts were noted on the abdomen, and multiple intact bullae were present on the extremities. No mucosal involvement was identified. Skin biopsy revealed a subepidermal blister with eosinophilic infiltration. Direct immunofluorescence demonstrated strong C3 deposition along the basement membrane, consistent with the diagnosis of bullous pemphigoid (BP).

Following hospitalization, rivaroxaban was discontinued, and therapy was switched to apixaban. The patient received systemic corticosteroids and adjunctive

Tabela 2. Lečenje i ishod pacijenta sa buloznim pemfigoidom povezanim sa primenom rivaroksabana

Datum	Terapija	Ishod
Mart 2020. godine	Apiksaban 5 mg dva puta dnevno	
Mart 2020. godine	Oralno primenjen prednizon 50 mg na dan, postepeno smanjen na 16 mg; nega rana	
Maj 2020. godine	Prednizon, azatioprin, doksiciklin	Značajno povlačenje lezija
Mart 2021. godine		Bez ponovnog javljanja lezija nakon više od godinu dana primene apiksabana

Table 2. Treatment and outcome of the patient with rivaroxaban-associated bullous pemphigoid

Date	Therapy	Outcome
March 2020	Apixaban 5 mg twice daily	
March 2020	Oral prednisone 50 mg daily, tapered to 16 mg; wound care	
May 2020	Prednisone, azathioprine, doxycycline	Significant lesion resolution
March 2021		No recurrence after > 1 year on apixaban

ponovnog započinjanja terapije rivaroksabanom, pacijentu su se na abdomenu pojavile napete bule, koje su potom progresivno prelazile u erozije pokrivene krastama i bulozne erupcije na ekstremitetima. U bolnicu je primljen 2. marta 2020. godine.

Pregledom su uočene ljubičaste naslage sa hemoragičnim krastama na abdomenu, dok su na ekstremitetima bile prisutne višestruke intaktne bule. Nije utvrđena zahvaćenost sluzokože. Biopsijom kože utvrđen je subepidermalni mehur sa eozinofilnom infiltracijom. Direktna imunofluorescencija pokazala je izražene depozite C3 duž bazalne membrane, što je u skladu sa dijagnozom buloznog pemfigoida (BP).

Nakon hospitalizacije, rivaroksaban je isključen i umesto njega je uveden apiksaban. Pacijent je lečen sistemskim kortikosteroidima uz dodatnu imunosupresivnu terapiju, uz postepeno kliničko poboljšanje. Vrednost Naranjo skora bila je +5, a apiksaban je uspešno primenjen bez ponovnog javljanja buloznih erupcija tokom jednogodišnjeg perioda praćenja. Imajući u vidu objedinjenu seriju slučajeva, primenjeni apiksaban je tokom ovog farmakovigilantnog pregleda procenjen kao potencijalni uzročnik nastanka neželjene reakcije. U Tabeli 2 prikazan je vremenski okvir i ishodi lečenja.

DISKUSIJA

Ovi izveštaji o proceni bezbednosnih signala u farmakovigilanci predstavljaju značajan doprinos jer objedinjuju 11 slučajeva ILD povezanih sa primenom DOAC lekova, te predstavljaju jedan izolovan slučaj buloznog pemfigoida izazvanog upotrebom rivaroksabana, čime postaju jedan od najopsežnijih kliničkih pregleda ovih retkih nehemoragičnih neželjenih reakcija. Ovi slučajevi ističu retke, ali ozbiljne neželjene reakcije povezane sa direktnim oralnim antikoagulantima i naglašavaju

immunosuppressive therapy, with progressive clinical improvement. The Naranjo score was +5 and apixaban was successfully administered without recurrence of bullous eruptions during the follow-up period of one year. Consistent with the collated series, the administered apixaban was assessed as having a possible causal relationship during this pharmacovigilance review. Table 2 summarizes the treatment timeline and outcomes.

DISCUSSION

These pharmacovigilance signal assessment reports make an important contribution by consolidating 11 ILD cases associated with DOACs, along with a distinct case of rivaroxaban-induced BP, representing one of the most comprehensive clinical overviews of these rare non-hemorrhagic toxicities to date. These cases highlight rare but serious adverse reactions associated with direct oral anticoagulants and underscore the importance of early recognition, appropriate management, and consideration of alternative therapies. Multiple single-case reports and small series have described ILD, often accompanied by diffuse alveolar hemorrhage, following exposure to NOACs. Importantly, this safety concern is not currently reflected in the European Union Summary of Product Characteristics (SmPC) or in most Risk Management Plans. The ILD findings align with pharmacovigilance data reported by Raschi et al. and others [4,8], suggesting that although infrequent, these pulmonary reactions can have severe outcomes. The consistent demographic pattern (elderly Asian males with comorbidities) points to potential population-specific susceptibility.

Additional support for this association comes from a single-center observational survey in Japan. Among 870 apixaban users, four developed ILD, correspond-

značaj ranog prepoznavanja, adekvatnog lečenja i razmatranja alternativnih terapija. Višestruki prikazi pojedinačnih slučajeva i male serije slučajeva opisali su ILD, često praćenu difuznim alveolarnim krvarenjem, nakon izlaganja NOAC lekovima. Važno je napomenuti da ovaj bezbednosni problem trenutno nije naveden u Sadržaju karakteristika leka (SmPC) u Evropskoj uniji niti u većini planova upravljanja rizicima. Nalazi u okviru ILD poklapaju se sa podacima farmakovigilance koje su objavili Raši i saradnici [4,8], što ukazuje na to da, iako retke, ove plućne reakcije mogu imati ozbiljne posledice. Dosledan demografski obrazac (stariji muškarci azijskog porekla sa pridruženim bolestima) ukazuje na potencijalnu populaciono osetljivu predispoziciju.

Dodatnu potvrdu da ova povezanost postoji pruža opservaciona studija sprovedena u pojedinačnom centru u Japanu. Među 870 korisnika apiksabana, četvoro je dobilo ILD, što odgovara učestalosti od približno 0,45%. Svi oboleli pojedinci bili su stariji japanski muškarci, a u tri od četiri slučaja simptomi su se razvili u roku od jedne nedelje od početka terapije. Uprkos lečenju pulsnom terapijom metilprednizolonom i mehaničkoj podršci, dva pacijenta su preminula. Ovi nalazi dodatno potvrđuju potencijalnu ozbiljnost ove neželjene reakcije i ukazuju na postojanje demografske predispozicije [9].

Iako je ILD i dalje retka neželjena reakcija kod svih DOAC lekova, opservacione studije i izveštaji farmakovigilance ukazuju na određenu varijabilnost rizika u zavisnosti od specifičnog agensa, demografskih karakteristika pacijenta i prisustva pridruženih bolesti. **Tabela 3** prikazuje dostupne dokaze o učestalosti ILD kada je

ing to an incidence of approximately 0.45%. All affected individuals were elderly Japanese men, and in three of the four cases symptoms developed within one week of drug initiation. Despite treatment with methylprednisolone pulse therapy and ventilatory support, two patients died. These findings further reinforce the potential seriousness of this adverse reaction and suggest a demographic susceptibility [9].

Although ILD remains an uncommon adverse event across all DOACs, observational studies and pharmacovigilance reports suggest some variability in risk depending on the specific agent, patient demographics, and comorbidities. **Table 3** summarizes the available evidence on the incidence of ILD among different DOACs and highlights key patient and drug-related factors.

The majority of reported cases involve elderly Asian males, and several clinical risk factors have been proposed, including renal impairment, pre-existing pulmonary disease, and a history of smoking. Drug-related factors may also contribute to the risk. Apixaban is associated with a higher potential for metabolic interactions, whereas rivaroxaban carries a higher risk of bleeding complications. Alveolar hemorrhage itself may mimic or precipitate interstitial lung disease, making the distinction between these entities clinically challenging. The relationship between hemorrhage and ILD remains an unresolved question [4,8].

At present, interstitial lung disease is not listed as an adverse reaction in the EU SmPC for any NOAC. In contrast, Japan introduced "important precautions" for rivaroxaban as early as February 2014, specifically

Tabela 3. Poređenje učestalosti i karakteristika ILD u slučaju primene različitih DOAC

DOAC	Prijavljena učestalost	Studija / Populacija	Osnovne karakteristike / Faktori rizika
Apiksaban	~0,45%	Japanska studija sprovedena u pojedinačnom centru (n = 870) [9]	Stariji muškarci; početak bolesti u roku od jedne nedelje kod većine; uobičajeno oštećenje bubrega i prethodna bolest pluća
Rivaroksaban	Retka / neodređena	Studije slučaja i analize farmakovigilance [4,8]	Povećan rizik od krvarenja; ILD se može javiti istovremeno sa difuznim alveolarnim krvarenjem
Dabigatran	Retka	Serijski slučajevi [4,8]	Uglavnom stariji muškarci; ograničen broj slučajeva
Edoksaban	Retka	Serijski slučajevi [4,8]	Rana obustava terapije uz primenu kortikosteroida povezana sa oporavkom

Table 3. Comparative incidence and characteristics of ILD among DOACs

DOAC	Reported Incidence	Study / Population	Key Notes / Risk Factors
Apixaban	~0.45%	Japanese single-center survey (n = 870) [9]	Elderly males; onset within 1 week in most; renal impairment and pre-existing lung disease common
Rivaroxaban	Rare / not quantified	Case reports and pharmacovigilance analyses [4,8]	Higher bleeding risk; ILD may overlap with diffuse alveolar hemorrhage
Dabigatran	Rare	Case series [4,8]	Mostly elderly males; limited number of cases
Edoxaban	Rare	Case series [4,8]	Early discontinuation + corticosteroid therapy associated with recovery

reč o različitim DOAC lekovima i ističe ključne faktore u vezi sa pacijentom i primenjenim lekom.

Većina prijavljenih slučajeva odnosi se na starije muškarce azijskog porekla, a istaknuti su brojni klinički faktori rizika, uključujući oštećenje bubrega, prethodnu bolest pluća i istoriju pušenja. Faktori povezani sa lekovima takođe mogu doprineti povećanju rizika. Apiksaban je povezan sa većim potencijalom za metaboličke interakcije, dok rivaroksaban nosi veći rizik od komplikacija krvarenja. Alveolarno krvarenje samo po sebi može da imitira ili izazove intersticijsku bolest pluća, zbog čega kliničko razdvajanje ovih entiteta predstavlja izazov. Odnos između krvarenja i intersticijske bolesti pluća i dalje je nerešeno pitanje [4,8].

Trenutno intersticijska bolest pluća nije navedena kao neželjena reakcija u Sadržaju karakteristika leka (SmPC) ni za jedan NOAC u EU. Nasuprot tome, Japan je još u februaru 2014. godine uveo „važne mere predostrožnosti“ za rivaroksaban, posebno ističući potencijalne plućne neželjene reakcije. Ova regulatorna mera verovatno je uticala na podizanje svesti i može delimično objasniti veću stopu prijavljivanja iz japanskih centara [4,6,9].

Kliničari treba da budu svesni da respiratorni simptomi, poput dispneje, mogu ukazivati na rani razvoj ILD kod pacijenata lečenih NOAC lekovima. Čini se da je ovaj rizik posebno izražen kod starijih muškaraca azijskog porekla, kao i kod osoba sa oštećenjem bubrega ili postojećom bolešću pluća. Hitna kompjuterizovana tomografija visoke rezolucije neophodna je kod simptomatskih pacijenata kako bi bilo moguće razlikovati ILD od difuznog alveolarnog krvarenja. Kada postoji ovakva sumnja, indikovana je hitna obustava primene NOAC leka koji se trenutno koristi, nakon čega se započinje lečenje velikim dozama kortikosteroida, uz mehaničku podršku u teškim slučajevima. Neophodno je sprovesti edukaciju lekara koji prepisuju lekove kako bi se podigla svest o tome da, iako retka, ILD predstavlja klinički značajnu komplikaciju terapije NOAC lekovima, pored dobro poznatih rizika od krvarenja [1,4,6,8–10].

Budući istraživački prioriteti uključuju analizu farmakovigilance velikih razmera u više regiona radi utvrđivanja stope učestalosti, zatim prospektivne kliničke studije u cilju razjašnjavanja osnovnih mehanizama, kao i fokusirano istraživanje relativnog doprinosa difuznog alveolarnog krvarenja u odnosu na imunološki posredovane neželjene reakcije u patogenezi ILD povezane sa upotrebom NOAC lekova.

Slučaj BP povezan sa rivaroksabanom, detaljno opisan u ovom izveštaju, prvobitno je identifikovan kao temeljno dokumentovan ICSR u našoj bazi podataka farmakovigilance, što naglašava praktičnu vrednost kontinuiranog otkrivanja bezbednosnih signala. Nje-

highlighting potential pulmonary adverse events. This regulatory action likely increased awareness and may partly explain the higher rate of reporting from Japanese centers [4,6,9].

Clinicians should be aware that respiratory symptoms such as dyspnea may signal an early development of ILD in patients treated with NOACs. This risk appears to be greatest in elderly Asian males, as well as in individuals with renal impairment or pre-existing lung disease. Prompt high-resolution computed tomography is warranted in symptomatic patients in order to differentiate ILD from diffuse alveolar hemorrhage. Once suspected, immediate discontinuation of the offending NOAC is indicated, followed by initiation of high-dose corticosteroid therapy, with ventilatory support in severe cases. Educating prescribers is essential to raise awareness that, although uncommon, ILD represents a clinically significant complication of NOAC therapy, in addition to the well-established bleeding risks [1,4,6,8–10].

Future research priorities include large-scale, multi-regional pharmacovigilance analyses to establish incidence rates, prospective clinical studies to elucidate underlying mechanisms, and focused investigations into the relative contributions of diffuse alveolar hemorrhage versus immune-mediated toxicity in the pathogenesis of NOAC-associated ILD.

The rivaroxaban-associated BP case detailed in this report was initially identified as a robust ICSR within our pharmacovigilance database, underscoring the practical output of ongoing signal detection. Its subsequent publication [6] provided a valuable opportunity for in-depth clinical analysis. While several other cases of DOAC-associated BP have been reported in the literature [7,11], this specific case was selected not as a literature review example, but because it represented a high-quality, data-rich signal from our internal monitoring system. The patient's clinical course, confirmed by biopsy and immunofluorescence, together with a positive rechallenge and a high Naranjo score (+5), provided strong evidence for a causal association. The successful transition to apixaban without recurrence further suggests that this adverse reaction may be molecule-specific rather than a class effect, providing a crucial insight for clinical management.

Accurate identification of rivaroxaban-associated BP requires careful clinical evaluation combined with immunofluorescence studies, which remain the definitive diagnostic method [6,7,11]. In this case, both the clinical presentation and immunopathological findings corroborated the diagnosis.

Timely recognition, immediate withdrawal of the suspected agent, and initiation of corticosteroid

govo naknadno objavljivanje [6] pružilo je dragocenu priliku za detaljnu kliničku analizu. Iako je u literaturi objavljeno nekoliko drugih slučajeva BP povezanih sa DOAC lekovima [7,11], ovaj konkretan slučaj izabran je ne kao primer za pregled literature, već zato što predstavlja visokokvalitetan, podacima bogat signal iz našeg internog sistema praćenja. Klinički tok pacijenta, potvrđen biopsijom i imunofluorescencijom, zajedno sa pozitivnim ponovnim izlaganjem i visokim Naranjo skorom (+5), pružio je snažne dokaze o uzročnoj povezanosti. Uspešan prelazak na apixaban bez recidiva dodatno ukazuje na to da bi ova neželjena reakcija mogla biti specifična za agens, a ne za celu grupu lekova, što je ključni podatak kada je reč o kliničkom lečenju.

Precizna identifikacija BP povezanog sa upotrebom rivaroksabana zahteva pažljivu kliničku procenu u kombinaciji sa imunofluorescentnim studijama, koje i dalje predstavljaju zlatni standard dijagnostike [6,7,11]. U ovom slučaju, i klinička slika i imunopatološki rezultati potvrdili su dijagnozu.

Blagovremeno prepoznavanje, momentalna obustava primene sumnjivog uzročnika i započinjanje terapije kortikosteroidima neophodni su za kontrolu progresije bolesti. Dok neki pacijenti pokazuju brzo poboljšanje nakon prekida terapije, drugima može biti potrebna produžena primena kortikosteroida i dodatni imunosupresori, kao što je ovde prikazano [7,11]. Naranjo skor je bio +5, što ukazuje na verovatnu uzročnu vezu između rivaroksabana i BP [6,7]. Naranjo algoritam, koji je u širokoj upotrebi u farmakovigilanci, pruža objektivnu i ponovljivu metodu za procenu uzročnosti, smanjujući subjektivnu pristrasnost pri oceni neželjenih reakcija na minimum. Kontinuirana antikoagulantna terapija predstavlja dodatni izazov. Kod ovog pacijenta, apixaban je uspešno primenjivan bez ponovnog javljanja buloznih erupcija duže od godinu dana, što ukazuje na to da bi ovaj lek mogao biti odgovarajuća alternativa za pacijente sa BP izazvanim upotrebom rivaroksabana [6,7].

Ovaj slučaj ističe potrebu za ranim prepoznavanjem BP izazvanog rivaroksabanom, momentalnim prekidom terapije i započinjanjem kortikosteroidne terapije. Uspešna primena apixabana kao alternative podržava hipotezu da je reč o reakcija specifičnoj za agens, a ne za celu grupu lekova.

Svi ovi slučajevi pokazuju kako nadzor nakon stavljanja leka u promet i farmakovigilanca prevazilaze praznine u znanju koje ostaju iza randomizovanih ispitivanja, koja retko beleže ovako retke događaje [4,5]. Povećana svest kod lekara, brza dijagnostička evaluacija i blagovremena intervencija i dalje su neophodni za svođenje morbiditeta i mortaliteta povezanih sa ovim reakcijama na minimum.

therapy are essential for controlling disease progression. While some patients show rapid improvement following drug cessation, others may need extended corticosteroid therapy and additional immunosuppressants, as seen here [7,11]. The Naranjo score was +5, indicating a probable causal relationship between rivaroxaban and BP [6,7]. The Naranjo algorithm, widely used in pharmacovigilance, offers an objective and reproducible method for assessing causality, minimizing subjective bias in adverse reaction evaluation.

Ongoing anticoagulation poses additional challenges. In this patient, apixaban was successfully administered without recurrence of bullous eruptions for more than one year, suggesting it may be a suitable alternative for patients with rivaroxaban-induced BP [6,7].

This case emphasizes the need for early recognition of rivaroxaban-induced BP, immediate discontinuation of the drug, and corticosteroid initiation. The successful use of apixaban as an alternative supports the hypothesis of a molecule-specific, rather than class-wide, reaction.

Together, these cases illustrate how post-marketing surveillance and pharmacovigilance bridge knowledge gaps left by randomized trials, which rarely capture such infrequent events [4,5]. Increased clinician awareness, prompt diagnostic evaluation, and timely intervention remain essential to minimize morbidity and mortality associated with these reactions.

This study is limited by the small number of cases, retrospective data collection, and an absence of a control group. Causality cannot be conclusively proven, and under-reporting remains a potential bias. Additionally, demographic overrepresentation (elderly males) may restrict generalizability. Nonetheless, these reports provide valuable real-world evidence and highlight the need for larger, multicenter studies. Our intention was to highlight the signal detection process using high-quality internal cases, rather than to provide a comprehensive review of all published DOAC-associated cases. While we focused on a small number of internally identified cases for detailed analysis, we acknowledge that additional cases exist in the literature.

Table 4 presents summary of signal detection reports and supporting external literature.

Although DOACs remain safer and more convenient alternatives to vitamin K antagonists, emerging evidence of rare non-hemorrhagic reactions such as ILD and BP warrants ongoing vigilance. Early imaging, immediate drug withdrawal, and corticosteroid therapy are critical for ILD management, while biopsy and immunofluorescence confirmation followed by immunosuppressive treatment are central to BP care. This

Tabela 4. Rezime izveštaja o otkrivanju bezbednosnih signala i pomoćne eksterne literature

Izvor	Referenca / Poreklo	Opis podataka	Ključni rezultati / Doprinos trenutnoj analizi
Interni signal farmakovigilance	Baza podataka PrimeVigilance (Datum zaključavanja podataka: 28. februar 2025. godine)	Objedinjena serija od 11 izveštaja o bezbednosti pojedinačnih slučajeva (ICSR)	- 11 starijih muškaraca (65-91 godina) je obolelo od ILD - U vezi sa upotrebom apiksabana, dabigatrana, edoksabana - Latentni period: 3 dana do 4 godine - Ishod: stanje 9 pacijenata se popravilo nakon obustavljanja terapije ± steroidi; 2 fatalna ishoda
Interni signal farmakovigilance	Baza podataka PrimeVigilance (Datum zaključavanja podataka: 28. februar 2025. godine)	Jedan dobro dokumentovan ICSR	- 86-godišnji muškarac je dobio bulozni pemfigoid - U vezi sa upotrebom rivaroksabana (pozitivno ponovno izlaganje leku) - Potvrđeno biopsijom i imunofluorescencijom - Potpuni oporavak nakon prelaska na apiksaban
Pomoćna eksterna literatura (ILD)	Raschi et al. Drug Saf. 2020 [4]	Analiza farmakovigilance	- Omogućena eksterna validacija signala ILD kod više DOAC lekova. - Razmatrani potencijalni mehanizmi i klinički izazovi.
Pomoćna eksterna literatura (ILD)	Tomari et al. J Stroke Cerebrovasc Dis. 2016 [9]	Pojedinačna studija slučaja	- Rana studija slučaja o ILD povezanom sa upotrebom apiksabana. - Potvrdila je ozbiljnost i brz razvoj reakcije.
Pomoćna eksterna literatura (ILD)	Chan et al. JAMA Netw Open. 2022 [10]	Opservaciona studija (Tajvan)	- Studija velikog obima koja pruža epidemiološke dokaze za povećan rizik od ILD uz upotrebu DOAC lekova nasuprot upotrebi varfarina.
Pomoćna eksterna literatura (BP)	Chohan et al. Clin Case Rep. 2020 [7]	Pojedinačna studija slučaja	- Nezavistan slučaj BP usled upotrebe rivaroksabana kod starijeg pacijenta sa pridruženim bolestima, koji potvrđuje utemeljenost bezbednosnog signala.
Pomoćna eksterna literatura (BP)	Stavropoulos et al. J Eur Acad Dermatol Venereol. 2014 [11]	Pregledni članak	- Obezbedio je kontekst za pemfigoid izazvan upotrebom lekova kao poznat fenomen, čime je potvrđena biološka utemeljenost.
Regulatorni kontekst	Evropska agencija za lekove (EMA) [5]	Regulatorni izveštaj o proceni	- Obezbedio je kontekst za regulatorni stav u EU, gde ILD trenutno nije naveden u Sadržaju karakteristika leka za DOAC.

Table 4. Summary of signal detection reports and supporting external literature

Source Type	Reference / Origin	Data Description	Key Findings / Contribution to Current Analysis
Internal Pharmacovigilance Signal	PrimeVigilance Safety Database (Data Lock Point: 28 Feb 2025)	Collated series of 11 Individual Case Safety Reports (ICSRs)	- 11 elderly male patients (65-91 yrs) developed ILD - Associated with apixaban, dabigatran, edoxaban - Latency: 3 days to 4 years - Outcome: 9 improved after drug withdrawal ± steroids; 2 fatal
Internal Pharmacovigilance Signal	PrimeVigilance Safety Database (Data Lock Point: 28 Feb 2025)	Single, well-documented ICSR	- 86-year-old male developed bullous pemphigoid - Associated with rivaroxaban (positive rechallenge) - Confirmed by biopsy and immunofluorescence - Full recovery after drug switch to apixaban
Supporting External Literature (ILD)	Raschi et al. Drug Saf. 2020 [4]	Pharmacovigilance analysis	- Provided external validation of the ILD signal across multiple DOACs. - Discussed potential mechanisms and clinical challenges.
Supporting External Literature (ILD)	Tomari et al. J Stroke Cerebrovasc Dis. 2016 [9]	Single case report	- Early case report of apixaban-associated ILD. - Supported the seriousness and rapid onset of the reaction.
Supporting External Literature (ILD)	Chan et al. JAMA Netw Open. 2022 [10]	Observational study (Taiwan)	- Large-scale study providing epidemiological evidence for increased ILD risk with DOACs vs. warfarin.
Supporting External Literature (BP)	Chohan et al. Clin Case Rep. 2020 [7]	Single case report	- Independent case of rivaroxaban-associated BP in an elderly patient with comorbidities, supporting the plausibility of the signal.
Supporting External Literature (BP)	Stavropoulos et al. J Eur Acad Dermatol Venereol. 2014 [11]	Review article	- Provided context for drug-induced pemphigoid as a known phenomenon, supporting biological plausibility.
Regulatory Context	European Medicines Agency (EMA) [5]	Regulatory assessment report	- Provided context on the regulatory stance in the EU, where ILD is not currently listed in the SmPC for DOACs.

Ova studija je ograničena malim brojem slučajeva, retrospektivnim prikupljanjem podataka i odsustvom kontrolne grupe. Uzročnost se ne može konačno dokazati, a nepotpuno prijavljivanje predstavlja moguću pristrasnost. Pored toga, prekomerna demografska zastupljenost (stariji muškarci) može ograničiti mogućnost generalizovanja rezultata. Ipak, ovi izveštaji pružaju vredne dokaze iz stvarnog sveta i ističu potrebu za većim, multicentričnim studijama. Naša namera bila je da ilustrujemo proces otkrivanja bezbednosnih signala koristeći visokokvalitetne interne slučajeve, a ne da pružimo sveobuhvatan pregled svih objavljenih slučajeva povezanih sa DOAC lekovima. Iako smo se usredsredili na mali broj internih slučajeva radi detaljne analize, priznajemo da u literaturi postoje i drugi slučajevi.

Tabela 4 predstavlja rezime izveštaja o otkrivanju bezbednosnih signala i pomoćne eksterne literature.

Iako su DOAC lekovi i dalje bezbednije i praktičnije alternative antagonistima vitamina K, noviji dokazi o retkim nehromoragičnim neželjenim reakcijama, kao što su ILD i bulozni pemfigoid, ukazuju na potrebu za stalnom budnošću. Rano snimanje, momentalna obustava leka i primena kortikosteroidne terapije ključni su za lečenje ILD, dok su biopsija i imunofluorescentna potvrda, uz odgovarajuću imunosupresivnu terapiju, od presudnog značaja za lečenje buloznog pemfigoida. Ovaj izveštaj o proceni bezbednosnog signala farmakovigilance popunjava praznine u znanju koje su ostale iza kliničkih ispitivanja, dok uočeni signali ističu vrednost farmakovigilance u otkrivanju retkih neželjenih reakcija i naglašavaju potrebu za daljim istraživanjima sa ciljem razjašnjenja mehanizama, faktora rizika i strategija za poboljšanje bezbednosti pacijenata.

pharmacovigilance signal assessment report bridges knowledge gaps left by clinical trials, while the signals detected underscore the value of pharmacovigilance in uncovering infrequent adverse events and call for further studies to clarify mechanisms, risk factors, and strategies for improved patient safety.

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BILATERALNA HIFEMA U NEONATALNOJ DOBI: REDAK SLUČAJ I KLINIČKE IMPLIKACIJE

PRIKAZ SLUČAJA

CASE REPORT

NEONATAL BILATERAL HYPHEMA: A RARE PRESENTATION AND CLINICAL IMPLICATIONS

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SAŽETAK

Uvod: Hifema u neonatalnoj dobi predstavlja retko stanje koje zahteva hitnu oftalmološku procenu. Za razliku od traumatske hifeme, koja je češća kod starije dece i odraslih, hifema u neonatalnoj dobi obično nastaje usled netraumatskih uzroka, uključujući porođajnu traumu, hematološke poremećaje, kongenitalne infekcije ili vaskularne anomalije. Bilateralna hifema je naročito retka i zahteva detaljan sistemski i oftalmološki pregled radi isključivanja ozbiljnih oboljenja.

Prikaz slučaja: Novorođenče ženskog pola rođeno je u terminu, spontanim vaginalnim porođajem, sa normalnim Apgar skorom i bez evidentnih perinatalnih komplikacija. Nedugo nakon rođenja, primećena je krv u prednjim očnim komorama oba oka, izraženije na desnom oku. Oftalmološkim pregledom potvrđena je bilateralna hifema uz očuvanu providnost rožnjače. Sprovedena je sistemska obrada, uključujući kompletnu krvnu sliku, koagulacione testove i *TORCH* serologiju, čime su isključene koagulopatije i kongenitalne infekcije. Lečenje je sprovedeno konzervativno, uz lokalnu kapljičnu primenu atropina i kortikosteroida. Tokom hospitalizacije, hifema se postepeno resorbovala bez znakova povećanog očnog pritiska ili formiranja sinehija. Novorođenče je otpušteno uz zakazane oftalmološke kontrole radi praćenja mogućih kasnijih komplikacija.

Zaključak: Ovaj slučaj naglašava značaj rane dijagnostike i multidisciplinarnog pristupa u lečenju hifeme u neonatalnoj dobi, naročito kada je prisutna bilateralna. Iako je porođajna trauma najčešći uzrok, neophodna je detaljna dijagnostika kako bi se isključili hematološki i infektivni faktori. S obzirom na retkost bilateralne hifeme u neonatalnoj dobi, potrebni su dalji prikazi slučajeva i studije kako bi se bolje razumela njena etiologija, terapijski pristupi i dugoročni ishodi.

Ključne reči: hifema u neonatalnoj dobi, intraokularno krvarenje, porođajna trauma, kongenitalne infekcije, neonatalni hematološki poremećaji

ABSTRACT

Introduction: Neonatal hyphema, defined as intraocular bleeding into the anterior chamber, is a rare condition that requires immediate ophthalmologic evaluation. Unlike traumatic hyphema commonly seen in older children and adults, neonatal hyphema is typically associated with non-traumatic etiologies such as birth-related mechanical stress, hematologic disorders, congenital infections, or vascular anomalies. Bilateral involvement is particularly uncommon and necessitates a comprehensive systemic and ophthalmologic workup to rule out serious underlying pathology.

Case report: A female neonate was delivered at term via spontaneous vaginal delivery with normal Apgar scores and without perinatal complications. Shortly after birth, blood was observed in the anterior chambers of both eyes, more prominently in the right eye. Ophthalmologic examination confirmed bilateral hyphema with preserved corneal clarity. Systemic evaluation including complete blood count, coagulation studies, and TORCH serology ruled out coagulopathies and congenital infections. The patient was treated conservatively with topical atropine and corticosteroids. During hospitalization, the hyphema gradually resolved without evidence of elevated intraocular pressure or synechiae formation. The newborn was discharged with scheduled ophthalmologic follow-up to monitor for potential late complications.

Conclusion: This case underscores the importance of early recognition and multidisciplinary management of neonatal hyphema, particularly when both eyes are affected. Although birth trauma remains a common cause, thorough diagnostic evaluation is essential to exclude hematologic and infectious etiologies. Given the rarity of bilateral neonatal hyphema, additional case reports and studies are needed to enhance understanding of its etiology, optimal management, and long-term outcomes.

Keywords: neonatal hyphema, intraocular hemorrhage, birth trauma, congenital infections, neonatal hematologic disorders

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UVOD

Hifema u neonatalnoj dobi je redak očni nalaz. Karakteriše ga postojanje krvi u prednjoj očnoj komori. Za razliku od češće prisutne traumatske hifeme kod starije dece i odraslih, hifema u neonatalnoj dobi obično nastaje usled netraumatskih uzroka kao što su porođajna trauma, poremećaji koagulacije ili vaskularne anomalije [1]. Prisustvo bilateralne hifeme kod novorođenčadi je naročito neuobičajeno i zahteva detaljnu evaluaciju kako bi se utvrdila ili isključila sistemska, odnosno očna oboljenja [2].

Porođajna trauma je vodeći uzrok hifeme u neonatalnoj dobi, koja često nastaje usled prolongiranog porođaja, upotrebe forcepsa ili vakuuma, ili prekomernog pritiska na glavu i oči novorođenčeta tokom vaginalnog porođaja [3]. Međutim, spontana hifema, bez jasne traumatske anamneze, izaziva sumnju na sistemska stanja kao što su nedostatak vitamina K, nedostatak faktora koagulacije ili kongenitalne infekcije [4]. Posebno je nedostatak vitamina K dobro dokumentovan uzrok neonatalnog krvarenja, koje se može manifestovati kao hifema, naročito u slučajevima kada je profilaktička primena vitamina K izostala ili bila neefikasna [5]. Ređe, urođene očne anomalije, poput juvenilnog ksantogranuloma, perzistentne fetalne vaskulature (PFV) u predelu dužice ili retinoblastoma, mogu da dovedu do razvoja hifeme, što zahteva dalju oftalmološku i sistemska evaluaciju [6].

Iako se blaži oblik hifeme u neonatalnoj dobi može resorbovati bez dugoročnih posledica, komplikacije kao što su hematokornea i sekundarni glaukom mogu nastati kada se stanje ne prepozna i ne leči pravovremeno [7]. Povišen intraokularni pritisak (IOP) usled začepljenja trabekularne mreže krvnim ugruškom predstavlja značajan problem i u težim slučajevima se rešava primenom lekova za snižavanje intraokularnog pritiska ili hirurškom intervencijom [8]. Hematokornea i formiranje sinehija dovode do trajnog oštećenja vida, ukoliko se pravovremeno ne leče [9]. Ovaj prikaz slučaja opisuje novorođenče sa bilateralnom hifemom, i stavlja akcenat na dijagnostički pristup, terapijske aspekte i kliničke implikacije za razvoj vida. Pisana informisana saglasnost roditelja novorođenčeta dobijena je za objavljivanje ovog prikaza slučaja i pratećih slika.

PRIKAZ SLUČAJA

Prikazujemo novorođenče ženskog pola rođeno u terminu spontanog vaginalnim porođajem nakon uredne trudnoće. Majka, stara 27 godina, bila je zdrava, bez istorije sistemskih bolesti, poremećaja koagulacije ili upotrebe lekova tokom trudnoće. Porođaj je protekao bez komplikacija, a Apgar skor deteta iznosio je 9/9. Pri rođenju, novorođenče je imalo normalne vitalne pa-

INTRODUCTION

Neonatal hyphema is a rare ocular finding. It is characterized by the presence of blood in the anterior chamber. In contrast to the more commonly encountered traumatic hyphema in older children and adults, neonatal hyphema is typically associated with non-traumatic etiologies such as birth-related trauma, coagulation disorders, or vascular anomalies [1]. The presence of bilateral hyphema in a neonate is particularly unusual and necessitates a thorough evaluation to identify or exclude underlying systemic or ocular disease [2].

Birth trauma is the leading cause of neonatal hyphema, often resulting from prolonged labor, forceps- or vacuum-assisted delivery, or excessive pressure on the infant's head and eyes during vaginal birth [3]. However, spontaneous hyphema without a clear traumatic history raises concern for systemic conditions such as vitamin K deficiency, clotting factor deficiencies, or congenital infections [4]. Vitamin K deficiency, in particular, is a well-documented cause of neonatal bleeding and may present as hyphema, especially when prophylactic vitamin K administration is omitted or ineffective [5]. More rarely, congenital ocular abnormalities such as juvenile xanthogranuloma, persistent fetal vasculature (PFV) involving the iris, or retinoblastoma can also result in hyphema, requiring further ophthalmologic and systemic evaluation [6].

Although mild neonatal hyphema may resolve spontaneously without long-term consequences, complications such as corneal blood staining and secondary glaucoma can occur if the condition is not promptly recognized and appropriately managed [7]. Increased intraocular pressure due to clot obstruction of the trabecular meshwork represents a significant concern and may require treatment with pressure-lowering medications or, in severe cases, surgical intervention [8]. Corneal blood staining and the formation of synechiae can lead to permanent visual impairment if not treated in a timely manner [9].

This case report describes a newborn with bilateral hyphema at birth, emphasizing the diagnostic approach, therapeutic considerations, and clinical implications for visual development. Written informed consent for publication of this case report and accompanying images was obtained from the infant's parents.

CASE REPORT

A female neonate was delivered at term via spontaneous vaginal delivery after an uneventful pregnancy. The 27-year-old mother was healthy, with no history of systemic disease, bleeding disorders, or medication use during pregnancy. The delivery was uncomplicated, and the infant's Apgar scores were 9/9. At birth, the

rametre, težilo je 3.360 g i procenjeno je kao klinički stabilno. Međutim, ubrzo nakon rođenja primećeno je prisustvo krvi u prednjim očnim komorama oba oka, sa izraženijim krvarenjem u desnom oku (Slika 1). Nisu uočeni spoljašnji znaci traume, periorbitalni edem niti subkonjunktivalna hemoragija. Crveni refleks je bio odsutan, naročito desno, gde je obilno krvarenje onemogućavalo vizualizaciju dubljih struktura.

Novorođenče je primljeno na Kliniku za očne bolesti Univerzitetskog Kliničkog centra Srbije, a radi dalje evaluacije i lečenja. Oftalmološkim pregledom pokazano je postojanje bilateralne hifeme, ali bez znakova zamućenja rožnjače. Reakcija leve zenice bila su usporene zbog hifeme, ali nije bilo aferentnog pupilarnog defekta. Reakcija desne zenice je procenjena indirektno u odnosu na levo oko. Prisustvo krvi ograničilo je pregled očnog dna, međutim, na levom oku nisu uočene vidljive patološke promene zadnjeg segmenta, dok dublje strukture desnog oka nisu bile vidljive. Ultrazvučni pregled potvrdio je odsustvo intraokularnog tumora.

Sprovedena je sveobuhvatna sistemska obrada radi isključivanja hematoloških i infektivnih uzroka. Rezultati kompletne krvne slike, koagulacionog profila i biohemijskih analiza bili su u granicama referentnih vrednosti, čime su isključeni poremećaji koagulacije,

newborn demonstrated normal vital signs, weighed 3360 g, and was assessed as clinically stable. However, shortly after birth, blood was noted in the anterior chambers of both eyes, with more pronounced hemorrhage in the right eye (Figure 1). There were no external signs of trauma, periorbital edema, or subconjunctival hemorrhage. The red reflex was absent, particularly in the right eye, where the extensive hemorrhage prevented visualization of deeper ocular structures.

The newborn was admitted to the University Eye Hospital for further evaluation and management. Ophthalmologic examination confirmed bilateral hyphema without corneal clouding. Pupillary reactions in the left eye were sluggish due to the hyphema but showed no afferent pupillary defect. The pupillary reaction in the right eye was assessed indirectly in comparison with the left eye. Visualization of the fundus was limited by the presence of blood; no posterior segment abnormalities were seen in the left eye, while the deeper structures of the right eye remained obscured. Ultrasonography confirmed the absence of intraocular tumors.

A comprehensive systemic workup was performed to exclude hematologic and infectious causes. Complete blood count, coagulation profile, and biochemical analyses were within normal limits, ruling out



Slika 1. Gornja fotografija: Novorođenče sa hifemom bez vidljive spoljašnje traume. Donja fotografija (nakon sedam dana): Vidljivo poboljšanje, uz značajnu resorpciju hifeme. Prednja očna komora izgleda bistrije, sa samo minimalnim zaostalim tragovima krvi

Figure 1. Top image: A neonatal eye presenting with spontaneous hyphema, characterized by the presence of blood in the anterior chamber without any apparent external trauma. Bottom image (7 days later): Noticeable improvement, with significant resorption of the hyphema. The anterior chamber appears clearer, with only minimal residual blood

kao što su nedostatak vitamina K ili poremećaji faktora zgrušavanja. TORCH serologija bila je negativna, čime su kongenitalne infekcije isključene kao moguća etiologija. Urađen je ultrazvučni pregled abdomena radi provere na hepatosplenomegaliju, koja nije ustanovljena, što je dodatno umanjilo verovatnoću sistemskog infektivnog ili metaboličkog poremećaja. Ukupni nalazi ukazivali su na to da je hifema verovatno nastala tokom porođaja, a ne kao posledica sistemskog oboljenja.

Novorođenče je lečeno lokalnom primenom atropina u koncentraciji od 0,25% (dva puta dnevno), u desno oko radi prevencije formiranja zadnjih sinehija, kao i lokalnom primenom prednizolon acetata u koncentraciji od 0,5% (četiri puta dnevno), u oba oka radi kontrole inflamacije i smanjenja rizika od komplikacija. Novorođenče je pažljivo praćeno na znakove povišenog intraokularnog pritiska ili pogoršanja krvarenja. Tokom narednih dana, hifema se postepeno resorbovala, uz delimično poboljšanje vizualizacije crvenog refleksa.

Nakon sedmodnevnog bolničkog lečenja, stanje novorođenčeta je ostalo stabilno, bez novih nalaza koji bi ukazivali na dodatnu očnu patologiju. Hifema je počela spontano da se povlači, a intraokularni pritisak ostao je u granicama normalnih vrednosti što je provereno u uslovima opšte anestezije ručnim aplanacionim tonometrom (IOP desno 14 mmHg, levo 15 mmHg). Novorođenče je otpušteno uz preporuku za nastavak lokalne kortikosteroidne terapije (4 puta dnevno u oba oka sledeće dve nedelje), upotreba cikloplegika je isključena posle 14 dana od početka primene. Zakazani su kontrolni oftalmološki pregledi radi praćenja mogućih komplikacija, kao što su sekundarni glaukom ili hematokornea.

DISKUSIJA

Hifema u neonatalnoj dobi je neuobičajen, ali klinički značajan nalaz koji zahteva hitnu oftalmološku procenu radi utvrđivanja osnovne etiologije i prevencije mogućih komplikacija. Dok je hifema kod starije dece i odraslih najčešće povezana sa povredom oka tupim predmetom, uzroci kod novorođenčadi su raznovrsniji i često netraumatske prirode. Najčešći uzroci su porođajna trauma, hematološki poremećaji, intrauterine infekcije, metaboličke abnormalnosti i kongenitalne vaskularne anomalije [1]. Bilateralna hifema u neonatalnoj dobi, koja je opisana u našem slučaju, naročito je retka i zahteva detaljnu sistemsku i oftalmološku evaluaciju kako bi se isključila ozbiljnija sistemska oboljenja.

Porođajna trauma se smatra vodećim uzrokom neonatalne hifeme, naročito u slučajevima vaginalnih porođaja sa prekomernim pritiskom na glavu i oči novorođenčeta tokom porođaja. Asistirani porođaji, poput onih uz vakuum-ekstrakciju ili upotrebu forcepsa, mogu dovesti do povišenog intraorbitalnog pritiska

coagulation disorders such as vitamin K deficiency or clotting factor abnormalities. TORCH serology was negative, excluding congenital infections as the underlying etiology. Abdominal ultrasonography revealed no hepatosplenomegaly, further reducing the likelihood of a systemic infectious or metabolic disorder. Overall, the findings suggested that the hyphema was most likely induced during birth rather than caused by an underlying systemic disease.

The patient was treated conservatively with topical atropine 0.25% twice daily in the right eye to prevent posterior synechiae formation and topical prednisolone acetate 0.5% four times daily in both eyes to control inflammation and reduce the risk of complications. The infant was closely monitored for signs of elevated intraocular pressure or progression of hemorrhage. Over the following days, the hyphema gradually began to resolve, with partial improvement in the red reflex.

After seven days of hospitalization, the infant remained clinically stable, with no new findings suggestive of additional ocular pathology. The hyphema continued to resolve spontaneously, and intraocular pressure remained within normal limits, measured under general anesthesia using a handheld applanation tonometer (14 mmHg in the right eye and 15 mmHg in the left eye). The patient was discharged with instructions to continue topical corticosteroid therapy (four times daily in both eyes for two additional weeks), while cycloplegic treatment was discontinued after 14 days. Follow-up ophthalmologic examinations were scheduled to monitor for potential complications such as secondary glaucoma or corneal blood staining.

DISCUSSION

Neonatal hyphema is an uncommon but clinically important finding that requires urgent ophthalmologic evaluation to identify the underlying etiology and prevent potential complications. While hyphema in older children and adults is most commonly associated with blunt ocular trauma, the causes in neonates are more diverse and often nontraumatic. The most frequent etiologies include birth trauma, hematologic disorders, intrauterine infections, metabolic abnormalities and congenital vascular anomalies [1]. Bilateral hyphema in the neonatal period, as described in this case, is particularly rare and requires a detailed systemic and ophthalmologic assessment to exclude serious systemic disease.

Birth trauma is considered the leading cause of neonatal hyphema, especially in vaginal deliveries where excessive pressure may be exerted on the infant's head and eyes during labor. Assisted deliveries, including vacuum extraction or forceps, can lead to elevated intraorbital pressure [2]. However, our case in-

[2]. Međutim, u našem slučaju radilo se o spontanom vaginalnom porođaju, što ukazuje da u retkim situacijama kao što je ova i prilikom spontanog vaginalnog porođaja može da dođe do razvoja hifeme.

Još jedan važan aspekt u razmatranju neonatalne hifeme odnosi se na hematološke poremećaje, uključujući krvarenje usled nedostatka vitamina K (engl. *vitamin K deficiency bleeding - VKDB*), trombocitopeniju ili urođene poremećaje faktora koagulacije, kao što su hemofilija A ili B [3]. VKDB je dobro dokumentovan uzrok spontanijih krvarenja kod novorođenčadi zbog nedovoljnih nivoa vitamina K pri rođenju, a može se manifestovati mukoznim ili intrakranijalnim krvarenjem, kao i intraokularnim hemoragijama [4]. Međutim, u ovom slučaju, novorođenče je na rođenju primilo profilaktički vitamin K, a koagulacioni testovi pokazali su normalan broj trombocita, normalno protrombinsko vreme i aktivirano parcijalno trombotoplastinsko vreme, čineći poremećaj koagulacije malo verovatnim.

Kongenitalne infekcije, naročito one iz TORCH grupe (toksoplazmoza, rubeola, citomegalovirus i herpes simpleks), takođe mogu dovesti do intraokularnog krvarenja usled pridruženog hiororetinitisa, abnormalnosti retinalnih krvnih sudova ili urođenog glaukoma [5]. Međutim, kod našeg pacijenta TORCH serologija je bila negativna, nisu postojali znaci sistemske infekcije niti očni nalazi koji bi ukazivali na urođeni retinitis ili inflamaciju, čime je infektivni uzrok praktično isključen.

Drugi mogući uzroci neonatalne hifeme uključuju urođene očne anomalije, poput PFV u predelu dužice, retinoblastoma ili urođenog glaukoma. PFV predstavlja razvojnu anomaliju nastalu neuspešnim povlačenjem fetalnog hijaloidnog vaskularnog sistema, što kod novorođenčadi može da dovede do intraokularnog krvarenja [7]. Retinoblastom, iako redak kod novorođenčadi, treba uzeti u obzir u slučajevima neobjašnjenog intraokularnog krvarenja, naročito ako je udružen sa leukokorijom [8]. Ipak, u našem prikazu rožnjača je bila providna, a ultrazvučnim pregledom nije potvrđeno postojanje intraokularnog tumora koji bi mogao dovesti do razvoja hifeme.

Glavne komplikacije hifeme u neonatalnoj dobi uključuju povišen intraokularni pritisak, hematokorneu, sekundarni glaukom što dugoročno može dovesti do oštećenja vida. Povišen intraokularni pritisak može da nastane usled začepljenja trabekularne mreže krvnim ćelijama ili inflamatornim detritusom, što može da dovede do sekundarnog glaukoma [9]. Hematokornea, koja nastaje usled produženog kontakta hemolizovanih eritrocita sa endotelom rožnjače, predstavlja značajni problem u slučajevima produžene ili ponovljene hifeme [10].

S obzirom na mogućnost komplikacija koje ugrožavaju vid, lečenje hifeme u neonatalnoj dobi prvenstveno

zavolava spontane vaginalni porođaj, ukazujući da hifema može da se javi čak i tokom nekomplikovanih porođaja.

Drugi važan aspekt u proceni neonatalne hifeme uključuje hematološke poremećaje, kao što su vitamin K deficijencija krvarenje (VKDB), trombocitopenija i kongenitalne defekcije faktora koagulacije uključujući hemofiliju A i B [3]. VKDB je dobro dokumentovani uzrok spontanog krvarenja kod novorođenčadi zbog niskih nivoa vitamina K pri rođenju, a može se manifestovati mukoznim ili intrakranijalnim krvarenjem, kao i intraokularnim hemoragijama [4]. U ovom slučaju, novorođenče je primilo profilaktički vitamin K pri rođenju, a koagulacioni testovi (broj trombocita, vreme protrombina i vreme aktiviranog parcijalnog trombotoplastina) bili su normalni, čime je verovatnoća za koagulacionu bolest izuzetno mala.

Kongenitalne infekcije, posebno one iz TORCH grupe (toxoplasmoza, rubeola, citomegalovirus i herpes simplex), mogu takođe dovesti do intraokularnog krvarenja usled pridruženog hiororetinitisa, abnormalnosti retinalnih krvnih sudova ili urođenog glaukoma [5]. Međutim, kod našeg pacijenta TORCH serologija je bila negativna, nisu postojali znaci sistemske infekcije niti očni nalazi koji bi ukazivali na urođeni retinitis ili inflamaciju, čime je infektivni uzrok praktično isključen.

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Glavne komplikacije neonatalne hifeme uključuju povišen intraokularni pritisak, krvavost rožnjače i sekundarni glaukom, sva tri stanja koja mogu dovesti do trajnog oštećenja vida. Povišen intraokularni pritisak može nastati zbog začepljenja trabekularne mreže krvnim ćelijama ili inflamatornim detritusom, što može dovesti do sekundarnog glaukoma [9]. Krvavost rožnjače nastaje usled produženog kontakta hemolizovanih eritrocita sa endotelom rožnjače, predstavlja značajni problem u slučajevima produžene ili ponovljene hifeme [10].

S obzirom na mogućnost komplikacija koje ugrožavaju vid, lečenje hifeme u neonatalnoj dobi prvenstveno

no se zasniva na pažljivom praćenju i suportivnoj terapiji. Konzervativno lečenje cikloplegicima (npr. atropin) uobičajeno se koristi radi prevencije formiranja zadnjih sinehija, dok kortikosteroidi (npr. prednizolon acetat) pomažu u smanjenju intraokularne inflamacije [11]. U ovom slučaju, novorođenče je lečeno atropinom u koncentraciji od 0,25% i prednizonom u koncentraciji od 0,5%, što je dovelo do postepene resorpcije hifeme bez razvoja komplikacija.

Iako je spontano povlačenje uobičajeno kod blagih hifema u neonatalnoj dobi, redovno oftalmološko praćenje je od ključnog značaja [12]. Praćenje intraokularnog pritiska takođe je neophodno zato što kod nekih novorođenčadi može da dođe do razvoja odloženog sekundarnog glaukoma, čak i nakon povlačenja hifeme.

ZAKLJUČAK

Ovaj slučaj ističe značaj sveobuhvatnog dijagnostičkog pristupa hifemi u neonatalnoj dobi, naročito kada je prisutna bilateralno. Iako porođajna trauma ostaje najverovatniji uzrok u slučajevima vaginalnih porođaja, bilateralna zahvaćenost zahteva detaljnu sistemsku obradu radi isključivanja hematoloških, infektivnih i urođenih očnih patologija. Konzervativno lečenje cikloplegicima i kortikosteroidima često je dovoljno, ali je neophodno pažljivo praćenje zbog mogućih komplikacija, kao što su povišen intraokularni pritisak i hematokornea. S obzirom na retkost bilateralne hifeme u neonatalnoj dobi, potrebni su dodatni prikazi slučajeva i studije kako bi se bolje razumela njena etiologija, klinički tok i optimalne strategije lečenja.

Sukob interesa: Nije prijavljen

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mation [11]. In this case the newborn was treated with atropine 0.25% and prednisolone 0.5%, which resulted in gradual resorption of the hyphema without complications.

Although spontaneous resolution is common in mild neonatal hyphema, regular ophthalmologic follow up remains essential [12]. Monitoring intraocular pressure is also required because some newborns may develop delayed secondary glaucoma even after the hyphema has resolved.

CONCLUSION

This case highlights the importance of a comprehensive diagnostic approach to neonatal hyphema, particularly when it presents bilaterally. Although birth trauma remains the most likely cause in vaginal deliveries, bilateral involvement requires a detailed systemic evaluation to exclude hematologic, infectious and congenital ocular pathologies. Conservative treatment with cycloplegics and corticosteroids is often sufficient, but careful monitoring is essential because of potential complications such as elevated intraocular pressure and corneal blood staining. Given the rarity of bilateral neonatal hyphema, additional case reports and studies are needed to improve understanding of its etiology, clinical course and optimal management strategies.

Conflict of interest: None declared.

UDRUŽENA POJAVA POLICITEMIJE VERE I MULTIPLOG MIJELOMA: PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

COEXISTENCE OF POLYCYTHEMIA VERA AND MULTIPLE MYELOMA: A CASE REPORT

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SAŽETAK

Uvod: Policitemija vera (PV) je hronična mijeloproliferativna neoplazma koju karakteriše klonalna proliferacija eritrocitne a neretko i mijeloide i megakariocitne loze, najčešće povezana sa pojavom mutacije u JAK2 genu. Multipli mijelom (MM), s druge strane, je maligna neoplazma koju karakteriše klonalna proliferacija plazma ćelija u koštanoj srži i sekrecija monoklonskog imunoglobulina. Koezistencija policitemije vere i multiplog mijeloma kod istog pacijenta je izuzetno retka, jer ovi poremećaji potiču od različitih hematopoetskih ćelijskih linija.

Prikaz slučaja: Predstavljamo slučaj pacijenta sa dugogodišnjom PV koji je tokom svog kliničkog toka razvio i sekundarni hematološki malignitet MM, ukazujući na izazove tokom dijagnostike i lečenja udružena dva hematološka maligniteta.

Zaključak: Prognoza pacijenata sa udruženim hematološkim malignitetima zavisi od tipa i agresivnosti oboljenja, stadijuma u trenutku otkrivanja i optimalnog terapijskog pristupa. Prikazani slučaj podseća da se klinički znaci i simptomi kod pacijenta sa već postojećom dijagnozom ne smeju tumačiti isključivo u okviru osnovne bolesti. Diferencijalna dijagnoza mora ostati široka, uz pojedinačno ispitivanje svakog novog simptoma, čime se omogućava rano prepoznavanje dodatne patologije i pravovremeno lečenje.

Ključne reči: multipli mijelom, policitemija vera, mijeloproliferativne neoplazme

ABSTRACT

Introduction: Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by the clonal proliferation of erythroid, myeloid, and megakaryocytic lineages, most commonly associated with the JAK2 V617F mutation. Multiple myeloma (MM), on the other hand, is a malignant plasma cell neoplasm characterized by clonal proliferation of plasma cells in the bone marrow and the secretion of monoclonal immunoglobulin. The coexistence of PV and MM in the same patient is extremely rare, as these disorders originate from distinct hematopoietic lineages.

Case report: We report the case of a patient with long-standing PV who subsequently developed MM, highlighting the diagnostic and therapeutic challenges of this unusual association.

Conclusion: The prognosis of patients with concomitant hematologic malignancies depends on the type and aggressiveness of the diseases, the clinical stage at the time of detection, and the adequacy of the therapeutic approach. This case highlights the importance of avoiding automatic attribution of new clinical symptoms to a pre-existing diagnosis. A broad differential diagnosis should always be maintained, with each new symptom evaluated individually, allowing for early recognition of additional hematologic pathology and timely initiation of appropriate treatment.

Keywords: multiple myeloma, polycythemia vera, myeloproliferative neoplasms

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UVOD

Policitemija vera (PV) je mijeloproliferativna neoplazma koju karakteriše klonalna eritrocitoza, dok druge karakteristike uključuju leukocitozu, trombocitozu, splenomegaliju, pruritus, konstitucionalne simptome, poremećaje mikrocirkulacije i povećan rizik od tromboze i progresije u mijelofibrozu (MF nakon PV) ili akutnu mijeloidnu leukemiju (AML) [1]. Više od 95% pacijenata ima mutaciju JAK2 gena, što pomaže u razlikovanju PV od sekundarnih uzroka eritrocitoze [2]. Mutacija JAK2 kinaze dovodi do poremećaja signalizacije koji rezultiraju nekontrolisanom proliferacijom eritroidnih progenitora. Zamena valina fenilalaninom na poziciji 617 JAK2 gena, ili JAK2V617F, uzrokuje konstitutivnu aktivaciju citokinskih receptora, nezavisno od prisustva eritropoetina [3]. Pored JAK2 mutacije, kod manjeg broja pacijenata mogu se javiti mutacije u TET2, DNMT3A i ASXL1 genima, koji doprinose heterogenosti kliničke slike i riziku progresije bolesti [4]. Klinički tok PV je hroničan i sporo progresivan, a glavne komplikacije uključuju tromboembolijske događaje, transformaciju u post-policitemijsku mijelofibrozu i akutnu mijeloidnu leukemiju. Postignut je značajan napredak u razvoju novih terapijskih pristupa za pacijente sa policitemijom verom (PV) [5,3]. Standardni terapijski pristup obuhvata terapijsku venepunkciju i citoreduktivnu terapiju (hidroksiurea) [5].

Multipli mijelom (MM), s druge strane, je maligni poremećaj plazma ćelija koji karakteriše klonalna proliferacija plazma ćelija unutar koštane srži, što dovodi do prekomerne proizvodnje monoklonskih imunoglobulina (M- proteina), osteolitičkih lezija, anemije, bubrežne slabosti i imunodeficijencije [6]. Multipli mijelom čini približno 10% hematoloških maligniteta i predstavlja drugi po učestalosti hematološki malignitet posle limfoma [7]. Bolest najčešće pogađa osobe starije od 60 godina i ima značajan uticaj na morbiditet i mortalitet. U patogenezi MM-a ključnu ulogu imaju genetske abnormalnosti, mikrookruženje koštane srži i disregulacija signalnih puteva koji stimulišu preživljavanje i proliferaciju plazma ćelija [8,9].

Policitemija vera i multipli mijelom predstavljaju hronične hematološke maligne bolesti koje potiču iz različitih hematopoteskih loza – mijeloidne i limfoidne, što čini njihovu koegzistenciju kod jednog pacijenta neuobičajenom i zanimljivom kliničkom pojavom. Uprkos različitom poreklu, obe bolesti mogu deliti zajedničke faktore rizika, uključujući izloženost jonizujućem zračenju, hroničnu stimulaciju hematopoetskih ćelija i akumulaciju somatskih mutacija tokom starenja [1,6,10]. Istovremena ili uzastopna pojava PV i MM je retka, sa samo ograničenim brojem slučajeva prijavljenih u literaturi. Precizni mehanizmi koji leže u osnovi

INTRODUCTION

Polycythemia vera (PV) is a myeloproliferative neoplasm distinguished by clonal erythrocytosis. Other features include leukocytosis, thrombocytosis, splenomegaly, pruritus, constitutional symptoms, microcirculatory disturbances, and an increased risk of thrombosis and progression to myelofibrosis (post-PV MF) or acute myeloid leukemia (AML) [1]. Over 95% of patients possess a JAK2 gene mutation, which helps differentiate PV from secondary erythrocytosis causes [2]. Mutations in the JAK2 kinase lead to signaling abnormalities that cause uncontrolled proliferation of erythroid progenitors. The substitution of valine with phenylalanine at position 617 of the JAK2 gene (JAK2V617F) results in constitutive activation of cytokine receptors, regardless of erythropoietin presence [3]. Besides JAK2 mutations, a smaller percentage of patients may have mutations in the TET2, DNMT3A, and ASXL1 genes, contributing to clinical heterogeneity and the risk of disease progression [4]. The clinical course of PV is chronic and slowly progressive, with major complications including thromboembolic events, transformation to post-polycythemic myelofibrosis, and acute myeloid leukemia. Significant progress has been made in developing new therapeutic approaches for patients with polycythemia vera [5,3]. The standard treatment includes therapeutic venesection and cytoreductive therapy (hydroxyurea) [5].

Multiple myeloma (MM), on the other hand, is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells within the bone marrow, leading to excessive production of monoclonal immunoglobulins (M protein), osteolytic lesions, anemia, renal impairment, and immunodeficiency [6]. Multiple myeloma accounts for approximately 10% of hematologic malignancies and represents the second most common hematologic malignancy after lymphoma [7]. The disease most commonly affects individuals older than 60 years and has a significant impact on morbidity and mortality. Genetic abnormalities, the bone marrow microenvironment, and dysregulation of signaling pathways that stimulate plasma cell survival and proliferation play a crucial role in the pathogenesis of MM [8,9].

Polycythemia vera and multiple myeloma are chronic hematologic malignancies originating from different hematopoietic lineages—myeloid and lymphoid—which makes their coexistence in a single patient an unusual and clinically intriguing phenomenon. Despite their different origins, both diseases may share common risk factors, including exposure to ionizing radiation, chronic stimulation of hematopoietic cells, and accumulation of somatic mutations during aging [1,6,10]. The simultaneous or sequential occurrence of PV and MM is rare, with

ove povezanosti ostaju nejasni [10]. Ovaj izveštaj predstavlja redak slučaj pacijenta kome je inicijalno dijagnostikovana policitemija vera, a koji je kasnije razvio multipli mijelom.

Cilj nam je da doprinesemo literaturi o ovoj neobičnoj koegzistenciji i da diskutujemo o mogućim patogenetskim mehanizmima i kliničkim implikacijama.

PRIKAZ SLUČAJA

Kod pacijenta starosti 54 godine postavljena je dijagnoza policitemije vere tokom 2010. godine, a nakon hematološke obrade koja je uključivala i biopsiju koštane srži. Od momenta postavljanja dijagnoze njegov tretman je uključivao acetilsalicilnu kiselinu (ASA) sa povremenom terapijskom flebotomijom koja se izvodi po potrebi radi kontrole nivoa hematokrita. Nakon 5 godina u terapiju uvedena i hidroksiureja (Litalir®). Bolest je ostala klinički stabilna 15 godina, uz redovno hematološko praćenje, a pacijent je bio bez tegoba. U ličnoj anamnezi: boluje od hipertenzije, i daje podatak da se ranije lečio od multiple skleroze, ali da je bolest u remisiji i da nema nikakvu terapiju, osim redovnih kontrola neurologa. U julu tekuće godine na jednoj od redovnih kontrola pacijent prijavljuje da je primetio krv u stolici (tada vrednost Hgb u krvnoj slici 120 g/l); nakon čega je upućen gastroenterologu i sprovedena je kompletna obrada. Od strane gastroenterologa potvrđeni su hemoroidi. Nakon mesec dana, na redovnoj kontroli registruje pad hemoglobina na 80 g/l, kao i abnormalnosti u rezultatima imunologije (IgG: 158,29 g/L, IgM: 0,22 g/L, C3:0,08 g/L, C4:0,03 g/L), ali i hiperproteinemija uz očuvanu bubrežnu funkciju. Pacijent se žali na opštu slabost i malaksalost, kao i na gubitak u telesnoj težini. Indikovana je hitna hospitalizacija radi evaluacije u pravcu multiplog mijeloma i daljeg lečenja. Pri prijemu, pacijent je bio afebrilan i hemodinamski stabilan. Tokom hospitalizacije sprovedena je dalja dijagnostika. U aspiratu koštane srži registrovano je 8–10% plazma ćelija. Testiranje fluorescentnom in situ hibridizacijom (FISH) bilo je negativno na citogenetske abnormalnosti ili mutacije visokog rizika. Elektroforezom seruma i urina dokazano je prisustvo M komponente u klasi IgG (kappa laki lanci). Urađen je niskodozni skener skeleta koji je pokazao višestruke osteolitičke lezije koje zahvataju aksijalni i apendikularni skelet. U bioptatu koštane srži, imunohistohemijski je dobijen sledeći fenotip: CD71+, MPO+, CD61+, CD34+ (< 5%), CD117+ (< 5%), CD56+ (35%), uz jasnu restrikciju kappa lakih lanaca 5:1. U zaključku takođe potvrđeno da je reč o istovremenom prisustvu policitemije vere i multiplog mijeloma. Tokom hospitalizacije, pacijent je podvrgnut terapijskoj plazmaferezi radi kontrole hiperproteinemije. Nakon

only a limited number of cases reported in the literature. The exact mechanisms underlying this association remain unclear [10]. This report presents a rare case of a patient initially diagnosed with polycythemia vera who subsequently developed multiple myeloma.

Our aim is to contribute to the literature on this unusual coexistence and to discuss possible pathogenetic mechanisms and clinical implications.

CASE REPORT

A 54-year-old patient was diagnosed with polycythemia vera in 2010 after a hematologic evaluation that included a bone marrow biopsy. Since diagnosis, treatment involved acetylsalicylic acid (ASA) with occasional therapeutic phlebotomy as needed to manage hematocrit levels. After five years, hydroxyurea (Litalir®) was added to the treatment plan. The disease remained clinically stable for 15 years with regular hematologic follow-up, and the patient was asymptomatic. Past medical history included arterial hypertension and multiple sclerosis, which was reported to be in remission, with no ongoing therapy besides regular neurological follow-up. In July of this year, during a routine follow-up visit, the patient reported noticing blood in the stool (hemoglobin level at that time was 120 g/L). He was referred to a gastroenterologist, and a complete diagnostic workup was performed, confirming hemorrhoids. One month later, during a scheduled follow-up, a further drop in hemoglobin to 80 g/L was observed, along with abnormalities in immunological parameters (IgG: 158.29 g/L, IgM: 0.22 g/L, C3: 0.08 g/L, C4: 0.03 g/L), as well as hyperproteinemia with preserved renal function. The patient reported general weakness, fatigue, and weight loss. Urgent hospitalization was recommended for evaluation of multiple myeloma and further management. Upon admission, the patient was afebrile and hemodynamically stable. Further diagnostic procedures were carried out during hospitalization. Bone marrow aspirate showed 8–10% plasma cells. Fluorescence in situ hybridization (FISH) testing was negative for cytogenetic abnormalities or high-risk mutations. Serum and urine protein electrophoresis revealed the presence of an M component in the IgG class (kappa light chains). Low-dose skeletal computed tomography identified multiple osteolytic lesions involving both the axial and appendicular skeleton. Immunohistochemical analysis of the bone marrow biopsy showed the following phenotype: CD71+, MPO+, CD61+, CD34+ (<5%), CD117+ (<5%), CD56+ (35%), with a clear kappa light chain restriction at a ratio of 5:1. The conclusion confirmed the simultaneous presence of polycythemia vera and multiple myeloma. During hospitalization, the patient received therapeutic

toga, započeta je hemoterapija prema VTD protokolu (bortezomib, talidomid, deksametazon). Pacijent trenutno prima četvrti ciklus terapije, nakon čega će se proceniti odgovor na lečenje i status bolesti.

DISKUSIJA

Istovremena pojava policitemije vere i multiplog mijeloma je izuzetno retka i predstavlja značajne dijagnostičke i terapijske izazove. PV nastaje iz klona mijeloidnih matičnih ćelija i u većini slučajeva je uzrokovana mutacijom JAK2 V617F, dok MM predstavlja neoplazmu limfocita-plazma ćelija [3,5]. Koegzistenciju multiplog mijeloma i policitemije vere prvi su opisali Lorens i Rozental 1948. godine [7,8]. Opisani su slučajevi poput našeg pacijenta gde je inicijalno postavljena dijagnoza policitemije, a zatim multiplog mijeloma, ali i slučajevi gde je redosled bolesti drugačiji, odnosno prvo MM, a zatim PV [8,11]. Takođe je opisan slučaj pacijentkinje kod koje je istovremeno postavljena dijagnoza PV i monoklonske gamopatije (MGUS) koja je kasnije progredirala u klinički manifestni multipli mijelom [11]. Pacijenti su lečeni primenom HU, koja je obustavljena nakon dijagnoze MM [9,11,12]. Lečenje multiplog mijeloma sprovedeno je primenom VCD (bortezomib + ciklofosamid + dexametazon) protokola kao prve terapijske linije [9–12]. U trenutku kada su ovi prikazi slučajeva objavljeni za dva pacijenta je učinjena procena terapijskog odgovora, i oni su bili u parcijalnoj remisiji [9,10]. U tabeli 1 su prikazane karakteristike pacijenata kod kojih su dijagnostikovane ove dve maligne hematološke bolesti. Zanimljivo je da su u pitanju 4 žene, prosečne starosti 70,75 godina [9–12].

Istovremeno postojanje ove dve bolesti kod jednog pacijenta sugerise ili razvoj dva nezavisna klona ili transformaciju zajedničke progenitorske ćelije sa multipotentnim potencijalom [9]. Predloženo je nekoliko mehanizama za objašnjenje ovog fenomena. Neki autori smatraju da oba poremećaja mogu nastati iz zajedničke pluripotentne hematopoetske matične ćelije sposobne da se diferencira i u mijeloidnu i

tic plasmapheresis to manage hyperproteinemia. Following this, chemotherapy was started using the VTD protocol (bortezomib, thalidomide, dexamethasone). The patient is now on the fourth cycle of treatment, and the response to therapy and disease status will be assessed afterward.

DISCUSSION

The simultaneous occurrence of polycythemia vera and multiple myeloma is extremely rare and represents a significant diagnostic and therapeutic challenge. PV arises from a clone of myeloid stem cells and in most cases is caused by the JAK2 V617F mutation, whereas MM is a neoplasm of lymphocytes-plasma cells [3,5]. The coexistence of multiple myeloma and polycythemia vera was first described by Lawrence and Rosenthal in 1948 [7,8]. Similar cases to our patient have been reported, where the initial diagnosis was polycythemia followed by multiple myeloma, as well as cases where the disease sequence was reversed, with MM preceding PV [8,11]. A case has also been documented of a female patient in whom PV and monoclonal gammopathy of undetermined significance (MGUS) were diagnosed simultaneously, later progressing to clinically evident multiple myeloma [11]. Patients were treated with hydroxyurea (HU), which was discontinued after diagnosing MM [9,11,12]. The treatment for multiple myeloma involved the VCD protocol (bortezomib + cyclophosphamide + dexamethasone) as the initial therapy [9–12]. At the time these case reports were published, treatment response had been evaluated in two patients, both of whom were in partial remission [9,10]. Table 1 presents the characteristics of patients diagnosed with these two malignant hematological diseases. Interestingly, all 4 reported patients were women, with a mean age of 70.75 years [9–12].

The simultaneous presence of these two diseases in a single patient suggests either the development of two independent clones or the transformation of a common progenitor cell with multipotent potential [9].

Tabela 1. Karakteristike pacijenata lečenih od MM i PV – podaci iz dosadašnje literature

Pol / Gender	Starost / Age	Dg MM u odnosu na PV / Dg MM in relation to PV	Th PV / Th PV	Th MM / Th MM	Th odgovor / Th response
Ženski / Female	81	Nakon 5 god / After 5 years	HU	VCD	PR nakon 9 cy / PR after 9 cy
Ženski / Female	70	Istovremeno / At the same time	Bez th / Without th	VCD	PR, bez podataka o broju cy / PR, without data on the number of cy
Ženski / Female	65	Nakon 5 god / After 5 years	venepunkcije / Venipuncture	VCD	bez podataka / Without data
Ženski / Female	67	Nakon 13 god / After 13 years	HU	VCD	Primila 1 cy / Received 1 cy

Table 1. Characteristics of patients treated for MM and PV – data from the existing literature

u limfoidnu lozu [7]. Drugi predlažu da koegzistencija može biti slučajna ili moguće povezana sa terapijom, posebno kod pacijenata lečenih citoreduktivnim agensima kao što je hidroksiureja [8]. U kliničkoj praksi, važno je razmotriti potencijalnu ulogu prethodne terapije citoreduktivnim lekovima, koja može delovati kao dodatni genotoksični stresori podstaći klonalnu evoluciju [13]. Sugerisano je da hronična stimulacija koštane srži, aktivacija inflamatornih citokina i izmenjeno mikrookruženje koštane srži kod PV mogu doprineti sekundarnoj klonalnoj evoluciji i proliferaciji plazma ćelija [9]. U novijim istraživanjima sugerise se mogućnost da hronična stimulacija hematopoetskih progenitora u uslovima povećane proliferativne aktivnosti kod PV može stvoriti mikrookruženje pogodno za nastanak sekundarnih klonalnih poremećaja, uključujući plazmocitne diskrazije [11,12]. Takođe, produžena izloženost citokinima kao što su IL-6 i TNF-alfa može doprineti aktivaciji signalnih puteva koji podstiču proliferaciju plazma ćelija. Klinički, rano prepoznavanje multiplog mijeloma kod pacijenata sa PV može biti teško, jer simptomi poput umora ili laboratorijskih abnormalnosti, kao što su povišeni nivoi proteina, u početku mogu biti pripisani primarnom mijeloproliferativnom poremećaju [7,8]. Sa dijagnostičkog aspekta, kod pacijenta sa poznatom PV, pojava hipergamaglobulinemije, bubrežne disfunkcije ili anemije koja nije u skladu sa osnovnim tokom bolesti treba da pobudi sumnju na moguću pojavu multiplog mijeloma [11,13]. Rano prepoznavanje ove asocijacije omogućava pravovremeno sprovođenje ciljane terapije i bolju kontrolu komplikacija. Sa terapijskog aspekta, neophodno je pažljivo balansirati između tretmana usmerenih na kontrolu eritrocitoze i onih koji ciljaju plazmocitnu proliferaciju, imajući u vidu moguću toksičnost i interakcije lekova [13].

Ovaj prikaz slučaja dodatno naglašava potrebu za dugoročnim praćenjem pacijenata sa mijeloproliferativnim neoplazmama, budući da klonalna evolucija može rezultirati pojavom sekundarnih maligniteta. U tom kontekstu, integracija molekularne dijagnostike, kao što su analiza JAK2 mutacije i detekcija monoklonalnog paraproteina, ima ključnu ulogu u ranoj dijagnostici i praćenju bolesti [10–12].

U našem slučaju, pojava novog kliničkog znaka, odnosno krvarenja u stolici, pokrenula je dodatna ispitivanja koja su uključivala i rutinsko biohemijsko praćenje, a koje je bilo ključno u otkrivanju hiperproteinemije, što je dovelo do blagovremene dijagnostičke evaluacije i identifikacije multiplog mijeloma. Lečenje takvih slučajeva zahteva individualizovan, multidisciplinarni pristup. Zbog retkosti ove dvostruke dijagnoze, optimalne strategije lečenja i dugoročni ishodi nisu

Several mechanisms have been proposed to explain this phenomenon. Some authors suggest that both disorders may originate from a common pluripotent hematopoietic stem cell capable of differentiating into both myeloid and lymphoid lineages [7]. Others propose that the coexistence may be coincidental or possibly related to therapy, particularly in patients treated with cytoreductive agents such as hydroxyurea [8]. In clinical practice, it is important to consider the potential role of prior cytoreductive therapy, which may act as an additional genotoxic stressor and promote clonal evolution [13]. It has been suggested that chronic bone marrow stimulation, activation of inflammatory cytokines, and an altered bone marrow microenvironment in PV may contribute to secondary clonal evolution and plasma cell proliferation [9]. More recent studies suggest that chronic stimulation of hematopoietic progenitors, driven by increased proliferative activity in PV, may create a microenvironment conducive to the development of secondary clonal disorders, including plasma cell dyscrasias [11,12]. In addition, prolonged exposure to cytokines such as IL-6 and TNF- α may contribute to the activation of signaling pathways that promote plasma cell proliferation. Clinically, early detection of multiple myeloma in patients with PV can be difficult because symptoms like fatigue or lab abnormalities, such as elevated protein levels, might initially be mistaken for the underlying myeloproliferative disorder [7,8]. From a diagnostic point of view, in a patient with known PV, the presence of hypergammaglobulinemia, renal dysfunction, or anemia that do not align with the expected disease course should raise suspicion of developing multiple myeloma [11,13]. Recognizing this association early allows for timely targeted therapy and improved management of complications. From a treatment perspective, it is crucial to carefully balance therapies aimed at controlling erythrocytosis with those targeting plasma cell proliferation, considering potential toxicity and drug interactions [13].

This case report further highlights the importance of long-term follow-up for patients with myeloproliferative neoplasms, as clonal evolution can lead to the development of secondary malignancies. In this context, incorporating molecular diagnostics, such as JAK2 mutation analysis and detection of monoclonal paraprotein, is essential for early diagnosis and ongoing disease monitoring [10–12].

In our case, the appearance of a new clinical sign-specifically, gastrointestinal bleeding-prompted additional investigations, including routine biochemical monitoring, which was crucial in detecting hyperproteinemia and led to timely diagnostic evaluation and the identification of multiple myeloma. Managing

precizno utvrđeni, a većina dokaza dolazi iz izolovanih izveštaja o slučajevima. Ovaj slučaj predstavlja neuobičajenu koegzistenciju policitemije vere i multiplog mijeloma, dva različita klonalna hematološka poremećaja sa različitim patofiziološkim poreklom.

ZAKLJUČAK

Ovaj slučaj doprinosi ograničenom broju izveštaja koji opisuju udruženu pojavu policitemije vere i multiplog mijeloma, naglašavajući potrebu za budnim dugoročnim praćenjem i sveobuhvatnom evaluacijom novih i neočekivanih znakova i simptoma, kao i hematoloških ili biohemijskih abnormalnosti kod pacijenata sa hroničnim mijeloproliferativnim neoplazmama. Rano prepoznavanje i odgovarajuća terapijska intervencija mogu poboljšati kliničke ishode i kvalitet života kod ovih kompleksnih pacijenata.

Sukob interesa: Nije prijavljen.

such cases requires an individualized, multidisciplinary approach. Due to the rarity of this dual diagnosis, optimal treatment strategies and long-term outcomes have not been clearly established, and most evidence comes from isolated case reports. This case illustrates an unusual coexistence of polycythemia vera and multiple myeloma, two distinct clonal hematological disorders with different pathophysiological origins.

CONCLUSION

This case contributes to the small number of reports documenting the coexistence of polycythemia vera and multiple myeloma. It emphasizes the importance of vigilant long-term follow-up and thorough evaluation of new and unexpected signs, symptoms, and hematological or biochemical abnormalities in patients with chronic myeloproliferative neoplasms. Early recognition and timely treatment may enhance clinical outcomes and improve quality of life for these complex patients.

Conflict of interest: None declared.

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ZAHVALNICA RECENZENTIMA

Urednici Srpskog medicinskog časopisa Lekarske komore izražavaju iskrenu zahvalnost recenzentima za njihovu posvećenost, stručnost i neprocenjiv doprinos očuvanju naučne vrednosti časopisa.

Na sledećem spisku, po abecednom redu, navedeni su recenzenti koji su tokom 2025. godine učestvovali u postupku recenziranja.

1. Aleksić-Babić Kristina
2. Andrejević Slađana
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36. Lešić Aleksandar
37. Makević Vedrana
38. Maksimović Nataša

REVIEWER ACKNOWLEDGMENT

The Editors of the Serbian Journal of the Medical Chamber express their sincere gratitude to the reviewers for their dedication, expertise and invaluable contribution to maintaining the scientific quality of the Journal.

The reviewers who contributed to the peer-review process during 2025 are listed below, in alphabetical order.

39. Mandić Danijela
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UPUTSTVO AUTORIMA ZA PRIPREMU RADOVA

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

Da bi se rad razmatrao za publikovanje neophodno je da bude pripremljen prema propozicijama ovog Časopisa. U suprotnom Urednik može da ga odbije, bez daljih objašnjenja. Objavljivanje radova se ne honorariše. Prilikom prihvatanja rada za publikovanje svi autori prenose svoja autorska prava na izdavača časopisa.

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OPŠTA UPUTSTVA

Tekst rada treba da bude napisan latinicom u programu za obradu teksta *Word*, fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve četiri margine treba podesiti na 25 mm, a veličinu stranice na format A4. Prored treba da bude 1,5, sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm. Ne treba da bude podeljenih reči (hifenacije). Ne treba koristiti tabulatore i uzastopne prazne karaktere (spejsove) radi poravnanja teksta, već alatke za kontrolu poravnanja u tulu. Za prelazak na novu stranu dokumenta koristi se isključivo *Page break*. Posle svakog znaka interpunkcije treba staviti samo jedan prazan karakter (spejs). Ako se u tekstu koriste specijalni znaci (simboli), koristite font iz paketa *Symbol*. Za nazive lekova koristite isključivo generička imena. Uređaji (aparati) se označavaju fabričkim nazivima, a ime i mesto proizvođača treba navesti u obliku zagradama. Ukoliko se u tekstu koriste oznake koje su spoj slova i brojeva potrebno je precizno napisati broj koji se javlja u superskriptu ili supskriptu (na pr. ⁹⁹Tc, IL-6, O₂, B12, CD8 itd.). Ukoliko se nešto uobičajeno piše kurzivom (*italic*) tako se i navodi (npr. nazivi gena). Neophodno je koristiti međunarodni sistem mernih jedinica (SI), uz izuzetak temperature (°C) i krvnog pritiska (mmHg). Ukoliko je rad deo magistarske teze, odnosno doktorske disertacije, ili je urađen u okviru naučnog projekta, to treba posebno naznačiti u Napomeni na kraju teksta.

Za izradu grafičkih priloga koristite standardne grafičke programe za vindows (*Windows*), najbolje iz programskih paketa mikrosoft ofisa (*Excel*, *Word Graph*). Izbegavajte upotrebu boja, naročito prelaze boja i senčenje.

PRIPREMA RADA

Delovi rada su: naslovna strana, sažetak sa ključnim rečima, tekst rada, zahvalnost (po želji), literatura i prilozi.

NASLOVNA STRANA (prva strana) sadrži naslov rada bez skraćenica, predlog kratkog naslova rada, puna imena i prezimena autora (bez titula) indeksirana brojevima, zvaničan naziv ustanova u kojima autori rade, mesto i državu (redosledom koji odgovara indeksiranim brojevima autora). Na dnu stranice navesti ime i prezime, adresu za kontakt, broj telefona, faksa i imejl adresu autora zaduženog za korespondenciju. Naslovna strana treba da bude na srpskom i engleskom jeziku (druga strana).

SAŽETAK treba da ima do 250 reči, uključujući skraćenice (treća strana). Za originalne radove, prethodno i kratko saopštenje, meta-analize i pregledne radove, sažetak treba da ima sledeću strukturu: Uvod, Cilj, Metode, Rezultati, Zaključak. Svaki od navedenih segmenata treba da bude napisan kao poseban pasus. Za prikaze slučajeva sažetak treba da ima sledeće delove: Uvod, Prikaz bolesnika, Zaključak. Svaki deo, takođe, pisati kao poseban pasus. Za ostale vrste radova sažetak nema posebnu strukturu. Ispod Sažetka navesti od tri do šest ključnih reči ili izraza. Ne tre-

INSTRUCTIONS FOR AUTHORS

The **Serbian Journal of the Medical Chamber** publishes previously unpublished, original professional and scientific papers, reviews, short communications, editorials, letters to the editor, meta-analyses, case reports, current topics, book reviews, papers on the history of medicine and more, from all fields of medicine, pharmacy and dentistry, therefore contributing to the promotion and development of the profession and science. The journal is published in print and electronic form four times per year.

In order for a paper to be considered for publication, it is necessary to prepare it according to the Journal's guidelines, otherwise the editor may reject it without further explanation. The publication of papers is not paid. When accepting a paper for publication, all authors transfer their copyrights to the Journal publisher.

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GENERAL INSTRUCTIONS

The paper should be submitted as a Microsoft Word document (.docx, .doc), using the Times New Roman font, size 12 pt. All four margins should be set to 25 mm and the page size to A4. The line spacing should be 1.5, with left alignment and 10 mm indentation of each paragraph. There should be no end-of-line hyphenation. The alignment tools should be used for aligning the text, not tabs or multiple spaces. Only the page-break should be used for a new page in the document. A single space should follow each punctuation mark. If special characters (symbols) are used in the text, use the font from the Symbol package. Use only generic names for drugs. Devices (equipment) should be identified using factory names, and the name and location of the manufacturer should be indicated in parentheses. If the text uses labels that are a combination of letters and numbers, it is necessary to appropriately write the number that appears in superscript or subscript (e.g. ⁹⁹Tc, IL-6, O₂, B12, CD8, etc.). If something is typically written in italic, it should be written so (e.g. gene names). International System of Units (SI) units should be used, with the exception of temperature (°C) and blood pressure (mmHg). If the paper is part of a master's thesis or doctoral dissertation, or was created within a scientific project, this should be specifically indicated in the Notes section, at the end of the text.

Graphics attachments should be created using standard graphics software for MS Windows, preferably from the MS Office suite (MS Excel, MS Word Graph). Use of colors should be avoided, especially gradients and shading.

PREPARING THE PAPER

The sections of the paper are: the cover page, the abstract and keywords, the text of the paper, acknowledgements (optional), literature, and attachments.

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.

PRILoge (tabele, grafikone, slike itd.) postaviti na kraj rukopisa, a u samom tekstu jasno naznačiti mesto koje se odnosi na dati prilog. Krajnja pozicija priloga biće određena u toku pripreme rada za publikovanje.

SKRAĆENICE. Koristiti samo kada je neophodno, i to za veoma dugačke nazive hemijskih jedinjenja, odnosno nazive koji su kao skraćenice već prepoznatljivi (standardne skraćenice, kao npr. DNK, sida, HIV). Za svaku skraćenicu pun termin treba navesti pri prvom navođenju u tekstu, sem ako nije standardna jedinica mere. U naslovi se ne koriste skraćenice. Izbegavati korišćenje skraćenica u sažetku, ali ako su neophodne, svaku skraćenicu objasniti pri prvom navođenju u tekstu.

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.

JEDINICE MERA. Dužinu, visinu, težinu i zapreminu izražavati u metričkim jedinicama (metar – m, kilogram (gram) – kg (g), litar – l) ili njihovim delovima. Temperaturu izražavati u stepenima Celzijusa (°C), količinu supstance u molima

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.

STATISTICAL METHODS, PRESENTATION AND INTERPRETATION OF RESULTS

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.

ATTACHMENTS (tables, graphs, pictures, etc.) should be placed at the end of the manuscript, while clearly indicating in the text the place that refers to the given attachment. The final position of the attachment will be defined during the preparation of the paper for publication.

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!).

SLIKE. Slike su svi oblici grafičkih priloga. Objavljaju se fotografije, crteži, sheme i grafikoni. Slike se označavaju arapskim brojevima prema redosledu navođenja u tekstu. Primaju se isključivo digitalne fotografije (crno-bele ili u boji) rezolucije najmanje 300 dpi i formata zapisa *tiff* ili *jpg* (male, mutne i slike lošeg kvaliteta neće se prihvatati za štampanje!). Ukoliko autori nemaju ili nisu u mogućnosti da dostave digitalne fotografije, onda originalne slike treba skenirati u rezoluciji 300 dpi i u originalnoj veličini. Ukoliko je rad neophodno ilustrovati sa više slika, u radu će ih biti objavljeno nekoliko, a ostale će biti u e-verziji članka kao PowerPoint prezentacija (svaka slika mora biti numerisana i imati legendu). U legendi slika treba napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu. Potrebno je priložiti nazive slika i legendu na srpskom i engleskom jeziku.

GRAFIKONI. Grafikoni treba da budu urađeni i dostavljeni u programu *Excel*, da bi se videle prateće vrednosti raspoređene po ćelijama. Iste grafikone prekopirati i u *Word*-ov dokument. Grafikoni se označavaju arapskim brojevima prema redosledu navođenja u tekstu. Svi podaci na grafikonu kucaju se u fontu *Times New Roman*. Korišćene skraćenice na grafikonu treba objasniti u legendi ispod grafikona. Priložite nazive grafikona i legendu na srpskom i engleskom jeziku.

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