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EDITORIJAL



„Mudar čovek treba da smatra zdravlje kao jedan od najvećih blagoslova, te da nauči kako da u vlastitim mislima izvuče korist iz svoje bolesti.”
Hipokrat

Poštovane kolegice i kolege, dragi prijatelji,

Velika mi je čast i zadovoljstvo da vam predstavim treći broj „Srpskog medicinskog časopisa Lekarske komore” u 2026. godini. Posebno mi je zadovoljstvo što imam priliku da, zajedno sa glavnom i odgovornom urednicom prof. dr Milenom Šantrić-Milićević i članovima Uredništva, učestvujem u radu i doprinosim razvoju i unapređenju našeg časopisa. Svaki novi broj predstavlja rezultat zajedničkog rada, posvećenosti i stručnosti autora, recenzenta i urednika.

U ovom broju Časopisa, kao i u svim prethodnim, nastojali smo da uz podršku i saradnju cenjenih kolega ponudimo sadržaje koji će opravdati poverenje i očekivanja naše čitalačke publike. Pred vama se nalaze naučni i stručni radovi naših uvaženih kolega, koji prikazuju aktuelne teme, savremene pristupe i rezultate istraživanja od značaja za unapređenje naučnog i stručnog rada.

Na početku bih istakao originalno istraživanje autorke Maje Kitić i saradnika, pod nazivom: „Primena KASRP upitnika u proceni znanja i stavova medicinskih sestara o bolu: preliminarni rezultati”. U ovoj studiji preseka je prikazano istraživanje sprovedeno među medicinskim sestrama – tehničarima na Institutu za onkologiju Vojvodine. Dobijeni nalazi predstavljaju preliminarne rezultate primene upitnika – *Anketa o znanju i stavovima o bolu* (engl. *Knowledge and Attitudes Survey Regarding Pain – KASRP*), koji mogu biti osnova za dalja istraživanja i psihometrijsku evaluaciju srpske verzije upitnika.

Originalni rad autora Mladena Kasalovića i saradnika „Prediktori inkarceracije kile i postoperativnog recidiva kile: analiza demografskih, kliničkih i hirurških faktora koji utiču na ishode lečenja”, predstavlja retrospektivnu studiju sprovedenu na Hirurškoj klinici KBC Kosovska Mitrovica. Analizom dobijenih rezultata, autori su zaključili da je uklještenje značajno povezano sa starijim godinama, komorbiditetima i tipom kile, dok recidiv kile pokazuje multifaktorsku prirodu, bez jasnih nezavisnih prediktora.

Cilj istraživanja predstavljenog u originalnom radu autorke Enite Nakaš i saradnika, „Teledentistika u Bosni i Hercegovini: analiza znanja, stavova i prakse među studentima stomatologije, stomatolozima i nastavnim kadrom na stomatološkim fakultetima zasnovana na upitniku”, bio je da se procene nivo znanja, stavovi i praksa u kontekstu implementacije telemedicine. Rezultati pokazuju da stomatolozi u Bosni i Hercegovini iskazuju pozitivne stavove prema primeni teledentistike, ali da imaju ograničeno znanje i praktične veštine, što ukazuju na potrebu da se studenti stomatologije, stomatolozi i nastavni kadar u BiH kontinuirano stručno usavršavaju u ovoj oblasti.

Pregledni rad autora Dražena Radanovića i saradnika „Litijum kao neuroregenerativni modulator u reparaciji perifernih nerava: mehanistički uvidi i strategije bioinženjerske isporuke – sistematski pregled”, analizira dokaze o

EDITORIAL

*"A wise man should consider that health is the greatest of human blessings,
and learn how by his own thought to derive benefit from his illnesses."*

Hippocrates

Dear Colleagues and Friends,

It is a great honor and pleasure to present to you the third issue of the *Serbian Journal of the Medical Chamber* in 2026. I am particularly pleased to have the opportunity, together with the Editor-in-Chief, Prof. Dr. Milena Šantrić-Milićević, and the members of the Editorial Board, to participate in the work and contribute to the development and advancement of our journal. Each new issue is the result of the joint work, dedication, and expertise of the authors, reviewers, and editors.

In this issue of the Journal, as in all previous issues, we have endeavored, with the support and collaboration of our esteemed colleagues, to offer content that will justify the trust and meet the expectations of our readers. Before you are scientific and professional papers by our distinguished colleagues that address current topics, contemporary approaches, and research findings significant to the advancement of scientific and professional work.

At the outset, I would like to highlight the original research by Maja Kitić et al., entitled "Using the KASRP questionnaire to assess nurses' knowledge and attitudes regarding pain: preliminary results." This cross-sectional study presents research conducted among nurses at the Institute of Oncology of Vojvodina. The findings are preliminary results of the application of the questionnaire – *Knowledge and Attitudes Survey Regarding Pain – KASRP* – which may provide a basis for further research and psychometric evaluation of the Serbian version of the questionnaire.

The original research article by Mladen Kasalović et al., "Predictors of hernia incarceration and postoperative recurrence: analysis of demographic, clinical, and surgical factors influencing treatment outcomes", reports on a retrospective study conducted at the Surgical Clinic, Clinical Hospital Center Kosovska Mitrovica. Based on the analysis of the findings, the authors conclude that incarceration is significantly associated with older age, comorbidities, and hernia type, while hernia recurrence appears to be multifactorial, without clear independent predictors.

The study presented in the original research article by Enita Nakaš et al., "Teledentistry in Bosnia and Herzegovina: a questionnaire-based analysis of knowledge, attitudes, and practices among dental students, dentists, and academic staff at dental faculties", aimed to assess knowledge levels, attitudes, and practices in the context of telemedicine implementation. The results show that dentists in Bosnia and Herzegovina have positive attitudes toward implementing teledentistry but limited knowledge and practical skills to that effect, indicating the need for continuous professional development in this field for dental students, dentists, and faculty members in Bosnia and Herzegovina.

uloži litijuma u regeneraciji perifernih nerava, sa fokusom na bioinženjerske strategije isporuke. Dobijeni rezultati ukazuju na to da biomaterijali sa litijumom, prema novijim istraživanjima, mogu da omoguće lokalnu i produženu isporuku uz smanjenje sistemske toksičnosti.

U preglednom radu autorke Jelene Bojković i saradnika „Otpornost lanaca snabdevanja lekovima i medicinskim sredstvima kao stub zdravstvene bezbednosti: integrativni pregled i okvir upravljanja zasnovan na iskustvima iz prakse“, autori su analizom literature zaključili da otpornost lanaca snabdevanja lekovima i medicinskim sredstvima treba posmatrati kao strateški prioritet zdravstvene bezbednosti.

Nesanica je čest poremećaj spavanja i predstavlja klinički značajan, ali često zanemaren faktor kardiovaskularnog rizika. Autor Petar Otašević i saradnici su u preglednom radu „Nesanica kao faktor rizika kod kardioloških bolesnika i terapijski pristup“, primenom deskriptivno-komparativne metode, analizirali dostupnu literaturu koja je ispitivala odnos nesanice, kardiovaskularnih ishoda i farmakološkog lečenja primenom benzodiazepina i Z-hipnotika. Autori zaključuju da se, u slučaju kada je farmakološko lečenje nesanice kod kardioloških bolesnika neophodno, Z-hipnotici mogu razmatrati kao povoljnija alternativa benzodiazepinima.

Interesovanje za uzročno-posledičnu povezanost između poremećaja iz spektra autizma i vakcinacije ne jenjava, te je pregledni rad autorke Aleksandre Ristić i saradnika „Poremećaj iz spektra autizma i vakcinacija: razbijanje mitova i predstavljanje činjenica“, još jedan doprinos gorućoj temi. Dostupni naučni dokazi nedvosmisleno pokazuju da MMR vakcina ne povećava rizik za nastanak poremećaja iz spektra autizma, te su autori zaključili da je kontinuirana medicinska edukacija zdravstvenih radnika i roditelja, bazirana na naučnim dokazima, ključna za suzbijanje dezinformacija i jačanje poverenja u vakcinaciju.

Predstavljamo vam i pregledni rad autorke Jelene Salatić, iz oblasti savremene otorinolaringologije, „Skriveni gubitak sluha – kohlearna sinaptopatija“. Nakon analize relevantne savremene literature, autorka je došla do zaključka da konvencionalni audiološki pristup nije dovoljan za detekciju kohlearne sinaptopatije, zbog čega je u kliničku praksu neophodno uvesti napredne elektrofiziološke i psihoakustičke testove.

Autor Lazar Jakšić i saradnici su u prikazu slučaja „Primena PENG i LFCN bloka za hiruršku korekciju kongenitalne dislokacije kuka kod deteta – prikaz slučaja“, opisali primer primene relativno nove tehnike regionalne anestezije čija je dobrobit u hirurgiji kuka kod odraslih dokazana, dok se kod dece i dalje ispituje.

Retka, ali potencijalno fatalna komplikacija sistemskog eritemskog lupusa, sindrom aktivacije makrofaga, opisana je kroz prikaz slučaja autorke Aleksandre Dašić i saradnika „Lupus in fabula“: Sistemski eritemski lupus komplikovan sindromom aktivacije makrofaga sa fatalnim ishodom“. Preklapanje kliničkih i laboratorijskih pokazatelja osnovne bolesti i njene komplikacije značajno utiču na pravovremeno postavljanje dijagnoze, dok poseban dijagnostički značaj ima koncentracija feritina sa vrednostima $> 10000 \mu\text{g/l}$ koje su visoko sugestivne za sindromom aktivacije makrofaga.

Još jedan redak i zanimljiv slučaj kongenitalne anomalije su prikazali autor Stefan Rošić i saradnici u radu „Prikaz slučaja jednostranog odsustva plućne arterije – radiološka dijagnoza retkog uzroka hemoptizija“. Jednosrano odsustvo plućne arterije može biti asimptomatsko, pa se dijagnoza često postavlja slučajno. S obzirom da može da izazove ozbiljne komplikacije, izuzetno je značajno da lekari imaju ovo na umu, posebno kod pacijenata sa hemoptizijama.

Verujemo da će sadržaj ovog broja privući vašu pažnju i da će vam biti od koristi kako u svakodnevnoj praksi, tako i u daljem profesionalnom usavršavanju. Ovom prilikom vas pozivam da nam se svojim radovima pridružite i u narednim brojevima.

Zahvaljujemo autorima i recenzentima na njihovom doprinosu i posvećenosti, kao i svima koji svojim radom i podrškom učestvuju u razvoju i unapređenju našeg časopisa.

S poštovanjem,
Doc. dr Mlađan Golubović
Pomoćnik glavnog i odgovornog urednika
Srpskog medicinskog časopisa Lekarske komore

The review article by Dražen Radanović et al., "Lithium as a neuroregenerative modulator in peripheral nerve repair: mechanistic insights and bioengineered delivery strategies – a systematic review", analyzes the evidence regarding the role of lithium in peripheral nerve regeneration, with a focus on bioengineering delivery strategies. The findings indicate that, according to recent research, lithium-containing biomaterials may enable localized and sustained delivery while reducing systemic toxicity.

In the review article by Jelena Bojković et al., "Pharmaceutical and medical device supply chain resilience as a pillar of healthcare security: an integrative review and practice-informed management framework", the authors concluded, based on a literature analysis, that the resilience of pharmaceutical and medical device supply chains should be regarded as a strategic priority for healthcare security.

Insomnia is a common sleep disorder and a clinically significant, yet often overlooked, cardiovascular risk factor. In their review article, "Insomnia as a risk factor in cardiac patients and the treatment approach", Petar Otašević et al. used a descriptive-comparative approach to analyze the available literature examining the relationship between insomnia, cardiovascular outcomes, and pharmacological treatment with benzodiazepines and Z-hypnotics. The authors conclude that, when pharmacological treatment of insomnia is necessary in cardiac patients, Z-hypnotics may be considered a more favorable alternative to benzodiazepines.

Interest in the causal relationship between autism spectrum disorder and vaccination has not waned. The review article by Aleksandra Ristić et al., "Autism spectrum disorder and vaccination: dispelling myths and presenting evidence", contributes further to this burning issue. Available scientific evidence unequivocally demonstrates that the MMR vaccine does not increase the risk of developing autism spectrum disorder, leading the authors to conclude that continuous medical education of healthcare professionals and parents, based on scientific evidence, is essential for countering misinformation and strengthening confidence in vaccination.

We also present a contemporary otorhinolaryngology review article by Jelena Salatić, "Hidden hearing loss – cochlear synaptopathy". Following an analysis of the relevant contemporary literature, the author concludes that the conventional audiological approach is insufficient in detecting cochlear synaptopathy, making it necessary to introduce advanced electrophysiological and psychoacoustic tests into clinical practice.

In their case report, "PENG and LFCN block for surgical correction of congenital hip dysplasia in a child – a case report", Lazar Jakšić et al. described the application of a relatively new regional anesthesia technique whose benefits in hip surgery in adults have been demonstrated, while its use in children continues to be investigated.

A rare but potentially fatal complication of systemic lupus erythematosus, macrophage activation syndrome, was described in the case report by Aleksandra Dašić et al., "*Lupus in fabula*: Systemic lupus erythematosus complicated by macrophage activation syndrome with a fatal outcome." The overlap of clinical and laboratory indicators of the underlying disease and its complication significantly affects timely diagnosis, while ferritin concentration has particular diagnostic significance, with values >10,000 µg/l being highly suggestive of macrophage activation syndrome.

Another rare and interesting case of a congenital anomaly was presented by Stefan Rošić et al. in the article "Case report of unilateral absence of pulmonary artery – radiological diagnosis of a rare cause of haemoptysis." Unilateral absence of the pulmonary artery may be asymptomatic, and the diagnosis is therefore often made incidentally. Given that it can cause serious complications, it is extremely important that physicians keep this condition in mind, particularly in patients presenting with hemoptysis.

We believe that the content of this issue will attract your attention and prove useful to you, both in everyday practice and in your continued professional development. On this occasion, I invite you to join us by contributing your own papers to future issues.

We would like to thank the authors and reviewers for their contribution and dedication, as well as everyone who, through their work and support, contributes to the development and improvement of our journal.

Yours sincerely,

Mlađan Golubović, Assistant Professor, PhD

Assistant Editor-in-Chief

Serbian Journal of the Medical Chamber

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PRIMENA KASRP UPITNIKA U PROCENI ZNANJA I STAVOVA MEDICINSKIH SESTARA O BOLU: PRELIMINARNI REZULTATI

ORIGINALNI RAD

ORIGINAL ARTICLE

USING THE KASRP QUESTIONNAIRE TO ASSESS NURSES' KNOWLEDGE AND ATTITUDES REGARDING PAIN: PRELIMINARY RESULTS

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SAŽETAK

Uvod/Cilj: Bol je neprijatno senzorno i emocionalno iskustvo povezano sa stvarnim ili potencijalnim oštećenjem tkiva. U sestrinskoj praksi bol se definiše kao „ono što osoba koja ga doživljava kaže da jeste i postoji kada god osoba kaže da postoji”. Cilj našeg istraživanja je bio da se izvrši procena primenljivosti upitnika – *Anketa o znanju i stavovima o bolu* (engl. *Knowledge and Attitudes Survey Regarding Pain – KASRP*), i prikažu preliminarni rezultati procene znanja i stavova medicinskih sestara – tehničara o bolu u odnosu na starost, godine radnog iskustva, stepen obrazovanja i organizacionu jedinicu u kojoj rade.

Materijali i metode: Istraživanje je sprovedeno kao studija preseka tokom novembra i decembra 2022. godine. Uzorak su činile medicinske sestre – tehničari zaposleni na Institutu za onkologiju Vojvodine. Podaci su prikupljeni pomoću *KASRP* upitnika. Ovaj upitnik sadrži 42 pitanja koja se odnose na sociodemografske karakteristike, kao i na znanje i stavove o bolu.

Rezultati: *KASRP* upitnik se pokazao primenljivim u ispitivanoj populaciji. Medicinske sestre – tehničari su pokazali prosečan nivo znanja i neutralan stav prema bolu (52,42%). Slabo znanje i negativan stav uočeni su u domenima bola povezanog sa malignim oboljenjima i procene bola, dok je u domenu farmakološkog lečenja zabeležen prosečan nivo znanja i neutralan stav, a u domenu zloupotrebe supstanci dobro znanje i pozitivan stav. Nije utvrđena statistički značajna povezanost skorova sa starošću, godinama radnog iskustva i stepenom obrazovanja, dok je značajna razlika uočena u odnosu na organizacionu jedinicu u kojoj su ispitanici zaposleni.

Zaključak: Dobijeni nalazi predstavljaju preliminarne rezultate primene *KASRP* upitnika i mogu da posluže kao osnova za dalja istraživanja i psihometrijsku evaluaciju srpske verzije upitnika.

Ključne reči: bol, stavovi, medicinske sestre – tehničari, ankete, upitnici

ABSTRACT

Introduction/Objective: Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. In nursing practice, pain is defined as “whatever the experiencing person says it is, existing whenever the person says it does”. This study aimed to assess the feasibility of applying the *Knowledge and Attitudes Survey Regarding Pain (KASRP)* questionnaire and to present preliminary results on nurses' knowledge and attitudes regarding pain, in relation to age, years of work experience, education level, and organizational unit of employment.

Materials and methods: This cross-sectional study was conducted in November and December 2022 among the nurses employed at the Institute of Oncology of Vojvodina. Data were collected using the *KASRP* questionnaire, consisting of 42 items assessing sociodemographic characteristics, knowledge, and attitudes regarding pain.

Results: The *KASRP* questionnaire proved feasible in the study population. Nurses demonstrated an average level of knowledge and neutral attitudes toward pain (52.42%). Poor knowledge and negative attitudes were observed in the domains of cancer-related pain and pain assessment; average knowledge was registered in the area of pharmacological management, while good knowledge was noted regarding substance abuse. *KASRP* scores were not significantly associated with age, years of work experience, or education level. However, they differed significantly in relation to the organizational unit of employment.

Conclusion: The findings represent preliminary results obtained using the *KASRP* questionnaire and may serve as a basis for further research and psychometric evaluation of its Serbian version.

Keywords: pain, attitudes, nurses, surveys, questionnaires

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UVOD

U zdravstvenoj zaštiti, jednu od najšire prihvaćenih definicija bola dala je Margo McCaffery: „Bol je sve ono što osoba koja ga doživljava kaže da jeste i postoji kad god osoba kaže da postoji“ [1]. Revidirana definicija bola – „neprijatno senzorno i emocionalno iskustvo povezano sa stvarnim ili potencijalnim oštećenjem tkiva, ili nalik iskustvu povezanom sa takvim oštećenjem“ – jednoglasno je usvojena od strane Saveta Međunarodnog udruženja za proučavanje bola (engl. *International Association for the Study of Pain – IASP*) početkom 2020. godine [2].

Približno 20% odraslih osoba u Evropi, odnosno oko 150 miliona ljudi, pati od umerenog do jakog hroničnog bola [3]. Kod pacijenata sa malignim bolestima, bol je prisutan u približno 30%–40% slučajeva u trenutku postavljanja dijagnoze, dok u uznapredovalim stadijumima oko 70%–80% onkoloških pacijenata oseća bol. Prema procenama SZO, približno 17 miliona ljudi širom sveta boluje od malignih bolesti, od kojih 12–13 miliona ima hronični bol povezan sa karcinomom. Od 1995. godine na ovamo, hronični bol se dovodi u vezu sa fizičkim i psihološkim posledicama, povećanim izdacima za zdravstvenu zaštitu, smanjenom produktivnošću i prevremenim penzionisanjem [4]. Jak bol takođe pogađa članove porodice pacijenata i druge osobe iz njihovog okruženja, što dodatno ukazuje na značaj ublažavanja bola kao ključnog izazova savremene medicine [3].

Pored primene neopiodnih i opiodnih analgetika, od ključnog značaja je odgovarajuća procena bola. Ona podrazumeva uzimanje detaljne anamneze, sa posebnim osvrtnom na lokalizaciju, raspodelu, intenzitet, kvalitet i vremenske karakteristike bola, kao i na faktore koji izazivaju ili pogoršavaju bol, uz pažljivo slušanje pacijenta [3,5]. Pored uzimanja anamneze, neophodni su i fizički pregled, dodatne procene i dijagnostičke procedure, kao i prepoznavanje i razlikovanje nociceptivnog i ne-nociceptivnog bola. Opšteprihvaćeni model podrazumeva prepoznavanje, procenu i lečenje (engl. *recognize, assess, and treat – RAT*) bola [3].

Bol predstavlja klinički problem koji zahteva saradnju lekara i medicinskih sestara – tehničara. Obrazovanje medicinskih sestara – tehničara omogućava im da samostalno procenjuju intenzitet bola i doprinesu poboljšanju komfora pacijenta i njegovog subjektivnog blagostanja. Kroz odnos zasnovan na poverenju, razumevanju i empatiji, medicinske sestre – tehničari obavljaju razgovore sa pacijentima, posmatraju ih, sprovedu procenu fizičkog stanja i prikupljaju podatke o prisustvu, intenzitetu, lokalizaciji, nastanku, širenju i kvalitetu bola. Intenzitet bola određuje hitnost intervencije, dozu farmakološke terapije i put primene leka [6].

Jedna studija iz Omana ispitala je faktore povezane sa postupcima medicinskih sestara u kontekstu

INTRODUCTION

In healthcare, one of the most widely accepted definitions of pain was given by Margo McCaffery: “Pain is whatever the experiencing person says it is, and it exists whenever the person says it does” [1]. The revised definition of pain – “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” – was unanimously adopted by the International Association for the Study of Pain (IASP) Council in early 2020 [2].

Approximately 20% of adults in Europe, or around 150 million people, are affected by moderate to severe chronic pain [3]. In patients with malignant disease, pain is present in approximately 30%–40% of cases at the time of diagnosis, while in the advanced stages, about 70%–80% of oncology patients experience pain. According to WHO estimates, approximately 17 million people worldwide suffer from malignant diseases, of whom 12–13 million experience chronic cancer pain. Since 1995, chronic pain has been associated with physical and psychological consequences, increased healthcare expenditures, reduced productivity, and early retirement [4]. Severe pain also affects patients' family members and others in their environment, further highlighting pain management as a key challenge in modern medicine [3].

In addition to non-opioid and opioid analgesic treatment, appropriate pain assessment is essential. This includes taking a detailed medical history, with particular attention to pain localization, distribution, intensity, quality, temporal characteristics, and factors that trigger or aggravate pain, together with careful listening to the patient [3,5]. Alongside history taking, physical examination, additional assessments, and diagnostic procedures are required, as well as the identification and differentiation of nociceptive and non-nociceptive pain. The generally accepted model is to recognize, assess, and treat (RAT) pain [3].

Pain is a collaborative clinical problem addressed by physicians and nurses. Nursing education enables nurses to independently assess pain intensity and contribute to improving patient comfort and subjective well-being. Through a relationship based on trust, understanding, and empathy, nurses conduct interviews, observe patients, perform physical assessments, and collect data on the presence, intensity, localization, onset, spread, and quality of pain. Pain intensity determines the urgency of intervention, the dose of pharmacological therapy, and the route of drug administration [6].

A study from Oman examined factors related to nurses' pain management practices and emphasized the role of knowledge and attitudes within the *Knowledge and Attitudes Survey Regarding Pain (KASRP)*

ublažavanja bola i istakla ulogu znanja i stavova unutar okvira *Ankete o znanju i stavovima o bolu* (engl. *Knowledge and Attitudes Survey Regarding Pain – KASRP*). Nalazi ove studije ukazuju na to da adekvatno znanje i odgovarajući stavovi omogućavaju medicinskim sestrama – tehničarima da efikasno tretiraju bol [7].

Naša studija se fokusira na znanje i stavove u vezi sa bolom među medicinskim sestrama – tehničarima zaposlenim u onkološkoj zdravstvenoj zaštiti, uz ispitivanje razlika u odnosu na starosno doba, godine radnog iskustva, stepen obrazovanja i organizacionu jedinicu u kojoj su učesnici studije zaposleni.

MATERIJALI I METODE

Etički odbor Instituta za onkologiju Vojvodine (br. 4/21/2-3993/2-6) i Etički odbor Medicinskog fakulteta Univerziteta u Novom Sadu (br. 01-39/165/2) dali su etičko odobrenje za sprovođenje istraživanja. Istraživanje je sprovedeno u Institutu za onkologiju Vojvodine.

Ova studija preseka sprovedena je tokom novembra i decembra 2022. godine. U istraživanje su bile uključene medicinske sestre – tehničari zaposleni na Institutu za onkologiju Vojvodine, i to u sledećim organizacionim jedinicama: Klinika za hiruršku onkologiju ($n = 29$), Klinika za internističku onkologiju ($n = 25$), Klinika za radioterapiju ($n = 25$) i Služba za anesteziju sa reanimatologijom ($n = 25$). Medicinske sestre – tehničari su dobrovoljno i anonimno učestvovali u istraživanju, nakon potpisivanja formulara o saglasnosti. Svim učesnicima je uručen osnovni istraživački instrument – KASRP upitnik, u papirnoj formi, koji su samostalno popunjavali 30 minuta pre ili nakon završetka smene.

KASRP upitnik je korišćen uz dozvolu njegove autorke, Beti Ferel. Sadržaj upitnika razvili su Svetska zdravstvena organizacija i Američko društvo za bol (engl. *American Pain Society – APS*), uz oslanjanje na Smernice za lečenje bola Nacionalne sveobuhvatne mreže za rak (engl. *National Comprehensive Cancer Network Pain Guidelines*). Upitnik je potvrđen kao validan i primenjen u brojnim međunarodnim istraživanjima [8,9]. U prethodnim istraživanjima utvrđena je zadovoljavajuća interna konzistentnost instrumenta, sa vrednostima Kronsbohovog alfa koeficijenta većim od 0,70 [10,11]. Sadržaj upitnika zasnovan je na međunarodno prihvaćenim smernicama za lečenje bola. Za potrebe ove studije, upitnik je preveden sa engleskog na srpski jezik i lingvistički prilagođen lokalnom kliničkom okruženju, kako bi se poboljšale jasnoća i primenljivost za učesnike. Formalna psihometrijska validacija srpske verzije nije sprovedena pre njene primene. Shodno tome, ova studija predstavlja preliminarne nalaze o primeni srpske verzije KASRP upitnika u ispitivanoj populaciji.

Bodovani segment upitnika sastojao se od 38 pitanja, uključujući 22 pitanja po tipu tačno/netačno, 14

framework. Its findings suggest that adequate knowledge and appropriate attitudes enable nurses to effectively manage pain [7].

The present study focuses on pain-related knowledge and attitudes among nurses working in oncology care and examines differences by age, work experience, education level, and department.

MATERIALS AND METHODS

The Ethics Committee of the Institute of Oncology of Vojvodina (No. 4/21/2-3993/2-6) and the Ethics Committee of the University of Novi Sad Faculty of Medicine (No. 01-39/165/2) granted ethical approval for the study. The study was performed at the Institute of Oncology of Vojvodina.

This cross-sectional study was carried out in November and December 2022. The study included nurses of both genders employed at the Institute of Oncology of Vojvodina, in the following organizational units: Clinic for Surgical Oncology ($n = 29$), Clinic for Medical Oncology ($n = 25$), Clinic for Radiotherapy ($n = 25$), and the Department of Anesthesiology with Resuscitation ($n = 25$). Nurses participated voluntarily and anonymously after signing the consent form. All participants were given the primary research instrument – the KASRP questionnaire, in paper form, which they completed independently, 30 minutes before or after the end of their shift.

The KASRP questionnaire was used with the permission of its author, Betty Ferrell. The content of the questionnaire was developed by the World Health Organization and the American Pain Society (APS), and informed by the National Comprehensive Cancer Network Pain Guidelines. The questionnaire has been validated and applied in numerous international studies [8,9]. Previous studies reported satisfactory internal consistency of the instrument, with Cronbach's alpha values above 0.70 [10,11]. The content of the questionnaire is based on internationally accepted pain management guidelines. For the purpose of this study, the questionnaire was translated from English into Serbian and linguistically adapted to the local clinical setting, in order to improve clarity and applicability for the participants. Formal psychometric validation of the Serbian version was not performed prior to its use. Accordingly, this study presents preliminary findings on the use of the Serbian version of the KASRP questionnaire in the study population.

The scored segment of the questionnaire consisted of 38 items, including 22 true/false items, 14 multiple-choice items, and two case-based questions. In addition to the 38 scored KASRP items, participants answered four additional questions related to so-

pitanja sa višestrukim izborom i dva pitanja zasnovana na prikazu slučaja. Pored 38 bodovanih KASRP pitanja, učesnici su odgovarali i na četiri dodatna pitanja koja su se odnosila na sociodemografske karakteristike, kako je opisano u nastavku. Ukupan skor izračunat je na osnovu 38 pitanja. Pitanja su bila koncipirana tako da se tačni odgovori zaokruže ili označe znakom „X“, tamo gde je to bilo naznačeno. Svaki tačan odgovor bodovan je jednim poenom, dok su netačni odgovori bodovani sa nula poena. Maksimalni mogući skor iznosio je 38 poena (100% tačnih odgovora), dok je minimalni mogući skor iznosio 0 poena. Budući da su autori KASRP upitnika naveli da pitanja koja se odnose na znanje i stavove prema bolu ne treba analizirati odvojeno, analiziran je ukupan procenat tačnih odgovora na KASRP upitniku. Procenat tačnih odgovora kategorisan je u tri grupe:

1. < 50% tačnih odgovora – nedovoljno znanje i negativan stav prema bolu
2. 50%–80% tačnih odgovora – prosečno znanje i neutralan stav prema bolu
3. ≥ 80% tačnih odgovora – dobro znanje i pozitivan stav prema bolu.

Navedenu kategorizaciju definisali su autori ove studije u svrhu interpretacije rezultata, dok je prag od ≥ 80% u skladu sa prethodnim istraživanjima koja ovaj nivo smatraju pokazateljem zadovoljavajućeg nivoa znanja i stavova [12,13].

Budući da su pitanja KASRP upitnika grupisana u četiri domena, odgovori medicinskih sestara – tehničara analizirani su i u odnosu na pojedinačne domene:

1. Pitanja o bolu povezanim sa karcinomom
 2. Pitanja o proceni bola
 3. Pitanja o farmakološkom lečenju bola
 4. Pitanja o zloupotrebi supstanci/fizičkoj zavisnosti
- Domen 1 obuhvatio je pitanja: 9, 27, 29, 32, 34.
Domen 2 obuhvatio je pitanja: 5, 6, 7, 8, 16, 35, 36, 41a i 42a.
Domen 3 obuhvatio je pitanja: 10, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 25, 28, 30, 31, 33, 38, 39, 40, 41b i 42b.
Domen 4 obuhvatio je pitanja: 24, 26, 37.

Za potrebe ove studije bilo je potrebno odgovoriti i na četiri dodatna pitanja koja su se odnosila na sociodemografske podatke (starost, godine radnog iskustva, stepen obrazovanja i organizaciona jedinica u kojoj su ispitanici zaposleni). Stepen obrazovanja medicinskih sestara – tehničara uključenih u istraživanje grupisan je u dve kategorije (srednje/više obrazovanje) za potrebe statističke analize. Medicinske sestre – tehničari sa diplomom srednje medicinske škole svrstani su u grupu sa srednjim obrazovanjem, dok su oni sa osnovnim strukovnim, osnovnim akademskim ili master akademskim stepenom obrazovanja iz oblasti zdravstvene nege svrstani u grupu sa višim stepenom obrazovanja.

ciodemographic characteristics, as described below. The overall score was generated from 38 questions. Questions were structured so that correct answers could be circled or marked with an “X”, where indicated. Each correct response was assigned one point, whereas incorrect responses were scored as zero. The maximum possible score was 38 points (100% correct answers), while the minimum possible score was 0 points. Since the authors of the KASRP questionnaire indicated that questions related to knowledge and attitudes toward pain should not be analyzed separately, we analyzed the overall percentage of correct answers in the KASRP questionnaire. The percentage of correct answers was categorized into three groups:

- 1) < 50% correct answers – poor knowledge and negative attitude toward pain
- 2) 50%–80% correct answers – average knowledge and neutral attitude toward pain
- 3) ≥ 80% correct answers – good knowledge and positive attitude toward pain.

This categorization was defined by the authors of the present study for interpretative purposes, while the ≥ 80% threshold is consistent with previous studies that consider this level to indicate satisfactory knowledge and attitudes [12,13].

As the KASRP questions were grouped into four domains, the nurses' responses were also analyzed by each domain:

- 1) Questions about cancer-related pain
- 2) Questions on pain assessment
- 3) Questions on pharmacological management
- 4) Questions on substance abuse/physical addiction

Domain 1 included questions: 9, 27, 29, 32, 34.

Domain 2 included questions: 5, 6, 7, 8, 16, 35, 36, 41a, and 42a.

Domain 3 included questions: 10, 11, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 25, 28, 30, 31, 33, 38, 39, 40, 41b, 42b.

Domain 4 included questions: 24, 26, 37.

For the purpose of this study, it was also necessary to answer four additional questions related to sociodemographic data (age, years of work experience, level of education, and organizational unit of employment). For the purpose of statistical analysis, the education level of the nurses who participated in the study was grouped into two categories (secondary/higher education). Nurses with a medical high school diploma were classified into the secondary education group, while those with basic vocational (associate degree), undergraduate academic (Bachelor of Science), or master's academic degrees in nursing were classified into the higher education group.

Odgovori (upitnici) koji nisu bili adekvatno popunjeni isključeni su iz uzorka istraživanja. Od ukupno 120 (100,0%) distribuiranih upitnika, 104 (86,7%) upitnika su bila adekvatno popunjena, zbog čega su rezultati istraživanja prikazani na osnovu analize 104 upitnika (100,0%). Primenljivost upitnika je procenjena na osnovu udela adekvatno popunjenih upitnika.

Statistička obrada podataka sprovedena je u programu SPSS, verzija 21. Kvantitativni podaci prikazani su kao aritmetička sredina $\pm$ standardna devijacija, dok su kvalitativni podaci izraženi kao frekvencije i procenti. Razlike između grupa u pogledu kontinuiranih ishoda ispitane su primenom t-testa ili jednofaktorskom analizom varijanse (ANOVA). Kada je rezultat ANOVA testa bio statistički značajan, primenjena je Bonferroni-jeva post hoc analiza radi utvrđivanja razlika između pojedinačnih parova grupa. Kategorijalne varijable poredene su primenom hi-kvadrat testa. Statistička značajnost definisana je kao $p < 0,05$. Rezultati su prikazani tabelarno i grafički.

REZULTATI

Od ukupno 120 distribuiranih KASRP upitnika, 104 (86,7%) je bilo adekvatno popunjeno i stoga su ovi upitnici uključeni u analizu. Analiza je zasnovana na odgovorima 104 medicinskih sestara – tehničara zaposlenih u Institutu za onkologiju Vojvodine. Većina (63,4%) ispitanika je bila starosti od 26 do 45 godina, dok je 13,5% njih bilo mlađe od 26 godina, a 23,1% starije od 46 godina. U pogledu radnog iskustva, 23,1% ispitanika je imalo manje od šest godina radnog iskustva, 19,2% između šest i deset godina, 20,2% između jedanaest i petnaest godina, dok je 37,5% imalo više od šesnaest godina radnog iskustva. U pogledu obrazovanja, većina (86,5%) učesnika je imala diplomu srednje medicinske škole, 3,8% je imalo završene osnovne strukovne studije, 8,7% osnovne akademske studije, dok je 1% imalo master akademski stepen iz oblasti zdravstvene nege.

U pogledu organizacione jedinice, najveći broj učesnika je radio na Klinici za hiruršku onkologiju (27,9%; $n = 29$); isti broj medicinskih sestara – tehničara je radio na Klinici za internističku onkologiju (24,0%; $n = 25$), Klinici za radioterapiju (24,0%; $n = 25$) i u Službi za anesteziju sa reanimatologijom (24,0%; $n = 25$) (Tabela 1).

Nijedan učesnik nije pokazao dobro znanje i pozitivan stav prema bolu. Većina (67,3%) medicinskih sestara – tehničara je imala prosečno znanje i neutralan stav, dok je 32,7% imalo nedovoljno znanje i negativan stav (Grafikon 1).

Ukupan KASRP skor je ukazao na prosečan nivo znanja i neutralan stav prema bolu (52,43%). Analiza prema domenima pokazala je nedovoljno znanje i negativne stavove u oblastima bola povezanog sa karci-

Responses (questionnaires) that were inadequately completed were excluded from the study sample. Out of a total of 120 (100.0%) questionnaires distributed, 104 (86.7%) questionnaires were appropriately completed, which is why the study results are presented based on the analysis of 104 questionnaires (100.0%). The feasibility of questionnaire application was assessed based on the proportion of adequately completed questionnaires.

Statistical processing was carried out in SPSS, Version 21. Quantitative data were summarized using mean values, standard deviations, while qualitative data were expressed as counts and percentages. Group differences in continuous outcomes were examined with t-test or one-way ANOVA. When the ANOVA result was statistically significant, Bonferroni post hoc analysis was applied to identify pairwise differences between groups. Categorical variables were compared using the chi-square test. Statistical significance was defined as $p < 0.05$. Results are presented in tables and graphs.

RESULTS

Of the 120 KASRP questionnaires distributed, 104 (86.7%) were completed appropriately and, therefore, included in the analysis. The analysis was based on responses from 104 nurses employed at the Institute of Oncology of Vojvodina. The majority of respondents were between 26 and 45 years of age (63.4%), while 13.5% were younger than 26 years and 23.1% were older than 46 years. Regarding work experience, 23.1% of nurses had less than six years of experience, 19.2% had between six and ten years of experience, 20.2% had between eleven and fifteen years, while 37.5% had more than sixteen years of professional experience. In terms of education, most participants (86.5%) had a medical high school diploma, 3.8% had a basic vocational degree, 8.7% had an undergraduate academic degree, while 1% held a master's degree in health care.

Regarding the organizational unit, the largest number of participants worked at the Clinic for Surgical Oncology (27.9%; $n = 29$); the same number of nurses worked at the Clinic for Medical Oncology (24.0%; $n = 25$), the Clinic for Radiotherapy (24.0%; $n = 25$), and the Department of Anesthesiology with Resuscitation (24.0%; $n = 25$) (Table 1).

No participants demonstrated good knowledge and a positive attitude toward pain. The majority of nurses (67.3%) had average knowledge and a neutral attitude, while 32.7% had poor knowledge and a negative attitude (Graph 1).

Tabela 1. Sociodemografske karakteristike ispitanika

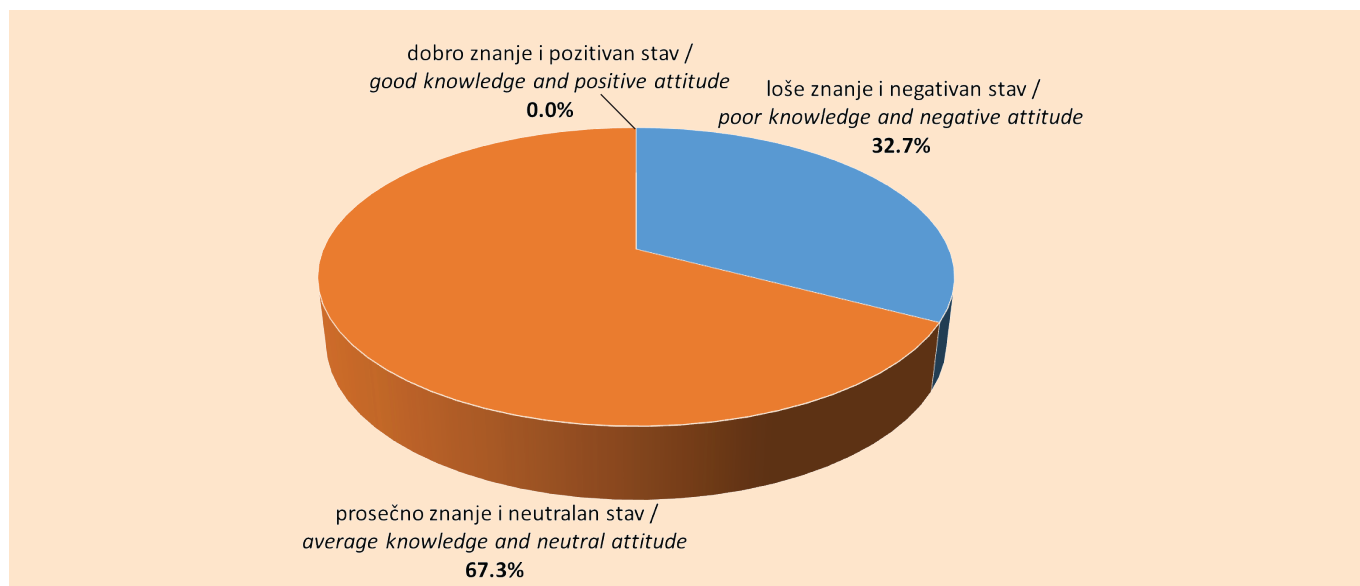
Pitanje / Question		N	%
Starost / Age	< 26	14	13.5%
	26–35	33	31.7%
	36–45	33	31.7%
	> 46	24	23.1%
Godine radnog iskustva / Years of work experience	< 6	24	23.1%
	6–10	20	19.2%
	11–15	21	20.2%
	> 16	39	37.5%
Stepen obrazovanja / Level of education	Srednja medicinska škola / Medical high school diploma	90	86.5%
	Osnovne strukovne studije / Basic vocational degree (Associate Degree in Nursing)	4	3.8%
	Osnovne akademske studije / Undergraduate academic degree (Bachelor of Science in Nursing)	9	8.7%
	Master akademske studije zdravstvene nege / Master's degree in health care/nursing	1	1.0%
Organizaciona jedinica / Department	Hirurška onkologija / Surgical Oncology	29	27.9%
	Internistička onkologija / Medical Oncology	25	24.0%
	Radioterapija / Radiotherapy	25	24.0%
	Služba anestezije / Anesthesiology and Resuscitation Department	25	24.0%

Table 1. Sociodemographic characteristics of the study participants

nomom (48,07%) i procene bola (39,30%). U domenu farmakološkog lečenja (55,56%), medicinske sestre – tehničari su pokazali prosečan nivo znanja i neutralne stavove, dok su dobro znanje i pozitivni stavovi uočeni u domenu zloupotrebe supstanci (80,13%).

Analiza odgovora na pitanja zasnovanih na prikazu slučaja (41a–42a) pokazala je teškoće u proceni bola u konkretnim kliničkim situacijama. U prvom prikazu slučaja (pitanje 41a), 91,3% medicinskih sestara netačno je procenilo intenzitet bola, dok je samo 8,7%

The overall KASRP score indicated an average level of knowledge and a neutral attitude toward pain (52.43%). Domain-specific analysis showed poor knowledge and negative attitudes in the areas of cancer-related pain (48.07%) and pain assessment (39.30%). In the pharmacological management domain (55.56%), nurses demonstrated an average level of knowledge and neutral attitudes, whereas good knowledge and positive attitudes were observed in the substance abuse domain (80.13%).



Grafikon 1. Znanje i stavovi medicinskih sestara – tehničara o bolu

Graph 1. Knowledge and attitudes of nurses about pain

Tabela 2. Razlike u tačnosti odgovora iz KASRP upitnika po organizacionim jedinicama

Pitanje / Question	Hirurška onkologija / Surgical Oncology n (%)	Internistička onkologija / Medical Oncology n (%)	Radioterapija / Radiotherapy n (%)	Anestezija sa reanimacijom / Anesthesia and Resuscitation n (%)	p
Vitalni znaci i intenzitet bola / Vital signs and pain intensity	11 (37.9%)	19 (76.0%)	15 (60.0%)	7 (28.0%)	0.003
Placebo test za „pravi” bol / Placebo test for “real” pain	12 (41.4%)	8 (32.0%)	6 (24.0%)	2 (8.0%)	0.045
Način primene opioida / Route of opioid administration	15 (51.7%)	10 (40.0%)	20 (80.0%)	7 (28.0%)	0.002
Analgetici kao lek izbora / Analgesics as the drug of choice	23 (79.3%)	19 (76.0%)	6 (24.0%)	11 (44.0%)	< 0.001
Respiratorna depresija / Respiratory depression	17 (58.6%)	6 (24.0%)	2 (8.0%)	5 (20.0%)	< 0.001
Rizik od zloupotrebe / Risk of abuse	15 (51.7%)	7 (28.0%)	20 (80.0%)	12 (48.0%)	0.003
Fizička zavisnost / Physical addiction	4 (13.8%)	14 (56.0%)	18 (72.0%)	11 (44.0%)	< 0.001
Subjektivna procena bola / Subjective pain assessment	13 (44.8%)	8 (32.0%)	19 (76.0%)	3 (12.0%)	< 0.001

* Prikazani su tačni odgovori kao n (%).

Table 2. Differences in correct answers to the KASRP questionnaire items by organizational units

*Correct answers are presented as n (%).

pravilno procenilo intenzitet bola. U drugom prikazu slučaja (pitanje 42a), 58,7% medicinskih sestara – tehničara je netačno procenilo intenzitet bola, dok je 41,3% imalo pravilnu procenu. Kada je reč o doziranju analgetika (pitanja 41b i 42b), samo 4,8% medicinskih sestara – tehničara je u prvom prikazu slučaja odabralo odgovarajuću dozu morfina za ublažavanje bola, dok je njih 20,2% to učinilo u drugom prikazu slučaja. Statistički značajne razlike u tačnosti odgovora između organizacionih jedinica utvrđene su za nekoliko stavki KASRP upitnika (Tabela 2).

Nisu utvrđene statistički značajne razlike u KASRP skorovima između starosnih grupa, ni u ukupnom skoroviti u analizama prema pojedinačnim domenima (Tabela 3).

Analysis of responses to the case study questions (41a–42a) revealed difficulties in pain assessment in specific clinical situations. In the first case study (question 41a), 91.3% of nurses incorrectly assessed pain intensity, whereas only 8.7% provided the correct assessment. In the second case study (question 42a), 58.7% of nurses incorrectly assessed pain intensity, while 41.3% assessed it correctly. Regarding analgesic dosing (questions 41b and 42b), only 4.8% of nurses in the first case study and 20.2% in the second one selected the appropriate morphine dose for pain relief. Statistically significant differences in response accuracy across organizational units were identified for several KASRP items (Table 2).

No statistically significant differences in KASRP scores were observed across age groups, either in the overall score or in the domain-specific analyses (Table 3).

Tabela 3. Znanje po starosnim grupama

Domen / Domain	< 26	26–35	36–45	> 46	p
Ukupno / Overall	50.0 ± 8.4	52.3 ± 10.4	53.3 ± 8.4	52.9 ± 7.5	0.703
Bol povezan sa kancerom / Cancer-related pain	48.6 ± 23.2	42.4 ± 23.9	50.9 ± 23.5	51.7 ± 18.6	0.365
Procena bola / Pain assessment	35.7 ± 12.5	40.1 ± 18.0	37.7 ± 13.3	42.6 ± 14.9	0.504
Primena lekova / Pharmacological management	53.3 ± 14.9	56.2 ± 11.6	56.8 ± 10.8	54.3 ± 9.6	0.720
Zloupotreba supstanci / Substance abuse	69.1 ± 24.3	82.8 ± 27.8	81.8 ± 25.1	80.6 ± 23.9	0.377

* Podaci su prikazani kao aritmetička sredina ± standardna devijacija (SD)

Table 3. Knowledge by age group

* Data are presented as mean ± standard deviation (SD)

Tabela 4. Znanje po godinama radnog iskustva

Domen / Domain	<6	6–10	11–15	>16	p
Ukupno / Overall	50.5 ± 10.1	53.9 ± 8.1	50.7 ± 8.9	53.8 ± 8.2	0.341
Bol povezan sa kancerom / Cancer-related pain	43.3 ± 21.8	44.0 ± 22.1	51.4 ± 25.0	51.3 ± 21.9	0.402
Procena bola / Pain assessment	40.7 ± 16.3	40.0 ± 15.5	33.3 ± 14.5	41.3 ± 14.4	0.242
Primena lekova / Pharmacological management	52.9 ± 14.2	58.3 ± 9.7	54.8 ± 10.5	56.2 ± 10.5	0.444
Zloupotreba supstanci / Substance abuse	75.0 ± 24.6	86.7 ± 25.1	74.6 ± 27.7	82.9 ± 25.2	0.301

* Podaci su prikazani kao aritmetička sredina ± standardna devijacija (SD)

Slično tome, godine radnog iskustva nisu bile povezane sa statistički značajnim razlikama ni u ukupnom skor u niti u bilo kom od procenjivanih domena (Tabela 4).

Stepen obrazovanja takođe nije bio statistički značajno povezan sa razlikama u ukupnom skor u niti u

Table 4. Knowledge by years of work experience

Domen / Domain	<6	6–10	11–15	>16	p
Ukupno / Overall	50.5 ± 10.1	53.9 ± 8.1	50.7 ± 8.9	53.8 ± 8.2	0.341
Bol povezan sa kancerom / Cancer-related pain	43.3 ± 21.8	44.0 ± 22.1	51.4 ± 25.0	51.3 ± 21.9	0.402
Procena bola / Pain assessment	40.7 ± 16.3	40.0 ± 15.5	33.3 ± 14.5	41.3 ± 14.4	0.242
Primena lekova / Pharmacological management	52.9 ± 14.2	58.3 ± 9.7	54.8 ± 10.5	56.2 ± 10.5	0.444
Zloupotreba supstanci / Substance abuse	75.0 ± 24.6	86.7 ± 25.1	74.6 ± 27.7	82.9 ± 25.2	0.301

* Data are presented as mean ± standard deviation (SD)

Similarly, years of work experience were not associated with significant differences in the overall score or in any of the assessed domains (Table 4).

Education level was also not significantly associated with differences in the overall score or any of the

Tabela 5. Razlika u znanju medicinskih sestara – tehničara o bolu u odnosu na stepen obrazovanja

Domen / Domain	Srednje obrazovanje / Secondary education	Više/Visoko obrazovanje / Higher education	p
Ukupno/ Overall	52.4 ± 8.5	52.7 ± 10.9	0.910
Bol povezan sa kancerom/ Cancer-related pain	48.2 ± 21.6	47.1 ± 28.9	0.869
Procena bola/ Pain assessment	39.2 ± 14.7	39.7 ± 18.4	0.923
Primena lekova/ Pharmacological management	55.6 ± 11.2	55.1 ± 12.5	0.857
Zloupotreba supstanci/ Substance abuse	79.6 ± 26.3	83.3 ± 21.7	0.617

* Podaci su prikazani kao aritmetička sredina ± standardna devijacija (SD).

Table 5. Differences in nurses' knowledge about pain by education level

* Data are presented as mean ± standard deviation (SD).

bilo kom od procenjivanih domena (Tabela 5). Nasuprot tome, statistički značajne razlike u KASRP skorovima utvrđene su između organizacionih jedinica, kako u ukupnom skor u, tako i u svim procenjivanim domenima (Tabela 6).

Tabela 6. Razlika u znanju medicinskih sestara – tehničara o bolu, ukupno i po domenima, i prema vrsti organizacione jedinice gde su zaposleni

Domen / Domain	Hirurška onkologija / Surgical oncology	Internistička onkologija / Medical oncology	Radioterapija / Radiotherapy	Anestezija sa reanimacijom / Anesthesia and resuscitation	p
Ukupno / Overall	49.6 ± 7.7	50.7 ± 8.3	56.2 ± 10.5	53.7 ± 7.4	0.026
Bol povezan sa kancerom / Cancer-related pain	61.4 ± 18.5	47.2 ± 18.1	44.8 ± 18.5	36.8 ± 27.5	<0.001
Procena bola / Pain assessment	37.5 ± 11.3	37.3 ± 13.2	48.0 ± 16.9	34.7 ± 16.5	0.008
Primena lekova / Pharmacological management	49.3 ± 11.0	54.3 ± 10.7	57.8 ± 12.4	61.8 ± 6.9	<0.001
Zloupotreba supstanci / Substance abuse	72.4 ± 28.3	70.7 ± 29.4	89.3 ± 18.6	89.3 ± 18.6	0.005

*Podaci su prikazani kao aritmetička sredina ± standardna devijacija).

*Data are presented as mean ± standard deviation.

assessed domains (Table 5). In contrast, statistically significant differences in KASRP scores were observed across organizational units in both the overall score and all assessed domains (Table 6).

Table 6. Differences in nurses' knowledge about pain, overall and by domains, and by the type of organizational unit of employment

DISKUSIJA

Ova studija prikazuje preliminarne rezultate primene upitnika pod nazivom: Anketa o znanju i stavovima o bolu (engl. *Knowledge and Attitudes Survey Regarding Pain – KASRP*) među medicinskim sestrama – tehničarima zaposlenim na Institutu za onkologiju Vojvodine. Visoki procenat adekvatno popunjenih upitnika ukazuje na to da je KASRP bio pogodan za primenu u ispitivanoj populaciji. Rezultati su pokazali prosečan nivo znanja i neutralne stavove prema bolu, što ukazuje na to da, iako su medicinske sestre – tehničari posedovali zadovoljavajući opšti nivo znanja, postoje značajni nedostaci u pojedinim oblastima lečenja bola.

KASRP upitnik ima široku primenu u proceni znanja i stavova o bolu među medicinskim sestrama – tehničarima, ali i drugim zdravstvenim radnicima u različitim zdravstvenim ustanovama [14–16]. Kao i u prethodnoj studiji sprovedenoj u Etiopiji, ova studija je bila posebno usmerena na medicinske sestre – tehničare koji rade u onkologiji [17]. Razlike između studija mogu se objasniti razlikama u zdravstvenim sistemima, obrazovanju medicinskih sestara i njihovim kliničkim odgovornostima u različitim zemljama. Dok su pojedine studije pokazale nedovoljno znanje i negativne stavove prema bolu [18,19], povoljniji rezultati opisani su u drugim populacijama medicinskih sestara – tehničara [15]. Ukupan KASRP skor utvrđen u ovoj studiji, koji ukazuje na prosečan nivo znanja i neutralne stavove prema bolu, uporediv je sa rezultatima studije sprovedene u Kini [20].

Većina ispitanika u ovoj studiji bila je uzrasta od 26 do 45 godina i imala je više od 16 godina radnog iskustva. Većina je imala diplomu srednje medicinske škole, dok je manji procenat imao više nivoe obrazovanja iz oblasti sestrinstva. Iako se kontinuirano profesionalno obrazovanje sve više prepoznaje kao važna komponenta sestrinske prakse i može doprineti većoj profesionalnoj autonomiji, rezultati ove studije ukazuju na potrebu za dodatnim obrazovanjem iz oblasti lečenja bola [21].

Najniži skorovi u ovoj studiji su zabeleženi u domenu bola povezanog sa karcinomom i domenu procene bola; prosečni skorovi su zabeleženi u domenu farmakološkog lečenja, dok su najviši skorovi zabeleženi u domenu zloupotrebe supstanci. Ovi preliminarni rezultati ukazuju na to da procena bola, naročito kod pacijenata sa karcinomom, ostaje oblast u kojoj je potrebna dodatna edukativna podrška.

Slični rezultati zabeleženi su i u Vijetnamu, gde su medicinske sestre – tehničari uglavnom bili upoznati sa analgeticima koji se koriste za dugotrajno lečenje bola kod pacijenata sa karcinomom, ali su pokazali ograničeno znanje u vezi sa preporučenim putem primene opioida kod perzistentnog bola povezanog sa karci-

DISCUSSION

This study presents preliminary results from administering the Knowledge and Attitudes Survey Regarding Pain (KASRP) questionnaire to nurses employed at the Institute of Oncology of Vojvodina. The high proportion of appropriately completed questionnaires indicates that the KASRP was feasible for use in the study population. The findings demonstrated an average level of knowledge and neutral attitudes toward pain, suggesting that although nurses possessed a satisfactory overall level of knowledge, important gaps remain in specific areas of pain management.

The KASRP questionnaire has been widely used to assess knowledge and attitudes relating to pain among nurses and other healthcare professionals in various healthcare settings [14–16]. As in a previous study conducted in Ethiopia, the present study focuses specifically on oncology nurses [17]. The differences between the studies may be explained by variations in healthcare systems, nursing education, and clinical responsibilities across countries. While some studies have reported insufficient knowledge and negative attitudes toward pain [18,19], more favorable results have been described in other nursing populations [15]. The overall KASRP score observed in the present study, indicating an average level of knowledge and neutral attitudes toward pain, is comparable to findings reported in a study conducted in China [20].

Most respondents in the present study were between 26 and 45 years old and had more than 16 years of professional experience. A majority of them had a secondary medical school diploma, while a smaller proportion had higher-level degrees in nursing education. Although continuing professional education is increasingly recognized as an important component of nursing practice and may support greater professional autonomy, the present findings suggest that additional education in pain management remains necessary [21].

The lowest scores in the present study were observed in the domains of cancer-related pain and pain assessment; average scores were recorded in pharmacological management, while the highest scores were found in the substance abuse domain. These preliminary findings suggest that pain assessment, particularly in patients with cancer, remains an area requiring additional educational support.

Similar findings have been reported in Vietnam, where nurses were generally familiar with analgesics used for long-term cancer pain, but demonstrated limited knowledge regarding the recommended route of administering opioids in persistent cancer pain. In the same study, fewer than half of the nurses correctly an-

nomom. U istoj studiji, manje od polovine medicinskih sestara – tehničara je tačno odgovorilo na pitanja koja su se odnosila na procenu bola, a samo četvrtina njih prepoznala je centralnu ulogu pacijenta u proceni sopstvenog bola [11].

U domenu farmakološkog lečenja, većina medicinskih sestara – tehničara je pravilno prepoznala da doze opioda treba prilagođavati u skladu sa odgovorom pacijenta. Međutim, manji broj učesnika prepoznao je korist od kombinovanja analgetika sa različitim mehanizmima dejstva, što može poboljšati kontrolu bola uz istovremeno smanjenje neželjenih efekata. Znanje o ekvivalentnom doziranju takođe je bilo ograničeno, budući da je samo jedna trećina učesnika pravilno identifikovala ekvivalentne intravenske i oralne doze morfina. U domenu zloupotrebe supstanci, većina medicinskih sestara – tehničara je prepoznala značaj procene stepena sedacije tokom terapije opiodima i pravilno razumela definiciju zavisnosti.

U našoj studiji, starost nije bila povezana sa KASRP skorovima. Slični rezultati zabeleženi su i u Saudijskoj Arabiji [12], dok je studija iz Nepala pokazala statistički značajne razlike u znanju i stavovima u vezi sa bolom u zavisnosti od životnog doba [22]. Takođe, ni godine profesionalnog iskustva ni nivo obrazovanja nisu bili povezani sa KASRP skorovima. Iako bi se moglo očekivati da duže profesionalno iskustvo i viši nivo obrazovanja doprinose boljem znanju i pozitivnijim stavovima, takva povezanost nije uočena u ovoj studiji. U studiji sprovedenoj u Libanu zabeleženi su bolji rezultati kod iskusnijih i bolje obrazovanih medicinskih sestara [23], dok su naši nalazi bili više u skladu sa rezultatima koje su objavili Šdaifat i saradnici [19]. Ovi nalazi ukazuju na to da formalno obrazovanje i godine profesionalnog iskustva sami po sebi možda nisu dovoljni ukoliko se znanje o lečenju bola kontinuirano ne unapređuje kroz strukturisanu edukaciju i kliničku obuku.

Uočene razlike između organizacionih jedinica ukazuju na to da razmena znanja može da doprinese ujednačenijoj praksi lečenja bola i smanjenju varijabilnosti u donošenju kliničkih odluka. Odgovori na pitanja zasnovana na prikazima slučajeva ukazuju na teškoće u proceni bola i donošenju odluka u vezi sa primenom opioda u konkretnim kliničkim situacijama. Samo mali procenat medicinskih sestara odabrao je odgovarajuću dozu analgetika za ublažavanje bola, što može da ukazuje na nesigurnost u prevođenju intenziteta bola koji pacijenti sami prijavljuju u odgovarajuće odluke o lečenju. Ovaj nalaz je klinički značajan jer neadekvatna analgezija može da produži patnju pacijenta, dok neodgovarajuće doziranje opioda može da poveća rizik od neželjenih efekata. Slični rezultati zabeleženi su u prethodnim studijama, u kojima su medicinske sestre

swered questions related to pain assessment, and only one quarter of them recognized the patient's central role in assessing their own pain [11].

In the domain of pharmacological management, most nurses correctly recognized that opioid doses should be adjusted according to the patient's response. However, fewer participants recognized the benefit of combining analgesics with different mechanisms of action, which may improve pain control while reducing adverse effects. Knowledge of equianalgesic dosing was also limited, as only one third of participants correctly identified equivalent intravenous and oral morphine doses. In the domain of substance abuse, most nurses recognized the importance of assessing sedation during opioid therapy and correctly understood the definition of addiction.

In the present study, age was not associated with KASRP scores. Similar findings were reported in Saudi Arabia [12], whereas a study from Nepal found significant differences in pain-related knowledge and attitudes according to age [22]. Likewise, neither years of professional experience nor education level were associated with KASRP scores. Although greater professional experience and a higher level of education might be expected to contribute to better knowledge and attitudes, such an association was not observed in the present study. A study conducted in Lebanon reported better outcomes among more experienced and better-educated nurses [23], whereas our findings were more consistent with those reported by Shdaifat et al. [19]. These findings suggest that formal education and years of professional practice alone may not be sufficient unless pain management is continuously reinforced through structured education and clinical training.

The observed differences between organizational units suggest that knowledge exchange may contribute to more consistent pain management practices and reduce variability in clinical decision-making. Responses to the case-based questions suggest difficulties in pain assessment and opioid-related decision-making in specific clinical situations. Only a small proportion of nurses selected the appropriate analgesic dose for pain relief, which may reflect uncertainty in translating patients' self-reported pain intensity into treatment decisions. This finding is clinically relevant because inadequate analgesia may prolong patient suffering, whereas inappropriate opioid dosing may increase the risk of adverse effects. Similar findings have been reported in previous studies, where nurses demonstrated better general knowledge of pain assessment and management than of opioid dosing and opioid-related adverse effects [24].

pokazale bolje opšte znanje o proceni i lečenju bola nego o doziranju opioda i neželjenim efektima povezanim sa primenom opioda [24].

U našoj studiji, utvrđene su razlike između organizacionih jedinica u nekoliko oblasti povezanih sa procenom bola i primenom opioda. Medicinske sestre – tehničari sa Klinike za radioterapiju i Klinike za medikalnu onkologiju češće su prepoznavali da sami vitalni znaci nisu pouzdani pokazatelji intenziteta bola nego medicinskih sestara – tehničara sa Klinike za hiruršku onkologiju i iz Službe anesteziologije sa reanimatologijom. Niža tačnost odgovora zabeležena je kod medicinskih sestara – tehničara iz Službe anesteziologije sa reanimatologijom u pogledu primene injekcija sterilne vode u proceni bola. Nasuprot tome, medicinske sestre – tehničari sa Klinike za radioterapiju češće su prepoznavali preporučeni put primene opioda kod perzistentnog bola povezanog sa karcinomom, dok su medicinske sestre – tehničari sa Klinike za medikalnu onkologiju i Klinike za hiruršku onkologiju češće prepoznavali morfin kao preferiranu terapijsku opciju za dugotrajni umereni do jaki bol povezan sa karcinomom. Medicinske sestre – tehničari sa Klinike za hiruršku onkologiju takođe su češće prepoznavali da je klinički značajna respiratorna depresija neuobičajena kod pacijenata sa karcinomom koji primaju stabilnu dugotrajnu terapiju opiodima.

Opstipacija, mučnina, sedacija, konfuzija, halucinacije, retencija urina i vrtoglavica spadaju među češće neželjene efekte povezane sa primenom opioda, dok se respiratorna depresija smatra neuobičajenom kada se opiodi titiraju na odgovarajući način u lečenju bola kod pacijenata sa karcinomom [25,26]. Prilagođavanje respiratornim efektima opioda tokom produžene terapije može dodatno da smanji rizik od klinički značajne respiratorne depresije [27,28].

Najveći udeo tačnih odgovora na pitanja koja su se odnosila na zloupotrebu alkohola i/ili droga zabeležen je među medicinskim sestrama – tehničarima sa Klinike za radioterapiju. Ispitanici iz ove organizacione jedinice takođe su češće prepoznavali manifestacije fizičke zavisnosti nakon naglog prekida primene opioda. Pored toga, medicinske sestre – tehničari sa Klinike za radioterapiju preciznije su procenjivali intenzitet bola primenom numeričke skale za procenu bola nego medicinske sestre – tehničari iz drugih organizacionih jedinica. Ove razlike mogu da odražavaju varijacije u kliničkoj izloženosti, obuci i praktičnom iskustvu između organizacionih jedinica.

U celini, preliminarni nalazi ukazuju na to da su medicinske sestre – tehničari zaposleni na onkologiji pokazali umereno znanje i uglavnom neutralne stavove prema lečenju bola povezanog sa karcinomom, uz niže

In the present study, differences between organizational units were observed in several areas related to pain assessment and opioid use. Nurses from the Clinic for Radiotherapy and the Clinic for Medical Oncology more frequently recognized that vital signs alone are not reliable indicators of pain intensity than was the case with the nurses working at the Clinic for Surgical Oncology and the Department of Anesthesiology with Resuscitation. Lower response accuracy was observed among nurses from the Department of Anesthesiology with Resuscitation regarding the use of sterile water injections in pain assessment. In contrast, nurses from the Clinic for Radiotherapy more frequently identified the recommended route of opioid administration for persistent cancer-related pain, while nurses from the Clinic for Medical Oncology and the Clinic for Surgical Oncology more often recognized morphine as the preferred treatment option for prolonged moderate to severe cancer pain. Nurses from the Clinic for Surgical Oncology also more frequently recognized that clinically significant respiratory depression is uncommon in cancer patients receiving stable long-term opioid therapy.

Constipation, nausea, sedation, confusion, hallucinations, urinary retention, and dizziness are among the more common opioid-related adverse effects, whereas respiratory depression is considered uncommon when opioids are appropriately titrated for cancer pain management [25,26]. Adaptation to the respiratory effects of opioids during prolonged therapy may further reduce the risk of clinically significant respiratory depression [27,28].

The highest proportion of correct responses to questions related to alcohol and/or drug abuse was observed among nurses from the Clinic for Radiotherapy. Participants from this organizational unit also more frequently recognized manifestations of physical dependence following abrupt opioid discontinuation. In addition, nurses from the Clinic for Radiotherapy assessed patients' pain intensity more accurately using the numerical pain rating scale than nurses from other organizational units. These differences may reflect variations in clinical exposure, training, and practical experience across organizational units.

Overall, preliminary findings suggest that oncology nurses demonstrated moderate knowledge and generally neutral attitudes toward cancer pain management, with lower scores particularly in the domains of pain assessment and opioid-related knowledge. From a clinical perspective, insufficient knowledge in these areas may affect timely pain recognition, treatment decisions, and patient comfort. Continuous professional education focused on evidence-based pain assessment, safe opioid use, and comprehensive

skorove naročito u domenima procene bola i znanja povezanog sa primenom opioda. Sa kliničkog aspekta, nedovoljno znanje u ovim oblastima može da utiče na pravovremeno prepoznavanje bola, donošenje odluka o lečenju i udobnost pacijenata. Kontinuirano profesionalno obrazovanje usmereno na procenu bola zasnovanu na dokazima, bezbednu primenu opioda i sveobuhvatno lečenje bola povezanog sa karcinomom stoga bi moglo da unapredi kliničku praksu. Veća saradnja i razmena iskustava između onkoloških, radio-terapijskih i anestezioloških jedinica takođe bi mogle da doprinesu ujednačenijoj praksi lečenja bola i povećanju sigurnosti medicinskih sestara – tehničara u donošenju kliničkih odluka.

Ova studija ima nekoliko ograničenja koja treba uzeti u obzir prilikom tumačenja rezultata. Istraživanje je sprovedeno u jednoj onkološkoj ustanovi, što može da ograniči mogućnost generalizacije rezultata na druga zdravstvena okruženja. Pored toga, podaci su prikupljeni primenom upitnika zasnovanog na samoproceni, na koji može uticati pristrasnost u davanju odgovora. Rezultati ukazuju na to da je KASRP upitnik pogodan za primenu u ovoj ispitivanoj populaciji. Ovi preliminarni rezultati mogu da predstavljaju osnovu za buduća istraživanja znanja i stavova u vezi sa bolom među medicinskim sestrama – tehničarima koji rade u onkologiji u Srbiji.

ZAKLJUČAK

KASRP upitnik se pokazao kao pogodan za primenu u ovoj ispitivanoj populaciji. Preliminarni rezultati ukazuju na to da su medicinske sestre – tehničari na Institutu za onkologiju Vojvodine pokazali prosečan nivo znanja i uglavnom neutralne stavove prema bolu, pri čemu su najniži rezultati zabeleženi u domenima bola povezanog sa karcinomom i procene bola, prosečni rezultati u domenu primene lekova, a najbolji rezultati u domenu zloupotrebe supstanci. Starost medicinskih sestara – tehničara, godine radnog iskustva i nivo obrazovanja nisu bili povezani sa znanjem i stavovima prema bolu. Nivo znanja o proceni i lečenju bola razlikovao se među medicinskim sestrama – tehničarima iz različitih klinika i službi. Niži skorovi na stavkama koje se odnose na kliničke scenarije mogu ukazivati na teškoće u proceni bola i donošenju kliničkih odluka u konkretnim situacijama.

Sukob interesa: Nije prijavljen.

cancer pain management may therefore improve clinical practice. Greater collaboration and experience exchange between oncology, radiotherapy, and anesthesiology units could also contribute to more consistent pain management practices and strengthen nurses' confidence in clinical decision-making.

This study has several limitations to be considered when interpreting the findings. The research was conducted in a single oncology institution, which may limit the generalizability of the results to other healthcare settings. In addition, data were collected using a self-reported questionnaire, which may be influenced by response bias. The findings suggest that the KASRP questionnaire is feasible for use in this study population. These preliminary results may provide a basis for future research on pain-related knowledge and attitudes among oncology nurses in Serbia.

CONCLUSION

The KASRP questionnaire proved feasible for use in this study population. The preliminary findings indicate that nurses at the Institute of Oncology of Vojvodina demonstrated average knowledge and generally neutral attitudes toward pain, with the lowest results in the domains of cancer-related pain and pain assessment, average results in medication use, and the best results in the domain of substance abuse. The nurses' age, years of work experience, and education level were not associated with knowledge and attitudes toward pain. The knowledge level regarding pain assessment and management varied among nurses from different clinics and departments. Lower scores on the items related to clinical scenarios may indicate difficulties in pain assessment and clinical decision-making in specific situations.

Conflict of interest: None declared.

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PREDIKTORI INKARCERACIJE KILE I POSTOPERATIVNOG RECIDIVA KILE: ANALIZA DEMOGRAFSKIH, KLINIČKIH I HIRURŠKIH FAKTORA KOJI UTIČU NA ISHODE LEČENJA

ORIGINALNI RAD

ORIGINAL ARTICLE

PREDICTORS OF HERNIA INCARCERATION AND POSTOPERATIVE RECURRENCE: ANALYSIS OF DEMOGRAPHIC, CLINICAL, AND SURGICAL FACTORS INFLUENCING TREATMENT OUTCOMES

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SAŽETAK

Uvod/Cilj: Hernije trbušnog zida predstavljaju čestu patologiju u opštoj hirurgiji, sa značajnim rizikom od inkarceracije, recidiva i produžene hospitalizacije. Cilj studije bio je da se analiziraju klinički i operativni faktori povezani sa inkarceracijom, recidivom i dužinom bolničkog lečenja kod operisanih pacijenata.

Materijal i metode: Retrospektivna studija obuhvatila je 230 pacijenata operisanih zbog hernije u Hirurškoj klinici KBC Kosovska Mitrovica. Analizirani su demografski podaci, prisustvo komorbiditeta, tip hernije, inkarceracija, operativna tehnika, vrsta anestezije, recidiv i trajanje hospitalizacije.

Rezultati: Prosečna starost ispitanika iznosila je $58,85 \pm 14,77$ godina, a muškarci su činili 85,7% uzorka. Najčešća je bila preponska hernija (85,7%), dok je Lichtenstein tehnika primenjena kod 83,9% pacijenata. Recidiv je registrovan kod 4,8%, a inkarceracija kod 16,1% bolesnika. Recidiv nije bio značajno povezan sa polom ($p = 0,164$), vrstom hernije ($p = 0,175$), niti komorbiditetima ($p = 0,110$). Inkarceracija je bila značajno češća kod žena (39,4% vs. 12,2%; $p < 0,001$), kao i kod pacijenata operisanih u opštoj endotrahealnoj anesteziji (25,4%; $p = 0,001$). Hospitalizacija je bila duža kod pacijenata sa inkarceracijom (8,22 vs. 6,86 dana; $p = 0,017$). Multivarijabilna analiza pokazala je da su starost ($OR = 1,035$; $p = 0,047$) i komorbiditeti ($OR = 3,073$; $p = 0,029$) nezavisni prediktori inkarceracije, dok je lokalna anestezija imala protektivni efekat ($OR = 0,315$; $p = 0,038$).

Zaključak: Recidiv kile pokazuje multifaktorsku prirodu bez jasnih nezavisnih prediktora. Inkarceracija je značajno povezana sa starijim godinama, komorbiditetima i tipom kile i dovodi do produžene hospitalizacije. Ovi nalazi odražavaju ishode primećene u hirurškoj bolnici koja radi u zdravstvenom okruženju sa ograničenim resursima.

Ključne reči: kila, inkarceracija, recidiv, hospitalizacija

ABSTRACT

Introduction/Objective: Hernias of the abdominal wall represent a frequent pathology in general surgery, with a significant risk of recurrence, incarceration, and prolonged hospitalization. The aim of the study was to analyze clinical and operative factors associated with incarceration, recurrence and length of hospital treatment in operated patients.

Materials and methods: A retrospective study included 230 patients operated on for hernia at the Surgical Clinic of CHC Kosovska Mitrovica. Demographic data, presence of comorbidities, type of hernia, incarceration, operative technique, type of anesthesia, recurrence and duration of hospitalization were analyzed.

Results: The average age of the respondents was 58.85 ± 14.77 years, and men made up 85.7% of the sample. The most common was groin hernia (85.7%), while the Lichtenstein technique was used in 83.9% of patients. Recurrence was registered in 4.8% and incarceration in 16.1% of patients. Recurrence was not significantly related to gender ($p = 0.164$), type of hernia ($p = 0.175$), or comorbidities ($p = 0.110$). Incarceration was significantly more common in women (39.4% vs. 12.2%; $p < 0.001$), as well as in patients operated on under general endotracheal anesthesia (25.4%; $p = 0.001$). Hospitalization was longer in patients with incarceration (8.22 vs. 6.86 days; $p = 0.017$). Multivariable analysis showed that age ($OR = 1.035$; $p = 0.047$) and comorbidities ($OR = 3.073$; $p = 0.029$) were independent predictors of incarceration, while local anesthesia had a protective effect ($OR = 0.315$; $p = 0.038$).

Conclusion: Hernia recurrence demonstrates a multifactorial nature with no clear independent predictors. Incarceration is significantly associated with older age, comorbidities, and hernia type and results in prolonged hospitalization. These findings reflect outcomes observed in a surgical hospital operating in a resource-limited healthcare setting.

Keywords: hernia, incarceration, relapse, hospitalization

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UVOD

Ingvinalne kile predstavljaju najčešći tip preponskih kila, manifestujući se kao ispupčenje u preponskoj regiji i potencijalno izazivajući bol, nelagodnost ili opstrukciju creva [1]. Operacija kile i dalje predstavlja jednu od najčešće izvođenih hirurških procedura širom sveta, iako pojedini aspekti zbrinjavanja kila i dalje zahtevaju dodatna istraživanja [2]. Preponske kile obuhvataju ingvinalne i femoralne kile, pri čemu femoralne kile čine približno 4% svih preponskih kila i češće se javljaju kod žena [1]. Femoralne kile su ređe od ingvinalnih kila, ali zbog urgentnosti operativnih zahvata i česte potrebe za resekcijom creva zauzimaju značajno mesto u hirurškoj praksi [3]. Ove kile se uglavnom javljaju kod starijih pacijentkinja [4].

Tokom godina razvijene su brojne hirurške tehnike za operativno zbrinjavanje ingvinalnih kila, sa različitim dugoročnim ishodima. Na osnovu aktuelnih dokaza, međunarodne smernice preporučuju otvorenu reparaciju uz primenu mrežice prema Lichtenstein tehnici i laparo-endoskopske pristupe (TAPP i TEP) kao preferirane opcije lečenja za većinu odraslih pacijenata sa ingvinalnom kilom. Shodno tome, ove tehnike postale su najšire primenjivane metode u savremenoj hirurgiji kila [5–7]. Operativno zbrinjavanje umbilikalnih i epigastričnih kila često se izvodi hirurškim putem, pri čemu izbor metode zavisi od veličine hernijalne kese i fascijalnog defekta [8].

Primena tehnike sa ugradnjom mrežice široko je prihvaćena kao efikasan način lečenja ventralnih i incizionih kila. Operativno zbrinjavanje ventralnih i incizionih kila predstavlja čest hirurški zahvat, sa značajnom učestalošću postoperativnih komplikacija i reintervencija [9]. Sintetička mrežica je široko prihvaćena u hirurgiji ventralnih kila, iako nije jasno da li pruža iste koristi kod pacijenata sa visokim rizikom ili u slučajevima sa kontaminacijom [10].

Poslednjih godina laparoskopski i robotski pristupi zauzimaju sve značajnije mesto u hirurgiji kila. Ipak, njihova primena i dalje zavisi od dostupnih lokalnih zdravstvenih resursa, infrastrukture i prakse zdravstvene ustanove. Budući da minimalno invazivna reparacija kila tokom perioda istraživanja nije bila rutinski dostupna u našoj ustanovi, svi pacijenti uključeni u ovu studiju podvrgnuti su otvorenoj reparaciji kile. Shodno tome, prikazani rezultati odražavaju ishode povezane sa otvorenim hirurškim lečenjem kila trbušnog zida.

Cilj ove studije bio je da se sprovede sveobuhvatna analiza kliničkih, demografskih i operativnih faktora kod pacijenata operisanih zbog kile, sa posebnim fokusom na identifikovanje prediktora postoperativnih ishoda, prvenstveno inkarceracije i recidiva. Istraživanje je takođe imalo za cilj da proceni uticaj tipa kile, ko-

INTRODUCTION

Inguinal hernias are the most common type of groin hernia, presenting as a protrusion in the groin region and potentially causing pain, discomfort, or intestinal obstruction [1]. Hernia repair remains one of the most frequently performed surgical procedures worldwide, although several aspects of hernia management continue to require further investigation [2]. Groin hernias include both inguinal and femoral hernias, with femoral hernias accounting for approximately 4% of all groin hernias and occurring more frequently in women [1]. Femoral hernias are less common than inguinal hernias, but due to the urgency of the procedures and frequent bowel resections, they occupy an important place in surgical practice [3]. These hernias mainly occur in elderly female patients [4].

Over the years, numerous surgical techniques have been developed for inguinal hernia repair, with varying long-term outcomes. Based on current evidence, international guidelines recommend mesh-based open repair using the Lichtenstein technique and laparo-endoscopic approaches (TAPP and TEP) as the preferred treatment options for most adult patients with inguinal hernia. Consequently, these techniques have become the most widely adopted methods in contemporary hernia surgery [5–7]. The procedure for umbilical and epigastric hernia repair is often performed surgically, with the choice of method being determined by the size of the hernial sac and fascial defect [8].

The application of the mesh technique is widely accepted as an effective treatment for ventral and incisional hernias. Ventral and incisional hernia repair is a frequent surgical procedure with a significant incidence of postoperative complications and reinterventions [9]. Synthetic mesh is widely accepted for ventral hernia surgery, although it is unclear whether it provides the same benefits in high-risk patients or in contaminated cases [10].

In recent years, laparoscopic and robotic approaches have gained an increasingly important role in hernia surgery. Nevertheless, their implementation remains dependent on local healthcare resources, infrastructure, and institutional practice. As minimally invasive hernia repair was not routinely available in our institution during the study period, all patients included in this study underwent open hernia repair. Consequently, the presented results reflect outcomes associated with open surgical management of abdominal wall hernias.

The aim of this study was to perform a comprehensive analysis of clinical, demographic, and operative factors in patients operated on for hernia, with a particular focus on identifying predictors of postoperative outcomes, primarily incarceration and recurrence. Also, the aim of the research was to evaluate the influence of type of hernia, the presence of comorbidities, different

morbiditeta, operativnih tehnika i anestezije na dužinu hospitalizacije i stopu komplikacija, kao i da utvrdi koji od navedenih faktora predstavljaju nezavisne prediktore nepovoljnih ishoda.

MATERIJAL I METODE

Ova retrospektivna studija ispitala je različite aspekte operacija kila analizom podataka prikupljenih iz medicinske dokumentacije i arhive Hirurške klinike KBC Kosovska Mitrovica. Uzorak je obuhvatio 230 pacijenata koji su podvrgnuti operaciji kile tokom jednogodišnjeg perioda. Istraživanje je sprovedeno uz odobrenje Etičkog odbora ustanove u kojoj je istraživanje realizovano, u skladu sa relevantnim etičkim smernicama i standardima. Sve procedure prikupljanja i analize podataka sprovedene su u skladu sa odobrenim protokolom istraživanja, uz poštovanje prava i dobrobiti svih učesnika. U svakom koraku istraživanja obezbeđena je zaštita privatnosti i poverljivosti podataka o pacijentima.

Demografske karakteristike pacijenata detaljno su analizirane. Podaci o starosti i polu pacijenata prikupljeni su i analizirani odvojeno za muškarce i žene. Izračunate su srednja vrednost starosti i standardna devijacija kako bi se dobio detaljan prikaz starosne strukture pacijenata podvrgnutih operaciji kile. Identifikovan je i analiziran tip kile. Izračunat je procenat za svaki tip kile kako bi se utvrdila učestalost i distribucija različitih tipova kila u uzorku.

Identifikovane su i analizirane operativne tehnike korišćene u operacijama kila. Takođe su analizirane učestalost i distribucija svake tehnike u uzorku. Izračunat je i prosečan broj primenjenih operativnih tehnika kako bi se procenila varijabilnost u njihovoj primeni. Pažljivo su praćeni ishodi hirurškog lečenja, uključujući recidiv kile i dužinu hospitalizacije. Pacijenti su grupisani prema prisustvu ili odsustvu inkarceracije i recidiva kile.

U istraživanju je primenjena deskriptivna statistika za analizu osnovnih karakteristika uzorka, uključujući srednje vrednosti, standardne devijacije i procentualne distribucije. Hi-kvadrat test korišćen je za analizu razlika u učestalosti recidiva kile prema polu, komorbiditetima i tipu kile, čime je omogućena procena statističke značajnosti razlika između kategorijalnih varijabli, kao i F-test. Takođe je primenjen Mann-Whitney U test, kao i multivarijabilna analiza. Varijable su uključene u multivarijabilnu logističku regresionu analizu na osnovu kliničke relevantnosti i rezultata univarijantne analize, a ne isključivo na osnovu statističke značajnosti. Starost, pol, komorbiditeti, vrsta anestezije i dužina hospitalizacije uključeni su kao potencijalne konfundirajuće varijable, jer mogu odražavati razlike u kliničkoj prezentaciji, perioperativnom zbrinjavanju i težini bolesti kod pacijenata sa kilom.

operative techniques, and anesthesia s on the duration of hospitalization and the occurrence of complications, as well as to determine which of these factors are independent predictors of an unfavorable outcome.

MATERIALS AND METHODS

A retrospective study investigated various aspects of hernia operations through the analysis of data collected from medical records and archives of the Surgical Clinic of CHC Kosovska Mitrovica. The sample included 230 patients who underwent hernia surgery over a period of one year. This research was conducted with the approval of the Ethics Committee of the institution where the research was conducted in accordance with relevant ethical guidelines and standards. All data collection and analysis procedures were conducted in accordance with the approved research protocol, respecting the rights and well-being of all participants. Each step of the research is conducted in a manner that ensures the protection of privacy and confidentiality of patient data.

The demographic characteristics of the patients were analyzed in detail. Data on patient age and gender were collected and analyzed separately for men and women. The mean age and standard deviation were calculated to obtain a detailed picture of the age structure of patients undergoing hernia surgery. The type of hernia was identified and analyzed. The percentage of each hernia type was calculated to determine the prevalence and distribution of different hernia types in the sample.

Operative techniques used in hernia operations were identified and analyzed. The frequency of application of each technique was analyzed as well as their distribution in the sample. The average number of operative techniques that were applied was also calculated in order to assess the variability in the application of different techniques. Outcomes of surgery, including hernia recurrence and length of hospitalization, were followed in detail. Patients were grouped according to the presence or absence of hernia incarceration and hernia recurrence.

The research used descriptive statistics to analyze the basic characteristics of the sample, including average values, standard deviations, and percentage distributions. The chi-square test was used to analyze the differences in the frequency of hernia recurrence according to gender, comorbidities, and type of hernia, which enabled the assessment of the statistical significance of the differences between categorical variables as well as the F-test. The Mann-Whitney U test was also applied, as well as multivariable analysis. Variables were included in the multivariable logistic regression analysis based on their clinical relevance and the results of the univariate analysis, rather than solely on statistical significance.

Iako neke varijable, kao što su starost i komorbidite- ti, nisu bile statistički značajne u univariabilnim analizi, uključene su u multivariabilni model zbog njihove dokazane kliničke značajnosti i potencijalnog uticaja na ishode lečenja. Istovremeno, nisu uključene sve dostupne varijable kako bi se izbeglo preopterećenje modela i povećanje rizika od overfittinga imajući u vidu veličinu uzorka, čime su očuvane stabilnost i interpretabilnost regresionog modela [11,12]. Ova kombinacija statističkih testova omogućila je sveobuhvatnu analizu uticaja različitih faktora na ishode lečenja kila u ispitivanoj populaciji. Svi statistički testovi interpretirani su uz nivo značajnosti od $p < 0,05$, što predstavlja standardni prag za statističku značajnost. Korišćen je softverski paket SPSS Statistics 20.

REZULTATI

Ova studija analizirala je podatke 230 pacijenata sa dijagnozom kila prednjeg trbušnog zida. Sociodemografski podaci pokazali su da je prosečna starost ispitanika iznosila $58,85 \pm 14,77$ godina, pri čemu su muškarci činili 85,7%, a žene 14,3% ispitanika; preostale varijable prikazane su u Tabeli 1.

U analizi dužine hospitalizacije i starosti u odnosu na recidiv, nije utvrđena statistički značajna razlika ($p = 0,757$; $p = 0,418$), što ukazuje na to da ovi faktori nisu povezani sa recidivom u ovoj studiji. Nije utvrđena statistički značajna povezanost između demografskih i kliničkih karakteristika i recidiva. Pol ($p = 0,164$), tip kile, operativna tehnika, vrsta anestezije, inkarceracija

Age, sex, comorbidities, type of anesthesia, and length of hospitalization were included as potential confounding variables because they may reflect differences in clinical presentation, perioperative management, and disease severity among patients with hernia.

Although some variables, such as age and comorbidity, did not show statistical significance in the univariable analysis, their inclusion in the multivariable model was considered justified due to their proven clinical significance and potential impact on the treatment results, while at the same time uncritical inclusion of all available variables was not carried out in order to avoid overloading the model and the risk of overfitting in relation to the sample size, thus preserving the stability and interpretability of the regression model [11,12]. This combination of statistical tests enabled a comprehensive analysis of the influence of various factors on hernia outcomes in the study population. All statistical tests were interpreted with the significance level set at $p < 0.05$, which is the standard threshold for statistical significance. The SPSS Statistics 20 software package was used.

RESULTS

In this study, data collected from 230 patients diagnosed with anterior abdominal wall hernias were analyzed. Socio-demographic data showed that the average age of the subjects was 58.85 ± 14.77 years, with a male and female percentage of 85.7% and 14.3%, respectively, while the remaining variables examined are shown in Table 1.

Tabela 1. Ispitivane varijable

Variable / Variables, medijana (opseg) / median (range)	n = 230
Starost, medijana (opseg) / Years of life, median (range)	61 (18–88)
Dužina hospitalizacije, med. (min-max) / Duration of hospitalization, med. (min-max)	6 (0–20)
Pol, n (%) / Sex, n (%)	
Muški / Male	197 (85.7)
Ženski / Female	33 (14.3)
Tip kile, n (%) / Type of hernia, n (%)	
Preponska / Groin	197 (85.7%)
Ventralna / Ventral	33 (14.3%)
Operativna tehnika, n (%) / Operative technique, n (%)	
Lichtenstein/Bassini / Lichtenstein/Bassini	193 (83.9%)
Lotheissen / Lotheissen	4 (1.7%)
Rives sublay/Mesh / Rives sublay/Mesh	33 (14.3%)
Recidiv kile, n (%) / Hernia recurrence, n (%)	
Da / Yes	11 (4.8)
Ne / No	219 (95.2)
Inkarceracija kile, n (%) / Incarceration of hernia, n (%)	
Da / Yes	37 (16.1)
Ne / No	193 (83.9)
Komorbiditeti, n (%) / Comorbidities, n (%)	
Da / Yes	95 (41.3)
Ne / No	135 (58.7)

Table 1. Tested variables

Tabela 2. Korelacija kliničkih karakteristika sa recidivom

Table 2. Correlation of clinical characteristics with recurrence

Varijable / Variables	Bez recidiva / Without recurrence n (%)	Sa recidivom / With recurrence n (%)	p
Pol / Sex			
Muški / Male	186 (94.4%)	11 (5.6%)	0.164
Ženski / Female	33 (100%)	0 (0%)	
Tip kile / Type of hernia			
Preponska / Groin	186 (94.4%)	11 (5.6%)	0.175
Ventralna / Ventral	33 (100%)	0 (0%)	
Operativna tehnika / Operative technique			
Lichtenstein / Bassini	182 (94.3%)	11 (5.7%)	0.548
Lotheissen / Lotheissen	4 (100%)	0 (0%)	
Rives sublay / Mesh	33 (100%)	0 (0%)	
Inkarceracija kile / Incarceration of hernia			
Ne / No	182 (94.3%)	11 (5.7%)	0.137
Da / Yes	37 (100%)	0 (0%)	
Anestezija / Anesthesia			
Lokalna / Local	121 (96.0%)	5 (4.0%)	0.548
Spinalna / Spinal	32 (97.0%)	1 (3.0%)	
GETA / GETA	66 (93.0%)	5 (7.0%)	
Komorbiditeti / Comorbidities			
Ne / No	126 (93.3%)	9 (6.7%)	0.110
Da / Yes	93 (97.9%)	2 (2.1%)	

GETA (opšta endotrahealna anestezija)

($p = 0,137$) i komorbiditeti nisu predstavljali značajne prediktore, iako su svi slučajevi recidiva zabeleženi kod muškaraca (Tabela 2).

Nije utvrđena statistički značajna razlika u starosti između pacijenata sa i bez inkarceracije ($p = 0,176$), iako je u grupi pacijenata sa inkarceracijom uočena tendencija ka većoj starosti. Nasuprot tome, pacijenti sa inkarceracijom imali su statistički značajno duže trajanje hospitalizacije ($p = 0,017$) (Tabela 3).

Utvrđena je statistički značajna povezanost između nekoliko kliničkih i operativnih karakteristika i pojave inkarceracije. Veća učestalost inkarceracije zabeležena je kod žena sa femoralnim kilama, kao i kod pacijenata operisanih primenom određenih operativnih tehnika i u opštoj endotrahealnoj anesteziji. Nasuprot tome, komorbiditeti i recidiv nisu bili statistički značajno povezani sa pojavom inkarceracije (Tabela 4).

GETA (general endotracheal anesthesia)

In the analysis of the duration of hospitalization and age in relation to the presence of recurrence, no statistically significant difference was found ($p = 0.757$; $p = 0.418$), which indicates that these factors are not related to the occurrence of recurrence in this study. No statistically significant association was found between demographic and clinical characteristics and recurrence. Gender ($p = 0.164$), type of hernia, operative technique, type of anesthesia, incarceration ($p = 0.137$), and comorbidities were not significant predictors, although all recurrences were recorded in men (Table 2).

No statistically significant difference in age was found between patients with and without incarceration ($p = 0.176$), although a tendency towards older age was noted in the group with incarceration. In contrast, the duration of hospitalization was significantly longer in patients with incarceration ($p = 0.017$) (Table 3).

Tabela 3. Poređenje starosti i dužine hospitalizacije u odnosu na prisustvo inkarceracije

Table 3. Comparison of age and duration of hospitalization according to the presence of incarceration

Parametar / Parameter	Bez inkarceracije / Without incarceration (n = 193)	Sa inkarceracijom / With incarceration (n = 37)	p
Starost / Years of life	60 (18–88)	63 (31–88)	0.176
Dužina hospitalizacije / Duration of hospitalization	6 (0–18)	7 (4–20)	0.017

Tabela 4. Kliničke karakteristike povezane sa pojavom inkarceracije

Table 4. Clinical characteristics associated with the occurrence of incarceration

Varijable / Variables	Bez recidiva / Without recurrence n (%)	Sa recidivom / With recurrence n (%)	p
Pol / Sex			
Muški / Male	173 (87.8%)	24 (12.2%)	< 0.001
Ženski / Female	20 (60.6%)	13 (39.4%)	
Tip kile / Type of hernia			
Preponska / Groin	169 (85.8%)	28 (14.2%)	0.057
Ventralna / Ventral	24 (72.7%)	9 (27.3%)	
Operativna tehnika / Operative technique			
Lichtenstein/Bassini / Lichtenstein/Bassini	169 (87.6%)	24 (12.4%)	0.001
Lotheissen / Lotheissen	0 (0%)	4 (100%)	
Rives sublay/Mesh / Rives sublay / Mesh	24 (72.7%)	9 (27.3%)	
Anestezija / Anesthesia			
Lokalna / Local	116 (92.1%)	10 (7.9%)	0.001
Spinalna / Spinal	24 (72.7%)	9 (27.3%)	
GETA / GETA	53 (74.6%)	18 (25.4%)	
Komorbiditeti / Comorbidities			
Ne / No	110 (81.5%)	25 (18.5%)	0.232
Da / Yes	83 (87.4%)	12 (12.6%)	
Recidiv kile / Hernia recurrence			
Ne / No	182 (83.1%)	37 (16.9%)	0.137
Da / Yes	11 (100%)	0 (0%)	

GETA (opšta endotrahealna anestezija)

GETA (general endotracheal anesthesia)

Izbor operativne tehnike bio je statistički značajno povezan sa dužinom hospitalizacije ($p = 0,016$). Pacijenti lečeni Rives sublay tehnikom imali su duži boravak u bolnici, dok su pacijenti kod kojih su primenjene manje kompleksne procedure reparacije kile imali kraći boravak. Starost pacijenata nije se statistički značajno razlikovala između grupa prema operativnoj tehnici ($p = 0,865$), što ukazuje na uporedivu starosnu distribuciju (Tabela 5).

U analizi povezanosti operativne tehnike sa kliničkim ishodima i karakteristikama pacijenata utvrđeno je da operativna tehnika nije bila statistički značajno povezana sa pojavom recidiva ($p = 0,657$). Nasuprot tome, operativna tehnika bila je statistički značajno povezana sa inkarceracijom ($p < 0,001$), što ukazuje na različitu distribuciju hirurških procedura u zavisnosti od

A statistically significant association was established between several clinical and operative characteristics and the occurrence of incarceration. A higher frequency was recorded in women with femoral hernias, as well as in patients operated on with certain techniques and under general endotracheal anesthesia. In contrast, comorbidities and recidivism were not significantly associated with incarceration (Table 4).

The choice of operative technique was significantly associated with the duration of hospitalization ($p = 0.016$). Longer hospital stays were observed in patients treated using the Rives sublay technique, whereas shorter stays were recorded following less extensive hernia repair procedures. Patient age did not differ significantly between operative technique groups ($p = 0.865$), indicating a comparable age distribution (Table 5).

Tabela 5. Starost i dužina hospitalizacije u odnosu na operativnu tehniku

Table 5. Age and duration of hospitalization according to operative technique

Operativna tehnika / Operative technique, as±SD/ mean±SD	n = 230	Starost / Years of life	Dužina hospitalizacije / Duration of hospitalization
Lichtenstein/Bassini / Lichtenstein/Bassini	193	59.03 ± 14.80	6.81 ± 2.78
Lotheissen / Lotheissen	4	56.25 ± 14.19	5.00 ± 0.00
Rives sublay/Mesh / Rives sublay/Mesh	33	58.12 ± 15.04	8.88 ± 4.57
p-vrednost / p-value		0.865	0.016

prisustva inkarceracije. Operativna tehnika je takođe bila statistički značajno povezana sa vrstom anestezije ($p < 0,001$), pri čemu su složenije tehnike češće izvođene u opštoj endotrahealnoj anesteziji. Utvrđena je izuzetno snažna povezanost između operativne tehnike i tipa kile ($p < 0,001$), što ukazuje na to da je izbor operativne tehnike u velikoj meri zavisio od tipa kile. Pored toga, operativna tehnika bila je statistički značajno povezana sa prisustvom komorbiditeta ($p = 0,009$). Ovi nalazi ukazuju na to da operativna tehnika nije nezavisan faktor u analizi ishoda, već da je u velikoj meri određena kliničkim karakteristikama pacijenata i tipom kile.

U analizi starosti pacijenata u odnosu na tip kile nije utvrđena statistički značajna razlika između posmatranih grupa ($p = 0,913$). Srednji rangovi starosti bili su slični među različitim tipovima kila, što ukazuje na to da starost pacijenata nije bila povezana sa tipom kile. Nasuprot tome, u analizi dužine hospitalizacije prema tipu kile utvrđena je statistički značajna razlika između grupa ($p < 0,001$). Ventralne kile (191,04) i ingvinskrotalne kile (170,62) imale su najviše srednje rangove dužine hospitalizacije, što ukazuje na duži boravak u bolnici kod ovih pacijenata. Femoralne kile imale su najniži srednji rang (85,00), dok su ingvinalne i umbilikalne kile imale međuvrednosti. Ovi rezultati ukazuju na to da tip kile značajno utiče na dužinu hospitalizacije.

Tip kile bio je statistički značajno povezan sa većinom demografskih, kliničkih i operativnih karakteristika. Pol ($p < 0,001$) i operativna tehnika ($p < 0,001$) pokazali su snažnu povezanost, pri čemu su ingvinalne i ingvinskrotalne kile preovlađivale kod muškaraca, a femoralne i ventralne kile kod žena. Nije utvrđena povezanost sa recidivom ($p = 0,458$), dok je utvrđena statistički značajna povezanost sa inkarceracijom ($p < 0,001$), vrstom anestezije ($p < 0,001$) i komorbiditetima ($p = 0,017$). Ovi rezultati ukazuju na to da je tip kile važan faktor u kliničkom toku bolesti i izboru terapije.

Komorbiditeti su bili statistički značajno povezani sa većom starošću i dužim trajanjem hospitalizacije (Tabela 6).

Prisustvo komorbiditeta nije bilo statistički značajno povezano sa polom ($p = 0,888$), recidivom ($p = 0,110$), inkarceracijom ($p = 0,232$) niti vrstom anestezije ($p = 0,321$). Nasuprot tome, utvrđena je statistički značajna povezanost sa operativnom tehnikom

In the analysis of the association of the operative technique with clinical outcomes and patient characteristics, it was determined that the operative technique was not significantly associated with the occurrence of recurrence ($p = 0.657$). In contrast, a statistically significant association between the operative technique and the occurrence of incarceration was determined ($p < 0.001$), which indicates a different distribution of surgical procedures depending on the presence of incarceration. Also, the operative technique was significantly related to the type of anesthesia ($p < 0.001$), whereby more complex techniques were more often performed under general endotracheal anesthesia. An extremely strong correlation was found between the operative technique and the type of hernia ($p < 0.001$), which indicates that the choice of operative technique largely depended on the type of hernia. In addition, operative technique was significantly associated with the presence of comorbidities ($p = 0.009$). These findings indicate that the operative technique is not an independent factor in the outcome analysis but is strongly determined by the clinical characteristics of the patients and the type of hernia.

In the analysis of the age of the patients in relation to the type of hernia, no statistically significant difference was found between the observed groups ($p = 0.913$). The mean age ranks were similar among the different types of hernias, indicating that the age of the patients was not related to the type of hernia. In contrast, in the analysis of the duration of hospitalization according to the type of hernia, a statistically significant difference between the groups was determined ($p < 0.001$). The highest median ranking of hospitalization duration was recorded for ventral (191.04) and inguinoscrotal hernias (170.62), which indicates a longer hospital stay in these patients. The lowest mean rank was recorded for femoral hernias (85.00), while inguinal and umbilical hernias had medium values. These results indicate that the type of hernia significantly affects the duration of hospitalization.

Hernia type was significantly associated with most demographic, clinical, and operative characteristics. Gender ($p < 0.001$) and operative technique ($p < 0.001$) showed a strong association, with inguinal and inguinoscrotal hernias predominating in men and femoral and ventral hernias in women. No association was found with

Tabela 6. Starost i dužina hospitalizacije u odnosu na prisustvo komorbiditeta

Parametar / Parameter medijana (opseg) / median (range)	Bez komorbiditeta (n = 135) / Without comorbidities (n = 135)	Sa komorbiditetima (n = 95) / With comorbidities (n = 95)	p
Starost / Years of life	58 (18–78)	67 (29–88)	< 0,001
Dužina hospitalizacije / Duration of hospitalization	6 (0–20)	7 (4–20)	0.002

Table 6. Age and duration of hospitalization according to the presence of comorbidities

Tabela 7. Multivarijabilna logistička regresija prediktora inkarceracije

Varijable / Variables	OR	95% CI	p
Starija životna dob / Old age	1.035	1.000–1.071	0.047
Dužina hospitalizacije / Duration of hospitalization	1.090	0.945–1.258	0.235
Pol / Sex	0.488	0.122–1.958	0.312
Anestezija (lokalna) / Anesthesia (local)	0.315	0.106–0.936	0.038
Komorbiditeti / Comorbidities	3.073	1.119–8.440	0.029

($p = 0,006$) i tipom kile ($p = 0,007$), što ukazuje na to da komorbiditeti ne utiču direktno na ishode, već mogu delovati kao konfundirajući faktori u analizi.

Multivarijabilna logistička regresija pokazala je da je model statistički značajan. Starost i prisustvo komorbiditeta identifikovani su kao nezavisni prediktori inkarceracije, pri čemu su komorbiditeti povećavali verovatnoću njenog nastanka približno tri puta. Vrsta anestezije bila je granično statistički značajna (lokalna anestezija kao protektivni faktor), dok dužina hospitalizacije, pol, tip kile i operativna tehnika nisu imali nezavisn uticaj (Tabela 7).

DISKUSIJA

Ova studija usmerena je na ishode hirurškog lečenja kila procenjene tokom jednogodišnjeg perioda praćenja. Analizom jednogodišnjeg perioda, u našoj studiji identifikovani su značajni trendovi i prognostički faktori koji utiču na uspešnost operacija kila. U ovoj diskusiji razmatramo implikacije naših nalaza u kontekstu postojećih istraživanja i njihovu relevantnost za kliničku praksu.

Kriterijumi za uključivanje i isključivanje iz studije imaju ključnu ulogu u definisanju uzorka i obezbeđivanju pouzdanih rezultata. U studiju su uključeni pacijenti stariji od 18 godina koji su podvrgnuti operaciji kile. Pored toga, bilo je neophodno da pacijenti imaju kompletnu medicinsku dokumentaciju dostupnu za analizu. Sa druge strane, iz studije su isključeni pacijenti mlađi od 18 godina, kao i oni koji nisu podvrgnuti operaciji kile u definisanom periodu. Isključeni su i pacijenti sa teškim komorbidnim stanjima koja bi mogla značajno uticati na interpretaciju ishoda hirurškog lečenja. Ovi kriterijumi obezbedili su odgovarajuću reprezentativnost uzorka i validnost rezultata istraživanja.

Prilikom analize recidiva kile kod naših pacijenata, uočili smo da većina njih (95,2%) nakon operacije nije imala recidiv kile, dok je samo mali procenat (4,8%) imao recidiv. Iako recidiv kile i dalje predstavlja važnu postoperativnu komplikaciju, tehnike reparacije uz primenu mrežice značajno su smanjile stope recidiva u poređenju sa tradicionalnim reparacijama tkivom, što

Table 7. Multivariable logistic regression for predictors of incarceration

Varijable / Variables	OR	95% CI	p
Starija životna dob / Old age	1.035	1.000–1.071	0.047
Dužina hospitalizacije / Duration of hospitalization	1.090	0.945–1.258	0.235
Pol / Sex	0.488	0.122–1.958	0.312
Anestezija (lokalna) / Anesthesia (local)	0.315	0.106–0.936	0.038
Komorbiditeti / Comorbidities	3.073	1.119–8.440	0.029

relapse ($p = 0.458$), while a significant association with incarceration ($p < 0.001$), type of anesthesia ($p < 0.001$), and comorbidities ($p = 0.017$) was found. These results indicate that the type of hernia is an important factor in the clinical course and the choice of therapy.

The presence of comorbidities was significantly associated with older age and longer duration of hospitalization (Table 6).

The presence of comorbidities was not significantly related to gender ($p = 0.888$), recurrence ($p = 0.110$), incarceration ($p = 0.232$), or type of anesthesia ($p = 0.321$). In contrast, a significant association with operative technique ($p = 0.006$) and hernia type ($p = 0.007$) was found, indicating that comorbidities do not directly affect outcomes but may act as confounders in the analysis.

Multivariable logistic regression showed that the model was statistically significant. Age and the presence of comorbidities were identified as independent predictors of incarceration, with comorbidities increasing the probability of its occurrence by about three times. The type of anesthesia was marginally significant (local protective), while the duration of hospitalization, sex, type of hernia, and operative technique had no independent influence (Table 7).

DISCUSSION

The present study focuses on hernia surgery outcomes assessed during a one-year follow-up period. Analyzing a one-year period, our study identified significant trends and prognostic factors affecting the success of hernia operations. Throughout this discussion, we will consider the implications of our findings in the context of existing research, as well as their relevance to clinical practice.

Study inclusion and exclusion criteria play a key role in defining the sample and ensuring reliable results. To enter the study, patients older than 18 years who underwent hernia surgery were included. Also, it was necessary for the medical data of these patients to be complete and available for analysis. On the other hand, patients under the age of 18, those who did not undergo hernia surgery in the specified period, were excluded from the study. Patients with severe comorbid conditions that could significantly affect the inter-

je pokazano u međunarodnim smernicama i velikim kliničkim studijama [7]. U našoj studiji, kao i u istraživanju Rodriguesa i sar. [13], uočavamo da je stopa reoperacija značajno niža od očekivane. Pored toga, tokom perioda istraživanja, recidivne ingvinalne kile činile su 13,5% svih kila [14]. Ova promena u hirurškoj praksi značajno doprinosi smanjenju opterećenja za pacijente, smanjujući potrebu za ponovljenim operacijama i poboljšavajući kvalitet života. Uvođenje mrežice kao standardne metode u hirurgiji ingvinalnih kila predstavlja korak ka uspešnijim i dugotrajnijim rezultatima.

U analizi starosne strukture između muškaraca i žena uočili smo razliku u stepenu varijabilnosti, pri čemu su muškarci pokazali nešto veću varijabilnost u distribuciji starosti u poređenju sa ženama, što je u skladu sa rezultatima istraživanja koja su identifikovala muški pol i starost kao faktore rizika za nastanak ingvinalne kile [5,15,16]. Nadalje, Aydin i sar. navode veću učestalost muškaraca (90,7%) [17]. Ovo naglašava značaj uzimanja u obzir pola i starosne strukture prilikom procene rizika i planiranja lečenja pacijenata sa ingvinalnim kilama. Femoralne kile, koje su retke među kilama, podvrgavaju se različitim dobro ustanovljenim tehnikama i u urgentnim i u elektivnim uslovima [18]. Iako femoralne kile čine samo mali deo slučajeva kila, ingvinalne kile predstavljaju najčešći tip, sa udelom od 76,1% svih slučajeva. Nasuprot tome, prisustvo femoralne kile zabeleženo je u samo 2,2% slučajeva [18]. Važno je napomenuti da se femoralne kile često operišu kao urgentni slučajevi [19]. Ova razlika u učestalosti između ingvinalnih i femoralnih kila može odražavati razlike u etiologiji, kliničkoj prezentaciji i pristupu lečenju.

Operacija umbilikalne kile predstavlja često izvođen hirurški zahvat; međutim, tačna zastupljenost prema polu i starosti ovih operacija na nivou cele zemlje ostaje nepoznata [20]. U studiji Deo i sar., ingvinalna kila bila je najčešći tip (77,25%), dok je umbilikalna kila zauzimala drugo mesto (8,61%), što je u skladu sa našim nalazima [2]. Analiza rezultata pokazuje da nije utvrđena statistički značajna razlika između pacijenata sa i bez recidiva kile prema polu ($p = 0,164$). Zanimljivo je da je stopa recidiva kile u retrospektivnoj studiji umbilikalnih kila iznosila 3%, što je slično studiji ventralnih kila, u kojoj je stopa recidiva iznosila 10% [8,10]. Ovi rezultati naglašavaju značaj kontinuiranog praćenja nakon operacije kile radi pravovremenog otkrivanja postoperativnih komplikacija i recidiva.

Lečenje ventralnih kila nastavlja da se unapređuje kako bi odgovorilo na nove zahteve i tehnološke inovacije u hirurgiji [21]. Ovaj kontinuirani razvoj odražava posvećenost medicinske zajednice unapređenju lečenja ventralnih kila i ishoda kod pacijenata.

Dobijeni rezultati ukazuju na to da starost nije bila

pretation of surgical outcomes were excluded from the analysis. These criteria were set in order to ensure the adequate representativeness of the sample and the validity of the research results.

When analyzing hernia recurrence in our patients, we observed that most of them (95.2%) did not have recurrence of hernia after surgery, while only a small percentage (4.8%) had recurrence. Although hernia recurrence remains an important postoperative complication, the introduction of mesh-based repair techniques has substantially reduced recurrence rates compared with traditional tissue-based repairs, as demonstrated in international guidelines and large clinical studies [7]. In our study, as well as in the research of Rodrigues et al. [13], we note that the percentage of reoperations is significantly lower compared to the expected values. Additionally, during the study period, recurrent inguinal hernias accounted for 13.5% of all hernias [14]. This change in surgical practice brings significant relief to patients, reducing the need for repeat operations and improving their quality of life. The introduction of mesh as a standard procedure in inguinal hernia surgery represents a step forward in achieving more successful and long-lasting results.

In the analysis of the age structure between men and women, we note a difference in the level of variability, whereby men showed a slightly greater variability in age distribution compared to women, which is in accordance with the results of research that identified male gender and age as risk factors for the occurrence of inguinal hernia [5,15,16]. Furthermore, in the study by Aydin et al., a higher frequency of men (90.7%) was observed [17]. This highlights the importance of considering gender and age structure when assessing risk and planning treatment in patients with inguinal hernias. Femoral hernias, which are rare among hernias, undergo a variety of well-established techniques in both emergency and elective settings [18]. Although femoral hernias make up only a small part of hernial cases, inguinal hernias are the most common type, accounting for 76.1% of all cases, while the presence of femoral hernia was noted in only 2.2% of cases [18]. It is notable that femoral hernias are often operated on as an emergency [19]. This difference in frequency between inguinal and femoral hernias may indicate differences in the etiology, clinical presentation, and treatment approach of these conditions.

Umbilical hernia repair is a frequently performed surgical procedure; however, the exact gender and age prevalence of these surgeries across the country remains unknown [20]. In the study by Deo et al., inguinal hernia was identified as the most common type (77.25%), while umbilical hernia took the second place in terms of prevalence (8.61%), which coincides with

statistički značajno povezana sa pojavom inkarceracije, iako je kod ovih pacijenata uočena tendencija ka većoj starosti. Slični nalazi opisani su u novijim studijama, u kojima starost nije uvek identifikovana kao nezavisan faktor rizika za inkarceraciju, već pre kao indirektan pokazatelj opšteg zdravstvenog stanja i prisustva drugih faktora rizika [22]. Nasuprot tome, ova studija je pokazala statistički značajno duže trajanje hospitalizacije kod pacijenata sa inkarceracijom, što je u skladu sa prethodnim istraživanjima koja pokazuju da inkarcerirane kile imaju teži klinički tok, češće zahtevaju urgentne intervencije i povezane su sa većom učestalošću postoperativnih komplikacija, što produžava boravak u bolnici [23]. Statistički značajna povezanost ženskog pola i femoralnih kila sa inkarceracijom u ovoj analizi takođe je potvrđena u literaturi. Studije pokazuju da su ženski pol i femoralni tip kile nezavisni faktori rizika za inkarceraciju, verovatno zbog anatomske specifičnosti i kasnijeg ispoljavanja simptoma [22].

Kada je reč o recidivu, rezultati nisu pokazali značajnu povezanost sa ispitivanim faktorima, što je u skladu sa istraživanjima koja naglašavaju multifaktorijalnu prirodu recidiva. Faktori kao što su starost, BMI, infekcija rane i širina defekta češće se izdvajaju kao značajni, dok pojedinačne kliničke varijable često nemaju nezavisan uticaj [24]. Nadalje, statistički značajna povezanost između operativne tehnike i dužine hospitalizacije, kao i drugih kliničkih karakteristika, u ovoj studiji podržava stav da hirurška metoda nije nezavisan faktor, već da je određena tipom kile i stanjem pacijenta. Takođe je uočena statistički značajna povezanost između operativne tehnike i vrste anestezije. Složenije procedure češće su izvođene u opštoj endotrahealnoj anesteziji, što je očekivano imajući u vidu duže trajanje operacije, veću hiruršku složenost i potrebu za optimalnim intraoperativnim uslovima. Nasuprot tome, manje zahtevne procedure češće su izvođene u lokalnoj anesteziji, što odražava savremene trendove u hirurgiji kila i individualizovani perioperativni pristup. Velike prospektivne studije ukazuju na to da faktori kao što su veličina defekta i tip kile značajno utiču na klinički tok i izbor terapije [25]. Konačno, identifikovanje starosti i komorbiditeta kao nezavisnih prediktora inkarceracije u multivarijabilnoj analizi u skladu je sa savremenim shvatanjem da sistemski faktori povezani sa pacijentom (opšte stanje, hronične bolesti) imaju značajnu ulogu u progresiji bolesti, čak i kada pojedinačne kliničke varijable nisu značajne u univarijantnim analizama [22].

Ovo istraživanje ima nekoliko prednosti, ali i određena ograničenja koja zahtevaju pažljivo razmatranje. Među prednostima istraživanja ističe se longitudinalni pristup, koji je omogućio praćenje ishoda operacija kila. Ova analiza pruža dublje razumevanje trendova

the findings of our study [2]. Analysis of the results indicates that there is no statistically significant difference between the groups of patients with and without hernia recurrence when it comes to gender ($p = 0.164$). It is interesting that the rate of hernia recurrence in a retrospective study of umbilical hernias was 3%, which is similar to the finding in a study of ventral hernias where the rate was 10% [8,10]. These results highlight the importance of continuous follow-up after hernia surgery in order to detect postoperative complications and recurrences in a timely manner.

Ventral hernia treatment is constantly being improved to meet new demands and technological innovations in surgery [21]. This continued development reflects the commitment of the medical community to improve the treatment of ventral hernias and provide better patient outcomes.

The obtained results indicate that age was not statistically significantly associated with the occurrence of incarceration, although a tendency towards older age was observed in these patients. Similar findings have been described in recent studies, where age is not always identified as an independent risk factor for incarceration, but rather as an indirect indicator of general health status and the presence of other risk factors [22]. In contrast, this study found a significantly longer duration of hospitalization in patients with incarceration, which is consistent with previous research showing that incarcerated hernias have a more severe clinical course, require emergency interventions more often, and are associated with greater postoperative complications, which prolongs hospital stay [23]. The significant association between female gender and femoral hernias with incarceration in this analysis was also confirmed in the literature. Studies show that female gender and femoral type of hernia are independent risk factors for incarceration, probably due to anatomical specificities and later onset of symptoms [22].

Regarding relapse, the results did not show a significant association with the examined factors, which is in line with research that emphasizes the multifactorial nature of relapse. Factors such as age, BMI, wound infection, and defect width are more often singled out as significant, while individual clinical variables by themselves often have no independent influence [24]. Furthermore, the significant association of the operative technique with the duration of hospitalization and other clinical characteristics in this study confirms the view that the choice of surgical method is not an independent factor but is determined by the type of hernia and the condition of the patient. A significant association was also observed between the operative technique and the type of anesthesia. More complex procedures were more

i razvoja lečenja kila tokom vremena. Velika veličina uzorka takođe omogućava pouzdanu statističku analizu i daje mogućnost generalizacije rezultata na širu populaciju. Međutim, ograničenja uključuju potencijalne pristrasnosti prilikom retrospektivnog prikupljanja podataka i nemogućnost kontrole faktora koji bi mogli uticati na ishode hirurškog lečenja kila. Ograničena dostupnost detaljnih podataka o pacijentima ili faktorima rizika takođe može uticati na dubinu analize. Stoga, uprkos značajnim nalazima, ova ograničenja treba uzeti u obzir prilikom interpretacije rezultata i izvođenja zaključaka.

ZAKLJUČAK

Ova studija nije pokazala značajnu povezanost između ispitivanih faktora i recidiva kile, što podržava njegovu multifaktorijalnu prirodu. Inkarceracija je bila statistički značajno povezana sa tipom kile i nekoliko kliničkih i operativnih karakteristika, dok su se starija životna dob i prisustvo komorbiditeta pokazali kao nezavisni prediktori u multivariabilnoj analizi. Pacijenti sa inkarceracijom imali su statistički značajno duži boravak u bolnici. Operativna tehnika bila je prvenstveno određena tipom kile i karakteristikama pacijenta, a ne nezavisnim uticajem na ishode. Ovi nalazi odražavaju ishode hirurškog lečenja kila u hirurškoj bolnici koja funkcioniše u uslovima ograničenih zdravstvenih resursa i naglašavaju značaj individualizovanog pristupa zbrinjavanju pacijenata.

Sukob interesa: Nije prijavljen.

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frequently performed under general endotracheal anesthesia, which is expected given the longer operative time, greater surgical complexity, and the need for optimal intraoperative conditions. Conversely, less demanding procedures were more often performed under local anesthesia, reflecting contemporary trends in hernia surgery and individualized perioperative management. Large prospective studies indicate that factors such as the size of the defect and the type of hernia have a dominant influence on the clinical course and the choice of therapy [25]. Finally, the identification of age and comorbidity as independent predictors of incarceration in multivariable analysis is consistent with the modern concept that systemic factors of the patient (general condition, chronic diseases) play a significant role in disease progression, even when individual clinical variables do not show significance in univariate analyses [22].

This research has a number of positive aspects but also challenges that require careful consideration. Among the advantages of the research, the longitudinal approach stands out, enabling the monitoring of the outcome of hernia operations. This analysis provides a deeper understanding of the trends and evolution of hernia treatment over time. Also, data that includes a large number of patients enables reliable statistical analysis and generalization of results to the wider population. However, challenges include potential biases in retrospective data collection, as well as the lack of ability to control for factors that could influence the outcomes of hernia surgeries. Limitations in the availability of detailed patient or risk factor information may also affect the depth of analysis. Therefore, despite the valuable findings, it is important to consider these aspects when interpreting the results and drawing conclusions.

CONCLUSION

In this study, no significant association was found between the examined factors and hernia recurrence, supporting its multifactorial nature. Incarceration was significantly associated with hernia type and several clinical and operative characteristics, while older age and the presence of comorbidities emerged as independent predictors in multivariable analysis. Patients with incarceration had significantly longer hospital stays. The choice of operative technique was primarily determined by hernia type and patient characteristics rather than representing an independent determinant of outcome. These findings reflect hernia surgery outcomes in a surgical hospital operating in a resource-limited healthcare setting and emphasize the importance of individualized patient management.

Conflict of interest: None declared

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TELEDENTISTIKA U BOSNI I HERCEGOVINI: ANALIZA ZNANJA, STAVOVA I PRAKSE MEĐU STUDENTIMA STOMATOLOGIJE, STOMATOLOZIMA I NASTAVNIM KADROM NA STOMATOLOŠKIM FAKULTETIMA ZASNOVANA NA UPITNIKU

ORIGINALNI RAD

ORIGINAL ARTICLE

TELEDENTISTRY IN BOSNIA AND HERZEGOVINA: A QUESTIONNAIRE-BASED ANALYSIS OF KNOWLEDGE, ATTITUDES AND PRACTICES AMONG DENTAL STUDENTS, DENTISTS AND ACADEMIC STAFF AT DENTAL FACULTIES

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SAŽETAK

Uvod/Cilj: Svetska zdravstvena organizacija nastoji da poboljša kvalitet zdravstvene zaštite kroz digitalnu transformaciju. U Bosni i Hercegovini nema dovoljno informacija o znanju, stavovima i praksi studenata stomatologije, stomatologa i nastavnog kadra na stomatološkim fakultetima u vezi sa telemedicinom. Cilj ove studije je da se procene nivo znanja, stavovi i praksa u kontekstu implementacije telemedicine.

Materijali i metode: Sprovedena je „onlajn“ anketa između aprila i juna 2025. godine među stomatolozima, studentima stomatologije i nastavnim kadrom na stomatološkim fakultetima širom Bosne i Hercegovine. Upitnik je sadržavao pitanja o znanju, stavovima i praksama povezanim sa teledentistikom.

Rezultati: Anketu je popunio ukupno 181 ispitanik, od kojih su 54,1% činili stomatolozi, 38,1% studenti stomatologije i 7,7% nastavni kadar na stomatološkim fakultetima širom Bosne i Hercegovine. Većina (89,5%) ispitanika nije bila upoznata s propisima koji regulišu telemedicinu. Oko 43% ispitanika je čulo za teledentistiku, dok je 96% ispitanika navelo da nema dovoljno znanja o teledentistici i izrazilo želju za formalnijim obrazovanjem iz ove oblasti. Među stomatolozima, 75% je izrazilo spremnost za pružanje određenih teledentističkih usluga u svojoj praksi.

Zaključak: Stomatolozi u Bosni i Hercegovini trenutno imaju ograničeno znanje i praktične veštine u području teledentistike, ali pokazuju pozitivne stavove prema njenoj primeni. Rezultati ukazuju na potrebu da studenti stomatologije, stomatolozi i nastavni kadar u BiH unaprede kompetencije iz oblasti teledentistike kroz kontinuirano stručno usavršavanje. Uspješna implementacija zahteva odgovarajuću digitalnu infrastrukturu, institucionalnu podršku i regulatorne okvire, kao i integraciju teledentistike u obrazovanje kroz mikrokvalifikacione programe.

Ključne reči: teledentistika, telemedicina, stomatolozi, studenti stomatologije

ABSTRACT

Introduction/Objective: The World Health Organization strives to improve the quality of healthcare through digital transformation. In Bosnia and Herzegovina, there is insufficient information about the knowledge, attitudes, and practices of dental students, dentists, and teaching staff at dental faculties in relation to telemedicine. The aim of this study was to assess the level of knowledge, attitudes, and practices in the context of telemedicine implementation.

Materials and methods: An online survey was conducted between April and June 2025 among dentists, dental students, and teaching staff at dental faculties across Bosnia and Herzegovina. The questionnaire included questions about knowledge, attitudes, and practices related to teledentistry.

Results: The survey was completed by a total of 181 respondents, of whom 54.1% were dentists, 38.1% were dental students, and 7.7% were teaching staff at dental faculties throughout Bosnia and Herzegovina. The majority of respondents (89.5%) were unaware of the regulations governing telemedicine. About 43% of respondents had heard of teledentistry, while 96% of respondents stated that they do not have enough knowledge about teledentistry and expressed a desire for a more formal education in this field. Among dentists, 75% expressed a willingness to provide certain teledentistry services in their practice.

Conclusion: Dentists in Bosnia and Herzegovina currently have limited knowledge and practical skills in the field of teledentistry, but they show positive attitudes towards its application. The results indicate the need for dental students, dentists, and teaching staff in BiH to improve competencies in the field of teledentistry through continuous professional development. Successful implementation requires adequate digital infrastructure, institutional support and regulatory frameworks, as well as the integration of teledentistry into education through micro-credential programs.

Keywords: teledentistry, telemedicine, dentists, dental students

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UVOD

Svetska zdravstvena organizacija (SZO) definiše telemedicinu kao primenu informacionih i komunikacionih tehnologija u razmeni validnih informacija u cilju dijagnostikovanja, lečenja i prevencije bolesti i povreda, istraživanja i evaluacije, kao i kontinuirane edukacije zdravstvenih radnika, a sve u interesu unapređenja zdravlja pojedinaca i njihovih zajednica. Teledentistika je oblast telemedicine, danas poznata i kao virtuelna stomatološka konsultacija, koja predstavlja inovativni pristup stomatološkoj zdravstvenoj zaštiti usmeren na povećanje dostupnosti stomatoloških usluga [1].

Teledentistika podrazumeva pružanje stomatoloških usluga putem informacionih i komunikacionih tehnologija, pri čemu se pružalac i korisnik zdravstvene zaštite nalaze na različitim mestima. Ovaj model smanjuje nejednakosti u pristupu stomatološkoj zdravstvenoj zaštiti, naročito kod starijih osoba, zatvorenika i stanovništva u udaljenim ruralnim područjima, dok dodatne prednosti uključuju smanjenje troškova i unapređenje kvaliteta stomatološke zdravstvene zaštite [2]. Pomoću teledentistike, stomatolozi mogu da pružaju savete, obavljaju trijažu, postavljaju preliminarne dijagnoze i edukuju pacijente putem različitih digitalnih komunikacionih kanala, uključujući pametne telefone, video-pozive i platforme društvenih mreža [3]. Pandemija bolesti KOVID-19 bila je značajan pokretač razvoja teledentistike. Tokom pandemije, zdravstveni sistemi su bili pod velikim pritiskom, dok je rizik od infekcije u stomatološkim ustanovama bio povećan [4]. U tom periodu, teledentistika je postala sve značajniji alat za praćenje pacijenata, davanje saveta i zbrinjavanje hitnih stomatoloških stanja, naročito kada je direktan kontakt bio ograničen [3,5].

Pružanje zdravstvene zaštite na daljinu uz podršku informacionih i komunikacionih tehnologija obuhvata različite modalitete, kao što su mobilno zdravstvo, elektronski zdravstveni kartoni, teleedukacija, telepraćenje, teledijagnostika, telekonsultacije i digitalna promocija oralnog zdravlja. Posebno se ističe i tzv. „gejmifikacija“, koja koristi elemente igara za menjanje zdravstvenih ponašanja i može se primenjivati na različitim digitalnim platformama [2]. U zavisnosti od vremenskog okvira prenosa informacija, teledentistika se deli na konsultacije u realnom vremenu, model „store-and-forward“ i komunikaciju u približno realnom vremenu [6]. U odnosu na oblast primene, razvijene su poddiscipline kao što su teleprotetička stomatologija, teleparodontologija, teleortodontija, teleoralna hirurgija i telepedodontologija [2].

Prednosti teledentistike uključuju rano otkrivanje i pravovremeno lečenje bolesti usta i zuba, bolju dostupnost zdravstvenih usluga i smanjenje profesionalne izolacije putem komunikacije i konsultacija sa kolega-

INTRODUCTION

The World Health Organization (WHO) defines telemedicine as the use of information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and continuing education of healthcare providers, all in the interest of advancing the health of individuals and their communities. Teledentistry is a field within telemedicine, today also known as virtual dental consultation, which represents an innovative approach to dental care aimed at increasing the accessibility of dental services [1].

Teledentistry refers to the provision of dental services through the use of information and communication technologies, where the provider and the recipient of care are located in different places. This model reduces inequalities in access to dental care, particularly for elderly individuals, prisoners, and populations in remote rural areas, while additional benefits include reduced costs and improved quality of dental care [2]. Through teledentistry, dentists can provide advice, perform triage, establish provisional diagnoses, and educate patients via various digital communication channels, including smartphones, video calls, and social media platforms [3]. The COVID-19 pandemic was a significant driver of teledentistry development. During the pandemic, healthcare systems were under substantial pressure, while the risk of infection in dental settings increased [4]. During this period, teledentistry became an increasingly important tool for monitoring patients, providing advice, and managing emergency dental conditions, particularly when direct contact was limited [3,5].

Remote healthcare delivery supported by information and communication technologies includes various modalities such as mobile health, electronic health records, tele-education, telemonitoring, telediagnos- tics, teleconsultations, and digital oral health promotion. Gamification is also highlighted, as it uses game elements to modify health behaviors and can be applied across different digital platforms [2]. Depending on the time frame of information transfer, teledentistry is divided into real-time consultations, the “store-and-forward” model, and near real-time communication [6]. In relation to the field of application, subdisciplines such as teleprosthodontics, teleperiodontology, teleorthodontics, teleoral surgery, and telepedodontics have been developed [2].

The advantages of teledentistry include early detection and timely treatment of oral diseases, improved access to healthcare services, and reduced professional isolation through communication and consultation with colleagues and specialists, which contributes to

ma i specijalistima, što doprinosi unapređenju kvaliteta zdravstvene zaštite pacijenata, uz istovremeno smanjenje lista čekanja i jačanje interdisciplinarnе saradnje [4]. Pacijenti generalno navode da su zadovoljni ovim oblikom zdravstvene zaštite, a pojedine studije ukazuju na pozitivnu korelaciju u poređenju sa tradicionalnim stomatološkim pregledom licem u lice [7]. Primena teledentistike naročito dolazi do izražaja kod trijaže pacijenata, pri konsultacijama i u edukaciji [8].

Mobilna tehnologija dodatno unapređuje dostupnost stomatološke zdravstvene zaštite, uz istovremeno smanjenje vremenskih i finansijskih troškova. Sistematski pregledi literature ukazuju na to da teledentistika doprinosi smanjenju indeksa dentalnog plaka, gingivalnog indeksa i učestalosti lezija bele mrlje. Nadalje, rezultati randomizovanih kontrolisanih studija pokazuju da intervencije sprovedene putem servisa za razmenu poruka na društvenim mrežama, uključujući nedeljne edukativne infografike, video-sadržaje i poruke podrške, imaju pozitivan efekat na ponašanja dece i roditelja u vezi sa oralnim zdravljem [9].

Dodatni dokazi potiču iz jedne studije sprovedene u vojnoj stomatološkoj ustanovi, koja je potvrdila da teledentistika može da predstavlja pouzdan alat za postavljanje dijagnoza i unapređenje stomatološke zdravstvene zaštite, u poređenju sa konvencionalnim kliničkim pregledima [1]. Dosadašnja literatura dodatno podržava teledentistiku kao efikasan alat za prevenciju bolesti, promociju oralnog zdravlja, dijagnostikovanje i rano otkrivanje karijesa [3]. Teledentistika obuhvata daljinski stomatološki skrining zasnovan na fotografskim podacima, koji predstavlja jednostavan i efikasan alat za rano otkrivanje bolesti usta i zuba [10].

Pandemija bolesti KOVID-19 je pokazala da teledentistika nije samo privremeno rešenje, već važna komponenta savremene stomatološke prakse [11]. Njena relevantnost potvrđena je u različitim zdravstvenim sistemima, uključujući sisteme u Australiji, Kanadi i Saudijskoj Arabiji [12]. Međutim, efikasna primena teledentistike u stomatološkoj praksi zavisi od odgovarajućeg znanja i obuke stomatoloških zdravstvenih radnika [3]. Stoga se naglašava da obrazovanje o teledentistici treba integrisati u planove i programe nastave na osnovnim studijama stomatologije kako bi se obezbedila njena pravilna i široko rasprostranjena primena u kliničkoj praksi [7].

S druge strane, primena teledentistike izaziva zabrinutost u pogledu zakonske regulative, licenci, zaštite podataka i integracije u rutinske kliničke tokove rada [2,5]. Identifikovane su i brojne prepreke, uključujući nedostatak poverenja među pacijentima i pružaocima zdravstvenih usluga, nedovoljnu digitalnu pismenost i zabrinutost u pogledu isplativosti. Potrebna su dalja

improved quality of patient care, while simultaneously reducing waiting lists and strengthening interdisciplinary collaboration [4]. Patients generally report satisfaction with this form of care, and some studies indicate a positive correlation compared to the traditional face-to-face dentist examination [7]. The applications of teledentistry are particularly evident in patient triage, consultations, and education [8].

Mobile technology further enhances access to dental care while reducing time and financial costs. Systematic literature reviews indicate that teledentistry contributes to reductions in the dental plaque index, gingival index, and the incidence of white spot lesions. Furthermore, results from randomized controlled trials (RCTs) demonstrate that interventions delivered via social media messaging services, including weekly educational infographics, video content, and supportive messages, have a positive effect on the oral health behaviors of children and parents [9].

Additional evidence comes from a study conducted in a military dental institution, which confirmed that teledentistry can be a reliable tool for establishing diagnoses and improving dental care, as compared to conventional clinical examinations [1]. Current literature further supports teledentistry as an effective tool for prevention, oral health promotion, diagnosis, and early detection of caries [3]. Teledentistry includes remote dental screening based on photographic data, which represents a simple and effective tool for early detection of oral diseases [10].

The COVID-19 pandemic demonstrated that teledentistry is not merely a temporary solution, but an important component of modern dental practice [11]. Its relevance has been confirmed in various healthcare systems, including Australia, Canada, and Saudi Arabia [12]. However, effective implementation of teledentistry in dental practice depends on adequate knowledge and training of dental professionals [3]. Therefore, it is emphasized that education on teledentistry should be integrated into undergraduate dental curricula to ensure its proper and widespread application in clinical practice [7].

On the other hand, the implementation of teledentistry raises concerns regarding legal regulations, licensing, data protection, and integration into routine clinical workflows [2,5]. Numerous barriers have also been identified, including lack of trust among patients and providers, insufficient digital literacy, and concerns regarding cost-effectiveness. Further research is needed on clinical implementation, policy evaluation, economic benefits, as well as data security and confidentiality [2]. Most studies on dentists' knowledge, attitudes, and skills regarding teledentistry have been

istraživanja kliničke primene, evaluacije politika, ekonomskih koristi, kao i bezbednosti i poverljivosti podataka [2]. Većina studija o znanju, stavovima i veštinama stomatologa u vezi sa teledentistikom sprovedena je u razvijenim zemljama, dok su podaci iz zemalja u razvoju ograničeni ili ne postoje [13].

Ova studija predstavlja prvu analizu znanja, stavova i prakse studenata stomatologije, stomatologa i nastavnog kadra u vezi sa teledentistikom u Bosni i Hercegovini, čime doprinosi boljem razumevanju njihove spremnosti za primenu digitalnih rešenja u zdravstvenoj zaštiti.

Zdravstveni sistem u Bosni i Hercegovini predstavlja dodatni kontekstualni izazov za primenu teledentistike. Naime, složena organizacija zdravstvenog sistema, podeljenog na dva entiteta i jedan distrikt, otežava ujednačenu primenu zdravstvenih politika i digitalnih rešenja. Pored toga, nejednak pristup zdravstvenoj zaštiti posebno je izražen u udaljenim ruralnim područjima, migrantskim kampovima, kazнено-popravnim ustanovama, kao i među starijim i ranjivim populacijama. Iako se elektronska komunikacija i konsultacije putem elektronske pošte i društvenih medija već koriste u praksi, nedostatak sistematskog pristupa, nedovoljno znanje i neadekvatan pravni okvir ograničavaju širu primenu teledentistike.

Iz navedenih razloga, cilj ove studije je da proceni znanje, stavove i praksu u vezi sa teledentistikom među studentima stomatologije, stomatolozima i nastavnim kadrom u Bosni i Hercegovini, kao i njihovu spremnost za prihvatanje digitalnih rešenja. Cilj studije jeste i da identifikuje ključne prepreke i mogućnosti za unapređenje edukacije o teledentistici, njenog prihvatanja i primene u okviru zdravstvenog sistema Bosne i Hercegovine.

MATERIJALI I METODE

Za prikupljanje podataka u ovoj studiji preseka korišćen je elektronski upitnik, koji je distribuiran putem zvaničnih internet stranica Komore doktora stomatologije Republike Srpske i Stomatološke komore Federacije Bosne i Hercegovine, kao i putem elektronske pošte i različitih platformi društvenih mreža (*WhatsApp*®, *Facebook*®, *Instagram*® i *LinkedIn*®). Pre distribucije upitnika, studenti stomatologije, stomatolozi i nastavni kadar su zamoljeni da daju informisani pristanak za dobrovoljno učešće u studiji. Studiju je odobrio Etički komitet Sarajevske škole za nauku i tehnologiju (br. SMS-180125, 18. februar 2025. godine). Za procenu znanja, stavova i prakse u vezi sa teledentistikom među studentima stomatologije, stomatolozima i nastavnim kadrom korišćen je prethodno validiran upitnik. Upitnik je prethodno korišćen u sličnoj studiji sprovedenoj u Francuskoj, čiji su originalni autori odobrili njegovu primenu [14].

conducted in developed countries, while data from developing countries remain limited or non-existent [13].

This study provides the first analysis of the knowledge, attitudes, and practices of dental students, dentists, and academic staff regarding teledentistry in Bosnia and Herzegovina, contributing to a better understanding of their readiness for the implementation of digital healthcare solutions.

The healthcare system in Bosnia and Herzegovina represents an additional contextual challenge for the implementation of teledentistry. Specifically, the complex organization of the healthcare system, divided into two entities and a district, hinders the uniform implementation of health policies and digital solutions. Furthermore, unequal access to healthcare is particularly pronounced in remote rural areas, migrant camps, correctional institutions, and among elderly and vulnerable populations. Although electronic communication and consultations via e-mail and social media are already used in practice, the lack of a systematic approach, insufficient knowledge, and an inadequate legal framework limit wider implementation of teledentistry.

For these reasons, this study aims to assess knowledge, attitudes, and practices regarding teledentistry among dental students, dentists, and academic staff in Bosnia and Herzegovina, as well as their readiness to adopt digital solutions. The study also aims to identify key barriers and opportunities for improving teledentistry education, acceptance, and implementation within Bosnia and Herzegovina's healthcare system.

MATERIALS AND METHODS

To collect data for this cross-sectional study, an electronic questionnaire was employed and disseminated via the official websites of both the Republic of Srpska Chamber of Doctors in Dentistry and the Dental Chamber of the Federation of Bosnia and Herzegovina, as well as via email and various social media platforms (*WhatsApp*®, *Facebook*®, *Instagram*®, and *LinkedIn*®). Before distributing the questionnaire, dental students, dentists, and academic staff were asked to provide informed consent to participate voluntarily in the study. The study was approved by the Ethics Committee of the Sarajevo School of Science and Technology (No. SMS-180125, February 18, 2025). A previously validated questionnaire was used to assess knowledge, attitudes, and practices regarding teledentistry among dental students, dentists, and academic staff. The questionnaire had previously been used in a similar French study, whose original authors approved its application [14].

The questionnaire was adapted to the local language and health environment in Bosnia and Herze-

Upitnik je prilagođen lokalnom jeziku i zdravstvenom okruženju u Bosni i Hercegovini, uz očuvanje originalne validirane strukture. Upitnik se sastojao od tri segmenta: procene znanja, stavova i prakse u vezi sa teledentistikom. U studiji je primenjen metod prigodnog uzorkovanja. Učešće je bilo u potpunosti dobrovoljno, a konačni uzorak činili su svi studenti stomatologije, stomatolozi i nastavnici koji su ispunjavali kriterijume za učešće i koji su popunili upitnik tokom perioda istraživanja. Veličina uzorka je stoga bila određena brojem ispitanika koji su ispunjavali kriterijume za učešće i dobrovoljno odgovorili na anketu.

Statističke analize sprovedene su korišćenjem softvera SPSS 23 (Armonk, NY: IBM Corp.). Rezultati anketnog upitnika prikazani su kao apsolutne i relativne učestalosti, dok je za poređenje podataka korišćen Fišerov egzaktni test. Kruskal–Wallisov test primenjen je za poređenje rednih odgovora na tvrdnje (merenih na petostepenoj Likertovoj skali, od 1 = „u potpunosti se slažem“ do 5 = „uopšte se ne slažem“) između tri podgrupe (studenata, stomatologa i nastavnog kadra). Post hoc parna poređenja statistički značajnih razlika sprovedena su korišćenjem Man–Vitnijevog U testa uz Bonferronijevu korekciju za višestruka poređenja, pri čemu je nivo statističke značajnosti postavljen na $p < 0,0167$ ($\alpha = 0,05/3$). Man–Vitnijev U test je takođe korišćen za poređenje rednih odgovora na određene tvrdnje između dve grupe: doktora i nastavnika koji su primenjivali teledentistiku i onih koji je nisu primenjivali. Nivo statističke značajnosti za sva merenja bio je postavljen na $p < 0,05$. Za prikaz podataka korišćen je Microsoft Excel 2010.

REZULTATI

U anketi je učestvovao ukupno 181 ispitanik. Učestvovala su i žene ($n = 115$; 63,5%) i muškarci ($n = 66$; 36,5%). Najveći broj ispitanika činili su stomatolozi ($n = 98$; 54,1%) i studenti stomatologije ($n = 69$; 38,1%). Nešto više od polovine ispitanika bilo je starosti između 31 i 60 godina (Tabela 1). Žene su bile zastupljenije u svim kategorijama ispitanika prema zanimanju. U grupi studenata stomatologije, približno 70% ($n = 48$) su činile žene; u grupi stomatologa, 59,2% ($n = 58$) su bile žene; a u grupi nastavnika/saradnika na stomatološkim fakultetima 64,3% ($n = 9$) su bile žene (Tabela 2). Više od polovine ispitanika u grupi studenata je bilo starosti od 20 do 25 godina (76,8%), dok je 81% stomatologa bilo starosti između 31 i 60 godina. Približno 71% nastavnika/saradnika na stomatološkim fakultetima je bilo starosti između 46 i 60 godina.

Znanje

Najveći broj ispitanika ($n = 85$; 47%) smatrao je da je telemedicina oblast primene e-zdravstva, dok je pri-

govina while preserving the original validated structure. The questionnaire consisted of three segments: assessment of knowledge, attitudes, and practices regarding teledentistry. The study used a non-probability convenience sampling method. Participation was entirely voluntary, and the final sample consisted of all eligible dental students, dentists, and academic staff who completed the questionnaire during the study period. The sample size was, therefore, determined by the number of eligible participants who voluntarily responded to the survey.

Statistical analyses were performed using SPSS 23 software (Armonk, NY: IBM Corp.). The results of the survey questionnaire are presented in absolute and relative frequencies, while Fisher's exact test was used to compare the data. The Kruskal–Wallis test was applied for comparing ordinal responses to the statements (measured on a five-point Likert scale ranging from 1 = "I completely agree" to 5 = "I completely disagree") across the three subgroups (students, dentists, and academic staff). Post hoc pairwise comparisons of statistically significant differences were performed using the Mann–Whitney U test with Bonferroni correction for multiple comparisons, with the level of statistical significance set at $p < 0.0167$ ($\alpha = 0.05/3$). The Mann–Whitney U test was also used for comparing the ordinal responses to the statements of two groups, doctors and academic staff who practiced teledentistry and those who did not. The significance level for all measurements was set at $p < 0.05$. Microsoft Excel 2010 was used to display data.

RESULTS

A total of 181 respondents completed the survey, including women ($n = 115$; 63.5%) and men ($n = 66$; 36.5%). The majority of respondents were dentists ($n = 98$; 54.1%) and dental students ($n = 69$; 38.1%). Slightly more than half of the respondents were between 31 and 60 years of age (Table 1). Women were more represented across respondent occupations. In the group of dental students, approximately 70% ($n=48$) were women; in the group of dentists, 59.2% ($n = 58$) were women; and in the group of academic staff /associates at dental universities 64.3% ($n = 9$) were women (Table 2). More than half of the respondents in the group of students were 20–25 years old (76.8%), while 81% of dentists were between 31 and 60 years old. Approximately 71% of academic staff /associates at dental universities were between 46 and 60 years of age.

Knowledge

The largest number of respondents ($n = 85$; 47%) considered telemedicine to be an area of application of

Tabela 1. Sociodemografske karakteristike ispitanika

	Ukupno / Total (N = 181)	
	n	%
Pol / Gender		
Muški / Male	66	36.5 %
Ženski / Female	115	63.5 %
Starosno doba (godine) / Age group (years)		
<20	3	1.7 %
20-25	53	29.3 %
26-30	28	15.5 %
31-45	56	30.9 %
46-60	37	20.4 %
>60	4	2.2 %
Zanimanje / Profession		
Student stomatologije / Student of dentistry	69	38.1 %
Doktor stomatologije / Dentist	98	54.1 %
Nastavnik/saradnik na stomatološkom fakultetu / Academic staff	14	7.7 %
Fakultet* / Faculty*		
Univerzitet u Sarajevu / University of Sarajevo	37	20.4 %
Univerzitet u Banjoj Luci / University of Banja Luka	56	30.9 %
Univerzitet u Istočnom Sarajevu / University of East Sarajevo	29	16.0 %
Sveučilište u Mostaru / University of Mostar	14	7.7 %
Internacionalni univerzitet u Sarajevu / International University of Sarajevo	1	0.6 %
Sarajevska škola za nauku i tehnologiju / Sarajevo School of Science and Technology	10	5.5 %
Univerzitet u Travniku / University of Travnik	7	3.9 %
Drugo / Other	27	14.9 %

* Fakultet koji pohađaju (studenti) ili koji su pohađali (doktori i nastavnici/suradnici)

Table 1. Sociodemographic characteristics of respondents

*Faculty they are attending (students) or have attended (doctors and academic staff)

bližno 34% ($n = 62$) smatralo da je e-zdravstvo oblast primene telemedicine (Slika 1). Manji broj ispitanika smatrao je da su obe tvrdnje tačne, dok je samo 1% ($n = 2$) ispitanika odabrao odgovor da su obe tvrdnje tačne uz tvrdnju da su telemedicina i e-zdravstvo sinonimi (sve tvrdnje su tačne).

Jednaki broj ispitanika (16%; $n = 29$) je smatrao da telekonsultacije i medicinska pomoć na daljinu predstavljaju oblasti telemedicine u praksi. Ukupno 13% ($n = 23$) ispitanika smatralo je da, pored navedenog, te-

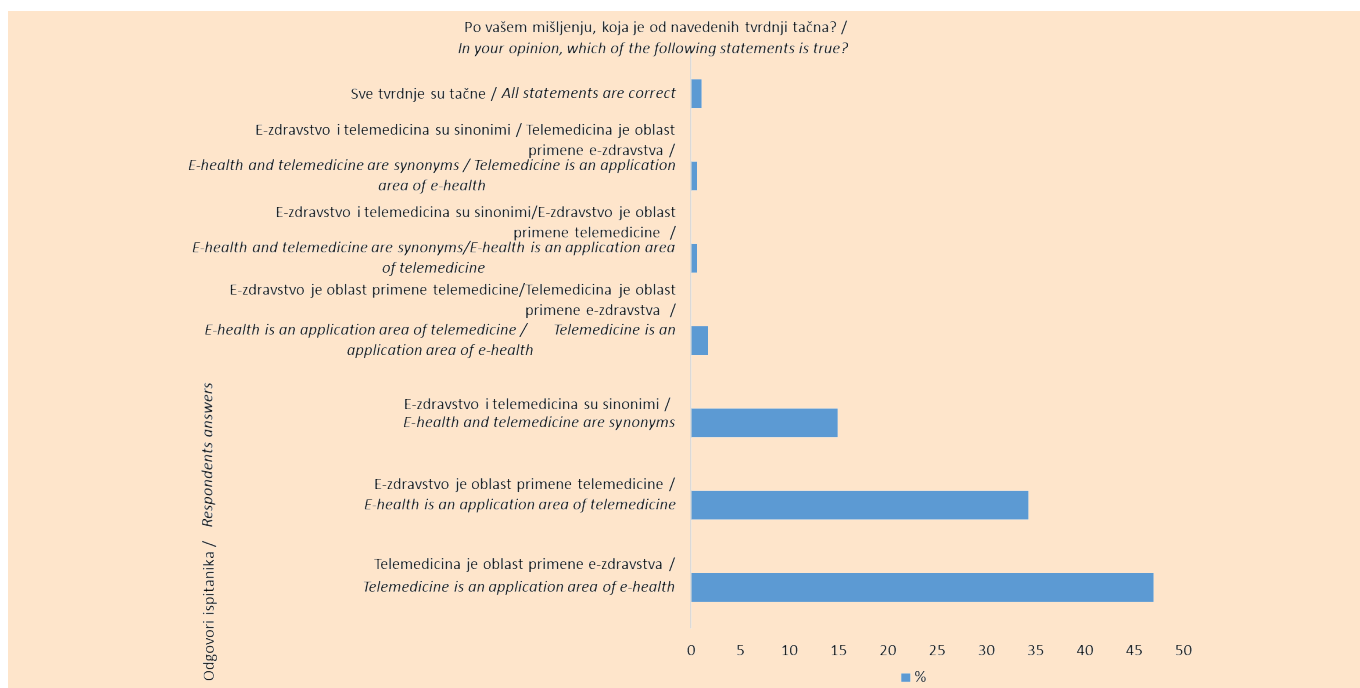
e-health, while approximately 34% ($n = 62$) believed that e-health is an area of application of telemedicine (Figure 1). A smaller number of respondents held the opinion that both statements are correct, while only 1% ($n = 2$) of respondents selected the opinion that both statements are correct along with the statement that telemedicine and e-health are synonyms (all statements are correct).

An equal number of respondents (16%; $n = 29$) considered teleconsultations and remote medical assistance to be areas of telemedicine in practice. A to-

Tabela 2. Odgovori u odnosu na razlike među polovima, prema zanimanju

Zanimanje / Profession	n	Muškarci / Male (n)	%	Žene / Female (n)	%
Student stomatologije / Student of dentistry	69	21	30%	48	70%
Doktor stomatologije / Dentist	98	40	40.81 %	58	59.2%
Nastavnik/saradnik na stomatološkom fakultetu / Academic staff	14	5	35.71 %	9	64.3 %

Table 2. Responses in relation to gender differences among professions

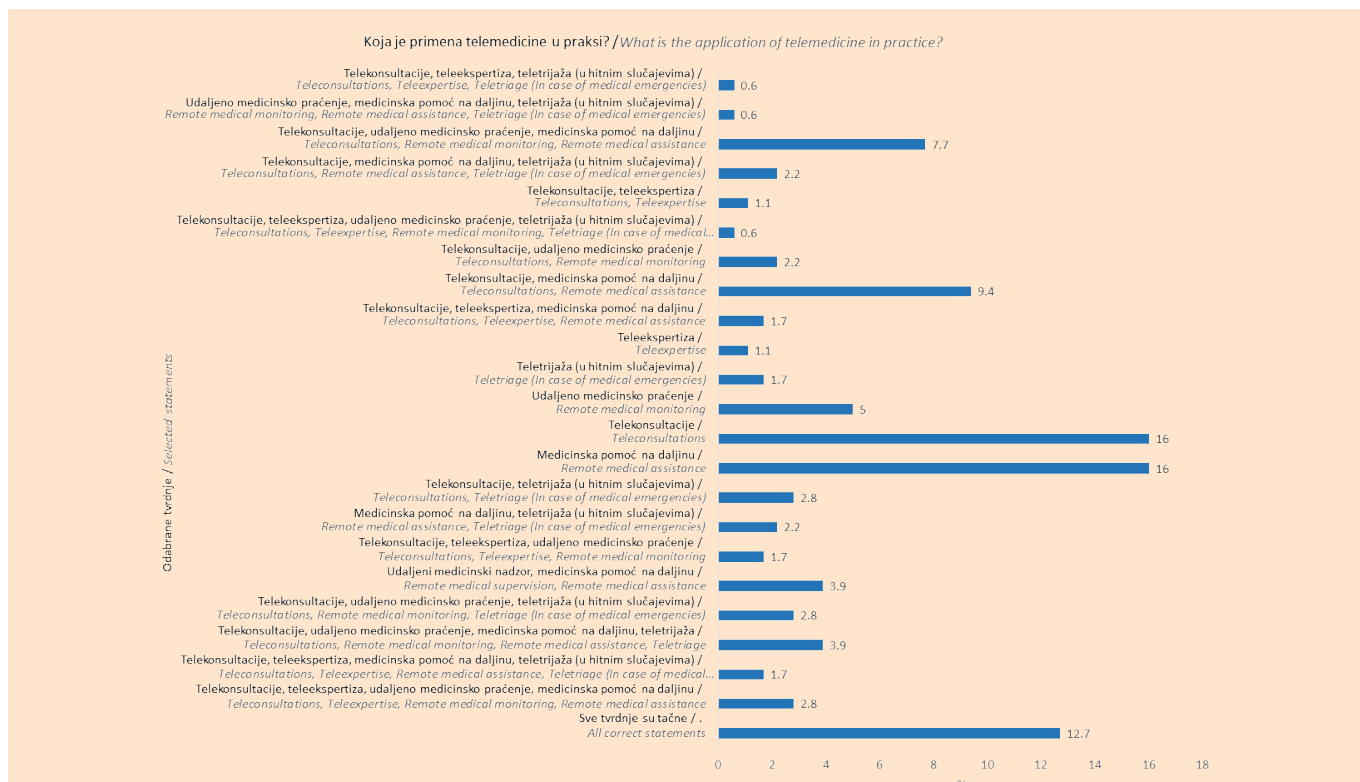


Slika 1. Respondents' attitudes towards the application of telemedicine and e-health

leekspertiza, daljinsko medicinsko praćenje i teletrižaža (u slučajevima hitnih medicinskih stanja) takođe predstavljaju sastavne delove telemedicines u praksi. Samo mali broj ispitanika odabrao je jednu ili najviše tri tačne tvrdnje (Slika 2).

Figure 1. PRISMA diagram of selected articles included in the analysis of the application of statistical methods in neurological research.

tal of 13% ($n = 23$) of the respondents believed that, in addition to the aforementioned, tele-expertise, remote medical monitoring, and tele-triage (in cases of medical emergencies) are also integral parts of telemedicine in practice. Only a small number of respondents selected one or up to three correct statements (Figure 2).



Slika 2. Stavovi ispitanika prema primeni telemedicines u praksi

Figure 2. Respondents' attitudes towards the application of telemedicine in practice

Velika većina ispitanika (89,5%) nije bila upoznata sa propisima koji regulišu telemedicinu u Bosni i Hercegovini. Oko 43% ispitanika je čulo za teledentistiku, dok je oko 35% čulo za neku od aktivnosti koje se primenjuju u teledentistici. Približno 20% njih upoznalo se sa tim aktivnostima putem internet stranica, oko 18% putem članaka, 17% na konferencijama, dok je oko 32% navelo druge izvore informacija. Kada je reč o aktivnostima o kojima su se informisali putem ovih izvora, najveći broj ispitanika je odabrao telekonsultacije (34%) i medicinsku pomoć na daljinu.

Samo 7% ispitanika je steklo znanje o teledentistici tokom formalnog obrazovanja, uglavnom u okviru izbornog predmeta (53%) ili tokom stažiranja (29,4%). Takođe, oko 96% ispitanika je smatralo da nema dovoljno znanja o teledentistici, dok je 86,2% izrazilo želju za dodatnim formalnim obrazovanjem ili obukom na ovu temu. Kao najpoželjniji oblici dodatnog obrazovanja su navedene konferencije (27,5%), onlajn nastava (34,6%) i kursevi (25%).

Nije utvrđena statistički značajna razlika u odgovorima na pitanja kojima je procenjavano znanje o teledentistici između studenata stomatologije, stomatologa i nastavnog kadra na stomatološkim fakultetima.

Obrazovanje

Više od polovine ispitanika (64,6%) nije pružilo nijednu uslugu teledentistike tokom studiranja, dok 25,4% nije bilo sigurno da li su pružili neku od ovih usluga ili ne. Samo 10% ispitanika potvrdilo je primenu teledentistike tokom studiranja, uključujući približno 15% stomatologa, 7% ($n = 1$) nastavnika/saradnika i 3% ($n = 2$) studena-

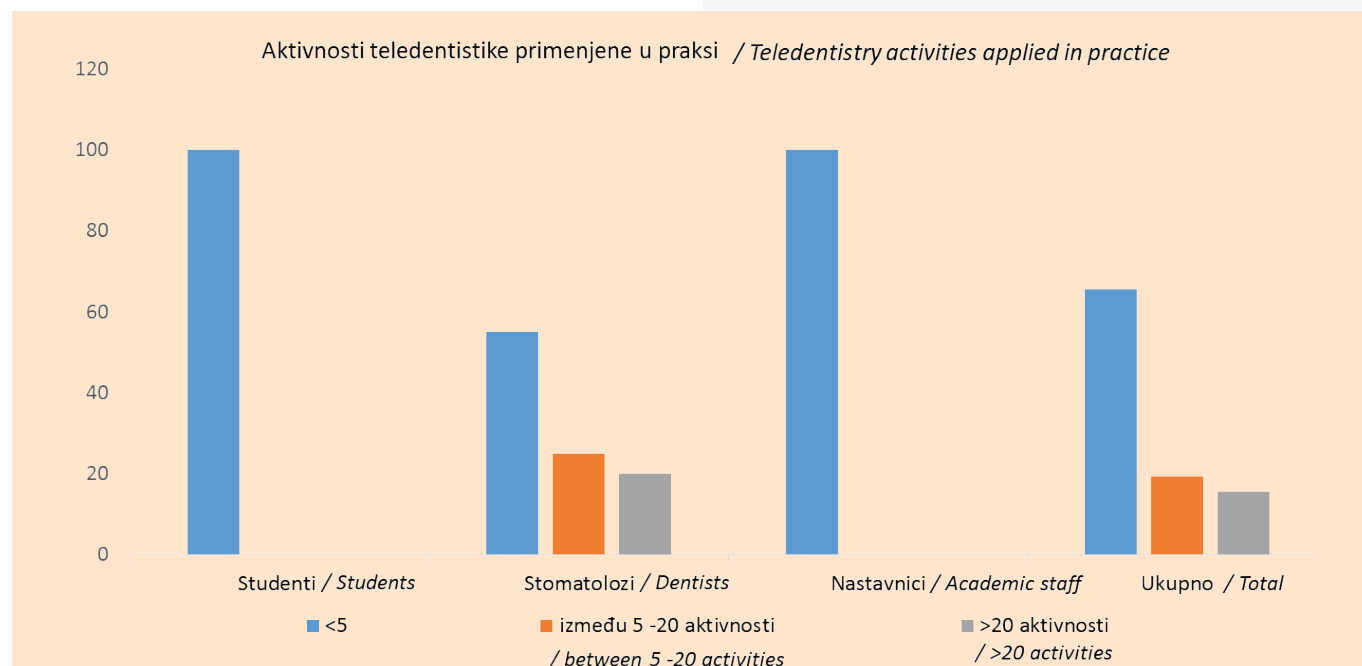
A vast majority of respondents (89.5%) were not familiar with telemedicine regulations in Bosnia and Herzegovina. About 43% of respondents had heard of teledentistry, while around 35% had heard of some activity applied in teledentistry. Approximately 20% of them became acquainted with these activities through websites, about 18% through articles, 17% at conferences, while around 32% indicated other sources of information. Regarding the activities they learned about through these sources, the largest number selected teleconsultations (34%) and remote medical assistance.

Only 7% of respondents acquired knowledge about teledentistry during their formal education, mostly within an elective course (53%) and internship (29.4%). Likewise, about 96% of respondents believed they did not have sufficient knowledge of teledentistry, while 86.2% expressed the desire to have more formal education or training on this topic. The preferred forms of additional education were conferences (27.5%), online teaching (34.6%), and courses (25%).

There was no significant difference in the responses to the questions assessing knowledge of teledentistry among dental students, dentists, and academic staff at dental universities.

Education

More than half of the respondents (64.6%) did not perform any teledentistry services during their studies, while 25.4% were not sure whether they had performed any or not. Only 10% of respondents confirmed the application of teledentistry during their studies, including approximately 15% of dentists, 7% ($n = 1$) of



Slika 3. Učestalost (%) odgovora na pitanje o broju aktivnosti teledentistike primenjenih u praksi

Figure 3. Frequency (%) of responses to the question about the number of teledentistry activities applied in practice

ta. Među ispitanicima koji su potvrdili primenu teledentistike u praksi, 20% je to činilo putem pisanog izveštaja, 13,3% putem obavezne sesije, a 57% kroz druge aktivnosti. Preostali ispitanici primenjivali su teledentistiku u praksi kroz kombinaciju prethodno navedenih aktivnosti.

Kada je reč o obimu primene teledentistike tokom studiranja, više od polovine ispitanika koji su potvrdili njenu primenu (65,4%) je navelo da je sprovedo manje od pet aktivnosti. Više od pet aktivnosti su obavili samo stomatolozi (Slika 3). Ipak, više od polovine njih (57,1%) je bilo veoma zadovoljno onim što je sprovedeno, dok je samo 7% bilo nezadovoljno. Nisu utvrđene statistički značajne razlike u zavisnosti od zanimanja ispitanika u pogledu broja aktivnosti ($p = 0,150$) niti u iskazanom stepenu zadovoljstva ($p = 0,170$).

Praksa

Približno 30% ($n = 34$) stomatologa je primenjivalo neki oblik teledentistike u svojoj praksi tokom godine koja je prethodila istraživanju. Najčešće primenjivana metoda su bile samo telekonsultacije (33,3%) ili telekonsultacije u kombinaciji sa teletrijažom i izdavanjem recepata (33,3%). Medicinsku pomoć na daljinu je pružalo 12% stomatologa, dok je jednak procenat (6%) primenjivao sve oblike telemedicine ili neki drugi oblik. Takođe, isti procenat stomatologa je naveo da je sproveo manje od pet intervencija teledentistike, odnosno između pet i 20 intervencija (39,4%). Slični rezultati su utvrđeni među nastavnicima/saradnicima na stomatološkim fakultetima, od kojih je oko 36% ($n = 5$) potvrdilo primenu teledentistike u praksi tokom godine koja je prethodila istraživanju, konkretno putem telekonsultacija i medicinske pomoći na daljinu. Nastavnici i saradnici su uglavnom bili veoma zadovoljni pruženim uslugama i sprovedenim intervencijama ($n = 4$).

Ukupno 12% ($n = 4$) stomatologa je izrazilo nezadovoljstvo teledentistikom i aktivnostima sprovedenim u okviru nje tokom godine koja je prethodila istraživanju, dok je većina stomatologa bila zadovoljna ili veoma zadovoljna (32,4% i 56%, redom). Pored toga, 75% stomatologa je izrazilo želju da u svojoj praksi pruža neki oblik usluge teledentistike. Kada je reč o aktivnostima teledentistike, najčešće su birane telekonsultacije, bilo samostalno ili u kombinaciji sa medicinskom pomoći na daljinu i teleekspertizom, kao i dostavljanje recepata putem elektronske pošte i teletrijaža. Najčešća sredstva za kontaktiranje oralnih hirurga i pacijenata bila su: telefon (82% i 87%, redom), Vajber (67% i 75,5%, redom) i elektronska pošta (54% i 58%, redom). SMS poruke su češće slane pacijentima (53%) nego oralnim hirurzima (24,5%).

Poznavanje propisa koji regulišu telemedicinu nije bilo povezano sa njenom primenom u praksi ($p = 0,159$) niti sa brojem sprovedenih intervencija ($p = 0,599$) (Tabela 3).

academic staff/associates, and 3% ($n = 2$) of students. Among the respondents who confirmed the application of teledentistry in practice, 20% did so through a written report, 13.3% through a mandatory session, and 57% through other activities. The remainder applied teledentistry in practice through a combination of the aforementioned activities.

Regarding the extent of teledentistry application during studies, more than half of the respondents who confirmed its application (65.4%) reported fewer than five activities. More than five activities were performed only by the dentists (Figure 3). Nevertheless, more than half of them (57.1%) were very satisfied with what had been done, and only 7% were dissatisfied. There were no significant differences depending on the respondent's occupation in the number of activities ($p = 0.150$) or in the expression of satisfaction ($p = 0.170$).

Practice

Approximately 30% ($N = 34$) of dentists performed some form of teledentistry in their practice during the year preceding the study. The most frequently applied method was teleconsultation alone (33.3%) or in combination with tele-triage and prescription delivery (33.3%). Remote medical assistance was provided by 12% of the dentists, while an equal proportion (6%) used all forms of telemedicine or something else. Likewise, the same proportion of dentists reported fewer than five teledentistry interventions and between five and 20 interventions (39.4%). Similar results were found among academic staff /associates at dental universities, about 36% ($n = 5$) of whom confirmed the application of teledentistry in practice during the year preceding the study, specifically through teleconsultations and remote medical assistance. Academic staff/associates were generally very satisfied with the services and interventions provided ($n = 4$).

A total of 12% ($n = 4$) of dentists expressed dissatisfaction with teledentistry and the activities performed within it in the year preceding the study, while a majority of dentists were satisfied or very satisfied (32.4% and 56%, respectively). Moreover, 75% of dentists expressed the desire to provide some form of teledentistry service in their practice. Regarding teledentistry activities, the most frequently selected were teleconsultations, either alone or in combination with remote medical assistance and tele-expertise, as well as prescription delivery via e-mail and tele-triage. The most common means of contacting oral surgeons and patients were the following: telephone (82% and 87%, respectively), Viber (67% and 75.5%, respectively), and e-mail (54% and 58%, respectively). SMS messages were sent more frequently to patients (53%) than to

Tabela 3. Povezanost poznavanja propisa telemedicine i primene teledentistike u prak

Da, dobro poznajem / Yes, I know it well n (%)		Poznavanje propisa telemedicine u Bosni i Hercegovini / Knowledge of telemedicine regulations in Bosnia and Herzegovina		
		Da, dobro poznajem / Yes, I know it well n (%)	Da, malo poznajem / Yes, I know a little n (%)	Ne poznajem / I don't know n (%)
Praktikovanje teledentistike / Practicing teledentistry	Da / Yes	2 (6.1%)	4 (12.1 %)	27 (81.8 %)
	Ne / No	1 (1.3%)	6 (7.6 %)	72 (91.1 %)
Broj aktivnosti / Number of activities	<5 intervencija / < 5 interventions	2 (15.4 %)	1 (7.7 %)	10 (76.9 %)
	5–20 intervencija / 5–20 interventions	0 (0 %)	3 (23.1 %)	10 (76.9 %)
	>20 intervencija / > 20 interventions	0 (0 %)	1 (14.3 %)	6 (85.7 %)

Table 3. Relationship between knowledge of telemedicine regulations and application of teledentistry in practice

Stavovi i uverenja

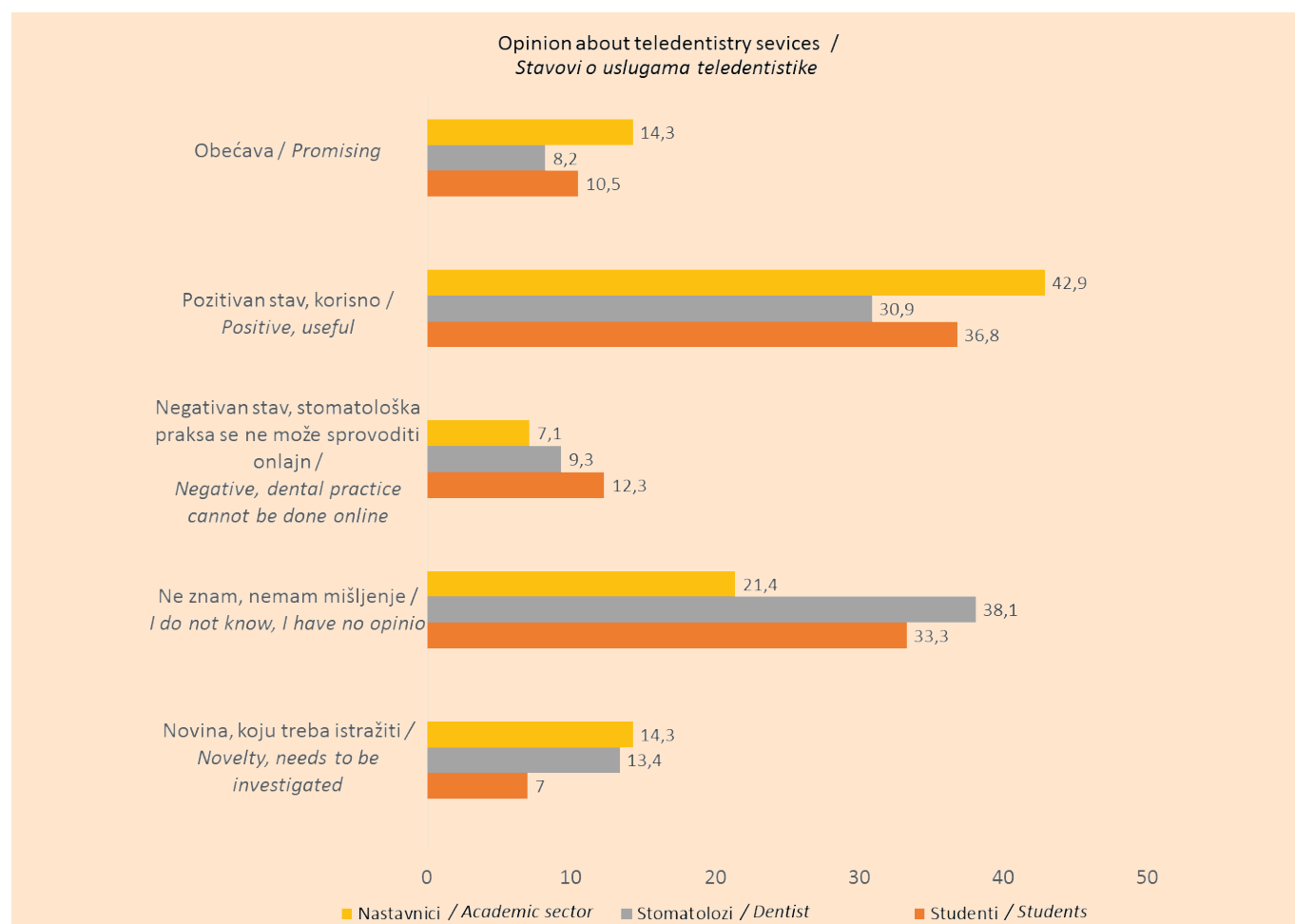
Oko 93% ispitanika je iznelo svoje opšte mišljenje o uslugama teledentistike, za koje su nezavisno formulisali odgovore. Identifikovani stavovi i uverenja su podeljeni u nekoliko kategorija. Približno 34% ispitanika je izrazilo pozitivan stav prema teledentistici, njenoj korisnosti i shvatanju teledentistike kao budućnosti stomatologije, dok je oko 10% bilo uvereno da teledentistika ima potencijal i perspektivu. Međutim, 10%

oral surgeons (24.5%).

Knowledge of telemedicine regulations was not associated with its application in practice ($p = 0.159$) or the number of interventions performed ($p = 0.599$) (Table 3).

Attitudes and beliefs

A total of about 93% of respondents expressed their general opinion on teledentistry services, for which they independently formulated answers. The identified atti-

**Slika 4.** Distribucija stavova i uverenja o teledentistici na osnovu percepcija ispitanika**Figure 4.** Distribution of attitudes and beliefs about teledentistry based on respondents' perceptions

ispitanika je imalo negativan stav, smatrajući da se stomatološka praksa ne može obavljati udaljeno preko interneta, dok značajan broj ispitanika (35%) nije imao stav, bilo zbog nedovoljnog razumevanja ove oblasti bilo zbog nenavođenja jasnog razloga. Nadalje, približno 11% ispitanika je smatralo da je teledentistika inovacija koju tek treba istražiti, ali je istovremeno verovalo da bi mogla biti korisna za pružanje manje pomoći ili konsultacija sa pacijentom. Nije utvrđena razlika u iskazanim stavovima u odnosu na zanimanje ispitanika ($p = 0,795$). Distribucija učestalosti iskazanih stavova o teledentistici prema zanimanju ispitanika je prikazana na [Slici 4](#).

Stavovi prema teledentistici su takođe procenjeni korišćenjem skupa tvrdnji, sa mogućnostima odgovora u rasponu od „u potpunosti se slažem“ do „uopšte se ne slažem“. Više od polovine ispitanika je izrazilo pozitivan stav u pogledu značaja teledentistike za unapređenje zdravstvene zaštite pacijenata i njihovog pristupa zdravstvenim uslugama, kao i za unapređenje stomatološke zdravstvene zaštite. Pored toga, približno 73% ispitanika je želelo da primenjuje teledentistiku u svom budućem profesionalnom radu, dok je oko 66% smatralo da pacijenti preferiraju usluge teledentistike ([Tabela 4](#)).

Nisu utvrđene statistički značajne razlike u zabeleženim učestalostima procenjivanih tvrdnji u odnosu na starosne grupe ispitanika ili potvrđeni nivo formalnog obrazovanja ($p > 0,05$). Međutim, stomatolozi i nastavnici/saradnici na univerzitetima koji su primenjivali teledentistiku, značajno su češće, u poređenju sa onima koji je nisu primenjivali, izražavali slaganje sa tim da je teledentistika rešenje za unapređenje zdravstvene zaštite pacijenata ($p < 0,001$), pristupa zdravstvenoj zaštiti ($p < 0,001$) i pružanja stomatološke zdravstvene zaštite ($p < 0,001$). Takođe su značajno češće smatrali da teledentistika predstavlja mogućnost za unapređenje stomatološke prakse ($p < 0,001$) i izražavali spremnost da je koriste u budućnosti ($p < 0,001$). Pored toga, doktori i nastavnici koji su primenjivali teledentistiku značajno su ređe ovaj oblik prakse doživljavali kao pretnju stomatološkoj praksi ($p = 0,023$). Nasuprot tome, doktori i nastavnici koji nisu primenjivali teledentistiku su imali tendenciju da izražavaju veće rezerve u pogledu svih procenjivanih tvrdnji.

Poređenje prema zanimanju ispitanika (studenti stomatologije, doktori stomatologije i nastavni kadar na univerzitetima) pokazalo je statistički značajne razlike u pogledu tvrdnji da je teledentistika rešenje za unapređenje zdravstvene zaštite pacijenata ($p = 0,039$), da predstavlja mogućnost za unapređenje stomatološke prakse ($p = 0,012$), da postoji želja za primenom teledentistike u budućnosti ($p = 0,008$) i da je pacijenti

tudes and beliefs were divided into several categories. Approximately 34% of respondents expressed a positive opinion about teledentistry, its usefulness, and its view as the future of dentistry, while around 10% were convinced of its potential and promising prospects. However, 10% of respondents held a negative opinion, believing that dental practice cannot be conducted online, while a considerable number (35%) had no opinion, either due to a lack of understanding of the field or without providing a clear reason. Furthermore, approximately 11% of respondents considered teledentistry to be an innovation that still needed to be explored but nonetheless believed it could be useful as a form of minor assistance or consultation with a patient. There was no difference in the expressed opinions in relation to the respondents' occupation ($p = 0.795$). The distribution of the frequencies of expressed opinions on teledentistry by respondent occupation is shown in [Figure 4](#).

Attitudes towards teledentistry were also assessed using a set of statements, with response options ranging from strongly agree to strongly disagree. More than half of the respondents expressed a positive attitude regarding the importance of teledentistry in improving patient care and access, as well as enhancing dental care. Moreover, approximately 73% wished to practice teledentistry in their future professional work, and around 66% believed that patients preferred teledentistry services ([Table 4](#)).

There were no significant differences in the recorded frequencies of the assessed statements with respect to respondent age groups or confirmed formal education level ($p > 0.05$). However, dentists and academic staff/associates at universities who had practiced teledentistry were significantly more likely than those who had not practiced it to agree that teledentistry is a solution for improving patient care ($p < 0.001$), access to care ($p < 0.001$), and the provision of dental care ($p < 0.001$). They were also significantly more likely to perceive teledentistry as an opportunity to enhance dental practice ($p < 0.001$) and to express a willingness to use it in the future ($p < 0.001$). In addition, doctors and academic staff who had practiced teledentistry were significantly less likely to perceive this form of practice as a threat to dental practice ($p = 0.023$). In contrast, doctors and academic staff who had not practiced teledentistry tended to express greater reservations across all assessed statements.

Comparison by the respondents' profession (dental students, doctors of dentistry and academic staff at universities) revealed statistically significant differences regarding the statements that teledentistry is a solution for improving patient care ($p = 0.039$), that it is an opportunity for improving dental practice

Tabela 4. Učestalosti i poređenje odgovora na tvrdnje o značaju teledentistike

Table 4. Frequencies and comparison of responses to statements about the importance of teledentistry

Tvrdnja / Statement	Ogovor / Answer	Ukupno / Total N = 181 n (%)	Student / Student n = 69 n (%)	Stomatolog / Dentist n = 98 n (%)	Nastavnik / Academic staff n = 14 n (%)*	p-value*
Teledentistika je relevantno rešenje za poboljšanje zdravstvene nege pacijenata. / Teledentistry is a relevant solution for improving patient care.	U potpunosti se slažem / I completely agree	76 (42.0%)	20 (29.30%)	50 (51.30%)	6 (42.9%)	0.039
	Slažem se / I agree	59 (32.6%)	29 (42%)	27 (27.6%)	3 (21.4%)	
	Uzdržan-a / Restrained	28 (15.5%)	11 (15.9%)	14 (14.3%)	3 (21.4%)	
	Ne slažem se / I don't agree	18 (9.9%)	9 (13%)	7 (7.1%)	2 (14.3%)	
	Uopšte se ne slažem / I completely disagree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Teledentistika je relevantno rešenje za poboljšanje pristupa zdravstvenoj nezi. / Teledentistry is a relevant solution for improving access to patient care.	U potpunosti se slažem / I completely agree	77 (42.5%)	21 (30.4%)	50 (51%)	6 (42.9%)	0.089
	Slažem se / I agree	64 (53.4%)	32 (46.4%)	28 (28.6%)	4 (28.6%)	
	Uzdržan-a / Restrained	26 (14.4%)	9 (13%)	15 (15.3) %	2 (14.3%)	
	Ne slažem se / I don't agree	14 (7.7%)	7 (10.1%)	5 (5.1%)	2 (14.3%)	
	Uopšte se ne slažem / I completely disagree	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Teledentistika je relevantno rešenje za poboljšanje pristupa stomatološkoj nezi. / Teledentistry is a relevant solution for improving access to dental care.	U potpunosti se slažem / I completely agree	77 (42.5%)	22 (31.9%)	49 (50%)	6 (42.9%)	0.144
	Slažem se / I agree	61 (33.7%)	29 (42%)	27 (27.6%)	5 (35.7%)	
	Uzdržan-a / Restrained	29 (16%)	11 (15.9%)	17 (17.3%)	1 (7.1%)	
	Ne slažem se / I don't agree	14 (7.7%)	7 (10.1%)	5 (5.1%)	2 (14.3%)	
	Uopšte se ne slažem / I completely disagree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Teledentistika je pretnja stomatološkoj praksi. / Teledentistry is a threat to dental practice.	U potpunosti se slažem / I completely agree	14 (7.7%)	2 (2.9%)	9 (9.2%)	3 (21.4%)	0.949
	Slažem se / I agree	31 (17.1%)	16 (23.2%)	14 (14.3%)	1 (7.1%)	
	Uzdržan-a / Restrained	43 (23.8%)	18 (26.1%)	23 (23.5%)	2 (14.3%)	
	Ne slažem se / I don't agree	92 (50.8%)	32 (46.4%)	52 (53.1%)	8 (57.1%)	
	Uopšte se ne slažem / I completely disagree	1 (0.6%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	
Teledentistika je prilika za unapređivanje stomatološke prakse. / Teledentistry is an opportunity to improve dental practice.	U potpunosti se slažem / I completely agree	85 (47%)	23 (33.3%)	56 (57.1%)	6 (42.9%)	0.012
	Slažem se / I agree	62 (34.3%)	28 (40.6%)	28 (28.6%)	6 (42.9%)	
	Uzdržan-a / Restrained	22 (12.2%)	13 (18.8%)	8 (8.2%)	1 (7.1%)	
	Ne slažem se / I don't agree	12 (6.6%)	5 (7.2%)	6 (6.1%)	1 (7.1%)	
	Uopšte se ne slažem / I completely disagree	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Želim da praktikujem teledentistiku u svojoj budućoj stomatološkoj praksi. / I want to practice teledentistry in my future dental practice.	U potpunosti se slažem / I completely agree	73 (40.3%)	18 (26.1%)	48 (49%)	7 (50%)	0.008
	Slažem se / I agree	60 (33.1%)	26 (37.7%)	29 (29.6%)	5 (35.7%)	
	Uzdržan-a / Restrained	31 (17.1%)	17 (24.6%)	13 (13.3%)	1 (7.1%)	
	Ne slažem se / I don't agree	17 (9.4%)	8 (11.6%)	8 (8.2%)	1 (7.1%)	
	Uopšte se ne slažem / I completely disagree	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Pacijenti preferiraju primenu teledentistike. / Patients prefer the use of teledentistry.	U potpunosti se slažem / I completely agree	42 (23.2%)	9 (13%)	29 (29.6%)	4 (28.6%)	0.012
	Slažem se / I agree	77 (42.5%)	28 (40.6%)	43 (43.9%)	6 (42.9%)	
	Uzdržan-a / Restrained	46 (25.4%)	25 (36.2%)	17 (17.3%)	4 (28.6%)	
	Ne slažem se / I don't agree	16 (8.8%)	7 (10.1%)	9 (9.2%)	– (–)	
	Uopšte se ne slažem / I completely disagree	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

* Kruskal–Wallis test / * Kruskal–Wallis Test

preferiraju ($p = 0,012$). Post hoc analiza, uz Bonferroni-korekciju ($\alpha = 0,0167$), pokazala je statistički značajne razlike između studenata i stomatologa za sve četiri tvrdnje ($p = 0,003$, $p = 0,001$, $p = 0,001$ i $p = 0,001$, redom). Nisu utvrđene statistički značajne razlike između studenata i nastavnog kadra niti između stomatologa i nastavnog kadra.

DISKUSIJA

Ova studija pruža sveobuhvatnu procenu znanja, stavova i prakse u vezi sa teledentistikom među studentima stomatologije, stomatolozima i nastavnim kadrom u Bosni i Hercegovini, ukazujući na potrebu za razvojem prilagođenih pristupa usmerenih na podsticanje primene teledentistike. Istraživanje pokazuje jasan raskorak između stavova i znanja. U našem uzorku, 73% odgovora je odražavalo zainteresovanost za teledentistiku, dok je samo 43% odgovora ukazivalo na stvarno znanje o teledentistici. Ovi nalazi ukazuju na to da je ovaj nivo znanja nedovoljan za uvođenje usluge teledentistike bez edukacije i sistemске podrške.

Čini se da prethodno iskustvo u teledentistici predstavlja važan faktor u oblikovanju pozitivnih stavova prema ovoj oblasti i njenom kliničkom značaju. Ispitanici koji su primenjivali teledentistiku su češće prepoznawali značaj teledentistike kao sredstva za unapređenje zdravstvene zaštite pacijenata, pristupa zdravstvenoj zaštiti i pružanja stomatološke zdravstvene zaštite, ali i kao mogućnosti za unapređenje stomatološke prakse, dok su je ređe doživljavali kao pretnju stomatološkoj praksi.

Kada je reč o profesionalnoj grupi, utvrđene su statistički značajne razlike između studenata stomatologije i stomatologa u njihovim stavovima prema teledentistici kao sredstvu za unapređenje zdravstvene zaštite pacijenata i stomatološke prakse, njihovoj spremnosti da je koriste u budućnosti, kao i u njihovim procenama preferencija pacijenata u pogledu njenog korišćenja. Međutim, nisu utvrđene statistički značajne razlike između studenata stomatologije i nastavnog kadra, niti između stomatologa i nastavnog kadra. Stoga se uočene razlike između studenata i stomatologa mogu više dovesti u vezu sa razlikama u kliničkoj izloženosti i praktičnom iskustvu nego sa samom profesionalnom grupom. Studenti stomatologije mogu da budu bolje upoznati sa digitalnim tehnologijama, ali da istovremeno imaju manje iskustva u njihovoj primeni u realnom kliničkom okruženju, dok stomatolozi imaju neposrednije iskustvo u pogledu praktičnih prednosti i ograničenja teledentistike.

Nalazi koji se odnose na zadovoljstvo ostvarenim uslugama teledentistike ukazuju na to da teledentistika može da predstavlja prihvatljivu i korisnu uslugu

($p = 0,012$), that there is a desire to practice teledentistry in the future ($p = 0,008$) and the preference for its use by patients ($p = 0,012$). Post hoc analysis with Bonferroni correction ($\alpha = 0,0167$) demonstrated statistically significant differences between students and dentists for all four statements ($p = 0,003$, $p = 0,001$, $p = 0,001$, and $p = 0,001$, respectively). No statistically significant differences were observed between students and academic staff or between dentists and academic staff.

DISCUSSION

The present study provides a comprehensive assessment of the knowledge, attitudes, and practices regarding teledentistry among dental students, dentists, and academic staff in Bosnia and Herzegovina, highlighting the necessity for developing customized approaches to promote the adoption of teledentistry. The research shows a clear gap between attitudes and knowledge. In our sample, 73% of responses reflected interest in teledentistry, whereas only 43% reflected actual knowledge about teledentistry. These findings suggest that this level of knowledge is insufficient to launch a teledentistry service without education and systemic support.

Previous experience with teledentistry appears to be an important factor in shaping positive attitudes towards teledentistry and its clinical relevance. Participants who had practiced teledentistry were more likely to recognize it as a means of improving patient care, access to healthcare, and the delivery of dental care, as well as an opportunity to enhance dental practice, while being less likely to perceive it as a threat to dental practice.

With regard to the professional group, statistically significant differences were observed between dental students and dentists in their perceptions of teledentistry as a means of improving patient care and dental practice, their willingness to use it in the future, and their perceptions of patients' preference for its use. However, no statistically significant differences were observed between dental students and academic staff or between dentists and academic staff. The differences observed between students and dentists may therefore be related more to differences in clinical exposure and practical experience than to professional affiliation itself. Dental students may be more familiar with digital technologies while having less experience in their application within real-world clinical settings, whereas dentists have more direct experience of the practical benefits and limitations of teledentistry.

The findings regarding satisfaction with teledentistry services suggest that teledentistry can represent an acceptable and useful service when appropriately implemented. No statistically significant differences

kada se primenjuje na odgovarajući način. Nisu utvrđene statistički značajne razlike u zadovoljstvu između ispitivanih profesionalnih grupa, pri čemu je više od polovine ispitanika navelo da je zadovoljno uslugama ostvarenim putem teledentistike. Ovi nalazi podržavaju potencijalnu prihvatljivost teledentistike među različitim profesionalnim grupama i ukazuju na to da ona može da predstavlja vrednu komponentu savremene stomatološke zdravstvene zaštite kada se na odgovarajući način primenjuje.

Rezultati naše studije su u skladu sa objavljenim rezultatima iz Francuske [14]. Nacionalno istraživanje sprovedeno u Sudanu je pokazalo je da je 59,8% stomatoloških radnika imalo pozitivan stav, što se naročito odnosilo na one sa postdiplomskim obrazovanjem i nastavničkim ulogama, dok su specijalisti bili manje skloni prihvatanju teledentistike [15]. Posmatrano u celini, ovi podaci ukazuju na to da raskorak između stavova i znanja nije specifičan za Bosnu i Hercegovinu, ali u sistemima sa ograničenim resursima i složenom administrativnom strukturom, kao što je Bosna i Hercegovina, njegove posledice po pružanje usluga mogu biti izraženije.

Pregled sproveden u 19 zemalja je pokazao ograničenu svakodnevnu kliničku primenu teledentistike, pri čemu je samo šest zemalja (31,6%) imalo uspostavljene politike i programe teledentistike, uz naglasak da je za prelazak sa pilot projekata na širu primenu potrebno uspostaviti odgovarajuće pravne okvire, mehanizme finansiranja i obuku zdravstvenih radnika [13].

Nismo prikupljali podatke o godinama radnog iskustva. Stoga nismo mogli direktno da ispitamo razlike povezane sa dužinom radnog staža. Buduće studije bi trebalo da prikupljaju ove podatke kako bi se uticaj faze profesionalne karijere mogao razgraničiti od uticaja iskustva iz prakse. Podjednako su važni strukturisani načini za razmatranje slučajeva između stomatologa, kao i za dobijanje drugog stručnog mišljenja. Podrška strukovnih udruženja i sekundarnih/tercijarnih službi potrebna je kako bi stomatološka zdravstvena zaštita na daljinu bila bezbedna i praktično izvodljiva [16]. Protokoli za trijažu i eskalaciju na nivou zdravstvene službe, uz jasno definisane uloge strukovnih udruženja i bolničkih službi, pokazuju na koji način se telekonsultacije mogu bezbedno i efikasno integrisati u zdravstvenu zaštitu [17].

Dostupnost stomatologa je neravnomerna u Bosni i Hercegovini, a većina stomatologa u Republici Srpskoj radi u privatnoj praksi (~60%). Na osnovu rezultata našeg istraživanja, potvrđena je potreba za uvođenjem teledentistike i uspostavljanjem standardizovanog puta e-konsultacija za konsultacije između stomatologa i dobijanje drugog stručnog mišljenja, kojim bi zajednički upravljale stomatološke komore i sekun-

in satisfaction were observed among the examined professional groups, with more than half of the participants reporting satisfaction with the services provided through teledentistry. These findings support the potential acceptability of teledentistry across different professional groups and suggest that, when appropriately implemented, it may be a valuable component of contemporary dental care.

Our study results are consistent with results published in France [14]. A national survey in Sudan showed that 59.8% of dental professionals expressed a positive attitude, especially those with postgraduate education and academic roles, while specialists were less accepting [15]. Taken together, these data suggest that the gap between attitudes and knowledge is not unique to Bosnia and Herzegovina, but in resource-constrained and administratively complex systems like Bosnia and Herzegovina, its consequences may be more pronounced for service delivery.

A 19-country review reported limited daily clinical use of teledentistry, with only six countries (31.6%) having established teledentistry policies and programs, and emphasized that moving beyond pilots requires enabling legal frameworks, funding mechanisms, and workforce training [13].

We did not collect data on the years of work experience. Therefore, we could not test work experience gradients directly. Future studies should collect this information to differentiate the impact of career stage from hands-on experience. Equally important are structured routes for dentist-to-dentist case discussion and for second opinions. Support from professional associations and secondary/tertiary services is needed to make remote dental care safe and workable [16]. Service-level triage and escalation protocols, with clear roles for professional associations and hospital services, demonstrate how remote consultations can be integrated safely and efficiently [17].

Dentist availability is uneven across Bosnia and Herzegovina, and most dentists in the Republic of Srpska work in private practice (~60%). Based on the results of our survey, the need for implementing teledentistry, establishing a standardized e-consultation pathway for consultations between dentists and for second opinions, jointly managed by dental associations and secondary/tertiary dental services, with on-call specialist input, and directly addressing the uneven distribution of dentists in Bosnia and Herzegovina, has been demonstrated. These findings highlight the importance of implementing additional preventive programs delivered through teledentistry to help prevent the development of various types of malocclusions such as those addressed in interceptive orthodontics.

darne/tercijarne stomatološke službe, uz mogućnost uključivanja dežurnog specijaliste, čime bi se direktno odgovorilo na neravnomernu distribuciju stomatologa u Bosni i Hercegovini. Ovi nalazi ukazuju na značaj uvođenja dodatnih preventivnih programa koji bi se realizovali putem teledentistike, kako bi se pomoglo u sprečavanju razvoja različitih vrsta malokluzija, poput onih kojima se bavi interceptivna ortodoncija. Naša studija je identifikovala nepostojanje politika, nedostatke u nastavnim planovima i programima i nejasnoće u regulativi kao faktore koji otežavaju primenu teledentistike [18,19].

Nizak nivo znanja stomatologa o teledentistici pripisuje se nedostatku formalnog obrazovanja na ovu temu. Istraživanje je pokazalo da je samo 7% ispitanika steklo znanja o teledentistici kroz formalno obrazovanje. Povećanje nivoa znanja i sticanje novih vještina povezanih sa teledentistikom su od ključnog značaja za njenu primenu u kliničkoj praksi. Međutim, naša studija nije direktno analizirala nastavne planove i programe osnovnih i postdiplomskih studija u Bosni i Hercegovini. Buduće studije bi trebalo da analiziraju i mapiraju sadržaje i ishode učenja koji se odnose na teledentistiku kroz sve cikluse stomatološkog obrazovanja, uključujući programe specijalizacije, kako bi se obezbedila precizna osnova za integraciju teledentistike u nastavne planove i programe i reformu politika. Naši rezultati potvrđuju da nedovoljna zastupljenost teledentistike u nastavnim planovima i programima dovodi do nedovoljnog znanja, zbog čega je neophodna njena integracija u kurikulum.

Kada je reč o stavovima prema teledentistici među ispitanicima iz različitih grupa, utvrđena je statistički značajna razlika. Razlike su uočene u percepciji teledentistike kao relevantnog rešenja za unapređenje zdravstvene zaštite pacijenata, u percepciji teledentistike kao mogućnosti za unapređenje stomatološke prakse, u spremnosti za prihvatanje teledentistike u budućnosti i u proceni preferencija pacijenata u pogledu korišćenja usluga teledentistike. Post hoc analiza je dodatno pokazala postojanje značajnih razlika između studenata i stomatologa, dok nisu utvrđene statistički značajne razlike između studenata i nastavnog kadra, niti između stomatologa i nastavnog kadra. Ovi nalazi ukazuju na to da se percepcija teledentistike razlikuje u zavisnosti od nivoa profesionalnog iskustva. Moguće je da su studenti, zbog veće izloženosti digitalnim tehnologijama, otvoreniji prema inovacijama u sistemima pružanja zdravstvene zaštite. Nasuprot tome, stomatolozi mogu imati drugačiju percepciju, budući da su neposrednije izloženi praktičnim, organizacionim i regulatornim izazovima povezanim sa implementacijom teledentistike.

Our study identified a policy vacuum, curricular deficit, and regulatory ambiguity as factors impeding the adoption of teledentistry [18,19].

Dentists' low knowledge of teledentistry is attributed to a lack of formal education on the subject. The survey revealed that only 7% of respondents learned about teledentistry through formal education. Increasing the level of knowledge and acquiring new skills related to teledentistry is crucial for its application in clinical practice. However, our study did not directly review the undergraduate and postgraduate curricula in Bosnia and Herzegovina. Future studies should review and map teledentistry content and learning outcomes across all cycles of dental education, including specialization programs, to provide a precise basis for curriculum integration and policy reform. Our results confirm that insufficient curriculum exposure to teledentistry results in poor knowledge, thus necessitating curriculum integration.

Regarding attitudes toward teledentistry among respondents from different groups, a statistically significant difference was observed. Differences were identified in the perception of teledentistry as a relevant solution for improving patient care, in the perception of teledentistry as an opportunity to enhance dental practice, in the willingness to adopt teledentistry in the future, and in the assessment of patient preferences for using teledentistry services. Post hoc analysis further revealed the presence of significant differences between students and dentists, whereas no statistically significant differences were found between students and academic staff, or between dentists and academic staff. These findings indicate that perceptions of teledentistry vary depending on the level of professional experience. Conceivably, students, due to greater exposure to digital technologies, are more open to innovations in healthcare delivery systems. In contrast, dentists may have a different perception, as they are more directly exposed to the practical, organizational, and regulatory challenges associated with the implementation of teledentistry.

The dental students' openness and acceptance of innovative digital solutions are rooted in their knowledge of clinical effectiveness, access to dental services, and the quality of care provided. Talla et al. highlighted the importance of perceiving teledentistry as a useful and easy-to-use dental service, which represents a key predictor of the intention to adopt teledentistry in future practice [20]. During their education and professional development, students are generally more open to innovation and its integration into clinical reasoning. Education plays a crucial role in shaping positive perceptions, as it provides opportunities to acquire knowl-

Otvorenost i prihvatanje inovativnih digitalnih rešenja među studentima stomatologije zasnivaju se na njihovom znanju o kliničkoj efikasnosti, dostupnosti stomatoloških usluga i kvalitetu pružene zdravstvene zaštite. Tala i saradnici su istakli značaj doživljavanja teledentistike kao korisne i jednostavne stomatološke usluge, što predstavlja ključni prediktor namere za prihvatanje teledentistike u budućoj praksi [20]. Tokom obrazovanja i stručnog usavršavanja, studenti su generalno otvoreniji prema inovacijama i njihovoj integraciji u kliničko rezonovanje. Edukacija ima ključnu ulogu u oblikovanju pozitivnih percepcija, jer pruža mogućnosti za sticanje znanja i veština u oblasti digitalnih zdravstvenih rešenja i podstiče spremnost za njihovu buduću primenu u stomatološkoj praksi.

Šire posmatrano, identifikovane prepreke – nedostaci u politikama, nedostaci u nastavnim planovima i programima i regulatorne nejasnoće – ukazuju na potrebu za koordinisanim delovanjem na nivou obrazovanja, regulative u profesiji i zdravstvene politike. Shodno tome, sistemi zdravstvene zaštite i obrazovanja moraju se prilagoditi novim tehnološkim dostignućima u kliničkoj praksi.

Složena organizacija zdravstvenog sistema, koji je u Bosni i Hercegovini podeljen na dva entiteta, jedan distrikt i nekoliko kantona, predstavlja prepreku jednostavnim rešenjima za primenu teledentistike. Međutim, teledentistika i dalje predstavlja sredstvo za ostvarivanje pristupa stomatološkoj zdravstvenoj zaštiti, dobijanje drugog stručnog mišljenja i profesionalnu saradnju, uprkos administrativnim izazovima. Prednosti ove studije uključuju dizajn studije preseka i primenu validiranog upitnika za procenu znanja, stavova i prakse u vezi sa teledentistikom. Ograničenja uključuju sprovođenje ankete putem interneta, što je moglo dovesti do prekomerne zastupljenosti stomatologa sa visokim nivoom informatičke pismenosti, kao i izostanak sistematske analize nastavnih planova i programa osnovnih i postdiplomskih studija, zbog čega stvarni obim formalne edukacije iz oblasti teledentistike može biti manji od prijavljenog.

ZAKLJUČAK

Studenti stomatologije, stomatolozi i nastavni kadar u Bosni i Hercegovini su pokazali ograničeno znanje i praktično iskustvo u pogledu teledentistikom, uz istovremeno ispoljavanje generalno pozitivnih stavova prema njenoj primeni.

Uspešna primena teledentistike u Bosni i Hercegovini zahteva adekvatnu digitalnu infrastrukturu, pouzdanu internet konekciju, institucionalnu podršku i odgovarajuće regulatorne okvire.

edge and skills in digital health solutions and fosters readiness for their future application in dental practice.

More broadly, the identified barriers – policy gaps, curriculum deficiencies and regulatory ambiguity – highlight the need for coordinated action at the education, professional regulation and health policy levels. Consequently, it follows that the health and education systems need to adapt to new technological advances in clinical practice.

The complex organization of the healthcare system, which is divided into two entities, one district and several cantons in BiH, presents an obstacle to simple solutions for the implementation of teledentistry. However, teledentistry remains a tool for accessing dental care, second opinions, and professional collaboration despite administrative challenges. The strengths of the present study include its cross-sectional design and the use of a validated questionnaire to assess knowledge, attitudes, and practices related to teledentistry. Limitations include the online administration of the survey, which may have resulted in the overrepresentation of IT-literate dentists, as well as the absence of a systematic review of undergraduate and postgraduate syllabi, which may mean that the actual extent of formal teledentistry education is lower than reported.

CONCLUSION

Dental students, dentists, and academic staff in Bosnia and Herzegovina demonstrated limited knowledge and practical experience regarding teledentistry, while maintaining generally positive attitudes towards its adoption.

The successful implementation of teledentistry in Bosnia and Herzegovina requires adequate digital infrastructure, reliable Internet connectivity, institutional support, and appropriate regulatory frameworks.

Integration of teledentistry into dental education and continuing professional development, including the introduction of micro-credential training, could contribute to improving competencies and readiness for its wider implementation.

Further research should examine patients' perspectives and evaluate the effectiveness and long-term sustainability of teledentistry services in Bosnia and Herzegovina.

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Integrisanje teledentistike u stomatološko obrazovanje i kontinuirano stručno usavršavanje, uključujući uvođenje programa obuke za sticanje mikroakreditacija (engl. *micro-credential training*), moglo bi doprineti unapređenju kompetencija i spremnosti za njenu širu primenu.

Buduća istraživanja bi trebalo da ispituju gledišta pacijenata i procene efikasnost i dugoročnu održivost usluga teledentistike u Bosni i Hercegovini.

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LITIJUM KAO NEUROREGENERATIVNI MODULATOR U REPARACIJI PERIFERNIH NERAVA: MEHANISTIČKI UVIDI I STRATEGIJE BIOINŽENJERSKE ISPORUKE – SISTEMATSKI PREGLED

PREGLEDNI RAD

REVIEW ARTICLE

LITHIUM AS A NEUROREGENERATIVE MODULATOR IN PERIPHERAL NERVE REPAIR: MECHANISTIC INSIGHTS AND BIOENGINEERED DELIVERY STRATEGIES – A SYSTEMATIC REVIEW

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SAŽETAK

Uvod: Povrede perifernih nerava (PNI) predstavljaju značajan klinički problem, sa ograničenim funkcionalnim oporavkom uprkos napretku mikrohkirurških tehnika. Litijum se poslednjih godina ispituje kao neuroaktivni agens sa efektima na preživljavanje neurona, funkciju Švanovih ćelija, regeneraciju aksona i remijelinizaciju. Ovaj pregled analizira dokaze o ulozi litijuma u regeneraciji perifernih nerava, sa fokusom na bioinženjerske strategije isporuke.

Metode: Sproveden je sistematski pregled literature prema PRISMA smernicama u bazama PubMed, Scopus i Web of Science, zaključno sa aprilom 2026. godine. Uključene su studije koje se bave litijumom u regeneraciji perifernih nerava, biologijom Švanovih ćelija, neuroprotektivnim efektima, remijelinizacijom i biomaterijalima za lokalnu isporuku. Podaci su kvalitativno analizirani sa fokusom na eksperimentalne modele i translacioni značaj.

Rezultati: Pretkliničke studije ukazuju na to da litijum može pospešiti regeneraciju perifernih nerava putem modulacije signalizacije glikogen-sintaza-kinaze-3β (GSK-3β), aktivacije pro-survival puteva, indukcije autofagije i regulacije proliferacije i mijelinizacije Švanovih ćelija. Većina dokaza potiče iz in vitro i životinjskih modela, sa poboljšanom regeneracijom aksona, remijelinizacijom i funkcionalnim oporavkom. Deo podataka potiče iz studija centralnog nervnog sistema i tumačen je oprezno zbog razlika u regenerativnom kapacitetu CNS i PNS. Novija istraživanja ukazuju na to da biomaterijali sa litijumom, uključujući hidrogelne, nervne konduite, adhezivne polimere i nanostrukturirane sisteme, mogu omogućiti lokalnu i produženu isporuku uz smanjenje sistemske toksičnosti.

Zaključak: Litijum predstavlja obećavajući dodatni neuroregenerativni modulator u modelima povrede perifernih nerava, naročito kada se primenjuje kroz lokalne bioinženjerske sisteme. Dokazi su i dalje pretežno pretklinički, a translacija je ograničena uskim terapijskim prozorom i sistemskom toksičnošću. Potrebne su dalje translacione i kliničke studije radi procene bezbednosti i terapijskog potencijala.

Ključne reči: litijum, periferni nervi, bioinženjering, GSK-3β, neuroregeneracija

ABSTRACT

Introduction: Peripheral nerve injuries (PNIs) remain a major clinical challenge with limited functional recovery despite advances in microsurgery. Lithium has emerged as a neuroactive agent with effects on neuronal survival, Schwann cell function, axonal regeneration, and remyelination. This review evaluates evidence on lithium in peripheral nerve regeneration, focusing on bioengineered delivery approaches.

Methods: A PRISMA-guided systematic review was performed using PubMed, Scopus, and Web of Science up to April 2026. Studies addressing lithium in peripheral nerve regeneration, Schwann cell biology, neuroprotection, remyelination, and biomaterial-based delivery systems were included. Data were synthesized qualitatively with emphasis on experimental and translational findings.

Results: Preclinical studies suggest lithium enhances peripheral nerve regeneration via modulation of glycogen synthase kinase-3β (GSK-3β), activation of pro-survival pathways, autophagy induction, and effects on Schwann cell proliferation and myelination. Most evidence comes from in vitro and animal models, showing improved axonal regrowth, remyelination, and functional recovery. Some supporting data derive from central nervous system models and were interpreted with caution due to inherent differences in regenerative capacity between the central and peripheral nervous systems. Newer studies indicate that lithium-loaded biomaterials, including hydrogels, nerve conduits, adhesive polymers, and nanostructured systems, may enable localized delivery with reduced systemic toxicity.

Conclusions: Lithium appears to be a promising adjunct in peripheral nerve repair, especially when delivered through bioengineered local systems. However, current evidence is largely preclinical, and translation is limited by a narrow therapeutic window and systemic toxicity. Further studies are needed to clarify safety and clinical applicability.

Keywords: lithium, peripheral nerves, bioengineering, GSK-3β, neuroregeneration

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UVOD

Povrede perifernih nerava (PNI) predstavljaju čest i klinički značajan problem u neurohirurgiji, ortopediji i traumatologiji, sa posledičnim motornim i senzitivnim deficitima koji često dovode do dugotrajne invalidnosti i smanjenja kvaliteta života pacijenata [1]. Uprkos napretku mikrohirurških tehnika rekonstrukcije nerva, uključujući direktne anastomoze, autologne nervne graftove i primenu nervnih konduita, funkcionalni oporavak ostaje nepredvidiv, naročito kod lezija sa većim defektom nervnog tkiva ili odloženom hirurškom intervencijom [2,3]. Glavno ograničenje savremenih terapijskih pristupa nije samo tehnička rekonstrukcija kontinuiteta nerva, već inherentno spor i često nepotpun biološki proces regeneracije aksona i reinervacije ciljnih struktura [4].

Nakon povrede perifernog nerva dolazi do Valerove degeneracije distalnog segmenta aksona, što uključuje fragmentaciju aksona i mijelina, kao i aktivaciju lokalnog imunološkog odgovora sa infiltracijom makrofaga koji učestvuju u čišćenju celularnog detritusa [5]. Paralelno sa ovim procesom, Švanove ćelije prolaze kroz značajno fenotipsko reprogramiranje i prelaze u tzv. stanje „popravke“, koje je ključno za uspešnu regeneraciju nerva. U ovom fenotipu, one gube mijelinizujuća svojstva i dobijaju regenerativni profil karakterisan povećanom proliferacijom, migracijom i ekspresijom neurotrofičnih faktora koji usmeravaju aksonski rast [6]. Takođe formiraju tzv. Bungnerove trake koje služe kao vodiči za regenerišuće aksone ka distalnim ciljnim strukturama, čime obezbeđuju prostornu i biohemijsku podršku procesu regeneracije [5]. Međutim, ovaj reparativni program je vremenski ograničen, a produžena denervacija dovodi do progresivnog gubitka fenotipske stabilnosti Švanovih ćelija, smanjenja njihove podrške aksonskom rastu i značajnog pada regenerativnog kapaciteta nerva [4].

METODOLOGIJA

Pretragom literature u bazama PubMed, Scopus i Web of Science identifikovano je ukupno 196 zapisa relevantnih za temu litijuma i regeneracije perifernih nerava. Nakon uklanjanja duplikata, za početni skrining ostalo je 158 publikacija.

Tokom faze skrininga izvršena je procena naslova i apstrakata svih identifikovanih radova. Isključena su 104 rada zbog nedovoljne povezanosti sa regeneracijom perifernih nerava, odsustva podataka o litijumu ili nedostatka eksperimentalne, translacione ili mehaničke relevantnosti za temu ovog pregleda.

Potpuna analiza teksta sprovedena je za 54 publikacije. Tokom procene podobnosti dodatno je isključeno 28 radova zbog preklapanja podataka, nedostatka originalnih nalaza, odsustva jasne veze sa perifernim

INTRODUCTION

Peripheral nerve injuries (PNIs) are a frequent and clinically significant problem in neurosurgery, orthopedics, and traumatology, often resulting in motor and sensory deficits that can lead to long-term disability and a reduction in patients' quality of life [1]. Despite advances in microsurgical nerve reconstruction techniques, including direct anastomosis, autologous nerve grafting, and the use of nerve conduits, functional recovery remains unpredictable, particularly in cases involving extensive nerve tissue defects or delayed surgical intervention [2,3]. The main limitation of current therapeutic approaches lies not only in the technical restoration of nerve continuity but also in the inherently slow and often incomplete biological processes of axonal regeneration and reinnervation of target structures [4].

Following peripheral nerve injury, Wallerian degeneration occurs in the distal axonal segment and is characterized by fragmentation of the axon and myelin, accompanied by activation of the local immune response and infiltration of macrophages, which contribute to the clearance of cellular debris [5]. In parallel, Schwann cells undergo significant phenotypic reprogramming and transition into a so-called "repair" state, which plays a crucial role in successful nerve regeneration. In this phenotype, they lose their myelinating properties and acquire a regenerative profile characterized by enhanced proliferation and migration, as well as increased expression of neurotrophic factors that support and guide axonal growth [6]. They also form the so-called Bands of Büngner, which serve as guiding structures for regenerating axons toward distal target tissues, providing essential spatial and biochemical support throughout the regeneration process [5]. However, this reparative program is time-limited, and prolonged denervation leads to progressive loss of Schwann cell phenotypic stability, reduced support for axonal growth, and a substantial decline in the nerve's regenerative capacity [4].

METHODOLOGY

A literature search of the PubMed, Scopus, and Web of Science databases identified 196 records relevant to lithium and peripheral nerve regeneration. Following the removal of duplicate records, 158 publications remained for initial screening.

During the screening phase, the titles and abstracts of all identified publications were evaluated. A total of 104 papers were excluded due to insufficient relevance to peripheral nerve regeneration, the absence of data on lithium, or a lack of experimental, translational, or mechanistic relevance to the scope of this review.

nervnim sistemom ili ograničene relevantnosti za regenerativne procese nakon povrede nerva.

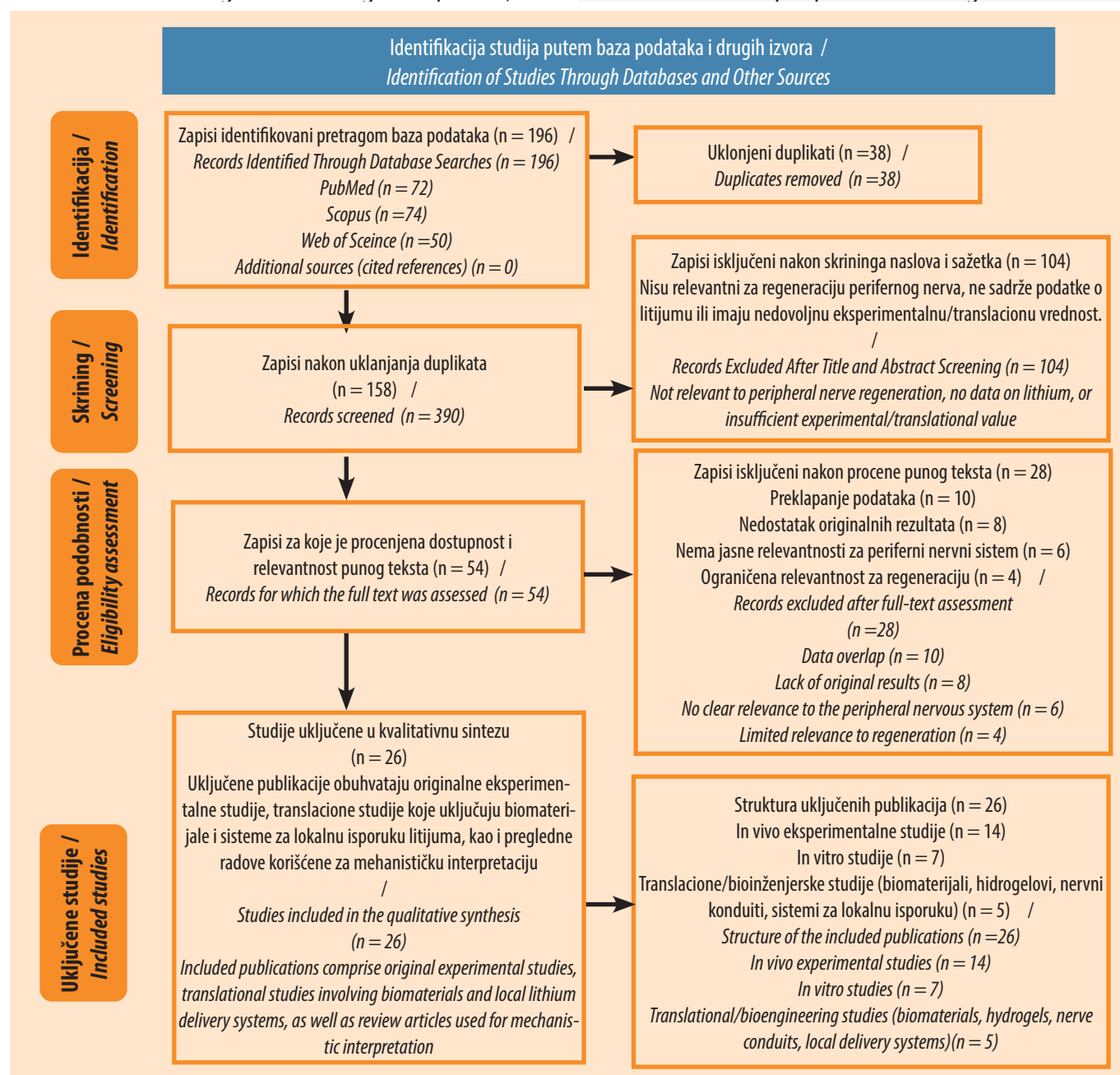
U konačnu kvalitativnu sintezu uključeno je 26 publikacija. Ovaj skup obuhvatao je originalne in vivo i in vitro eksperimentalne studije, translacione studije koje su analizirale biomaterijale i sisteme lokalne isporuke litijuma, kao i odabrane pregledne radove korišćene za interpretaciju mehanizama delovanja litijuma, biologije Švanovih ćelija i translacionog značaja regeneracije perifernih nerava.

Struktura uključenih publikacija obuhvatala je:

- 14 in vivo eksperimentalnih studija;
- 7 in vitro studija sa fokusom na Švanove ćelije, neuronske kulture i regenerativne signalne puteve;

Full-text analysis was conducted for 54 publications. During the eligibility assessment, an additional 28 papers were excluded due to overlapping data, lack of original findings, absence of a clear association with the peripheral nervous system, or limited relevance to regenerative processes following nerve injury.

Twenty-six publications were included in the final qualitative synthesis. The selected studies comprised original in vivo and in vitro experimental research, translational studies investigating biomaterials and localized lithium delivery systems, and selected review articles used to contextualize the mechanisms of action of lithium, Schwann cell biology, and the translational relevance of peripheral nerve regeneration.



Slika 1. PRISMA dijagram toka studija kroz faze identifikacije, selekcije i uključivanja. (PRISMA 2020 Flow Diagram).

Figure 1. PRISMA study flow diagram through the stages of identification, selection, and inclusion (PRISMA 2020 Flow Diagram).

- 5 translacionih i bioinženjerskih studija koje su analizirale biomaterijale, hidrogelove, nervne konduite i sisteme lokalne isporuke litijuma.

Proces identifikacije, selekcije, procene podobnosti i uključivanja studija prikazan je u PRISMA dijagramu (Slika 1).

REZULTATI

Neuroregenerativni i neuroprotektivni efekti litijuma u perifernom nervnom sistemu

Dostupna literatura ukazuje na to da litijum poseduje višestruke biološke efekte koji mogu biti relevantni za regeneraciju perifernih nerava, uključujući modulaciju neuronskog preživljavanja, aksonskog rasta i regenerativnog odgovora glijalnih ćelija [7,8]. Iako je prvobitno korišćen u psihijatriji, sve veći broj eksperimentalnih studija ukazuje na njegov širi neurobiološki potencijal, posebno u kontekstu regenerativne medicine [9].

U eksperimentalnim modelima povrede perifernih nerava, litijum je povezan sa poboljšanjem aksonske regeneracije i funkcionalnog oporavka, što je posebno istaknuto u studijama koje analiziraju njegov efekat na regeneraciju nakon traumatske lezije nerva [1]. Ovi efekti se povezuju sa njegovim delovanjem na intracelularne signalne puteve uključene u kontrolu neuronske plastičnosti i preživljavanja, pri čemu se posebno ističe inhibicija GSK-3 β i modulacija pro-survival signalizacije [10].

Pored direktnog uticaja na neurone, litijum ispoljava značajan efekat na glijalne ćelije, naročito Švanove ćelije, koje su ključne u procesu regeneracije perifernih nerava. In vitro studije pokazuju da litijum može stimulisati proliferaciju Švanovih ćelija uz istovremenu inhibiciju njihove migracije, što može doprineti stabilnijem regenerativnom mikrokruženju [11]. Ova promena ćelijskog ponašanja smatra se važnom za organizaciju regenerativnih puteva i podršku aksonskom rastu.

Dodatno, eksperimentalni podaci ukazuju na to da litijum utiče i na procese remijelinizacije, što je potvrđeno u modelima povrede nervnih korena, gde je uočeno poboljšanje funkcionalnog motornog oporavka nakon primene litijuma [3]. Ovi rezultati sugerišu da litijum ne deluje samo na fazu aksonskog rasta, već i na kasnije faze regeneracije, uključujući reorganizaciju mijelinske strukture. Značajan deo njegovog regenerativnog potencijala povezan je i sa indukcijom autofagije, koja je prepoznata kao važan mehanizam u održavanju ćelijske homeostaze i regenerativnog odgovora nakon nervne povrede. Studije ukazuju na to da aktivacija autofagije doprinosi neuroprotektivnim efektima litijuma i unapređuje funkcionalni oporavak nakon povrede nervnog sistema [12,13].

Iako većina dokaza potiče iz perifernih nervnih

The included publications comprised:

- 14 in vivo experimental studies;
- 7 in vitro studies focusing on Schwann cells, neuronal cultures, and regenerative signaling pathways;
- 5 translational and bioengineering studies investigating biomaterials, hydrogels, nerve conduits, and localized lithium delivery systems.

The process of study identification, selection, eligibility assessment, and inclusion is presented in the PRISMA flow diagram (Figure 1).

RESULTS

Neurodegenerative and neuroprotective effects of lithium in the peripheral nervous system

The available literature indicates that lithium exerts multiple biological effects that may be relevant to peripheral nerve regeneration, including the modulation of neuronal survival, axonal growth, and the regenerative responses of glial cells [7,8]. Although originally used in psychiatry, a growing body of experimental evidence suggests that it has broader neurobiological potential, particularly in the field of regenerative medicine [9].

In experimental models of peripheral nerve injury, lithium has been associated with enhanced axonal regeneration and improved functional recovery, with particularly notable effects reported in studies investigating its role following traumatic nerve injury [1]. These effects are associated with its influence on intracellular signaling pathways involved in the regulation of neuronal plasticity and survival, with inhibition of GSK-3 β and modulation of pro-survival signaling pathways being particularly prominent [10].

In addition to its direct effect on neurons, lithium exerts significant effects on glial cells, particularly Schwann cells, which play a central role in peripheral nerve regeneration. In vitro studies indicate that lithium can promote Schwann cell proliferation while simultaneously reducing their migratory activity, potentially contributing to the establishment of a more stable regenerative microenvironment [11]. This change in cellular behavior is thought to play an important role in the organization of regenerative pathways and the support of axonal growth.

Additionally, experimental evidence indicates that lithium may also influence remyelination processes, as demonstrated in nerve root injury models in which lithium administration was associated with improved functional motor recovery [3]. These findings suggest that lithium may influence not only axonal growth but also later stages of regeneration, including the reorganization of myelin structure. A substantial component of its regenerative potential may also be related

modela, deo mehanističkih uvida dolazi iz studija centralnog nervnog sistema, uključujući modele retinalne degeneracije i moždanog udara, gde je takođe zabeležen neuroprotektivni efekat litijuma [2,14]. Međutim, ovi rezultati se moraju tumačiti sa oprezom, s obzirom na fundamentalne razlike u regenerativnom kapacitetu centralnog i perifernog nervnog sistema.

Pored klasičnih farmakoloških oblika, novija istraživanja ukazuju i na potencijal savremenih formulacija litijuma, uključujući nano-strukturisane sisteme i biomaterijale, koji omogućavaju lokalizovano delovanje i produženo oslobađanje leka, čime se dodatno poboljšava njegov regenerativni efekat uz smanjenje sistemске izloženosti [15,16].

Uloga litijuma u funkciji Švanovih ćelija i procesu remijelinizacije

Švanove ćelije predstavljaju centralni celularni element regeneracije perifernog nervnog sistema, jer nakon povrede prolaze kroz proces fenotipske transformacije u tzv. stanje „popravke“ koje omogućava podršku aksonskom rastu, fagocitozu mijelinskih ostataka i formiranje regenerativnih puteva [4,5]. Ovaj adaptivni odgovor, iako visoko efikasan u ranoj fazi regeneracije, ostaje vremenski ograničen i podložan progresivnoj disfunkciji u uslovima produžene denervacije, što direktno kompromituje ishod nervne reparacije [6].

U ovom kontekstu, litijum se pojavljuje kao farmakološki modulatorski agens koji utiče na proliferativno i funkcionalno ponašanje Švanovih ćelija. In vitro studije pokazuju da litijum može značajno povećati proliferaciju Švanovih ćelija uz istovremenu supresiju njihove migracije, što se interpretira kao stabilizacija ćelijskog odgovora u regenerativnom mikrookruženju [11]. Ovakav efekat može doprineti efikasnijem usmeravanju regenerišućih aksona i očuvanju strukturalne organizacije regenerativnih traktova.

Pored uticaja na ćelijsku dinamiku, litijum ima značajnu ulogu u procesima remijelinizacije. U eksperimentalnom modelu povrede nervnih korena, primena litijuma je dovela do ubrzane remijelinizacije regenerišućih aksona, uz korelaciju sa poboljšanjem funkcionalnog motornog oporavka [3]. Ovi rezultati govore da litijum ne deluje isključivo na ranu fazu regeneracije, već i na kasniju fazu reorganizacije mijelinske ovojnice, što je ključno za obnovu brzine i efikasnosti nervne provodljivosti.

Dodatno, noviji podaci ukazuju na to da litijum može indirektno uticati na Švanove ćelije kroz modulaciju autofagije, čime se poboljšava njihova metabolička adaptacija i regenerativni kapacitet. Aktivacija autofagičnih puteva povezana je sa održavanjem ćelijske homeostaze i efikasnijim odgovorom na povredu, što dodatno doprinosi regeneraciji nervnog tkiva [12,13].

to the induction of autophagy, which is recognized as an important mechanism for maintaining cellular homeostasis and supporting the regenerative response following nerve injury. Studies suggest that autophagy activation contributes to the neuroprotective effects of lithium and may enhance functional recovery after nervous system injury [12,13].

Although most of the available evidence is derived from peripheral nerve models, some mechanistic insights come from studies of the central nervous system, including models of retinal degeneration and stroke, in which lithium has also demonstrated neuroprotective effects [2,14]. However, these findings should be interpreted with caution, given the fundamental differences in the regenerative capacity of the central and peripheral nervous systems.

In addition to conventional pharmacological formulations, recent research highlights the potential of advanced lithium delivery systems, including nano-structured formulations and biomaterials, which enable localized action and sustained drug release. These approaches may enhance the regenerative effects of lithium while minimizing systemic exposure [15,16].

The role of lithium in Schwann cell function and remyelination

Schwann cells are the central cellular mediators of peripheral nervous system regeneration. Following injury, they undergo phenotypic reprogramming into a so-called “repair” state that enables them to support axonal growth, facilitate the clearance of myelin debris through phagocytosis, and form regenerative pathways [4,5]. This adaptive response, although highly effective during the early stages of regeneration, is time-limited and progressively deteriorates with prolonged denervation, thereby compromising the overall outcome of nerve repair [6].

In this context, lithium appears to act as a pharmacological modulator of Schwann cell proliferation and function. In vitro studies indicate that lithium can significantly enhance Schwann cell proliferation while simultaneously suppressing their migratory activity, which may contribute to stabilization of the cellular response within the regenerative microenvironment [11]. This effect may contribute to more efficient guidance of regenerating axons and preservation of the structural organization of regenerative pathways.

In addition to modulating cellular dynamics, lithium appears to play a significant role in the remyelination process. In an experimental model of nerve root injury, lithium administration accelerated the remyelination of regenerating axons and was associated with improved functional motor recovery [3]. These findings indicate that lithium may influence not only the early

Savremeni pristupi takođe ukazuju na značaj kombinacije litijuma sa biomaterijalnim nosačima, pri čemu lokalna isporuka omogućava direktnu modulaciju Švanovih ćelija u zoni povrede. Biomaterijali kao što su hidrogelni sistemi i kompozitne strukture omogućavaju kontrolisano oslobađanje litijuma i stvaranje mikrookruženja pogodnog za Švanovu ćelijsku diferencijaciju i regeneraciju [15,16]. U takvim sistemima zabeležena je poboljšana interakcija između Švanovih ćelija i regenerišućih aksona, što dodatno podržava funkcionalni oporavak.

Sveukupno, dostupni podaci ukazuju na to da litijum deluje na više nivoa Švanove biologije, od proliferacije i fenotipske stabilizacije, preko regulacije autofagije, do podrške remijelinizaciji, čime se pozicionira kao potencijalni farmakološki modulatorski faktor u strategijama regeneracije perifernih nerava.

Eksperimentalni modeli i translacioni dokazi o efektima litijuma

Eksperimentalni dokazi o ulozi litijuma u regeneraciji nervnog sistema najvećim delom potiču iz in vivo modela povrede perifernih nerava, gde se procenjuju aksonski rast, remijelinizacija i funkcionalni oporavak nakon traume. U modelima avulzije i reimplantacije nervnih korenova, primena litijuma je bila povezana sa ubrzanjem funkcionalnog motornog oporavka, pri čemu se ovaj efekat dovodi u vezu sa poboljšanom remijelinizacijom regenerisanih aksona [3]. Ovi rezultati ukazuju na to da litijum može imati značajan uticaj ne samo na ranu fazu regeneracije, već i na kvalitet ponovnog uspostavljanja nervne provodljivosti.

U modelima povrede perifernog nerva kod glodara, dodatno je pokazano da kombinovana primena litijuma i neurotrofnih faktora, kao što je glijalni neurotrofni faktor (GDNF), može imati sinergistički efekat na regeneraciju nerva, što se ogleda u poboljšanoj reorganizaciji regenerativnih vlakana i funkcionalnom ishodu [17]. Ovi podaci sugerišu da se efekti litijuma mogu dodatno potencirati u kombinovanim terapijskim strategijama koje ciljaju više komponenti regenerativnog mikrookruženja.

Pored klasičnih modela perifernih nerava, deo eksperimentalnih dokaza potiče i iz studija na optičkom nervu i retinalnim ganglijskim ćelijama. U tim modelima litijum je bio povezan sa povećanim preživljavanjem ganglijskih ćelija i delimičnom stimulacijom aksonskog rasta nakon povrede optičkog nerva. Iako ovi nalazi potvrđuju neuroprotektivni potencijal litijuma, njihova direktna primena na periferne nerve mora se tumačiti sa oprezom zbog fundamentalnih razlika u regenerativnim sposobnostima centralnog i perifernog nervnog sistema [2,18].

phase of nerve regeneration but also the later stages of myelin sheath reorganization, which are crucial for restoring the speed and efficiency of nerve conduction.

Additionally, recent evidence suggests that lithium may indirectly influence Schwann cells by modulating autophagy, thereby enhancing their metabolic adaptation and regenerative capacity. Activation of autophagic pathways contributes to the maintenance of cellular homeostasis and promotes a more effective response to injury, further supporting peripheral nerve tissue regeneration [12,13].

Modern approaches also highlight the importance of combining lithium with biomaterial-based delivery systems, in which localized drug release enables direct modulation of Schwann cells at the site of injury. Biomaterials such as hydrogels and composite scaffolds can facilitate controlled lithium release while creating a regenerative microenvironment conducive to Schwann cell differentiation and peripheral nerve repair [15,16]. In such systems, enhanced interactions between Schwann cells and regenerating axons have been reported, further supporting functional recovery.

Overall, the available evidence indicates that lithium acts at multiple levels of Schwann cell biology, ranging from the regulation of proliferation and phenotypic stabilization to the modulation of autophagy and support of remyelination. These multifaceted effects position lithium as a potential pharmacological modulator in strategies aimed at promoting peripheral nerve regeneration.

Experimental models and translational evidence for the effects of lithium

Experimental evidence supporting a role for lithium in nervous system regeneration derives mostly from in vivo models of peripheral nerve injury, in which axonal growth, remyelination, and functional recovery after trauma are evaluated. In models of nerve root avulsion and reimplantation, lithium administration was associated with accelerated functional motor recovery, this effect being attributed to enhanced remyelination of regenerated axons [3]. These findings indicate that lithium may exert a significant influence not only during the early stages of regeneration but also on the quality of restored nerve conduction.

In rodent models of peripheral nerve injury, combined administration of lithium and neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), has further been shown to exert synergistic effects on nerve regeneration, as evidenced by enhanced reorganization of regenerating nerve fibers and improved functional outcomes [17]. These findings suggest that the effects of lithium may be further potentiated through

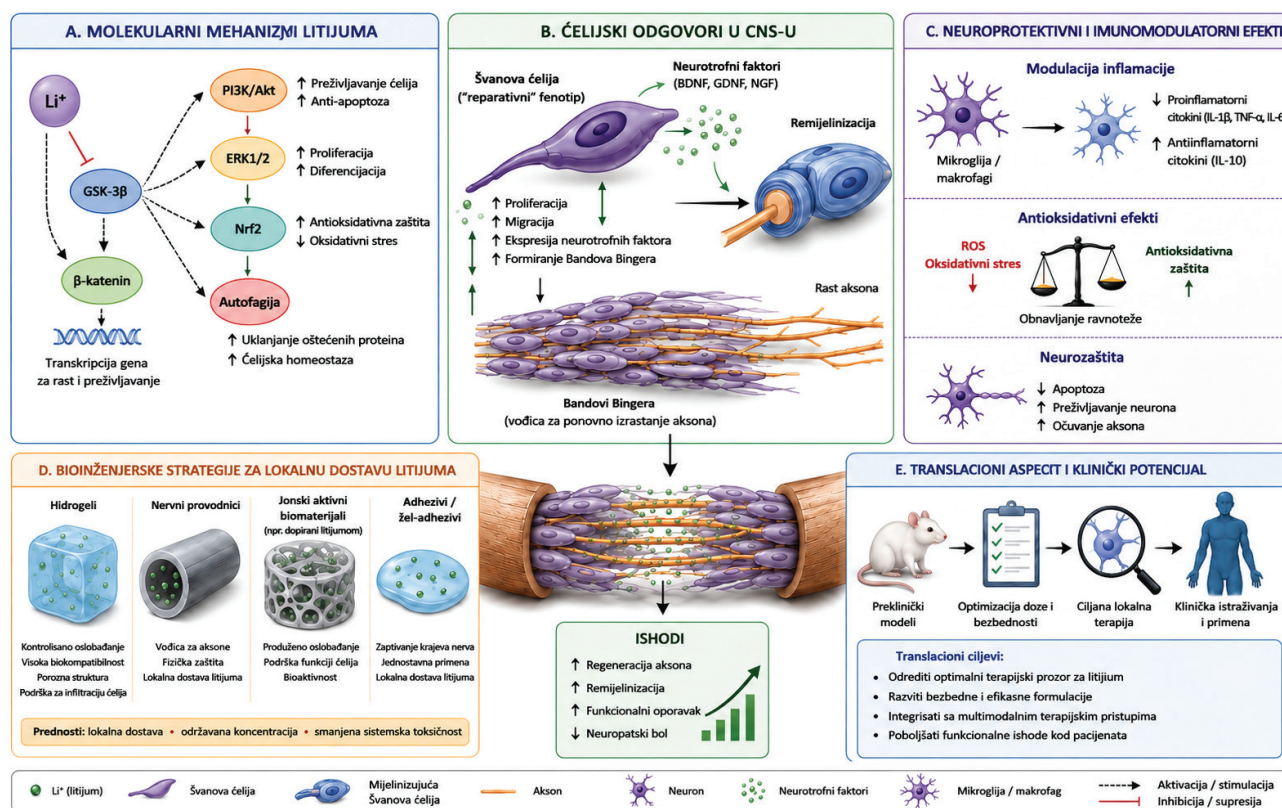
Dodatni translacioni uvidi potiču iz studija moždanog udara i spinalne povrede, gde je litijum pokazao sposobnost da modulira neuroinflamaciju i aktivira pro-survival signalne puteve, uključujući povećanje ekspresije miR-124 i inhibiciju GSK-3 β zavisnih i nezavisnih mehanizama. Iako ovi podaci nisu direktno vezani za periferne nerve, oni pružaju mehanističku osnovu za razumevanje šireg neuroprotektivnog delovanja litijuma [14].

U novijim istraživanjima naglasak se pomera ka bioinženjerskim strategijama koje omogućavaju lokalizovanu isporuku litijuma u zoni povrede. Upotreba adhezivnih sistema i biomaterijala sa inkorporiranim litijumom pokazala je poboljšanje regeneracije aksona i ponovnog uspostavljanja nervnog kontinuiteta u eksperimentalnim modelima transekcije nerva. Slično tome, primena hidrogelnih i kompozitnih sistema omogućava stvaranje stabilnog mikrookruženja koje podržava regeneraciju i funkciju ćelija uključenih u proces oporavka [15,16].

combination therapeutic strategies targeting multiple components of the regenerative microenvironment.

In addition to classical models of peripheral nerve injury, experimental evidence has also been derived from studies of the optic nerve and retinal ganglion cells. In these models, lithium administration was associated with increased ganglion cell survival and partial stimulation of axonal growth following optic nerve injury. Although these findings further support the neuroprotective potential of lithium, their direct extrapolation to peripheral nerve regeneration should be interpreted with caution, given the fundamental differences in the regenerative capacities of the central and peripheral nervous systems [2,18].

Additional translational insights come from studies of stroke and spinal cord injury, in which lithium has been shown to modulate neuroinflammatory responses and activate pro-survival signaling pathways, including the upregulation of miR-124 expression and the inhibition of both GSK-3 β -dependent and GSK-3 β -in-



Slika 2. Mehanički pregled uloge litijuma u regeneraciji perifernih nerava.

Prikazani su ključni molekularni, ćelijski i translacioni mehanizmi delovanja litijuma u regeneraciji perifernog nervnog sistema. Litijum inhibicijom GSK-3 β i modulacijom signalnih puteva PI3K/Akt, ERK1/2 i β -katenina podstiče ćelijsko preživljavanje, neuroplastičnost, proliferaciju Švanovih ćelija i aksonalni rast. Pored toga, aktivacijom autofagije, smanjenjem oksidativnog stresa i regulacijom neuroinflamacije stvara povoljno mikrookruženje za regeneraciju nervnog tkiva. Savremene bioinženjerske strategije, uključujući hidrogelove, nervne konduite, jonski aktivne biomaterijale i bioadhezive sa litijumom, omogućavaju lokalnu i kontrolisanu isporuku litijuma na mestu povrede, što može doprineti efikasnijoj remijelinizaciji, funkcionalnom oporavku i smanjenju sistemske toksičnosti.

Napomena: Slika je generisana korišćenjem alata zasnovanih na veštačkoj inteligenciji za potrebe vizuelne sinteze dostupnih naučnih podataka i naknadno pregledana i prilagođena od strane autora u skladu sa literaturom analiziranom u ovom radu. Prikaz služi isključivo kao konceptualna ilustracija i ne predstavlja originalne eksperimentalne rezultate.

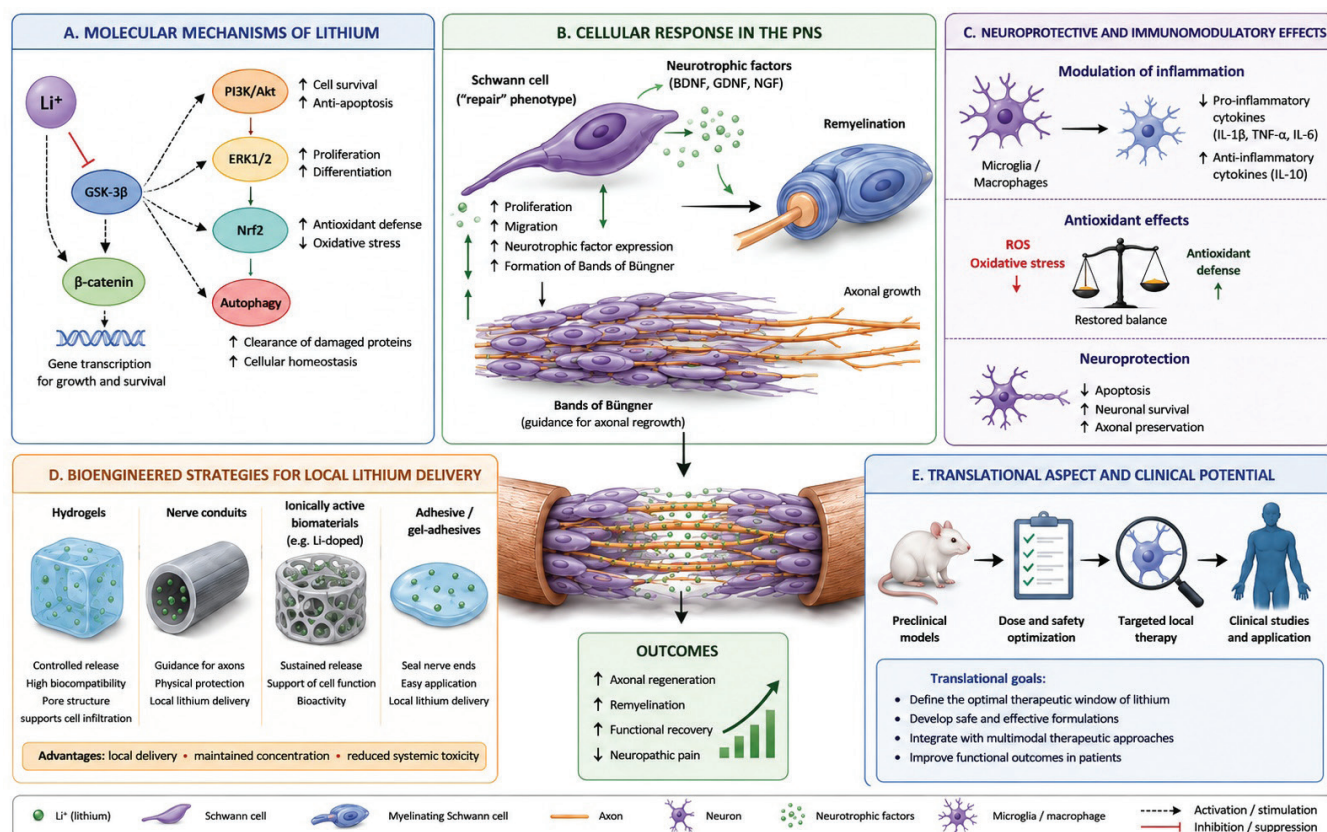


Figure 2. A mechanistic overview of the role of lithium in peripheral nerve regeneration.

The key molecular, cellular, and translational mechanisms of lithium action in peripheral nervous system regeneration are presented. By inhibiting GSK-3 β and modulating the PI3K/Akt, ERK1/2, and β -catenin signaling pathways, lithium promotes cell survival, neuroplasticity, Schwann cell proliferation, and axonal growth. In addition, by activating autophagy, reducing oxidative stress, and regulating neuroinflammation, it creates a favorable microenvironment for nerve tissue regeneration. Modern bioengineering strategies, including hydrogels, nerve conduits, ionically active biomaterials, and lithium-containing bioadhesives, enable the local and controlled delivery of lithium at the site of injury, which may contribute to more efficient remyelination, functional recovery, and reduced systemic toxicity.

Note: The image was generated using artificial intelligence-based tools for the visual synthesis of available scientific data and was subsequently reviewed and adjusted by the authors in accordance with the literature analyzed in this paper. The image is intended solely as a conceptual illustration and does not represent original experimental results.

U širem kontekstu, savremeni biomaterijali kao što su hidrogelovi i konduiti sa jonskom provodljivošću dodatno doprinose optimizaciji lokalne isporuke i biološke kompatibilnosti regenerativnih sistema, čime se otvara mogućnost precizne kontrole mikrookruženja nervne regeneracije [19].

Sveukupno posmatrano, eksperimentalni podaci ukazuju na to da litijum pokazuje konzistentne neuroregenerativne i neuroprotektivne efekte u različitim modelima, pri čemu su najizraženiji rezultati uočeni u perifernim nervnim modelima i u kombinaciji sa bioinženjerskim strategijama lokalne isporuke. Sažeti prikaz najvažnijih molekularnih, ćelijskih i tkivnih mehanizama putem kojih litijum doprinosi regeneraciji perifernih nerava prikazan je na Slici 2.

Molekularni mehanizmi delovanja litijuma u regeneraciji perifernih nerava

Molekularni efekti litijuma predstavljaju osnovu njegovog neuroprotektivnog i neuroregenerativnog poten-

dependent mechanisms. Although these findings are not directly related to peripheral nerve regeneration, they provide a mechanistic basis for understanding the broader neuroprotective effects of lithium [14].

Recent research has increasingly focused on bioengineering strategies that enable the localized delivery of lithium to the site of nerve injury. The use of lithium-incorporated adhesive systems and biomaterials has been shown to enhance axonal regeneration and facilitate the restoration of nerve continuity in experimental models of nerve transection. Similarly, hydrogel-based and composite systems can establish a stable microenvironment that supports the regeneration and functional activity of cells involved in the recovery process [15,16].

In a broader context, advanced biomaterials, including hydrogels and ionically conductive nerve conduits, may further optimize the localized delivery and biocompatibility of regenerative systems, thereby offering the potential for precise modulation of the microenvironment during nerve regeneration [19].

cijala. Iako je litijum decenijama korišćen kao stabilizator raspoloženja u psihijatriji, savremena istraživanja pokazala su da njegovo delovanje obuhvata veliki broj intracelularnih signalnih puteva uključenih u preživljavanje neurona, aksonski rast, plastičnost nervnog sistema i odgovor glijalnih ćelija na povredu [7,8].

Najistraženiji mehanizam delovanja litijuma jeste inhibicija glikogen sintaza kinaze-3 β (GSK-3 β), enzima koji ima centralnu ulogu u regulaciji ćelijskog rasta, diferencijacije i apoptotskih procesa. Inhibicijom GSK-3 β dolazi do aktivacije Wnt/ β -katenin signalnog puta, što rezultuje povećanom ekspresijom gena odgovornih za ćelijsko preživljavanje, proliferaciju i regeneraciju nervnog tkiva [9,10]. Aktivacija ovog signalnog sistema posebno je značajna nakon povrede nerva, kada je neophodno obezbediti održavanje regenerativnog fenotipa Švanovih ćelija i stimulisati produžavanje aksona.

Pored GSK-3 β signalizacije, litijum utiče i na PI3K/Akt i ERK1/2 puteve, koji predstavljaju ključne regulatorne sisteme ćelijskog preživljavanja. Aktivacijom ovih signalnih kaskada povećava se otpornost neurona na oksidativni stres i smanjuje aktivacija proapoptotskih mehanizama, čime se stvara povoljnije mikrookruženje za regeneraciju [7,10]. Ovakvi efekti imaju poseban značaj u ranim fazama nakon povrede kada sekundarna degeneracija može značajno ograničiti regenerativni potencijal nerva.

Jedan od najznačajnijih molekularnih efekata litijuma odnosi se na regulaciju ekspresije antiapoptotskog proteina Bcl-2. Sprovedena studija pokazala je da litijum povećava ekspresiju Bcl-2, što rezultuje povećanim preživljavanjem neurona i stimulacijom aksonske regeneracije nakon povrede optičkog nerva [2]. Ovi rezultati kasnije su potvrđeni i u drugim modelima nervnog oštećenja, sugerišući da Bcl-2 predstavlja jednu od ključnih molekularnih karika preko kojih litijum ostvaruje svoje neuroprotektivne efekte.

Poslednjih godina posebna pažnja usmerena je na ulogu autofagije u regeneraciji nervnog sistema. Autofagija omogućava uklanjanje oštećenih organela i proteinskih agregata, čime doprinosi održavanju ćelijske homeostaze i metaboličke stabilnosti. Litijum aktivira autofagične procese putem mehanizama koji delimično zavise od inhibicije inozitol-monofosfataze i modulacije mTOR signalizacije [13]. Eksperimentalne studije pokazale su da ovakva aktivacija autofagije doprinosi očuvanju funkcije Švanovih ćelija, povećava otpornost neurona na stres i poboljšava funkcionalni oporavak nakon povrede nervnog sistema [12,16].

Dodatno, litijum pokazuje sposobnost regulacije neuroinflamatornih procesa. Nakon povrede perifernog nerva aktiviraju se brojni inflamatorni medijatori koji mogu imati i protektivne i štetne efekte. Litijum

Taken together, the experimental evidence indicates that lithium exerts consistent neuroregenerative and neuroprotective effects across a range of experimental models, with the most pronounced effects observed in peripheral nerve injury models and in combination with bioengineered strategies for localized delivery. A summary of the principal molecular, cellular, and tissue-level mechanisms through which lithium contributes to peripheral nerve regeneration is presented in Figure 2.

Molecular mechanisms underlying the effects of lithium on peripheral nerve regeneration

The molecular effects of lithium are the basis of its neuroprotective and neuroregenerative potential. Although lithium has been used as a mood stabilizer in psychiatry for decades, contemporary research has demonstrated that its effects involve multiple intracellular signaling pathways that regulate neuronal survival, axonal growth, nervous system plasticity, and glial responses to injury [7,8].

The most extensively investigated mechanism of lithium action is the inhibition of glycogen synthase kinase-3 β (GSK-3 β), an enzyme that plays a central role in regulating cellular growth, differentiation, and apoptotic processes. Inhibition of GSK-3 β activates the Wnt/ β -katenin signaling pathway, thereby promoting the expression of genes involved in cell survival, proliferation, and neural tissue regeneration [9,10]. Activation of this signaling pathway is particularly important following nerve injury, when the maintenance of the regenerative phenotype of Schwann cells and the stimulation of axonal elongation are essential for effective nerve regeneration.

In addition to GSK-3 β signaling, lithium also modulates the PI3K/Akt and ERK1/2 pathways, which constitute key regulatory systems governing cellular survival. Activation of these signaling cascades enhances neuronal resistance to oxidative stress and attenuates pro-apoptotic mechanisms, thereby creating a more favorable microenvironment for nerve regeneration [7,10]. These effects are particularly important during the early stages following nerve injury, when secondary degeneration can substantially compromise the regenerative capacity of the nerve.

One of the most significant molecular effects of lithium involves the regulation of the anti-apoptotic protein Bcl-2. Studies have demonstrated that lithium increases Bcl-2 expression, thereby promoting neuronal survival and stimulating axonal regeneration following optic nerve injury [2]. These findings were subsequently corroborated in other models of nerve injury, suggesting that Bcl-2 represents a key molecular mediator through which lithium exerts its neuroprotective effects.

utiče na ekspresiju mikroRNK, posebno miR-124, koja učestvuje u kontroli neuroinflamatornog odgovora i smanjenju ekspresije proinflamatornih transkripcijskih faktora [14]. Time se omogućava uspostavljanje povoljnijeg regenerativnog mikrokruženja koje podržava aksonski rast i remijelinizaciju.

Posmatrano u celini, litijum deluje kao višeciljni molekularni regulator koji istovremeno moduliše procese ćelijskog preživljavanja, plastičnosti, autofagije, neuroinflamacije i regeneracije. Upravo ova sposobnost integracije različitih bioloških puteva razlikuje litijum od većine konvencionalnih neuroprotektivnih agenasa i predstavlja osnovu njegovog potencijala u regenerativnoj medicini perifernog nervnog sistema.

Biomaterijali i sistemi lokalne isporuke litijuma

Jedan od glavnih izazova u translaciji litijuma iz eksperimentalnih modela u kliničku praksu jeste postizanje dovoljne koncentracije u zoni povrede uz istovremeno minimiziranje sistemske izloženosti i mogućih neželjenih efekata. Zbog toga se poslednjih godina intenzivno razvijaju bioinženjerski sistemi za lokalnu i kontrolisanu isporuku litijuma, koji omogućavaju produženo oslobađanje leka direktno u regenerativnom mikrokruženju [15,20].

Među najperspektivnijim pristupima izdvajaju se hidrogelni sistemi. Hidrogelovi predstavljaju trodimenzionalne biomaterijalne mreže sposobne da apsorbuju velike količine vode i istovremeno obezbede fizičku podršku ćelijama uključenim u regeneraciju. Babaei i saradnici pokazali su da kompozitni hidrogelovi sa inkorporiranim litijum-hloridom mogu stimulisati proliferaciju neuralnih matičnih ćelija, njihovu diferencijaciju i rast neurita, stvarajući mikrokruženje pogodno za regeneraciju nervnog tkiva [20]. Kontrolisano oslobađanje litijuma iz hidrogelova omogućava dugotrajan biološki efekat bez potrebe za visokim sistemskim dozama.

Pored hidrogelova, značajan napredak ostvaren je u razvoju adhezivnih biomaterijala. Bu i saradnici razvili su bioadhezivnu platformu zasnovanu na poli(e-tilen-glikolu) sa inkorporiranim litijumom, koja omogućava povezivanje presečenih nervnih segmenata uz istovremeno lokalno oslobađanje jona litijuma [15]. U eksperimentalnim modelima ovaj sistem doveo je do značajnog poboljšanja aksonske regeneracije i funkcionalnog oporavka. Savremeni trendovi uključuju i upotrebu nanomaterijala kao nosača litijuma. Primer su upravo karbonizovane polimerne nanočestice dopirane litijumom koje aktiviraju autofagiju Švanovih ćelija i pospešuju regeneraciju perifernih nerava [16]. Ovakvi sistemi omogućavaju precizniju kontrolu kinetike oslobađanja litijuma i potencijalno smanjenje sistemske toksičnosti.

In recent years, increasing attention has been directed toward the role of autophagy in nervous system regeneration. Autophagy facilitates the removal of damaged organelles and protein aggregates, thereby contributing to the maintenance of cellular homeostasis and metabolic stability. Lithium promotes autophagic activity through mechanisms that are partially dependent on the inhibition of inositol monophosphatase and modulation of mTOR signaling [13]. Experimental studies have demonstrated that activation of autophagy contributes to the preservation of Schwann cell function, enhances neuronal resistance to cellular stress, and promotes functional recovery following nervous system injury [12,16].

Additionally, lithium has been shown to modulate neuroinflammatory processes. Following peripheral nerve injury, numerous inflammatory mediators are activated, exerting both protective and detrimental effects. Lithium influences the expression of microRNAs, particularly miR-124, which plays a role in regulating the neuroinflammatory response and suppressing the expression of pro-inflammatory transcription factors [14]. This contributes to the establishment of a more favorable regenerative microenvironment that supports axonal growth and remyelination.

Taken together, the available evidence indicates that lithium functions as a multi-target molecular regulator, simultaneously modulating cellular survival, plasticity, autophagy, neuroinflammation, and regenerative processes. This capacity to influence multiple interconnected biological pathways distinguishes lithium from many conventional neuroprotective agents and underpins its potential application in the regenerative medicine of the peripheral nervous system.

Biomaterials and localized lithium delivery systems

One of the main challenges in translating lithium from experimental models to clinical practice lies in achieving adequate lithium concentrations at the site of injury while minimizing systemic exposure and the associated risk of adverse effects. Consequently, recent years have witnessed intensive development of bioengineering-based systems for the localized and controlled delivery of lithium, designed to facilitate its sustained release directly within the regenerative microenvironment [15,20].

Hydrogel-based systems represent one of the most promising approaches in this field. Hydrogels are three-dimensional biomaterial networks capable of absorbing substantial amounts of water while simultaneously providing structural support for cells involved in tissue regeneration. Babaei et al. demonstrated that composite hydrogels incorporating lithium chloride can

Posebnu pažnju privukli su grafenski biomaterijali zbog svojih mehaničkih, električnih i bioloških karakteristika. Grafenski kompoziti mogu služiti kao provodljive platforme koje istovremeno podržavaju rast neurita i omogućavaju inkorporaciju bioaktivnih molekula, uključujući litijum [19,21]. Slično tome, savremena istraživanja nanomaterijala ukazuju na to da kombinacija litijuma sa nano-strukturisanim biomaterijalima može dodatno stimulirati neuritogenezu i ćelijsku diferencijaciju [20,22].

Novi razvojni pravac predstavljaju jonski provodljivi nervni konduiti. Huang i saradnici pokazali su da hidrogelom ispunjeni konduiti sa sposobnošću jonske provodljivosti stvaraju mikrokruženje koje oponaša fiziološke karakteristike nervnog tkiva i značajno poboljšavaju regeneraciju perifernih nerava [19]. Integracija litijuma u ovakve sisteme mogla bi predstavljati sledeći korak u razvoju inteligentnih biomaterijala za regenerativnu medicinu.

Sveukupno, biomaterijali omogućavaju prelazak sa sistemske primene litijuma ka preciznoj lokalnoj terapiji. Kombinacija kontrolisanog oslobađanja, biokompatibilnosti i sposobnosti modulacije ćelijskog mikrokruženja čini ove sisteme jednim od najvažnijih translacionih pravaca budućeg razvoja regenerativnih terapija perifernih nerava.

Kombinovane i sinergističke regenerativne strategije: litijum kao centralni neuromodulator

Savremeni koncept regenerativne medicine sve više napušta pristup zasnovan na pojedinačnim terapijskim agensima i usmerava se ka kombinovanim strategijama koje simultano deluju na više bioloških mehanizama uključenih u regeneraciju nervnog tkiva. U tom kontekstu litijum se izdvaja kao posebno zanimljiv kandidat zbog svoje sposobnosti da istovremeno moduliše neuronsko preživljavanje, Švanovu ćelijsku plastičnost, neuroinflamaciju, autofagiju i remijelinizaciju [1,10,13].

Jedan od prvih dokaza o potencijalnoj sinergiji litijuma sa drugim regenerativnim pristupima prikazan je u studiji Lin i saradnika, gde je kombinacija litijum-hlorida i GDNF-a dovela do izraženijeg aksonskog rasta i funkcionalnog oporavka u odnosu na pojedinačne terapije. Ovi rezultati ukazuju na to da litijum može pojačavati efekte neurotrofičnih faktora i time doprineti stvaranju efikasnijeg regenerativnog mikrokruženja [17].

Posebno značajan doprinos ovom konceptu predstavlja hipoteza trojne neuromodulatorne ose. U ovom modelu litijum se posmatra kao centralni regulator koji deluje sinergistički sa ekstraktima gljive *Hericium erinaceus* i vitaminom B12. Prema ovoj hipotezi, svaka od tri komponente cilja različite, ali međusobno povezane biološke procese. Litijum dominantno moduliše intra-

stimulate the proliferation and differentiation of neural stem cells, as well as neurite outgrowth, thereby establishing a microenvironment suitable for nerve tissue regeneration [20]. Controlled lithium release from hydrogel-based systems enables long-lasting biological effect while minimizing the need for high systemic doses.

In addition to hydrogels, considerable progress has been made in the development of adhesive biomaterials. Bu et al. developed a bioadhesive platform based on lithium-incorporated poly(ethylene glycol), which enables the approximation and connection of severed nerve segments while simultaneously providing localized release of lithium ions [15]. In experimental models, this system led to significant improvements in axonal regeneration and functional recovery. Contemporary approaches also include the use of nanomaterials as lithium carriers. One such example is represented by carbonized polymer nanoparticles doped with lithium, which activate autophagy in Schwann cells and promote peripheral nerve regeneration [16]. These systems offer more precise control over lithium release kinetics and may thereby contribute to reducing systemic toxicity.

Graphene-based biomaterials have attracted particular attention owing to their mechanical, electrical, and biological properties. Graphene composites can function as conductive platforms that support neurite outgrowth while also enabling the incorporation of bioactive molecules, including lithium [19,21]. Similarly, current research on nanomaterials indicates that combining lithium with nanostructured biomaterials can further enhance neuritogenesis and cellular differentiation [20,22].

A further emerging direction involves the development of ion-conducting nerve conduits. Huang et al. demonstrated that hydrogel-filled conduits with ionic conductivity create a microenvironment that mimics the physiological characteristics of nerve tissue and significantly enhances peripheral nerve regeneration [19]. The integration of lithium into such systems could represent a further step in the development of intelligent biomaterials for regenerative medicine.

Overall, biomaterials facilitate the transition from systemic lithium administration to precise local therapy. The combination of controlled release, biocompatibility, and the capacity to modulate the cellular microenvironment makes these systems one of the most important translational directions for the future development of peripheral nerve regenerative therapies.

Combined and Synergistic Regenerative Strategies: Lithium as a Central Neuromodulator

The contemporary concept of regenerative medicine is increasingly moving beyond the use of individual therapeutic agents toward combined strategies that

celularnu signalizaciju, autofagiju i ćelijsko preživljavanje; *Hericium erinaceus* stimuliše sintezu neurotrofičnih faktora i neuritogenezu; vitamin B12 podržava remijelinizaciju, metabolički integritet neurona i regeneraciju nervnog vlakna [23].

Koncept trojne neuromodulatorne ose posebno je značajan jer prevazilazi tradicionalni redukcionistički pristup regeneraciji perifernih nerava. Umesto fokusiranja na jedan signalni put ili jednu ćelijsku populaciju, predloženi model integriše više nivoa biološke organizacije, od molekularnih signalnih mreža do funkcionalnog oporavka nerva. Takav pristup je u skladu sa savremenim shvatanjem da uspešna regeneracija zahteva koordinisanu interakciju neurona, Švanovih ćelija, imunoloških ćelija i ekstracelularnog matriksa [4,6].

Dodatni potencijal ovakvih kombinovanih strategija proizlazi iz mogućnosti njihove integracije sa savremenim biomaterijalima. Litijum, neurotrofični faktori i metabolički modulatori mogu se inkorporirati u hidrogelove, nervne konduite ili nano-strukturisane sisteme za lokalnu isporuku, čime se postiže prostorno i vremenski kontrolisana terapijska aktivnost. Na taj način moguće je objediniti farmakološku modulaciju i bioinženjersku podršku regenerativnom procesu [15,19,20].

Posmatrano iz translacione perspektive, litijum se sve više pozicionira ne samo kao samostalni neuroregenerativni agens, već kao centralna komponenta multimodalnih terapijskih strategija. Njegova sposobnost da poveže neurotrofične, metaboličke, glijalne i imunološke mehanizme čini ga pogodnim kandidatom za razvoj sledeće generacije personalizovanih regenerativnih terapija. U tom smislu, hipoteza trojne neuromodulatorne ose predstavlja važan teorijski okvir za buduća eksperimentalna i klinička istraživanja usmerena ka optimizaciji oporavka nakon povreda perifernih nerava.

DISKUSIJA

Rezultati ovog sistematskog pregleda ukazuju na to da litijum predstavlja jedan od najperspektivnijih farmakoloških modulatora regeneracije perifernih nerava među trenutno dostupnim eksperimentalnim terapijama. Za razliku od pristupa koji ciljaju pojedinačne komponente regenerativnog odgovora, litijum deluje na više međusobno povezanih bioloških nivoa, uključujući preživljavanje neurona, plastičnost Švanovih ćelija, remijelinizaciju, aksonalni rast, autofagiju i regulaciju inflamatornog odgovora [1,7–10,13].

Ovakva multimodalnost može predstavljati značajnu prednost u poređenju sa strategijama koje se oslanjaju isključivo na neurotrofne faktore ili biomaterijalne platforme. Jedan od najkonzistentnijih rezultata analiziranih studija odnosi se na uticaj litijuma na Švanove ćelije, koje predstavljaju centralne efektorske

simultaneously target multiple biological mechanisms involved in nerve tissue regeneration. In this context, lithium represents a particularly promising candidate owing to its ability to simultaneously modulate neuronal survival, Schwann cell plasticity, neuroinflammation, autophagy, and remyelination [1,10,13].

One of the earliest indications of the potential synergy between lithium and other regenerative approaches was provided by a study by Lin et al., in which the combination of lithium chloride and GDNF resulted in more pronounced axonal growth and functional recovery compared with either treatment alone. These findings indicate that lithium may enhance the effects of neurotrophic factors and thereby contribute to the development of a more effective regenerative microenvironment [17].

A particularly significant contribution to this concept is the hypothesis of a triple neuromodulatory axis. Within this model, lithium is regarded as a central regulator that acts synergistically with extracts of the mushroom *Hericium erinaceus* and vitamin B12. According to this hypothesis, each of the three components targets distinct but interrelated biological processes. Lithium predominantly modulates intracellular signaling, autophagy, and cell survival; *Hericium erinaceus* stimulates the synthesis of neurotrophic factors and neuritogenesis; and vitamin B12 supports remyelination, neuronal metabolic integrity, and nerve fiber regeneration [23].

The concept of the triple neuromodulatory axis is particularly significant because it extends beyond the traditional reductionist approach to peripheral nerve regeneration. Rather than focusing on a single signaling pathway or cell population, the proposed model integrates multiple levels of biological organization, ranging from molecular signaling networks to functional nerve recovery. This approach is consistent with the contemporary understanding that successful regeneration requires coordinated interactions among neurons, Schwann cells, immune cells, and the extracellular matrix [4,6].

The further potential of such combined strategies lies in their integration with modern biomaterials. Lithium, neurotrophic factors, and metabolic modulators can be incorporated into hydrogels, nerve conduits, or nanostructured systems for local delivery, thereby enabling spatially and temporally controlled therapeutic activity. In this way, pharmacological modulation can be combined with bioengineering support for the regenerative process [15,19,20].

From a translational perspective, lithium is increasingly regarded not only as a stand-alone neuroregenerative agent but also as a central component of multimodal therapeutic strategies. Its ability to influence neurotrophic, metabolic, glial, and immune mechanisms

ćelije regeneracije perifernih nerava. Nakon povrede nerva, Švanove ćelije prolaze kroz proces dediferencijacije i prelaska u reparativni fenotip koji omogućava uklanjanje ostataka mijelina, lučenje neurotrofnih faktora i usmeravanje regenerišućih aksona [4–6].

Jedna studiji je pokazala da litijum povećava proliferaciju Švanovih ćelija i istovremeno reguliše njihovu migraciju, čime doprinosi formiranju organizovanog regenerativnog mikrokruženja [11]. Ovi rezultati su dodatno potvrđeni studijama koje ukazuju na to da litijum aktivira autofagiju u Švanovim ćelijama i na taj način održava njihovu funkcionalnu stabilnost tokom procesa reparacije [16]. Posmatrano zajedno, dostupni dokazi ukazuju na to da Švanove ćelije predstavljaju jednu od glavnih ćelijskih meta regenerativnog delovanja litijuma.

Pored efekata na glijalne ćelije, litijum direktno utiče i na neurone i regeneraciju aksona. Ključni molekularni mehanizam povezan je sa inhibicijom glikogen-sintaza-kinaze-3 β (GSK-3 β), što dovodi do aktivacije Wnt/ β -katena signalizacije, povećane ekspresije Bcl-2 proteina i stimulacije puteva odgovornih za ćelijsko preživljavanje i rast aksona [2,9,10]. Pojedine studije su pokazale da litijum ubrzava funkcionalni oporavak nakon avulzije ventralnog korena kroz unapređenje remijelinizacije i regeneracije aksona [3], dok je Kuffler istakao da litijum deluje istovremeno na neurone i ćelije mikrokruženja, čime povećava verovatnoću uspostavljanja funkcionalnih nervnih veza nakon povrede [1]. Iako deo ovih mehanističkih saznanja potiče iz modela centralnog nervnog sistema, uključujući retinu i optički nerv [2,18], osnovni signalni putevi uključeni u neuroprotekciju i aksonalni rast pokazuju visok stepen konzerviranosti i verovatno imaju značaj i u perifernom nervnom sistemu.

Savremena istraživanja dodatno ukazuju na to da regenerativni efekti litijuma ne zavise samo od direktne stimulacije ćelijskog rasta, već i od njegove sposobnosti da reguliše ćelijsku homeostazu i energetske metabolizam. Litijum aktivira autofagiju i pospešuje uklanjanje oštećenih organela, čime poboljšava otpornost neurona i Švanovih ćelija tokom perioda intenzivne regeneracije [12,13]. Istovremeno, modulacijom PI3K/Akt, ERK1/2 i CREB/BDNF puteva doprinosi održavanju neurotrofne signalizacije i metaboličke stabilnosti [10,14]. Ovakav integrativni efekat može objasniti zbog čega litijum pokazuje regenerativni potencijal u različitim modelima neurološkog oštećenja.

Poseban značaj analiziranih studija ogleda se u činjenici da se poslednjih godina fokus istraživanja pomera sa sistemske primene litijuma ka lokalnim bioinženjerskim sistemima isporuke. Ovakav pristup predstavlja direktan odgovor na jedno od najvećih

makes it a suitable candidate for the development of next-generation personalized regenerative therapies. In this context, the triple neuromodulatory axis hypothesis represents an important theoretical framework for future experimental and clinical research aimed at optimizing recovery following peripheral nerve injuries.

DISCUSSION

The findings of this systematic review indicate that lithium represents one of the most promising pharmacological modulators of peripheral nerve regeneration among currently available experimental therapies. Unlike approaches that target individual components of the regenerative response, lithium acts across multiple interrelated biological processes, including neuronal survival, Schwann cell plasticity, remyelination, axonal growth, autophagy, and regulation of the inflammatory response [1,7–10,13].

Such multimodal activity may represent a significant advantage over strategies that rely solely on neurotrophic factors or biomaterial platforms. One of the most consistent findings across the analyzed studies concerns the effect of lithium on Schwann cells, which represent key effector cells in peripheral nerve regeneration. Following nerve injury, Schwann cells undergo dedifferentiation and transition to a reparative phenotype that facilitates the removal of myelin remnants, the secretion of neurotrophic factors, and the guidance of regenerating axons [4–6].

One study demonstrated that lithium increases Schwann cell proliferation while simultaneously regulating their migration, thereby contributing to the formation of an organized regenerative microenvironment [11]. These findings were further supported by studies indicating that lithium activates autophagy in Schwann cells, thereby maintaining their functional stability during the repair process [16]. Taken together, the available evidence indicates that Schwann cells represent one of the principal cellular targets of lithium's regenerative effects.

In addition to its effects on glial cells, lithium directly influences neurons and axonal regeneration. A key molecular mechanism involves the inhibition of glycogen synthase kinase-3 β (GSK-3 β), resulting in activation of Wnt/ β -catena signaling, increased expression of Bcl-2 proteins, and stimulation of pathways involved in cell survival and axonal growth [2,9,10]. Several studies have shown that lithium accelerates functional recovery following ventral root avulsion by promoting remyelination and axonal regeneration [3], while Kuffler reported that lithium acts simultaneously on neurons and cells within the microenvironment, thereby by increasing the likelihood of establishing functional

ograničenja kliničke primene litijuma – njegov uski terapijski prozor i mogućnost razvoja renalne, endokrine i neurološke toksičnosti pri dugotrajnoj sistemskej ekspoziciji [2,16,17]. Litijum-ugrađeni bioadhezivi, hidrogelovi, nanočestice i nervni konduiti omogućavaju postizanje visokih lokalnih koncentracija u zoni povrede uz minimalnu sistemske izloženost [15,16,20].

Posebno su značajni noviji jonski provodni nervni konduiti i hidrogelovi koji omogućavaju istovremenu mehaničku podršku, usmeravanje aksonalnog rasta i kontrolisano oslobađanje litijuma tokom dužeg vremenskog perioda. Ovakve platforme predstavljaju jedan od najvažnijih translacionih pravaca razvoja regenerativne neurologije [19].

U tom kontekstu, posebno mesto zauzima nedavno predstavljena hipoteza "Triple Neuromodulatory Axis". Ovaj koncept integriše tri međusobno komplementarne komponente, litijum, *Hericium erinaceus* i vitamin B12 u jedinstven neuroregenerativni model. Prema ovoj hipotezi, *Hericium erinaceus* primarno stimuliše produkciju neurotrofina, uključujući NGF i BDNF, litijum stabilizuje i pojačava nizvodnu signalizaciju putem inhibicije GSK-3 β i aktivacije CREB-zavisnih mehanizama, dok vitamin B12 obezbeđuje metaboličku i epigenetsku podršku neophodnu za održavanje remijelinizacije i regeneracije aksona. Iako za sada predstavlja teorijski model koji zahteva eksperimentalnu potvrdu, ova hipoteza nudi zanimljiv okvir za razvoj budućih kombinovanih terapijskih strategija zasnovanih na sinergiji farmakoloških, nutritivnih i bioinženjerskih intervencija [23].

Uprkos ohrabrujućim rezultatima, nekoliko važnih ograničenja mora biti uzeto u obzir prilikom interpretacije dostupnih dokaza. Većina studija sprovedena je na glodarima, dok direktni klinički podaci kod pacijenata sa povredama perifernih nerava praktično ne postoje. Dodatno, prisutna je značajna heterogenost u eksperimentalnim modelima, dozama litijuma, dužini terapije i metodama procene regeneracije, što otežava poređenje rezultata između studija. Deo mehaničkih zaključaka zasniva se na istraživanjima centralnog nervnog sistema, koja, iako pružaju značajne uvide u osnovne signalne puteve, ne mogu biti u potpunosti preneti na periferni nervni sistem zbog fundamentalnih razlika u regenerativnom potencijalu i glijalnoj organizaciji [2,12–14,18].

Sveukupno posmatrano, dostupni dokazi podržavaju koncept da litijum predstavlja značajnog farmakološkog kandidata za unapređenje regeneracije perifernih nerava. Njegova sposobnost simultane modulacije neurotrofnih, glijalnih, metaboličkih i inflamatornih procesa razlikuje ga od većine pojedinačnih regenerativnih agenasa. Dalji napredak u razvoju

nervne connections after injury [1]. Although some of these mechanistic insights come from central nervous system models, including the retina and optic nerve [2,18], the basic signaling pathways involved in neuroprotection and axonal growth exhibit a high degree of conservation and are therefore likely to be relevant to the peripheral nervous system as well.

Contemporary research further indicates that the regenerative effects of lithium depend not only on the direct stimulation of cellular growth but also on its ability to regulate cellular homeostasis and energy metabolism. Lithium activates autophagy and promotes the removal of damaged organelles, thereby enhancing the resilience of neurons and Schwann cells during periods of intensive regeneration [12,13]. At the same time, by modulating the PI3K/Akt, ERK1/2, and CREB/BDNF pathways, it contributes to the maintenance of neurotrophic signaling and metabolic stability [10,14]. This integrative effect may explain the regenerative potential of lithium observed across various models of neurological injury.

The particular significance of the analyzed studies is reflected in the shift in research focus in recent years from systemic lithium administration toward local bioengineering-based delivery systems. This approach directly addresses one of the major limitations of lithium's clinical application – its narrow therapeutic window and the potential for renal, endocrine, and neurological toxicity during prolonged systemic exposure [2,16,17]. Lithium-embedded bioadhesives, hydrogels, nanoparticles, and nerve conduits enable the attainment of high local lithium concentrations at the site of injury while minimizing systemic exposure [15,16,20].

Of particular interest are emerging ion-conducting nerve conduits and hydrogels that enable the simultaneous provision of mechanical support, guidance of axonal growth, and controlled release of lithium over an extended period. Such platforms represent one of the most important translational directions in the development of regenerative neurology [19].

In this context, a particular place is occupied by the recently proposed "Triple Neuromodulatory Axis" hypothesis. This concept integrates three mutually complementary components, lithium, *Hericium erinaceus*, and vitamin B12, into a unified neuroregenerative model. According to this hypothesis, *Hericium erinaceus* primarily stimulates the production of neurotrophins, including NGF and BDNF, lithium stabilizes and enhances downstream signaling through inhibition of GSK-3 β and activation of CREB-dependent mechanisms, while vitamin B12 provides the metabolic and epigenetic support necessary to maintain axonal remyelination and regeneration. Although this hypothesis currently rep-

lokalnih sistema isporuke, preciznom definisanju regenerativnih doza i validaciji kombinovanih terapijskih pristupa mogao bi omogućiti prelazak litijuma iz eksperimentalnog okruženja u kliničku praksu regenerativne neurologije.

Pored direktnih eksperimentalnih dokaza o regeneraciji perifernih nerava, pojedini radovi dodatno proširuju translacioni kontekst primene litijuma. Na osnovu toga konstatovano je da litijum pokazuje potencijalne neuroprotektivne efekte i u okviru neurodegenerativnih bolesti, što podrazumeva i Alchajmerovu bolest, pri čemu se njegovo delovanje povezuje sa regulacijom autofagije, neuroinflamacije, oksidativnog stresa i ćelijskog preživljavanja. Iako se radi o drugačijem patofiziološkom okruženju, brojni molekularni putevi identifikovani u neurodegeneraciji preklapaju se sa mehanizmima koji učestvuju u regeneraciji perifernih nerava. Istovremeno, razvoj savremenih biomaterijala otvara nove mogućnosti za lokalnu i kontrolisanu primenu litijuma [24].

U drugoj studiji je pak ustanovljeno da nanohidroksiapatit poseduje povoljne biološke karakteristike za regeneraciju nervnog tkiva i predstavlja potencijalnu platformu za buduće funkcionalizovane sisteme isporuke bioaktivnih molekula [25]. Međutim, sa druge pak strane, konstatovano je da biološki efekti litijuma zavise od koncentracije i dužine trajanja ekspozicije, te da pri neadekvatnim dozama mogu biti u korelaciji sa neurotoksičnim mehanizmima i disbalansom homeostaze ćelija [26]. Ovi rezultati dodatno potvrđuju značaj razvoja preciznih sistema lokalne isporuke i optimizacije doziranja, kako bi se maksimalno iskoristio regenerativni potencijal litijuma uz minimizaciju mogućih neželjenih efekata.

Ograničenja i buduće perspektive

I pored sve većeg broja eksperimentalnih dokaza koji ukazuju na litijum kao potencijalni neuroregulator u regeneraciji perifernih nerava, potrebno je naglasiti nekoliko značajnih ograničenja. Prvo, najveći deo dostupnih podataka potiče iz in vitro sistema i životinjskih modela, koji, iako pružaju važan uvid u mehanizme delovanja, ne odražavaju u potpunosti kompleksnost kliničkih stanja kod ljudi, posebno u kontekstu hroničnih lezija, komorbiditeta i heterogenosti povreda. Drugo, značajan deo mehanističkih zaključaka zasniva se na studijama centralnog nervnog sistema, uključujući modele retine, kičmene moždine i ishemijskog oštećenja mozga. Iako ove studije potvrđuju konzerviranost ključnih signalnih puteva (GSK-3 β / β -katenin, PI3K/Akt, ERK1/2), njihova direktna translacija na periferne nerve mora biti interpretirana oprezno zbog fundamentalnih razlika u glijalnoj arhitekturi i regenerativnom potencijalu

represents a theoretical model that requires experimental confirmation, it provides an interesting framework for the development of future combined therapeutic strategies based on the synergy of pharmacological, nutritional, and bioengineering interventions [23].

Despite these encouraging findings, several important limitations should be considered when interpreting the available evidence. Most studies have been conducted on rodents, while direct clinical data from patients with peripheral nerve injuries remain practically nonexistent. Furthermore, considerable heterogeneity exists in experimental designs, lithium doses, treatment duration, and methods used to assess regeneration, making comparisons across studies difficult. Some mechanistic conclusions are based on studies of the central nervous system, which, although providing valuable insights into fundamental signaling pathways, cannot be fully extrapolated to the peripheral nervous system because of fundamental differences in regenerative capacity and glial organization [2,12–14,18].

Taken together, the available evidence supports the concept that lithium represents an important pharmacological candidate for enhancing peripheral nerve regeneration. Its ability to simultaneously modulate neurotrophic, glial, metabolic, and inflammatory processes distinguishes it from most single regenerative agents. Further advances in the development of local delivery systems, precise definition of regenerative doses, and validation of combined therapeutic approaches could facilitate the transition of lithium from the experimental setting to clinical practice in regenerative neurology.

In addition to direct experimental evidence of peripheral nerve regeneration, some papers further broaden the translational context of lithium application. On this basis, lithium has been considered to have potential neuroprotective effects in neurodegenerative diseases, including Alzheimer's disease, where its effects are associated with the regulation of autophagy, neuroinflammation, oxidative stress, and cell survival. Although these represent distinct pathophysiological settings, numerous molecular pathways identified in neurodegeneration overlap with mechanisms involved in peripheral nerve regeneration. At the same time, the development of modern biomaterials opens new possibilities for the local and controlled delivery of lithium [24].

Another study found that nanohydroxyapatite possesses favorable biological characteristics for nerve tissue regeneration and represents a potential platform for future functionalized delivery systems for bioactive molecules [25]. However, it has also been established that the biological effects of lithium depend on

CNS-a i PNS-a. Treće, ne postoji standardizovan terapijski protokol za primenu litijuma u regenerativne svrhe, naročito u kontekstu mikrodoziranja i lokalne isporuke putem biomaterijala, što ograničava uporedivost rezultata između studija. Konačno, klinički dokazi u oblasti povreda perifernih nerava su i dalje oskudni, a većina dostupnih podataka dolazi iz psihijatrijskih ili neurodegenerativnih populacija, a ne iz ciljnih PNS modela.

Buduće istraživanje trebalo bi da bude usmereno ka dobro dizajniranim translacionim studijama koje povezuju prekliničke nalaze sa kliničkom primenom. Poseban fokus treba staviti na razvoj lokalnih bioinženjerskih sistema za isporuku, kao što su hidrogelovi, nervni konduiti i jonski aktivni biomaterijali, koji omogućavaju kontrolisano oslobađanje litijuma direktno u zoni povrede uz minimalizaciju sistemske toksičnosti. Takođe je neophodno precizno definisati odnose doza–efekat u regenerativnom kontekstu, naročito u domenu mikrodoziranja i hormetskih efekata. Na kraju, integrativni terapijski pristupi koji kombinuju litijum sa neurotrofnim i metaboličkim modulacijama predstavljaju obećavajući pravac razvoja sledeće generacije strategija za reparaciju perifernih nerava i funkcionalni oporavak pacijenata.

ZAKLJUČAK

Litijum predstavlja mehanistički utemeljen i eksperimentalno potkrepljen jonski modulator regeneracije perifernih nerava. Dostupni preklinički podaci ukazuju na to da njegovo delovanje obuhvata ključne procese nervne reparacije, uključujući preživljavanje neurona, modulaciju i proliferaciju Švanovih ćelija, aksonalni rast i remijelinizaciju regenerisanih vlakana. Ovi efekti su pre svega posredovani inhibicijom GSK-3 β i aktivacijom nizvodnih signalnih puteva koji uključuju Wnt/ β -katenin, PI3K/Akt i CREB/BDNF osovino, čime se stvara povoljno mikrokruženje za organizovanu regeneraciju nervnog tkiva. Uprkos snažnoj biološkoj osnovi, litijum se ne može posmatrati kao samostalna terapijska strategija, već kao centralni regulatorni element unutar složenih regenerativnih mreža koje uključuju glijalnu podršku, neurotrofne signale i metaboličku stabilizaciju. Njegov puni regenerativni potencijal najverovatnije dolazi do izražaja tek u kombinaciji sa komplementarnim biološkim i inženjerskim pristupima, posebno u okviru lokalnih sistema za kontrolisanu isporuku. Posebno obećavajućim pravcem budućih istraživanja nameće se razvoj multimodalnih terapijskih strategija zasnovanih na konceptu trojne neuromodulatorne ose (litijum–Hericium erinaceus–vitamin B12), koje bi mogle objediniti neurotrofičnu, metaboličku i glijalnu podršku regeneraciji perifernih nerava. Iako su rezultati prekliničkih studija obećavajući, klinička validacija u

the concentration and duration of exposure, and that inadequate doses may be associated with neurotoxic mechanisms and disruption of cellular homeostasis [26]. These findings further underscore the importance of developing precise local delivery systems and optimizing dosing to maximize the regenerative potential of lithium while minimizing potential adverse effects.

Limitations and future perspectives

Despite the growing body of experimental evidence supporting lithium as a potential neuroregulator in peripheral nerve regeneration, several important limitations should be emphasized. First, most of the available evidence come from in vitro systems and animal models, which, although providing important insights into mechanisms of action, do not fully reflect the complexity of human clinical conditions, particularly in the context of chronic lesions, comorbidities, and injury heterogeneity. Second, a substantial proportion of the mechanistic conclusions are based on studies of the central nervous system, including models of retinal, spinal cord, and ischemic brain injury. Although these studies support the conservation of key signaling pathways, including GSK-3 β / β -catenin, PI3K/Akt, and ERK1/2, their direct extrapolation to peripheral nerves should be approached with caution because of fundamental differences in glial architecture and regenerative potential between the CNS and PNS. Third, no standardized therapeutic protocol has been established for the use of lithium for regenerative purposes, particularly with regard to microdosing and local delivery through biomaterials, limiting the comparability of findings across studies. Finally, clinical evidence in the field of peripheral nerve injury remains scarce, with most available data derived from psychiatric or neurodegenerative populations rather than from targeted PNS models.

Future research should focus on well-designed translational studies that bridge preclinical findings and clinical application. Particular attention should be directed toward the development of local bioengineered delivery systems, such as hydrogels, nerve conduits, and ionically active biomaterials, which enable the controlled release of lithium directly at the site of injury while minimizing systemic toxicity. Precise characterization of dose–effect relationships in the regenerative context is also necessary, particularly with regard to microdosing and hormetic effects. Finally, integrative therapeutic approaches combining lithium with neurotrophic and metabolic modulation represent a promising direction for the development of next-generation strategies for peripheral nerve repair and functional recovery in patients.

kontekstu povreda perifernih nerava ostaje ograničena. Na osnovu trenutno dostupnih dokaza, litijum se izdvaja kao jedan od najperspektivnijih farmakoloških modulatora regeneracije perifernih nerava, naročito u kombinaciji sa savremenim sistemima lokalne isporuke i multimodalnim regenerativnim strategijama. Potrebna su dodatna translaciona istraživanja kako bi se definisali optimalni terapijski protokoli, bezbednosni profili i realni funkcionalni ishodi u humanoju populaciji.

Sukob interesa: Nije prijavljen.

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CONCLUSION

Lithium is a mechanistically grounded and experimentally supported ionic modulator of peripheral nerve regeneration. Available preclinical data indicate that its effects involve key processes of nerve repair, including neuronal survival, modulation and proliferation of Schwann cells, axonal growth, and remyelination of regenerated fibers. These effects are primarily mediated through inhibition of GSK-3 β and activation of downstream signaling pathways, including Wnt/ β -catenin, PI3K/Akt, and the CREB/BDNF axis, thereby creating a favorable microenvironment for organized nerve tissue regeneration. Despite its strong biological basis, lithium should not be regarded as an independent therapeutic strategy but rather as a central regulatory element within complex regenerative networks involving glial support, neurotrophic signaling, and metabolic stabilization. Its full regenerative potential is likely to be realized only in combination with complementary biological and engineering approaches, particularly within local controlled-delivery systems. A particularly promising direction for future research is the development of multimodal therapeutic strategies based on the concept of a triple neuromodulatory axis (lithium–*Hericium erinaceus*–vitamin B12), which could integrate neurotrophic, metabolic, and glial support for peripheral nerve regeneration. Although preclinical findings are promising, clinical validation in the context of peripheral nerve injuries remains limited. Based on the currently available evidence, lithium stands out as one of the most promising pharmacological modulators of peripheral nerve regeneration, particularly when combined with modern local delivery systems and multimodal regenerative strategies. Further translational research is needed to define optimal therapeutic protocols, safety profiles, and realistic functional outcomes in human populations.

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OTPORNOST LANACA SNABDEVANJA LEKOVIMA I MEDICINSKIM SREDSTVIMA KAO STUB ZDRAVSTVENE BEZBEDNOSTI: INTEGRATIVNI PREGLED I OKVIR UPRAVLJANJA ZASNOVAN NA ISKUSTVIMA IZ PRAKSE

PREGLEDNI RAD

REVIEW ARTICLE

PHARMACEUTICAL AND MEDICAL DEVICE SUPPLY CHAIN RESILIENCE AS A PILLAR OF HEALTHCARE SECURITY: AN INTEGRATIVE REVIEW AND CASE-INFORMED GOVERNANCE FRAMEWORK

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SAŽETAK

Uvod/Cilj: Otpornost lanaca snabdevanja farmaceutskim proizvodima i medicinskim sredstvima postala je ključna odrednica funkcionisanja zdravstvenog sistema, kontinuiteta zdravstvene zaštite i bezbednosti pacijenata. Nedavni globalni poremećaji razotkrili su značajne strukturne ranjivosti lanaca snabdevanja u zdravstvu, ukazujući na potrebu da se upravljanje lancima snabdevanja posmatra kao suštinska komponenta bezbednosti u zdravstvu. Cilj ovog rada je da pruži pregled savremene literature o otpornosti lanaca snabdevanja lekovima i medicinskim sredstvima, te da osmisli model upravljanja koji je zasnovan na iskustvima iz prakse i primenljiv u zdravstvenim sistemima suočenim sa poremećajima u snabdevanju.

Materijali i metode: Sproveden je narativni integrativni pregled literature usmeren na prevazilaženje nestašica, regulisanje javnih nabavki, otpornost logističkih sistema, mogućnost digitalnog praćenja, te pripremljenost zdravstvenih sistema za krizne situacije.

Rezultati: Analizirana literatura ukazuje na to da otpornost lanaca snabdevanja u zdravstvu zavisi od diversifikacije dobavljača, formiranja strateških rezervi, unapređenja sistema javnih nabavki, razvoja regionalnih proizvodnih kapaciteta, digitalne vidljivosti lanca snabdevanja, regulatorne fleksibilnosti i institucionalne pripremljenosti. Najčešće uočene slabosti obuhvataju prekomernu zavisnost od pojedinačnih dobavljača, koncentraciju proizvodnje, ograničenu transparentnost, fragmentisano upravljanje, te nedovoljne kapacitete za odgovor u vanrednim situacijama.

Zaključak: Otpornost lanaca snabdevanja lekovima i medicinskim sredstvima treba posmatrati kao strateški prioritet zdravstvene bezbednosti. Jačanje otpornosti zahteva integrisano upravljanje, proaktivno planiranje i koordinisano delovanje u oblastima javnih nabavki, logistike, proizvodnje, regulative i pripremljenosti za vanredne situacije.

Ključne reči: otpornost lanca snabdevanja lekovima, lanac snabdevanja medicinskim sredstvima, bezbednost u zdravstvu, nestašica, pripremljenost za vanredne situacije

ABSTRACT

Introduction/Objective: The resilience of pharmaceutical and medical device supply chains has become a critical determinant of healthcare system performance, continuity of care, and patient safety. Recent global disruptions have exposed major structural vulnerabilities in health-related supply networks, highlighting the need to view supply chain management as a core component of healthcare security. The objective of this article is to review the contemporary literature on pharmaceutical and medical device supply chain resilience and develop a case-informed governance framework applicable to healthcare systems facing supply disruptions.

Materials and methods: A narrative integrative review of the literature was conducted, focusing on shortage management, procurement governance, logistics resilience, digital traceability, and crisis preparedness in healthcare systems.

Results: The literature indicates that resilient healthcare supply chains depend on supplier diversification, strategic reserves, procurement redesign, regional manufacturing capacity, digital visibility, regulatory flexibility, and institutional preparedness. Common vulnerabilities include the following: overreliance on single-source suppliers, production concentration, limited transparency, fragmented governance, and inadequate surge-response capacity.

Conclusion: Pharmaceutical and medical device supply chain resilience should be treated as a strategic priority within healthcare security policy. Strengthening resilience requires integrated governance, anticipatory planning, and system-wide coordination in the areas of procurement, logistics, manufacturing, regulation, and emergency preparedness.

Keywords: pharmaceutical supply chain resilience, medical device supply chain, healthcare security, shortage, crisis preparedness

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UVOD

Kontinuitet pružanja zdravstvene zaštite ne zavisi samo od kliničke stručnosti i institucionalnih kapaciteta, već i od pouzdanog pristupa lekovima, medicinskom potrošnom materijalu, dijagnostičkim materijalima i ključnim medicinskim sredstvima. Poslednjih godina, ponovljene nestašice lekova, poremećaji izazvani pandemijom i geopolitička nestabilnost pokazali su da lanci snabdevanja lekovima i medicinskim sredstvima predstavljaju ključnu, mada često potcenjenu komponentu bezbednosti zdravstvenog sistema [1–3].

Pandemija bolesti KOVID-19 je naročito razotkrila ranjivost sistema snabdevanja medicinskim proizvodima. Nagli porast potražnje, uska grla u proizvodnji, ograničenja izvoza i nedovoljna transparentnost na različitim nivoima lanca snabdevanja poremetili su dostupnost osnovnih proizvoda u mnogim zemljama [1,4,5]. Međutim, pandemija nije stvorila ove slabosti; ona je, pre svega, učinila vidljivim dugotrajne strukturne slabosti koje su već bile prepoznate u literaturi o nestašicama lekova i rizicima u farmaceutskim lancima snabdevanja [2,3,6–9].

U okvirima zdravstvene zaštite, poremećaji u lancu snabdevanja imaju posledice koje daleko prevazilaze operativnu neefikasnost. Za razliku od većine industrijskih sektora, nestašice lekova i medicinskih sredstava mogu neposredno ugroziti bezbednost pacijenata, odložiti lečenje, smanjiti broj dostupnih terapijskih opcija i oslabiti kapacitet za odgovor u vanrednim situacijama [3,9–11]. Zbog toga otpornost u ovoj oblasti ne treba shvatiti samo kao logistički cilj, već kao jedan od ključnih stubova bezbednosti zdravstvene zaštite.

Cilj ovog preglednog rada jeste da objedini postojeće dokaze o otpornosti lanaca snabdevanja lekovima i medicinskim sredstvima, te da predloži, okvir upravljanja koji je zasnovan na realnim slučajevima iz prakse i primenljiv na zdravstvene sisteme, bolnice, regulatorna tela i farmaceutsku praksu. Rad integriše konceptualnu literaturu o otpornosti sa empirijskim dokazima o nestašicama, odgovoru na krize, modelovanju otpornosti i digitalnoj transformaciji, kako bi predstavio sažet i praktičan okvir relevantan za savremeni menadžment u zdravstvu [4,12–23].

MATERIJALI I METODE

Dizajn studije

Ova studija je osmišljena kao narativni integrativni pregled sa ciljem da objedini savremene dokaze o otpornosti lanaca snabdevanja lekovima i medicinskim sredstvima u širem kontekstu bezbednosti zdravstvene zaštite. Za razliku od sistematskih pregleda literature, koji prvenstveno nastoje da odgovore na usko definisana klinička

INTRODUCTION

The continuity of healthcare delivery depends not only on clinical expertise and institutional capacity, but also on reliable access to medicines, medical consumables, diagnostic materials, and essential devices. In recent years, repeated medicine shortages, pandemic-related disruptions, and geopolitical instability have demonstrated that pharmaceutical and medical device supply chains represent a critical, though often underestimated component of health system security [1–3].

The COVID-19 pandemic particularly exposed the fragility of medical product supply systems. Sudden increases in demand, production bottlenecks, export restrictions, and limited transparency across supply tiers disrupted the availability of essential products in many countries [1,4,5]. However, the pandemic did not create these weaknesses; rather, it made visible the long-standing structural vulnerabilities already recognized in the literature on drug shortages and pharmaceutical supply risk [2,3,6–9].

In the healthcare context, supply chain disruption has consequences that extend far beyond operational inefficiency. Unlike most industrial sectors, shortages in pharmaceuticals and medical devices may immediately compromise patient safety, delay treatment, reduce therapeutic options, and weaken emergency response capacity [3,9–11]. This is why resilience in this domain should be understood not simply as a logistical objective, but as a core pillar of healthcare security.

This review aims to synthesize the current evidence on pharmaceutical and medical device supply chain resilience and to propose a case-informed governance framework suitable for healthcare systems, hospitals, regulators, and pharmacy practice. The article integrates conceptual resilience literature with empirical evidence on shortages, crisis response, resilience modeling, and digital transformation, in order to present a concise and practical framework relevant to contemporary healthcare management [4,12–23].

MATERIALS AND METHODS

Study design

This study was designed as a narrative integrative review aimed at synthesizing contemporary evidence on pharmaceutical and medical device supply chain resilience within the broader context of healthcare security. Unlike systematic reviews, which primarily seek to answer narrowly defined clinical questions through quantitative evidence synthesis, an integrative review combines empirical research, conceptual analyses, policy literature, and governance-oriented publications to provide a comprehensive understanding of a complex, multidisciplinary topic.

pitanja putem kvantitativne sinteze dokaza, integrativni pregled objedinjuje empirijska istraživanja, konceptualne analize, literaturu iz oblasti javnih politika i publikacije usmerene na upravljanje, kako bi se obezbedilo sveobuhvatno razumevanje složene, multidisciplinarne teme.

Metodološki pristup odabran je zato što otpornost lanca snabdevanja u zdravstvu obuhvata međusobno povezane logističke, organizacione, regulatorne, tehnološke i javnozdravstvene dimenzije koje se ne mogu adekvatno obuhvatiti jedinstvenim dizajnom studije. Shodno tome, ovaj pregled integriše dokaze prikupljene iz više metodoloških obtazaca kako bi identifikovao zajedničke mehanizme otpornosti i principe upravljanja koji se mogu primeniti u različitim zdravstvenim okruženjima.

Strategija za pretraživanje literature

Sprovedena je strukturisana pretraga literature korišćenjem elektronskih baza podataka *PubMed*, *Scopus* i *Google Scholar*. Pretraga je obuhvatila recenzirane radove objavljene zaključno sa decembrom 2025. godine, bez geografskih ograničenja.

Strategija pretraživanja kombinovala je kontrolisani rečnik (gde je bio primenljiv) i ključne reči u slobodnom tekstu, uz korišćenje logičkih – Bulovih operatora („I“, „ILI“ – engl. „AND“, „OR“).

Reprezentativni termini za pretragu bili su:

- otpornost lanca snabdevanja farmaceutskim proizvodima
- lanac snabdevanja medicinskim sredstvima
- nestašice medikamenata (engl. *medicine shortages*)
- nestašice lekova (engl. *drug shortages*)
- bezbednost zdravstvene zaštite
- otpornost zdravstvene zaštite
- otpornost zdravstvenog sistema
- farmaceutska logistika
- upravljanje nabavkom
- pripremljenost za katastrofe
- pripremljenost za vanredne situacije
- upravljanje lancem snabdevanja
- industrija 4.0
- digitalni lanac snabdevanja
- digitalni blizanac
- otpornost zaliha
- modelovanje otpornosti

Različite kombinacije ovih ključnih reči korišćene su u zavisnosti od sistema indeksiranja pojedinačne baze podataka, kako bi se maksimalno povećao obuhvat relevantne literature.

Pored pretraživanja elektronskih baza podataka, sprovedli smo i ručni pregled spiskova referenci u publikacijama od visokog značaja, kako bismo identifikovali još relevantnih studija koje nisu pronađene tokom prvobitne pretrage.

The methodological approach was selected because healthcare supply chain resilience encompasses interconnected logistical, organizational, regulatory, technological, and public health dimensions that cannot be adequately captured through a single study design. Consequently, the review integrates evidence from multiple methodological traditions to identify common resilience mechanisms and governance principles applicable across different healthcare settings.

Literature search strategy

A structured literature search was performed using the electronic databases *PubMed*, *Scopus*, and *Google Scholar*. The search included peer-reviewed articles published up to December 2025, without geographical restrictions.

The search strategy combined controlled vocabulary (where applicable) and free-text keywords using Boolean operators (“AND”, “OR”).

Representative search terms included:

- pharmaceutical supply chain resilience
- medical device supply chain
- medicine shortages
- drug shortages
- healthcare security
- healthcare resilience
- health system resilience
- pharmaceutical logistics
- procurement governance
- disaster preparedness
- emergency preparedness
- supply chain governance
- industry 4.0
- digital supply chain
- digital twin
- inventory resilience
- resilience modelling

Different combinations of these keywords were used, depending on the database indexing system, to maximize retrieval of relevant literature.

In addition to electronic database searches, we manually screened reference lists in highly relevant publications to identify additional eligible studies not retrieved during the initial search.

Eligibility criteria

Publications fulfilling one or more of the criteria listed below were considered eligible.

The publications:

- addressed pharmaceutical or medical device supply chains within healthcare systems
- investigated medicine shortages or medical device shortages

Kriterijumi za uključivanje u pregled literature

Publikacije koje su ispunjavale jedan ili više kriterijuma navedenih u nastavku smatrane su prihvatljivim.

Publikacije su:

- obrađivale lance snabdevanja lekovima ili medicinskim sredstvima u okviru zdravstvenih sistema
- istraživale nestašice lekova ili medicinskih sredstava
- procenjivale otpornost, pripremljenost, nabavku, upravljanje, logistiku ili digitalne tehnologije relevantne za kontinuitet snabdevanja u zdravstvu
- predlagale konceptualne okvire, modele otpornosti, analize javnih politika ili empirijska istraživanja povezana sa otpornošću lanca snabdevanja u zdravstvu
- bile objavljene u recenziranim naučnim časopisima.

Sledeći tipovi publikacija su isključeni:

- sažeci sa konferencija bez dovoljno metodoloških informacija
- uvodnici bez suštinske naučne analize
- nerecenzirani izveštaji
- studije usmerene isključivo na industrijsku ili komercijalnu logistiku bez direktne relevantnosti za pružanje zdravstvene zaštite
- publikacije koje se isključivo bave optimizacijom izdavanja lekova u apotekama bez širih implikacija po zdravstveni sistem
- duplikati publikacija.

Odabir studija i narativna sinteza

Nakon pretraživanja baza podataka, pregledani su naslovi i sažeci radi procene relevantnosti u odnosu na ciljeve rada. Potom je izvršena procena punog teksta onih publikacija koje su potencijalno ispunjavale definisane kriterijume.

Umesto kvantitativne sinteze dokaza ili meta-analize, odabrane studije analizirane su primenom pristupa narativne tematske sinteze. Publikacije su međusobno poređene u odnosu na:

- osnovno istraživačko pitanje
- metodološki pristup
- tip zdravstvene zaštite
- razmatrane dimenzije otpornosti
- prijavljene slabosti
- predložene intervencije za jačanje otpornosti
- implikacije za upravljanje.

Identifikovani dokazi su potom organizovani u glavne tematske oblasti:

- strukturne ranjivosti
- nestašice lekova
- kapaciteti otpornosti
- nabavka i upravljanje zalihamama
- digitalna transformacija
- regulatorna pripremljenost
- integracija farmaceutskih radnika.

- evaluated resilience, preparedness, procurement, governance, logistics, or digital technologies relevant to healthcare supply continuity
- proposed conceptual frameworks, resilience models, policy analyses, or empirical investigations related to healthcare supply chain resilience
- were published in peer-reviewed scientific journals.

The following publication types were excluded:

- conference abstracts without sufficient methodological information
- editorials lacking substantive scientific analysis
- non-peer-reviewed reports
- studies focused exclusively on industrial or commercial logistics without direct relevance to healthcare delivery
- publications dealing solely with community pharmacy dispensing optimization without broader healthcare system implications
- duplicate publications.

Study selection and narrative synthesis

Following the database search, titles and abstracts were screened for relevance to the review objectives. Potentially eligible publications subsequently underwent full-text assessment.

Rather than performing quantitative evidence synthesis or meta-analysis, the selected studies were analyzed using a narrative thematic synthesis approach. Publications were compared according to:

- the principal research question
- the methodological approach
- the healthcare setting
- the resilience dimensions addressed
- the reported vulnerabilities
- the proposed resilience interventions
- the governance implications.

The identified evidence was subsequently organized into major thematic domains, including:

- structural vulnerabilities
- medicine shortages
- resilience capabilities
- procurement and inventory management
- digital transformation
- regulatory preparedness
- pharmacy workforce integration.

These domains provided the conceptual structure for the Results and Discussion sections.

Development of the case-informed governance framework

The governance framework proposed in this review was developed through iterative thematic integration

Ove oblasti obezbedile su konceptualnu strukturu za poglavlja: Rezultati i Diskusija.

Razvijanje okvira upravljanja zasnovanog na iskustvima iz prakse

Okvir upravljanja predložen u ovom pregledu razvijen je kroz iterativnu tematsku integraciju koncepata koji se ponavljaju, identifikovanih u literaturi uključenoj u analizu.

Umesto da bude izveden iz jedne studije slučaja, okvir je zasnovan na nalazima iz više dokumentovanih poremećaja u snabdevanju u zdravstvu, uključujući:

- nestašice lekova i medicinskih sredstava povezane sa pandemijom bolesti KOVID-19
- poremećaje povezane sa odgovorom na vanredne situacije i katastrofe
- ponovljene globalne nestašice lekova
- geopolitičke poremećaje i poremećaje u snabdevanju lekovima povezane sa sankcijama
- objavljene studije modelovanja otpornosti.

Principi upravljanja koji su više puta uočeni u ovim heterogenim kontekstima uporedno su analizirani kako bi se identifikovali zajednički mehanizmi otpornosti.

Pet oblasti upravljanja dosledno se izdvojilo u pregledanim dokazima:

1. Strateška pripremljenost
2. Operativna otpornost
3. Regulatorna i politička koordinacija
4. Digitalna otpornost i infrastruktura
5. Integracija farmaceutskih radnika

U tom kontekstu, predloženi okvir je okarakterisan kao zasnovan na iskustvima iz prakse, što govori da je izveden iz ponovljenih empirijskih iskustava opisanih u više scenarija poremećaja u zdravstvenoj zaštiti, a ne iz jednog empirijskog slučaja.

Konceptualni osnov: zašto je otpornost lanca snabdevanja pitanje bezbednosti zdravstvene zaštite

Otpornost lanca snabdevanja generalno se shvata kao sposobnost mreže snabdevanja da se pripremi za poremećaje, apsorbuje potrebe, održi ključne funkcije, obnovi performanse i prilagodi budućoj neizvesnosti [21–23]. U opštoj literaturi o logistici, otpornost se često opisuje u kontekstu kapaciteta kao što su fleksibilnost, redundantnost, vidljivost, saradnja i agilnost [21,22].

Međutim, u zdravstvu je značaj otpornosti dalekosežniji. Lanci snabdevanja lekovima i medicinskim sredstvima obezbeđuju proizvode za koje je blagovremeno snabdevanje neretko od ključnog značaja, koji

of recurring concepts identified across the literature included in the analysis.

Rather than being derived from a single case study, the framework was informed by multiple documented healthcare supply disruptions, including:

- COVID-19-related shortages of medicines and medical devices
- disruptions associated with emergency and disaster response
- recurrent global medicine shortages
- geopolitical and sanction-related pharmaceutical supply disruptions
- published resilience modelling studies.

Recurring governance principles observed across these heterogeneous contexts were comparatively analyzed to identify common resilience mechanisms.

Five governance domains consistently emerged across the reviewed evidence:

1. Strategic preparedness
2. Operational resilience
3. Regulatory and policy coordination
4. Digital resilience infrastructure
5. Pharmacy workforce integration

Accordingly, the proposed framework is described as case-informed, reflecting its derivation from recurring empirical experiences reported across multiple healthcare disruption scenarios rather than from a single empirical case.

Conceptual background: why supply chain resilience is a healthcare security issue

Supply chain resilience is generally understood as the capacity of a supply network to prepare for disruption, absorb shocks, maintain critical functions, recover performance, and adapt to future uncertainty [21–23]. In general logistics literature, resilience is often described in terms of capabilities such as flexibility, redundancy, visibility, collaboration, and agility [21,22].

In healthcare, however, the meaning of resilience is more consequential. Pharmaceutical and medical device supply chains support products that are often time-sensitive, clinically irreplaceable, and tightly regulated. Their disruption may lead not only to economic loss, but also to treatment interruption, medication errors, substitution with less familiar alternatives, and avoidable harm [2,3,8–11]. Therefore, resilience in this context should be interpreted as a protective system function that safeguards continuity of care.

The healthcare relevance of this perspective was strongly reinforced during the COVID-19 pandemic. Miller et al. [1] described the vulnerability of the medical product supply chain as a “wake-up call” for health

su klinički nezamenljivi i strogo regulisani. Poremećaj može dovesti ne samo do ekonomskih gubitaka već i do prekida lečenja, grešaka u primeni lekova, zamenje manje poznatim alternativama i štete koja se može izbeći [2,3,8–11]. Stoga, otpornost u ovom kontekstu treba tumačiti kao zaštitnu funkciju sistema koja obezbeđuje kontinuitet zdravstvene zaštite.

Relevantnost ovog pristupa u kontekstu zdravstva nedvosmisleno je potvrđena tokom pandemije bolesti KOVID-19. Miler i sar. [1] su opisali ranjivost lanca snabdevanja medicinskim proizvodima kao „trenutak otrežnjenja“ za zdravstvene sisteme. Oni tvrde da bezbednost pružanja zdravstvene zaštite zavisi od žilavosti struktura snabdevanja na višim instancama u lancu. Slično tome, skoping pregled (engl. *scoping review*) Ahmada Hamdija i sar. [4] pokazao je da upravljanje u farmaceutskom poslovanju u kontekstu pripremljenosti i odgovora na katastrofe zahteva koordinisano planiranje pre, tokom i nakon poremećaja.

Shodno tome, otpornost lanca snabdevanja lekovima i medicinskim sredstvima treba smatrati delom infrastrukture bezbednosti zdravstvene zaštite. To nije samo pitanje efikasnosti nabavke već i spremnosti sistema, zaštite pacijenata i kontinuiteta funkcionisanja institucija pod pritiskom [1,2,4,21–23].

Ključne ranjivosti i uzročnici poremećaja

Glavni izvor ranjivosti u lancima snabdevanja lekovima i medicinskim sredstvima predstavlja koncentracija proizvodnje. Mnogi esencijalni proizvodi zavise od ograničenog broja proizvođača, proizvodnih lokacija ili dobavljača na višim nivoima lanca za aktivne farmaceutske supstance i specijalizovane komponente [1,2,9]. Iako ova struktura može povećati troškovnu efikasnost u stabilnim periodima, ona stvara sistemsku krhkost kada kvarovi u proizvodnji, prekidi transporta ili ograničenja izvoza pogode kritične tačke u lancu.

Jaberidost i sar. [6] su identifikovali širok spektar rizika u lancu snabdevanja farmaceutskim proizvodima, uključujući otkazivanje dobavljača, neizvesnost potražnje, regulatorne prepreke, informacionu asimetriju, ograničenja u skladištenju, poremećaje u transportu i probleme povezane sa kvalitetom. Njihovi nalazi ostaju veoma relevantni jer pokazuju da poremećaj u snabdevanju retko nastaje usled samo jednog faktora. Umesto toga, nestašice obično nastaju usled međusobnog delovanja više operativnih, ekonomskih i regulatornih pritisaka.

Nestašice lekova predstavljaju najvidljiviju posledicu ovih strukturnih slabosti. Akosta i sar. [2] su naglasili da su nestašice lekova globalni fenomen kojeg karakterišu značajne razlike među zemljama u sistemima izveštavanja, definicijama i politikama za ublažavanje posledica. Foks i sar. [3] opisali su nestašice kao složenu

systems. They assert that the security of healthcare delivery depends on the robustness of upstream supply structures. Likewise, the scoping review by Ahmad Hamdi et al. [4] showed that pharmaceutical operations management in preparedness and disaster response requires coordinated planning before, during, and after disruption.

Consequently, pharmaceutical and medical device supply chain resilience should be regarded as part of healthcare security infrastructure. It is not only a matter of procurement efficiency, but also of system readiness, patient protection, and institutional continuity under pressure [1,2,4,21–23].

Key vulnerabilities and drivers of disruption

A major source of vulnerability in pharmaceutical and medical device supply chains is production concentration. Many essential products depend on a limited number of manufacturers, production sites, or upstream suppliers of active ingredients and specialized components [1,2,9]. Although this structure may improve cost efficiency in stable periods, it creates systemic fragility when production failures, transport interruptions, or export restrictions affect critical nodes.

Jaberidoost et al. [6] identified a wide range of pharmaceutical supply chain risks, including supplier failure, demand uncertainty, regulatory barriers, information asymmetry, storage limitations, transportation disruptions, and quality-related problems. Their findings remain highly relevant because they show that supply disruption is rarely caused by a single factor. Instead, shortages usually emerge from the interaction of multiple operational, economic, and regulatory pressures.

Drug shortages are the most visible consequence of these structural weaknesses. Acosta et al. [2] emphasized that medicine shortages are a global phenomenon characterized by substantial variation in reporting systems, definitions, and mitigation policies across countries. Fox et al. [3] described shortages as a complex healthcare crisis that affects therapeutic decisions, clinical workflow, and costs, while Ventola [9] highlighted the roles of manufacturing quality failures, limited profitability of older generics, raw material scarcity, and regulatory delays. Hospital-level studies in Europe have further confirmed that shortages create a significant burden for pharmacists, who must continuously manage substitutions, communication, and risk reduction under constrained conditions [7,8].

Some shortages are especially dangerous because they affect products with limited substitutability. Mazer-Amirshahi and Fox illustrated this problem with saline shortages, showing how the lack of even basic

krizu u zdravstvu koja utiče na terapijske odluke, klinički proces rada i troškove, dok je Ventola [9] istakla značaj kvalitativnih grešaka u proizvodnji, ograničene profitabilnosti starijih generičkih lekova, nestašice sirovina i regulatornih kašnjenja. Studije sprovedene na nivou bolnica u Evropi dodatno su potvrdile da nestašice stvaraju značajno opterećenje za farmaceute, koji moraju kontinuirano da rukovode zamenama, komunikacijom i smanjenjem rizika u uslovima ograničenih resursa [7,8].

Neke nestašice su naročito opasne jer se odnose na proizvode sa ograničenom mogućnošću zamene. Mazer-Amirshahi i Foks su ilustrovali ovaj problem nestašicama fiziološkog rastvora, pokazujući kako nedostatak čak i osnovnih bolničkih potrepština može da predstavlja veliku pretnju kontinuitetu zdravstvene zaštite [10]. Slično tome, Mazer-Amirshahi i sar. naveli su da nestašice lekova u toksikologiji i urgentnoj medicini mogu da ugroze pravovremeno lečenje i primoraju zdravstvene radnike da koriste manje poznate alternative [11].

Literatura takođe pokazuje da geopolitički i političko-ekonomski uslovi mogu da pojačaju nestabilnost snabdevanja. U kontekstu Irana, Bastani i sar. su pokazali da sankcije mogu da ugroze dostupnost lekova usled ograničenja uvoza, prepreka u finansiranju i poremećaja kanala nabavke [12]. Ovi dokazi su posebno važni jer proširuju diskusiju o otpornosti izvan pandemija i uobičajenih logističkih neuspeha, ukazujući i na potrebu pripreme za hronične geopolitičke stresore.

Sve u svemu, dokazi ukazuju na to da su lanci snabdevanja lekovima i medicinskim sredstvima ranjivi zbog koncentrisane proizvodnje, fragmentisane vidljivosti, ekonomskih struktura sklonih nestašicama, regulatorne rigidnosti i nedovoljne pripremljenosti za poremećaje proistekle iz više izvora [1,2,6,9–12].

Osnovni kapaciteti za otpornost u lancima snabdevanja lekovima i medicinskim sredstvima

Literatura o otpornosti dosledno pokazuje da se žilavi sistemi snabdevanja ne definišu odsustvom poremećaja, već posjedovanjem kapaciteta prilagođavanja [21–23]. U lancima snabdevanja lekovima i medicinskim sredstvima nekoliko kapaciteta se pokazuje naročito važnim. Vidljivost predstavlja osnovni kapacitet. Zdravstveni sistemi često imaju nepotpun uvid u međuzavisnosti na višim nivoima lanca, koncentraciju proizvodnje ili stanje zaliha izvan neposrednih interfejsa za nabavku [1,2,18,20]. Ograničena vidljivost odlaže otkrivanje problema i slabi sposobnost predviđanja nestašica. Stoga su veća transparentnost među dobavljačima, distributerima, bolničkim sistemima i regulatornim telima od ključnog značaja za rano upozoravanje i koordinisani odgovor.

hospital supplies can pose a major threat to care continuity [10]. Similarly, Mazer-Amirshahi et al. reported that drug shortages in toxicology and emergency care may compromise timely treatment and force the use of unfamiliar alternatives [11].

The literature also shows that geopolitical and politico-economic conditions may intensify supply instability. In the Iranian context, Bastani et al. demonstrated that sanctions could impair pharmaceutical access through import restrictions, financing barriers, and disruption of procurement pathways [12]. This evidence is especially important because it expands the resilience discussion beyond pandemics and routine logistics failures, highlighting the need to prepare for chronic geopolitical stressors as well.

Overall, the evidence indicates that pharmaceutical and medical device supply chains are vulnerable due to concentrated production, fragmented visibility, shortage-prone economics, regulatory rigidity, and insufficient preparedness for multi-source disruption [1,2,6,9–12].

Core resilience capabilities in pharmaceutical and medical device supply chains

The resilience literature consistently shows that robust supply systems are not defined by the absence of disruption but by the presence of adaptive capabilities [21–23]. In pharmaceutical and medical device supply chains, several capabilities appear especially important. Visibility is a foundational capability. Health systems often have incomplete insight into upstream dependencies, production concentration, or inventory conditions beyond immediate procurement interfaces [1,2,18,20]. Limited visibility delays problem detection and weakens the ability to anticipate shortages. Greater transparency across suppliers, distributors, hospital systems, and regulatory bodies is therefore central to early warning and coordinated response.

Redundancy remains essential despite its cost implications. While efficiency-oriented models often minimize inventory and supplier overlap, healthcare systems require strategic redundancy in critical products, alternative sourcing arrangements, and, where feasible, reserve capacity [21–23]. In healthcare, the cost of insufficient redundancy may be clinically unacceptable.

Flexibility is equally important. This includes the ability to switch suppliers, substitute therapeutically appropriate alternatives, adapt formularies, modify procurement pathways, and redistribute stock across institutions [4,5,12,18]. Flexibility is particularly valuable during acute shortages, when rigid administrative structures may delay response, even when physical stock exists elsewhere in the system.

Redundantnost ostaje od suštinskog značaja uprkos implikacijama po pitanju troškova. Dok modeli usmereni na efikasnost često nastoje da na minimum svedu zalihe i preklapanje dobavljača, zdravstveni sistemi zahtevaju stratešku redundantnost kritičnih proizvoda, alternativne aranžmane za nabavku i, gde je to izvodljivo, kapacitet za stvaranje rezervi [21–23]. U zdravstvu, cena nedovoljne redundantnosti može biti klinički neprihvatljiva.

Fleksibilnost je podjednako važna. Ona uključuje sposobnost da se promene dobavljači, izvrši zamena terapijski odgovarajućim alternativama, prilagode registri lekova, izmene putevi nabavke i preraspodele zaliha između institucija [4,5,12,18]. Fleksibilnost je od naročitog značaja tokom akutnih nestašica kada krute administrativne strukture mogu da odlože odgovor čak iako fizičke zalihe postoje drugde u sistemu.

Prilagodljivo upravljanje zalihama pojavilo se kao značajan mehanizam otpornosti u novijim studijama modelovanja. Pati i Rahimian [15] su predložili otporni pristup upravljanju zalihama za lance snabdevanja farmaceutskim proizvodima u uslovima poremećaja potražnje, ukazujući na značaj dinamičkih strategija upravljanja zalihama umesto pretpostavki o statičkom obnavljanju zaliha. Slično tome, Badeho i Ierapetrito su pokazali [14] da višekriterijumska optimizacija koja uzima u obzir poremećaje može da poboljša otpornost uspostavljanjem ravnoteže između troškova, kontinuiteta pružanja usluga i uspešnosti oporavka. Ovi nalazi podržavaju prelazak sa modela zaliha zasnovanih isključivo na principu optimizacije, odnosno poslovanja bez gubitaka (engl. *lean inventory models*) na politike zaliha prilagođenim riziku, zasnovanim na kritičnom značaju proizvoda, vremenu izvršenja nabavke i potencijalu naglog povećanja potražnje.

Noviji radovi su takođe ojačali analitičku osnovu za oblikovanje kapaciteta otpornosti. Kumar i sar. su modelovali otpornost i pouzdanost u lancima snabdevanja farmaceutskim proizvodima, dok su Žu i sar. koristili simulaciju za ispitivanje otpornosti iz perspektive kapaciteta zasnovanog na faktorima uticaja [16,17]. Ove studije dodatno potvrđuju da se otpornost može sistematski procenjivati i projektovati, umesto da se tretira kao apstraktna menadžerska težnja.

Konačno, saradnja i koordinisano upravljanje predstavljaju kapacitete koji su od značaja na svim nivoima. Nijedan pojedinačni akter ne kontroliše celokupan lanac snabdevanja lekovima ili medicinskim sredstvima. Proizvođači, veleprodaje, bolnice, apoteke, regulatorna tela i javnozdravstvene institucije, svi snose svoj deo odgovornosti [1,4,5,21–23]. Otpornost stoga zavisi od koordinisane razmene informacija, mehanizama eskalacije i jasno definisanih uloga pre nego što dođe do poremećaja.

Adaptive inventory management has emerged as a major resilience mechanism in recent modeling studies. Pathy and Rahimian [15] proposed a resilient inventory approach for pharmaceutical supply chains under demand disruption, demonstrating the importance of dynamic stock strategies rather than static replenishment assumptions. Similarly, Badejo and Ierapetritou showed [14] that disruption-aware multi-objective optimization can improve resilience by balancing cost, service continuity, and recovery performance. These findings support a shift from purely lean inventory models toward risk-adjusted inventory policies based on criticality, lead time, and surge potential.

Recent publications have also strengthened the analytical basis for designing resilience capabilities. Kumar et al. modeled resilience and reliability in pharmaceutical supply chains, while Zhu et al. used simulation to examine resilience from an impact-factor capability perspective [16,17]. These studies reinforce the idea that resilience can be systematically assessed and engineered rather than treated as an abstract managerial aspiration.

Finally, collaboration and coordinated governance are cross-cutting capabilities. No single actor controls the full pharmaceutical or medical device supply chain. Manufacturers, wholesalers, hospitals, pharmacies, regulators, and public health authorities all hold partial responsibilities [1,4,5,21–23]. Resilience, therefore, depends on coordinated information sharing, escalation pathways, and clearly defined roles before disruption occurs.

Digitalization, preparedness, and the role of pharmacists

Digital transformation is increasingly recognized as a major enabler of supply chain resilience. Industry 4.0 technologies, including data integration, predictive analytics, automation, digital traceability, and simulation, can improve visibility, forecasting, and responsiveness across healthcare supply networks [18–20]. Although much of the broader literature comes from manufacturing, its relevance to healthcare is substantial, especially where demand volatility and product criticality intersect.

Reza et al. [18], in their systematic review, highlighted that Industry 4.0 has significant implications for supply chain resilience by enhancing information flow, reducing uncertainty, and improving adaptive decision-making during disruptions. Badhotiya et al. [19] also showed that resilience assessment in disrupted supply systems benefits from structured capability evaluation. A particularly important conceptual contribution comes from Ivanov and Dolgui [20], who

Digitalizacija, pripremljenost i uloga farmaceuta

Digitalna transformacija se sve više prepoznaje kao važan faktor koji omogućava otpornost lanaca snabdevanja. Tehnologije Industrije 4.0, uključujući integraciju podataka, prediktivnu analitiku, automatizaciju, mogućnost digitalnog praćenja i simulaciju, mogu poboljšati vidljivost, prognoziranje i sposobnost odgovora u zdravstvenim mrežama snabdevanja [18–20]. Iako veliki deo šire literature potiče iz oblasti proizvodnje, njena relevantnost za zdravstvo je značajna, naročito tamo gde se ukrštaju varijabilnost potražnje i kritični značaj proizvoda.

Reza i sar. [18], u svom sistematskom pregledu, istakli su da Industrija 4.0 ima značajne implikacije za otpornost lanca snabdevanja kroz unapređenje protoka informacija, smanjenje neizvesnosti i poboljšanje adaptivnog donošenja odluka tokom poremećaja. Badhotija i sar. [19] su takođe pokazali da je strukturisana procena kapaciteta korisna za procenu otpornosti u poremećenim sistemima snabdevanja. Posebno važan konceptualni doprinos dali su Ivanov i Dolgui [20], koji su predložili uspostavljanje tzv. digitalnog blizanca lanca snabdevanja kao alat za prevazilaženje rizika od poremećaja i otpornošću u eri Industrije 4.0. U kontekstu zdravstvene zaštite, ovaj pristup bi mogao da podrži modelovanje scenarija dostupnosti lekova i medicinskih sredstava od kritičnog značaja, alternativnih izvora snabdevanja i planiranja raspodele u uslovima naglog povećanja potražnje.

Međutim, sami digitalni alati nisu dovoljni bez operativne pripremljenosti i integracije na profesionalnom nivou. Literatura jasno ukazuje na to da farmaceuti imaju ključnu ulogu u otpornim sistemima snabdevanja u zdravstvu, naročito tokom kriza [5,24–26]. Aruru i sar. su predložili okvir pod nazivom *Pharmacy Emergency Preparedness and Response (PEPR)*¹, koji proširuje uloge farmaceuta izvan izdavanja lekova i uključuje podršku trijaži, hitnu logistiku, komunikaciju sa javnošću i odgovorno upravljanje primenom lekova [5]. Buhari i sar. [24] su dodatno istakli ulogu farmaceuta koji su radili na prvoj liniji tokom pandemije bolesti KOVID-19.

Regulatorna prilagodljivost je takođe značajna. Merks i sar. [25] su pokazali da su zakonska proširenja ovlašćenja farmaceuta tokom pandemije poboljšala sposobnost odgovora i kontinuitet pružanja usluga. Slično tome, Kadka i sar. [26] su istakli ulogu farmaceuta u prevazilaženju katastrofa, naročito u održavanju dostupnosti lekova u nestabilnim uslovima. Posmatrano zajedno, ove studije pokazuju da otpornost zdravstvenih radnika nije odvojena od otpornosti lanca sna-

proposed the digital supply chain twin as a tool for managing disruption risk and resilience in the Industry 4.0 era. In the healthcare context, this approach could support scenario modeling for critical medicine and device availability, alternative sourcing, and surge allocation planning.

However, digital tools alone are insufficient without operational preparedness and professional integration. The literature strongly indicates that pharmacists play a crucial role in resilient healthcare supply systems, particularly during crises [5,24–26]. Aruru et al. proposed the Pharmacy Emergency Preparedness and Response (PEPR) framework, which expands pharmacists' roles beyond dispensing to include triage support, emergency logistics, public communication, and medication stewardship [5]. Bukhari et al. [24] further emphasized the frontline role of pharmacists during the COVID-19 pandemic.

Regulatory adaptability is also important. Merks et al. [25] demonstrated that legal extensions of pharmacists' roles during the pandemic improved responsiveness and service continuity. Khadka et al. [26] similarly highlighted the pharmacists' role in disaster management, particularly in maintaining medication access under unstable conditions. Taken together, these studies show that workforce resilience is not separate from supply chain resilience; it is one of its enabling prerequisites.

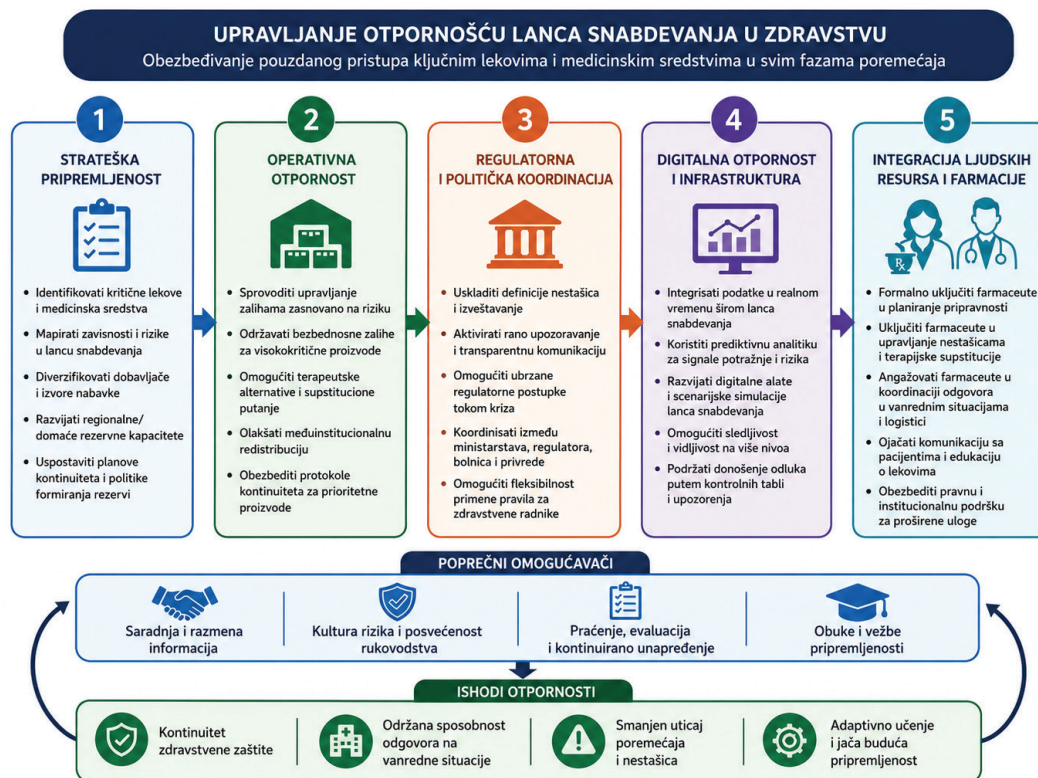
Case-informed governance framework for healthcare supply resilience

Based on the reviewed literature, pharmaceutical and medical device supply chain resilience can be organized into a practical five-level governance framework suitable for health systems, hospitals, and regulatory institutions. The proposed framework is summarized in Figure 1, illustrating the interdependent strategic, operational, regulatory, digital, and workforce dimensions required to strengthen healthcare supply continuity under conditions of disruption.

First, strategic preparedness should include identification of critical medicines and devices, tiered risk mapping of supply dependencies, diversified sourcing strategies, and, where feasible, regional or domestic backup capacity [1,2,4,12,18,21]. This level addresses structural exposure before disruption occurs.

Second, operational resilience should focus on risk-adjusted inventory policies, emergency substitution pathways, inter-institutional redistribution mechanisms, and continuity protocols for high-priority clinical products [3,10,11,14–17]. Hospitals should not rely exclusively on standard replenishment logic for products with high criticality and limited substitutability.

¹ Farmaceutska pripremljenost za odgovor u vanrednim situacijama, prim. prev.



Slika 1. Okvir upravljanja zasnovan na iskustvima iz prakse za otpornost lanca snabdevanja farmaceutskim proizvodima i medicinskim sredstvima u zdravstvenim sistemima

Okvir konceptualizuje otpornost lanca snabdevanja u zdravstvu kao višeslojni model upravljanja, a ne isključivo kao operativnu funkciju javnih nabavki. Pet međusobno povezanih oblasti, strateška pripravnost, operativna otpornost, regulatorna i politička koordinacija, digitalna otpornost i infrastruktura i integracija farmaceutskih radnika, zajednički doprinose sposobnosti zdravstvenih sistema da predvide poremećaje, apsorbuju potrese u lancima snabdevanja, očuvaju kontinuitet zdravstvene zaštite i prilagode se budućim neizvesnim situacijama.

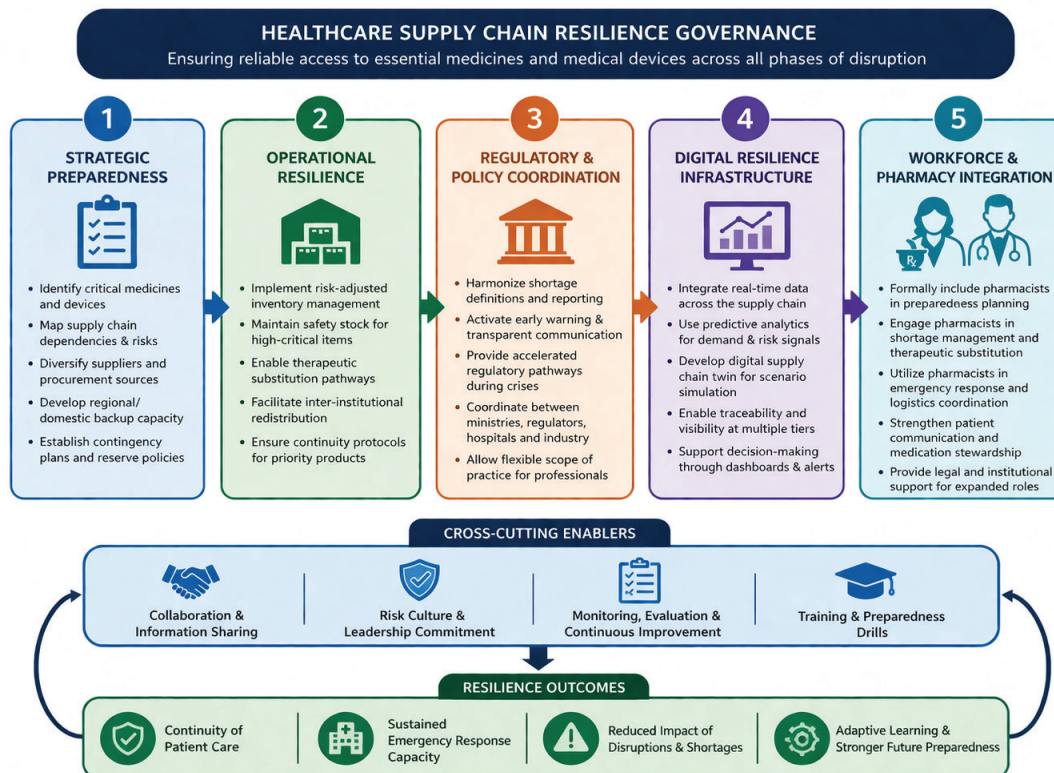


Figure 1. Case-informed governance framework for pharmaceutical and medical device supply chain resilience in healthcare systems

The framework conceptualizes healthcare supply chain resilience as a multi-level governance construct rather than a purely operational procurement function. Five interconnected domains, strategic preparedness, operational resilience, regulatory and policy coordination, digital resilience infrastructure, and pharmacy workforce integration, collectively support the ability of healthcare systems to anticipate disruptions, absorb supply shocks, maintain continuity of care, and adapt to future uncertainty.

Tabela 1. Ključne tematske oblasti identifikovane u pregledanoj literaturi i njihove implikacije na otpornost lanaca snabdevanja lekovima i medicinskim sredstvima kao komponentu bezbednosti zdravstvene zaštite

Tematska oblast	Ključni rezultati iz pregledane literature	Implikacije otpornosti na zdravstvene sisteme	Reprezentativni literaturni izvori
Globalna ranjivost lanaca snabdevanja lekovima i medicinskim sredstvima	Zdravstveni sistemi zavise od složenih, globalno distribuiranih mreža snabdevanja koje su podložne poremećajima, naročito tokom pandemija, vanrednih situacija i međudržavnih ograničenja.	Nacionalna i institucionalna pripremljenost bi trebalo da obuhvati kontinuitet snabdevanja kao komponentu bezbednosti zdravstvene zaštite, a ne isključivo kao pitanje efikasnosti nabavke.	Miler i sar. [1]; Ahmad Hamdi i sar. [4]; Hop i sar. [29]
Nestašice lekova kao sistemska pretnja po zdravstvenu zaštitu	Nestašice lekova se ponavljaju, one su multifaktorske i klinički značajne. Utiču na bezbednost pacijenata, kontinuitet lečenja, funkcionisanje bolnica i rad farmaceutskih službi.	Trebalo bi institucionalizovati mehanizme prevazilaženja nestašica putem sistema ranog upozoravanja, puteva za terapijsku zamenu, koordinisanih protokola za eskalaciju i strukturisanih strategija za ublažavanje posledica.	Akosta i sar. [2]; Foks i sar. [3]; Pauels i sar. [7]; Bogert i sar. [8]; Ventola [9]; Mazer-Amiršahi i sar. [10,11]
Strukturni faktori rizika u lancima snabdevanja	Ključne slabosti uključuju koncentraciju dobavljača, poremećaje u proizvodnji, oskudice u sirovinama, regulatorne prepreke, poremećaje u transportu, informacionu asimetriju i ekonomski krhke proizvodne modele.	Mapiranje rizika bi trebalo da identifikuje zavisnosti od kritičnog značaja i da kao prioritete utvrdi diversifikaciju, alternativne izvore snabdevanja i zaštitu kategorija lekova i medicinskih sredstava sa visokim rizikom.	Miler i sar. [1]; Akosta i sar. [2]; Jaberidost i sar. [6]; Ventola [9]; Bastani i sar. [12]
Geopolitički poremećaji i poremećaji uzrokovani sankcijama	Politička nestabilnost, sankcije, trgovinska ograničenja i prepreke u finansiranju mogu značajno da otežaju dostupnost lekova i medicinskih proizvoda.	Planiranje otpornosti bi trebalo da obuhvati hronične geopolitičke stresore i dugoročnu neizvesnost u snabdevanju, a ne samo akutne krize događaje.	Bastani i sar. [12]
Osnovni kapaciteti otpornosti	Otpornost lanaca snabdevanja zavisi od vidljivosti, redundantnosti, fleksibilnosti, saradnje, agilnosti i adaptivnog kapaciteta za oporavak. U zdravstvu su ovi kapaciteti neposredno povezani sa kontinuitetom zdravstvene zaštite.	Zdravstveni sistemi bi trebalo da prevaziđu modele stroge optimizacije i pređu na modele otpornosti prilagođene riziku, naročito kada je reč o proizvodima od kritičnog kliničkog značaja.	Petit i sar. [21]; Tukamuhabva i sar. [22]; Ponomarov i Holkom [23];
Otpornost i optimizacija zaliha	Statični ili strogo optimizovani („lean“) sistemi upravljanja zalihama nisu dovoljni tokom naglih poremećaja potražnje. Noviji modeli podržavaju dinamičke strategije upravljanja zalihama, optimizaciju koja uzima u obzir poremećaje i planiranje sa više ciljeva.	Lekovi i medicinska sredstva od kritičnog značaja bi trebalo da budu obuhvaćeni diferenciranim politikama upravljanja zalihama, zasnovanim na kliničkom prioritetu, vremenu nabavke, mogućnosti zamene i uticaju nestašice.	Badeho i Ierapetrto [14]; Pati i Rahimian [15]; Kumar i sar. [16]; Žu i sar. [17]
Digitalizacija i alati Industrije 4.0 za jačanje otpornosti	Mogućnost digitalnog praćenja, prediktivna analitika, integrisani sistemi podataka i digitalni blizanci mogu da unaprede vidljivost, predviđanja i odgovore na poremećaje.	Digitalna infrastruktura trebalo bi da podrži praćenje u realnom vremenu, modelovanje scenarija, prediktivno donošenje odluka i koordinisani odgovor na krize.	Reza i sar. [18]; Badhotija i sar. [19]; Ivanov i Dolgui [20]; Ivanov [32]
Farmaceuti kao nosioci otpornosti	Farmaceuti imaju ključnu ulogu u ublažavanju posledica nestašica, upravljanju terapijskim zamenama, odgovoru u vanrednim situacijama, odgovornom upravljanju primenom lekova i komunikaciji sa pacijentima tokom kriza.	Farmaceuti bi trebalo da budu formalno uključeni u planiranje pripremljenosti, prevazilaženje nestašica i institucionalne okvire za odgovor u vanrednim situacijama.	Aruru i sar. [5]; Buhari i sar. [24]; Merks i sar. [25]; Kadka i sar. [26];
Upravljanje i koordinacija regulative	Otpornost zavisi od koordinisanog delovanja regulatornih tela, bolnica, dobavljača, apoteke i organa javnog zdravlja. Regulatorna rigidnost može da odloži mere za ublažavanje posledica čak i kada postoje alternative.	Delotvorna otpornost zahteva upravljanje na više nivoa, usaglašeno izveštavanje o nestašicama, ubrzane regulatorne postupke, institucionalnu odgovornost i koordinisane mehanizme pripremljenosti.	Akosta i sar. [2]; Ahmad Hamdi i sar. [4]; Pauels i sar. [7]; Bogert i sar. [8]; Merks i sar. [25]; Bočenek i sar. [31]

Table 1. Key thematic domains identified in the reviewed literature and their implications for pharmaceutical and medical device supply chain resilience as a component of healthcare security

Thematic domain	Key findings from the reviewed literature	Resilience implications for healthcare systems	Representative references
Global pharmaceutical and medical device supply vulnerability	Healthcare systems depend on complex, globally distributed supply networks that are vulnerable to disruption, particularly during pandemics, emergencies, and cross-border restrictions.	National and institutional preparedness should incorporate supply continuity as a component of healthcare security rather than solely as a procurement efficiency issue.	Miller et al. [1]; Ahmad Hamdi et al. [4]; Hopp et al. [29]
Drug shortages as a systemic healthcare threat	Medicine shortages are recurrent, multifactorial, and clinically disruptive. They affect patient safety, treatment continuity, hospital workflow, and pharmacy operations.	Shortage management should be institutionalized through early warning systems, therapeutic substitution pathways, coordinated escalation protocols, and structured mitigation strategies.	Acosta et al. [2]; Fox et al. [3]; Pauwels et al. [7]; Bogaert et al. [8]; Ventola [9]; Mazer-Amirshahi et al. [10,11]
Structural risk factors in supply chains	Key vulnerabilities include supplier concentration, manufacturing failures, raw material scarcity, regulatory barriers, transportation disruption, information asymmetry, and economically fragile production models.	Risk mapping should identify critical dependencies and prioritize diversification, alternative sourcing, and protection of high-risk categories of medicines and devices.	Miller et al. [1]; Acosta et al. [2]; Jaberidoost et al. [6]; Ventola [9]; Bastani et al. [12]
Geopolitical and sanction-related disruptions	Political instability, sanctions, trade restrictions, and financing barriers can significantly impair access to medicines and medical products.	Resilience planning should incorporate chronic geopolitical stressors and long-term supply uncertainty, not only acute crisis events.	Bastani et al. [12]
Core resilience capabilities	Supply chain resilience depends on visibility, redundancy, flexibility, collaboration, agility, and adaptive recovery capacity. In healthcare, these capabilities are directly linked to continuity of care.	Healthcare systems should move beyond purely lean models toward risk-adjusted resilience architectures, particularly for clinically critical products.	Pettit et al. [21]; Tukamuhabwa et al. [22]; Ponomarov and Holcomb [23];
Inventory resilience and optimization	Static or purely lean inventory systems are insufficient during demand shocks. Recent models support dynamic inventory strategies, disruption-aware optimization, and multi-objective planning.	Critical medicines and devices should be managed through differentiated inventory policies based on clinical priority, lead time, substitutability, and shortage impact.	Badejo and Ilerapetritou [14]; Pathy and Rahimian [15]; Kumar et al. [16]; Zhu et al. [17]
Digitalization and Industry 4.0 resilience tools	Digital traceability, predictive analytics, integrated data systems, and digital twins can improve visibility, forecasting, and disruption response.	Digital infrastructure should support real-time monitoring, scenario modelling, predictive decision-making, and coordinated crisis response.	Reza et al. [18]; Badhotiya et al. [19]; Ivanov and Dolgui [20]; Ivanov [32]
Pharmacists as resilience actors	Pharmacists play a central role in shortage mitigation, substitution management, emergency response, medication stewardship, and patient communication during crises.	Pharmacists should be formally integrated into preparedness planning, shortage governance, and institutional emergency response frameworks.	Aruru et al. [5]; Bukhari et al. [24]; Merks et al. [25]; Khadka et al. [26];
Governance and regulatory coordination	Resilience depends on the coordinated action of regulators, hospitals, suppliers, pharmacies, and public health authorities. Regulatory rigidity may delay mitigation even when alternatives exist.	Effective resilience requires multi-level governance, harmonized shortage reporting, rapid regulatory pathways, institutional accountability, and coordinated preparedness mechanisms.	Acosta et al. [2]; Ahmad Hamdi et al. [4]; Pauwels et al. [7]; Bogaert et al. [8]; Merks et al. [25]; Bochenek et al. [31]

bdevanja; ona predstavlja jedan od uslova koji omogućavaju njegovu otpornost.

Okvir upravljanja za otpornost snabdevanja u zdravstvu zasnovan na iskustvima iz prakse

Na osnovu pregledane literature, otpornost lanaca snabdevanja lekovima i medicinskim sredstvima može se organizovati u praktičan petostepeni okvir upravljanja pogodan za zdravstvene sisteme, bolnice i regulatorne institucije. Predloženi okvir prikazan je na **Slici 1**, koja ilustruje međuzavisne strateške, operativne, regulatorne, digitalne i kadrovske dimenzije potrebne za jačanje kontinuiteta snabdevanja u zdravstvu u uslovima poremećaja.

Prvo, strateška pripremljenost treba da obuhvati identifikovanje lekova i medicinskih sredstava od kritičnog značaja, višestepeno mapiranje rizika zavisnosti u lancu snabdevanja, strategije diversifikacije izvora snabdevanja i, gde je izvodljivo, regionalne ili domaće rezervne kapacitete [1,2,4,12,18,21]. Ovaj nivo odnosi se na strukturnu izloženost pre nego što dođe do poremećaja.

Drugo, operativna otpornost treba da bude usmerena na politike stvaranja zaliha prilagođene riziku, putove hitne zamene, mehanizme preraspodele između institucija i protokole kontinuiteta za kliničke proizvode visokog prioriteta [3,10,11,14–17]. Bolnice ne bi trebalo da se oslanjaju isključivo na standardnu logiku obnavljanja zaliha kada su u pitanju proizvodi od visokog kritičnog značaja sa ograničenom mogućnošću zamene.

Treće, regulatorna i politička koordinacija treba da obuhvati rano prijavljivanje nestašica, usklađene definicije nestašica, ubrzane postupke regulatorne procesne tokom kriznih uslova, transparentne kanale komunikacije i strukturisanu koordinaciju između ministarstava, regulatornih tela, bolničkih sistema i stručnih organizacija [2,7–9,25]. Bez regulatorne agilnosti, čak i mere za ublažavanje posledica koje su tehnički dostupne mogu da budu odložene.

Četvrto, infrastruktura digitalne otpornosti treba da podrži vidljivost u realnom vremenu, prediktivno praćenje, simulaciju scenarija i integrisanu podršku odlučivanju [18–20]. Digitalne alate treba projektovati ne samo radi efikasnosti nabavke već i radi ranog upozoravanja i koordinacije u kriznim situacijama.

Peto, integracija farmaceutskih radnika treba da omogućiti formalno prepoznavanje farmaceuta kao aktera od ključnog značaja za pripremljenost, prevazilaženje nestašica, terapijsku zamenu, komunikaciju sa pacijentima i odgovor na katastrofe [5,24–26]. Ovo je naročito važno u bolnicama, gde su farmaceuti često primarna operativna spona između poremećaja u snabdevanju i kontinuiteta kliničkog rada.

Ovaj okvir je „zasnovan na iskustvima iz prakse“ zato što odražava obrasce koji se ponavljaju u pandemijskim

Third, regulatory and policy coordination should include early shortage reporting, harmonized shortage definitions, accelerated review pathways during crisis conditions, transparent communication channels, and structured coordination between ministries, regulators, hospital systems, and professional bodies [2,7–9,25]. Without regulatory agility, even technically available mitigation options may be delayed.

Fourth, digital resilience infrastructure should support real-time visibility, predictive monitoring, scenario simulation, and integrated decision support [18–20]. Digital tools should be designed not merely for procurement efficiency, but for early warning and crisis coordination.

Fifth, pharmacy workforce integration should formally recognize pharmacists as core actors in preparedness, shortage management, therapeutic substitution, patient communication, and disaster response [5,24–26]. This is especially important in hospitals, where pharmacists are often the primary operational interface between supply disruption and clinical continuity.

This framework is “case-informed” because it reflects recurrent patterns observed across pandemic disruptions, disaster response, chronic shortages, and sanction-related supply stress [1–5,9–12]. Its main value lies in integrating resilience as a governance function rather than limiting it to isolated procurement measures.

DISCUSSION AND PRACTICAL IMPLICATIONS

The reviewed literature supports a clear conclusion: pharmaceutical and medical device supply chain resilience should be treated as an essential component of healthcare security. Recurrent shortages, pandemic stress, and geopolitical instability have shown that disruptions in supply systems can rapidly undermine clinical care, emergency preparedness, and institutional reliability [1–3,7–11].

A key practical implication is that healthcare systems must move beyond a narrow efficiency paradigm. Procurement models built primarily around price minimization and lean inventory may appear rational in stable periods, but they often increase fragility under pressure [1,3,9]. In the healthcare setting, resilience requires a deliberate rebalancing toward strategic redundancy, risk-adjusted stock policies, and diversified sourcing for clinically critical products [14,15,21–23].

Another important implication relates to governance fragmentation. Because no single actor controls the full chain, resilience depends on coordinated action among regulators, manufacturers, distributors, hospitals, pharmacies, and emergency planners [1,2,4,5]. In practice, this means that shortage preparedness should be embedded in institutional policy, not left to

poremećajima, odgovoru na katastrofe, hroničnim nestašicama i stresu u snabdevanju povezanom sa sankcijama [1–5,9–12]. Njegova glavna vrednost ogleda se u integrisanju otpornosti kao funkcije upravljanja, umesto njenog ograničavanja na izolovane mere nabavke.

DISKUSIJA I PRAKTIČNE IMPLIKACIJE

Analizirana literatura podržava jasan zaključak: otpornost lanaca snabdevanja lekovima i medicinskim sredstvima treba tretirati kao suštinsku komponentu bezbednosti zdravstvene zaštite. Ponavljene nestašice, pandemijski pritisak i geopolitička nestabilnost pokazali su da poremećaji u sistemima snabdevanja mogu brzo da ugroze kliničku zdravstvenu zaštitu, pripremljenost za vanredne situacije i pouzdanost funkcionisanja institucija [1–3,7–11].

Ključna praktična implikacija jeste da zdravstveni sistemi moraju da se izdignu iznad uske paradigme efikasnosti. Modeli nabavke zasnovani prvenstveno na minimizaciji cena i optimizovanim (*lean*) zalihama mogu da deluju racionalno u stabilnim periodima, ali često povećavaju krhkost sistema pod pritiskom [1,3,9]. U kontekstu zdravstva, otpornost zahteva namerno uspostavljanje ravnoteže u korist strateške redundantnosti, politika zaliha prilagođenih riziku i diversifikovanih izvora snabdevanja za proizvode od kritičnog kliničkog značaja [14,15,21–23].

Druga važna implikacija odnosi se na fragmentisanost upravljanja. Budući da nijedan pojedinačni akter ne kontroliše celokupni lanac, otpornost zavisi od koordinisanog delovanja regulatornih tela, proizvođača, distributera, bolnica, apoteka i aktera odgovornih za planiranje odgovora na vanredne situacije [1,2,4,5]. U praksi, to znači da pripremljenost za nestašice treba da bude ugrađena u institucionalnu politiku, a ne da bude prepuštena *ad hoc* odgovoru na krizu. Bolnice i zdravstvene vlasti treba unapred da definišu liste prioriternih proizvoda, puteve eskalacije, protokole zamene i procedure komunikacije.

Ovaj pregled literature takođe ukazuje na to da se otpornost jača kada se farmaceuti tretiraju kao strateški učesnici, a ne samo kao izvršioci izdavanja lekova. Njihove uloge u ublažavanju posledica nestašica, odgovornom upravljanju primenom lekova, komunikaciji sa pacijentima i odgovoru na vanredne situacije više puta su naglašene u literaturi [5,7,24–26]. U mnogim sistemima farmaceuti već neformalno obavljaju ove funkcije. Formalno priznavanje njihovih uloga i regulatorna podrška poboljšali bi doslednost i pripremljenost.

Najzad, digitalizaciji treba pristupiti kao faktoru koji omogućava otpornost, a ne kao isključivo tehnološkom trendu. Integracija podataka u realnom vremenu, prediktivno praćenje i digitalno modelovanje lanaca

ad hoc crisis response. Hospitals and health authorities should define priority product lists, escalation pathways, substitution protocols, and communication procedures in advance.

The review also suggests that resilience is strengthened when pharmacists are treated as strategic participants rather than merely medicine dispensers. Their roles in shortage mitigation, medication stewardship, patient communication, and emergency response have been repeatedly emphasized across the literature [5,7,24–26]. In many systems, pharmacists already perform these functions informally. Formal recognition and regulatory support would improve consistency and preparedness.

Finally, digitalization should be approached as a resilience enabler rather than a purely technological trend. Real-time data integration, predictive monitoring, and digital supply chain modeling can improve preparedness, but only if embedded within clear governance structures and interoperable institutional workflows [18–20].

Alignment of the proposed governance framework with international medicines policy principles and pharmaceutical system resilience

The proposed governance framework should be interpreted as an extension of established principles of national medicines policies rather than as a replacement of existing pharmaceutical governance approaches. The World Health Organization (WHO) has traditionally emphasized the importance of equitable access to essential medicines, assurance of medicine quality, rational use, and the development of sustainable pharmaceutical systems, as fundamental components of national medicines policies [27,28]. However, the growing complexity of global pharmaceutical supply networks has shown that achieving these objectives increasingly depends on healthcare systems' ability to anticipate, absorb, and adapt to external disruptions.

Although traditional medicines policy frameworks have primarily focused on regulatory oversight, procurement mechanisms, affordability, and appropriate utilization of medicines, recent global events have highlighted additional determinants of pharmaceutical security. The COVID-19 pandemic exposed vulnerabilities related to global manufacturing concentration, dependence on limited suppliers, insufficient supply chain visibility, and delayed recognition of emerging shortages [1,29]. Consequently, medicine availability can no longer be considered solely a function of national procurement capacity but rather an outcome of interconnected international production, regulatory, logistical, and organizational processes. In this context, pharmaceutical resilience may be defined as the

snabdevanja mogu da poboljšaju pripremljenost, ali samo ako su ugrađeni u jasne strukture upravljanja i interoperabilne institucionalne radne procese [18–20].

Usklađenost predloženog okvira upravljanja sa međunarodnim principima politike o lekovima i otpornošću farmaceutskog sistema

Predloženi okvir upravljanja treba tumačiti kao proširenje ustanovljenih principa nacionalnih politika o lekovima, a ne kao zamenu za postojeće pristupe upravljanju farmaceutskim sistemom. Svetska zdravstvena organizacija (SZO) tradicionalno naglašava značaj pravičnog pristupa esencijalnim lekovima, obezbeđivanja kvaliteta lekova, racionalne upotrebe lekova i razvoja održivih farmaceutskih sistema kao osnovnih komponenti nacionalnih politika o lekovima [27,28]. Međutim, sve veća složenost globalnih mreža snabdevanja farmaceutskim proizvodima pokazala je rastuću zavisnost ovih ciljeva od sposobnosti zdravstvenih sistema da predvide, apsorbuju i prilagode se spoljnim poremećajima.

Iako su se tradicionalni okviri politika o lekovima prvenstveno usredsređivali na regulatorni nadzor, mehanizme nabavke, pristupačnost i odgovarajuću primenu lekova, nedavni globalni događaji istakli su dodatne determinante farmaceutске bezbednosti. Pandemija bolesti KOVID-19 razotkrila je ranjivosti povezane sa globalnom koncentracijom proizvodnje, zavisnošću od ograničenog broja dobavljača, nedovoljnom vidljivošću lanaca snabdevanja i zakasnelim prepoznavanjem novih nestašica [1,29]. Shodno tome, dostupnost lekova se ne može više posmatrati isključivo kao funkcija nacionalnog kapaciteta za nabavku, već kao ishod međusobno povezanih međunarodnih proizvodnih, regulatornih, logističkih i organizacionih procesa. U tom kontekstu, farmaceutska otpornost može se definisati kao sposobnost ekosistema snabdevanja lekovima da predvidi poremećaje, pripremi se za njih, apsorbuje ih, prilagodi im se i oporavi se od njih, uz istovremeno održavanje kontinuiranog pristupa esencijalnim lekovima [21–23].

Nestašice lekova predstavljaju višedimenzionalni sistemski problem, a ne izolovani operativni neuspeh. Prethodne analize pokazale su da nestašice nastaju kao rezultat kombinacije proizvodnih ograničenja, ekonomskih faktora, regulatornih prepreka, tržišne dinamike i neadekvatne koordinacije među relevantnim zainteresovanim stranama [2,30]. Stoga savremeno upravljanje farmaceutskim sistemom zahteva prelazak sa pretežno reaktivnih pristupa prevazilaženju nestašica ka proaktivnim modelima pripremljenosti koji su u stanju da identifikuju slabosti pre nego što dođe do poremećaja. U tom kontekstu, predloženi okvir uključuje otpornost kao dodatnu dimenziju

capacity of the medicines supply ecosystem to anticipate, prepare for, absorb, adapt to, and recover from disruptions while maintaining continuous access to essential medicines [21–23].

Medicine shortages represent a multidimensional systemic problem rather than an isolated operational failure. Previous analyses have demonstrated that shortages arise from a combination of manufacturing constraints, economic factors, regulatory barriers, market dynamics, and inadequate coordination among relevant stakeholders [2,30]. Therefore, contemporary pharmaceutical governance requires a transition from predominantly reactive shortage-management approaches toward proactive preparedness models capable of identifying vulnerabilities before disruption occurs. In this context, the proposed framework incorporates resilience as an additional dimension of pharmaceutical system performance, complementing existing WHO objectives with mechanisms aimed at maintaining continuity of medicine supply under uncertain conditions.

The concept of resilience applied within supply chain management emphasizes the capacity of systems to anticipate risks, withstand disruptions, adapt to changing conditions, and recover while maintaining essential functions [21–23].

Unlike robustness, which primarily refers to a system's ability to withstand predefined disturbances, resilience incorporates adaptive capacity, learning mechanisms, and the ability to reorganize after unexpected disruptions. Therefore, resilient pharmaceutical systems are not only designed to resist failures but also to evolve in response to emerging challenges.

Applying these principles to pharmaceutical systems provides a theoretical basis for integrative preparedness strategies, diversified supply mechanisms, adaptive regulatory responses, and coordinated institutional action. The proposed five-level governance framework reflects this approach by incorporating strategic preparedness, operational adaptation, regulatory coordination, digital monitoring, and workforce integration as interconnected components of pharmaceutical resilience.

Regulatory authorities represent a critical component of pharmaceutical resilience by enabling timely information exchange, coordinated shortage mitigation strategies, regulatory flexibility during emergencies, and maintenance of quality standards despite supply disruptions [31].

A particularly important aspect of contemporary resilience strategies is the integration of digital technologies that can improve supply chain transparency and predictive decision-making. Digital supply chain

uspešnosti farmaceutskog sistema, dopunjujući postojeće ciljeve SZO mehanizmima usmerenim na održavanje kontinuiteta snabdevanja lekovima u uslovima neizvesnosti.

Koncept otpornosti primenjen u okviru upravljanja lancem snabdevanja naglašava sposobnost sistema da predvide rizike, izdrže poremećaje, prilagode se promenljivim uslovima i oporave se uz održavanje osnovnih funkcija [21–23].

Za razliku od žilavosti, koja se prvenstveno odnosi na sposobnost sistema da izdrži unapred definisane poremećaje, otpornost uključuje adaptivni kapacitet, mehanizme učenja i sposobnost reorganizacije nakon neočekivanih poremećaja. Stoga otporni farmaceutski sistemi nisu samo projektovani da se odupru neuspesima već i da se razvijaju kao odgovor na nove izazove.

Primena ovih principa na farmaceutske sisteme pruža teorijsku osnovu za integrativne strategije pripremljenosti, diversifikovane mehanizme snabdevanja, adaptivne regulatorne odgovore i koordinisano institucionalno delovanje. Predloženi petostepeni okvir upravljanja odražava ovaj pristup uključivanjem strateške pripremljenosti, operativnog prilagođavanja, regulatorne koordinacije, digitalnog praćenja i integracije farmaceutskih radnika kao međusobno povezanih komponenti farmaceutske otpornosti.

Regulatorna tela predstavljaju komponentu od ključnog značaja za farmaceutsku otpornost jer omogućavaju pravovremenu razmenu informacija, koordinisane strategije za ublažavanje nestašica, regulatornu fleksibilnost tokom vanrednih situacija i održavanje standarda kvaliteta uprkos poremećajima u snabdevanju [31].

Posebno važan aspekt savremenih strategija otpornosti jeste integracija digitalnih tehnologija koje mogu poboljšati transparentnost lanca snabdevanja i prediktivno donošenje odluka. Digitalni modeli lanca snabdevanja, uključujući koncepte kao što su digitalni blizanci i sistemi praćenja u realnom vremenu, predloženi su kao alati za identifikovanje rizika od poremećaja, poboljšanje vidljivosti kroz složene mreže i podršku intervencijama zasnovanim na dokazima tokom kriza [20]. Nadalje, održivi modeli lanca snabdevanja naglašavaju da budući farmaceutski sistemi moraju istovremeno da ostvare agilnost, otpornost i održivost kako bi ostali funkcionalni u uslovima produžene neizvesnosti [32].

Iz farmaceutske perspektive, pouzdanost mreža snabdevanja predstavlja kritičnu determinantu dostupnosti lekova. Studije modelovanja ukazuju na to da slabosti u konfiguraciji lanca snabdevanja, nedovoljna redundantnost i ograničen kapacitet oporavka mogu direktno da doprinesu nastanku i produženom

models, including concepts such as digital twins and real-time monitoring systems, have been proposed as tools for identifying disruption risks, improving visibility across complex networks, and supporting evidence-based interventions during crises [20]. Furthermore, viable supply chain models emphasize that future pharmaceutical systems must simultaneously achieve agility, resilience, and sustainability to remain functional under prolonged uncertainty [32].

From a pharmaceutical perspective, reliability of supply networks represents a critical determinant of medicine availability. Modelling studies indicate that weaknesses in supply chain configuration, insufficient redundancy, and limited recovery capacity may directly contribute to the development and persistence of drug shortages [33]. Therefore, strengthening pharmaceutical resilience requires not only emergency response mechanisms but also long-term structural interventions involving supply diversification, improved information exchange, regulatory collaboration, and strategic planning.

Recent international policy discussions have increasingly emphasized strategic autonomy in pharmaceutical supply chains, specifically diversifying manufacturing sources, reducing excessive dependence on single suppliers, strengthening regional production capacities, and developing critical medicine monitoring mechanisms.

The proposed framework also recognizes that resilience is not solely dependent on infrastructure and technology but requires active participation of healthcare professionals. During recent global health emergencies, pharmacists and other healthcare workers have demonstrated an expanded role in maintaining medication continuity, supporting emergency preparedness, and implementing adaptive solutions within healthcare systems [5,24]. Regulatory adaptations and broader professional responsibilities introduced during the COVID-19 pandemic have further emphasized the importance of integrating healthcare workforce capabilities into national preparedness strategies [25].

Future implementation of such governance frameworks should include measurable resilience indicators, including supplier diversification, time to detect shortages, recovery time after disruptions, inventory adequacy, digital monitoring capacity, and stakeholder coordination performance. These indicators could enable comparative evaluation of pharmaceutical system resilience across different healthcare settings.

Accordingly, the proposed governance framework extends conventional national medicines policy principles by introducing resilience as a central component of pharmaceutical security. This approach shifts the

trajanju nestašica lekova [33]. Stoga, jačanje farmaceutske otpornosti zahteva ne samo mehanizme odgovora na vanredne situacije već i dugoročne strukturne intervencije koje uključuju diversifikaciju snabdevanja, unapređenje razmene informacija, regulatornu saradnju i strateško planiranje.

Tekuće međunarodne diskusije o javnim politikama sve više naglašavaju stratešku autonomiju u lancima snabdevanja farmaceutskim proizvodima, posebno diversifikaciju izvora proizvodnje, smanjenje prekomerne zavisnosti od pojedinačnih dobavljača, jačanje regionalnih proizvodnih kapaciteta i razvoj mehanizama za praćenje lekova od kritičnog značaja.

Predloženi okvir takođe prepoznaje da otpornost ne zavisi isključivo od infrastrukture i tehnologije, već zahteva aktivno učešće zdravstvenih radnika. Tokom nedavnih globalnih zdravstvenih vanrednih situacija, farmaceuti i drugi zdravstveni radnici pokazali su širu ulogu u održavanju kontinuiteta dostupnosti lekova, podršci u pripremljenosti za vanredne situacije i primeni adaptivnih rešenja unutar zdravstvenih sistema [5,24]. Izmene u regulativi i šire profesionalne odgovornosti uvedene tokom pandemije bolesti KOVID-19 su dodatno istakle značaj integrisanja kapaciteta zdravstvenih radnika u nacionalne strategije pripremljenosti [25].

Buduća primena takvih okvira upravljanja treba da obuhvati merljive pokazatelje otpornosti, uključujući diversifikaciju dobavljača, vreme potrebno za otkrivanje nestašica, vreme oporavka nakon poremećaja, adekvatnost zaliha, kapacitet za digitalno praćenje i uspešnost koordinacije zainteresovanih strana. Ovi pokazatelji mogli bi da omoguće komparativnu procenu otpornosti farmaceutskih sistema u različitim zdravstvenim okruženjima.

Shodno tome, predloženi okvir upravljanja proširuje konvencionalne principe nacionalnih politika o lekovima uvođenjem otpornosti kao centralne komponente farmaceutske bezbednosti. Ovaj pristup pomera perspektivu dostupnosti lekova sa statičkog cilja, prvenstveno usmerenog na pristup i nabavku, ka dinamičkom modelu zasnovanom na pripremljenosti, prilagodljivosti, digitalnoj inteligenciji i koordinisanom upravljanju. Takva integracija može da predstavlja osnovu za transformaciju farmaceutskih sistema od reaktivnog odgovora na nestašice u proaktivne strategije osmišljene za očuvanje dostupnosti lekova i kontinuiteta zdravstvene zaštite tokom budućih poremećaja.

Međutim, predloženi okvir predstavlja konceptualni model upravljanja i pre šire primene zahteva potvrdu kroz empirijske studije, komparativne analize između zdravstvenih sistema i procenu merljivih ishoda otpornosti.

medicine availability perspective from a static objective, focused primarily on access and procurement, towards a dynamic model based on preparedness, adaptability, digital intelligence, and coordinated governance. Such integration may provide the foundation for transforming pharmaceutical systems from reactive responses to shortages towards proactive strategies designed to preserve medicine availability and healthcare continuity during future disruptions.

However, the proposed framework represents a conceptual governance model and requires validation through empirical studies, comparative analyses between healthcare systems, and evaluation of measurable resilience outcomes before broader implementation.

CONCLUSION

Pharmaceutical and medical device supply chain resilience has become an essential component of modern healthcare security. The increasing frequency of medicine shortages, pandemic-related disruptions, geopolitical instability, and structural dependencies within global manufacturing networks demonstrates that ensuring continuity of healthcare delivery requires approaches extending beyond traditional procurement and shortage management strategies. This review highlights that resilient healthcare supply systems depend on the integration of multiple interconnected capabilities, including strategic preparedness, operational flexibility, regulatory coordination, digital visibility, and workforce engagement. The proposed five-level governance framework provides a conceptual approach for organizing these capabilities into a coordinated model that enables healthcare systems to anticipate disruptions, maintain essential supply continuity, and adapt effectively to conditions of uncertainty.

Rather than replacing established principles of national medicines policies, resilience-oriented governance represents an evolution of these principles by incorporating preparedness, adaptability, and system-level risk management into pharmaceutical security strategies. Future implementation of such frameworks should focus on measurable resilience indicators, empirical validation across different healthcare settings, and development of coordinated policies involving regulators, healthcare institutions, industry stakeholders, and healthcare professionals.

Ultimately, the future of pharmaceutical and medical device supply security will depend not only on maintaining sufficient access to products during stable periods, but on building adaptive systems capable of protecting patients and sustaining healthcare delivery when disruptions occur.

ZAKLJUČAK

Otpornost lanaca snabdevanja lekovima i medicinskim sredstvima postala je suštinska komponenta savremene bezbednosti zdravstvene zaštite. Sve veća učestalost nestašica lekova, poremećaji povezani sa pandemijama, geopolitička nestabilnost i strukturne zavisnosti unutar globalnih proizvodnih mreža pokazuju da obezbeđivanje kontinuiteta pružanja zdravstvene zaštite zahteva pristupe koji prevazilaze tradicionalne strategije nabavke i prevazilaženja nestašica. Ovaj pregled ističe da otporni sistemi snabdevanja u zdravstvu zavise od integracije više međusobno povezanih kapaciteta, uključujući stratešku pripremljenost, operativnu fleksibilnost, regulatornu koordinaciju, digitalnu vidljivost i angažovanje zdravstvenih radnika. Predloženi petostepeni okvir upravljanja pruža konceptualni pristup organizovanju ovih kapaciteta u koordinisani model koji zdravstvenim sistemima omogućava da predvide poremećaje, održe kontinuitet snabdevanja osnovnim proizvodima i efikasno se prilagode uslovima neizvesnosti.

Umesto zamene ustanovljenih principa nacionalnih politika o lekovima, upravljanje usmereno na otpornost predstavlja pretvaranje tih principa u strategije farmaceutske bezbednosti, kroz uključivanje pripremljenosti, prilagodljivosti i prevazilaženja rizika na nivou sistema. Buduća primena takvih okvira treba da bude usmerena na merljive pokazatelje otpornosti, empirijsku potvrdu u različitim zdravstvenim okruženjima i razvoj koordinisanih politika koje uključuju regulatorna tela, zdravstvene institucije, aktere iz farmaceutske industrije i zdravstvene radnike.

U zaključku, budućnost bezbednosti snabdevanja lekovima i medicinskim sredstvima zavisice ne samo od održavanja dovoljne dostupnosti proizvoda tokom stabilnih perioda već i od izgradnje adaptivnih sistema sposobnih da zaštite pacijente i održe pružanje zdravstvene zaštite kada dođe do poremećaja.

Izjava o korišćenju veštačke inteligencije

Alati veštačke inteligencije korišćeni su isključivo za jezičko doterivanje i pomoć u organizaciji rukopisa. Sve naučne interpretacije, evaluacija literature, zaključci i konačne odluke u vezi sa sadržajem rukopisa izvršili su i proverili autori.

Sukob interesa: Nije prijavljen.

Artificial intelligence statement

Artificial intelligence tools were used only for language refinement and manuscript organization support. All scientific interpretations, literature evaluation, conclusions, and final decisions regarding manuscript content were performed and verified by the authors.

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NESANICA KAO FAKTOR RIZIKA KOD KARDIOLOŠKIH BOLESNIKA I TERAPIJSKI PRISTUP

PREGLEDNI RAD

REVIEW ARTICLE

INSOMNIA AS A RISK FACTOR IN CARDIAC PATIENTS AND THE TREATMENT APPROACH

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SAŽETAK

Uvod/Cilj: Nesanica je čest poremećaj spavanja koji prevazilazi subjektivni osećaj neispavanosti i predstavlja stanje perzistentne fiziološke hiperbudnosti sa značajnim uticajem na kardiovaskularno zdravlje. Cilj ovog preglednog rada bio je da prikaže patofiziološke mehanizme povezanosti nesanice i kardiovaskularnih bolesti, kao i da uporedi kliničke aspekte primene benzodiazepina i Z-hipnotika u lečenju nesanice kod kardioloških bolesnika.

Metode: Korišćenjem deskriptivno-komparativne metode analizirani su dostupni pregledni radovi, meta-analize, kohortne i opservacione studije koje su ispitivale odnos nesanice, kardiovaskularnih ishoda i farmakološkog lečenja, sa posebnim fokusom na razlike između primene benzodiazepina i Z-hipnotika u pogledu efikasnosti i bezbednosti kod kardioloških bolesnika.

Rezultati: Analizirani podaci ukazuju na to da nesanica, putem autonomne, neuroendokrine, inflamatorne i metaboličke disregulacije, doprinosi razvoju arterijske hipertenzije, atrijske fibrilacije i srčane slabosti, pri čemu se najveći rizik beleži kod fenotipa nesanice sa objektivno kratkim trajanjem sna. Noviji longitudinalni podaci dodatno ukazuju na to da perzistentni simptomi nesanice nose veće kardiovaskularno opterećenje. U terapijskom kontekstu, benzodiazepini su kod kardioloških bolesnika povezani sa većom učestalošću nepovoljnih događaja, uključujući rehospitalizacije zbog srčane slabosti, iznenadni srčani zastoj i kardiovaskularni mortalitet, dok dostupni podaci za Z-hipnotike ukazuju na povoljniji ili neutralniji profil.

Zaključak: Nesanica predstavlja klinički značajan, ali često zanemaren faktor kardiovaskularnog rizika. Kod kardioloških bolesnika, njeno prepoznavanje i lečenje treba da budu sastavni deo sveobuhvatnog kliničkog pristupa, uz prednost nefarmakoloških mera i pažljivo odabranu farmakoterapiju. Kada je farmakološko lečenje nesanice neophodno, Z-hipnotici se mogu razmatrati kao povoljnija alternativa benzodiazepinima, pri čemu se zopiklon posebno izdvaja zbog svojih farmakoloških i kliničkih karakteristika.

Ključne reči: poremećaji spavanja, kardiovaskularne bolesti, benzodiazepini, z-hipnotici

ABSTRACT

Introduction/Objective: Insomnia is a common sleep disorder that extends beyond the subjective feeling of poor sleep and represents a state of persistent physiological hyperarousal with important cardiovascular consequences. This review aimed to summarize the pathophysiological links between insomnia and cardiovascular disease and to compare the clinical implications of benzodiazepines and Z-hypnotics in the treatment of insomnia in cardiac patients.

Methods: Using a descriptive-comparative approach, we analyzed review articles, meta-analyses, cohort studies, and observational studies addressing the relationship between insomnia, cardiovascular outcomes, and pharmacological treatment, with particular focus on differences between benzodiazepines and Z-hypnotics in cardiac patients.

Results: The available evidence indicates that insomnia, through autonomic, neuroendocrine, inflammatory, and metabolic dysregulation, contributes to the development of hypertension, atrial fibrillation, and heart failure, with the greatest risk observed in insomnia with objectively short sleep duration. Longitudinal studies further suggest that persistent insomnia symptoms are associated with greater cardiovascular burden. In therapeutic terms, benzodiazepines in cardiac patients are associated with higher rates of adverse events, including heart failure rehospitalization, sudden cardiac arrest, and cardiovascular mortality, whereas available data on Z-hypnotics suggest a more favorable or neutral profile.

Conclusion: Insomnia is a clinically important yet often overlooked cardiovascular risk factor. In cardiac patients, its recognition and treatment should be part of a comprehensive clinical approach, prioritizing non-pharmacological measures and carefully selected pharmacotherapy. When drug treatment is necessary, Z-hypnotics may be considered a more favorable alternative to benzodiazepines, with zopiclone standing out because of its pharmacological and clinical characteristics.

Keywords: sleep-wake disorders, cardiovascular diseases, benzodiazepines, Z-hypnotics

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UVOD

Spavanje je visoko organizovano ponašanje koje se karakteriše relativnim odvajanjem od spoljašnjeg sveta i smanjenjem reagovanja na različite draži. U pitanju je fiziološko besvesno stanje koje nastaje u samom mozgu i doprinosi poboljšanju njegovih integrativnih funkcija kao što su učenje, pamćenje i asocijativno mišljenje. S druge strane, premalo spavanja (nesanica) dvostruko povećava rizik od nastanka malignih ili sistemskih bolesti, doprinosi pojavi degenerativne demencije, remeti regulaciju šećera u krvi, predstavlja nezavisni faktor rizika za pojavu kardiovaskularnih bolesti i psihijatrijskih poremećaja [1].

Kada smo budni a kada spavamo

Dva najbitnija činioca koja određuju kada smo budni a kada spavamo su cirkadijalni ritam i homeostatski nagon za spavanjem. Cirkadijalni ritam (ili unutrašnji časovnik) šalje mozgu i ostalim organima signale kada treba da budemo budni, dok se homeostatski nagon za spavanjem povećava tokom budnosti, a smanjuje tokom spavanja [2].

Spavanje je organizovano u dve faze koje se smenjuju u cikličnim intervalima, sporotalasno spavanje (NREM) i spavanje sa brzim pokretima očiju (REM) (Slika 1). Kod ljudi, NREM spavanje se javlja kao posledica slabljenja mehanizama održavanja budnosti i aktivacije inhibitornog uticaja na aktivacioni sistem moždanog stabla [3]. REM san predstavlja aktivan oblik spavanja i karakteriše ga niskovoltirana iregularna i brza aktivnost (paradoksalno spavanje) povezana sa atonijom popreč-

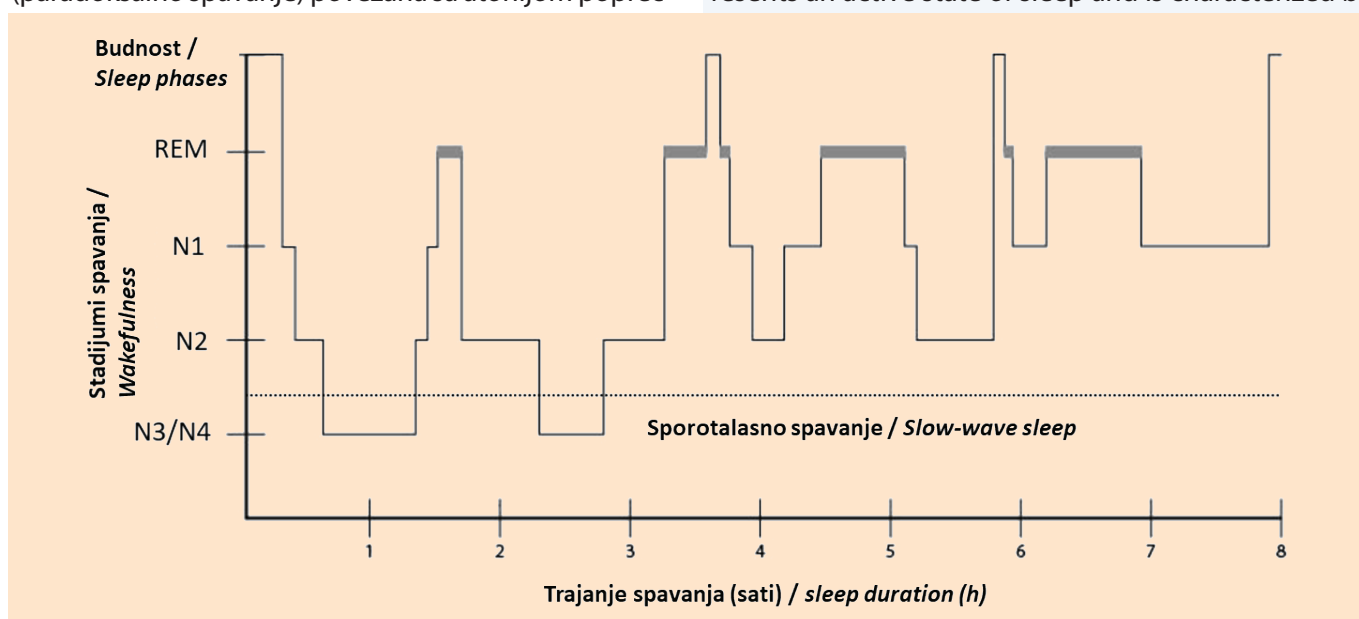
INTRODUCTION

Sleep is a highly organized behavior characterized by relative isolation from the external environment and reduced responsiveness to various stimuli. It is a physiological state of unconsciousness that originates within the brain itself and contributes to the improvement of its integrative functions, including learning, memory, and associative thinking. On the other hand, insufficient sleep (insomnia) is associated with a twofold increased risk of developing malignant or systemic diseases, contributes to the onset of degenerative dementia, disrupts blood glucose regulation, and constitutes an independent risk factor for the development of cardiovascular diseases and psychiatric disorders [1].

Wakefulness and sleep

The two principal factors determining the timing of wakefulness and sleep are the circadian rhythm and the homeostatic sleep drive. The circadian rhythm (or internal biological clock) sends signals to the brain and other organs indicating when we should be awake, whereas the homeostatic drive to sleep increases during wakefulness and decreases during sleep [2].

Sleep is organized into two phases that alternate at cyclical intervals: slow-wave sleep (NREM) and rapid eye movement (REM) sleep (Figure 1). In humans, NREM sleep occurs as a result of the weakening of the mechanisms responsible for maintaining wakefulness, accompanied by the activation of inhibitory influences on the brainstem arousal system [3]. REM sleep represents an active state of sleep and is characterized by



Slika 1. Grafički prikaz (hipnogram) strukture spavanja baziran na polisomnografskom zapisu, tokom 8 sati noćnog spavanja (N1, N2 – površni stadijumi spavanja, N3/N4 – dublji stadijumi spavanja, REM – spavanje sa brzim pokretima očiju). Autorski modifikovana slika iz reference 3

Figure 1. Graphical representation of sleep structure based on a polysomnographic recording over five nocturnal cycles, each lasting approximately 90 minutes on average (N1, N2 light sleep stages, N3/N4 deep sleep stages, REM – rapid eye movement sleep). Image from reference 3 modified by the author.

no-prugastih mišića i brzim pokretima očiju. Smatra se da se većina snova dešava tokom ove faze spavanja [4].

NREM–REM ciklus se obično ponavlja četiri do šest puta tokom tipične noći spavanja. Ujutru se obično budimo iz REM faze [5].

Funkcija spavanja

Iako ne postoji široko rasprostranjena saglasnost o tome zašto je san važan, jasno je da lišavanje sna (ili hronično nedovoljno spavanje) dovodi do povećane pospanosti i smanjenog funkcionisanja [6]. Danas je poznato nekoliko hipoteza o funkciji sna, na prvom mestu u očuvanju metaboličke energije i kognicije. U sporotalasnom spavanju uklanja se adenozin iz mozga putem aktivacije glimfatičkog sistema. Sporotalasno spavanje je takođe zaduženo za uklanjanje bespotrebnih konekcija i informacija, a sa druge strane ima ulogu u konsolidaciji novoupamćenog materijala [7,8]. U REM fazi se učvršćuju proceduralna, perceptualna i emocionalna memorija. Novoupamćeni materijal se inkorporira u već poznate sadržaje i dobija se sasvim nov kvalitet u formi iskustvenog pamćenja i asocijativnog mišljenja [9].

Spavanje je posebno važno za restoraciju fiziološke kontrole kardiovaskularnog sistema, naročito posle fizičkog napora. U sporotalasnom spavanju se stabilizuje simpatička aktivnost na nivou opuštene budnosti, pojačava parasimpatička aktivnost i povećava varijabilnost srčanog rada (HRV) čime se omogućava veća adaptibilnost srca na različite nivoe rada. Posledice su smanjenje krvnog pritiska, srčane frekvence i perifernog vaskularnog otpora što sve zajedno smanjuje opterećenje srčanog rada i indukuje autonomnu stabilnost. U REM spavanju dolazi do faznog pojačanja simpatičke aktivnosti (skokovi krvnog pritiska), dok se smanjuju parasimpatička aktivnost i HRV (postoji opasnost od pojave srčanih aritmija) [10].

Da li dovoljno spavamo?

Nesanica (insomnia), može se slobodno reći, danas predstavlja najčešći poremećaj spavanja i verovatno najčešću bolest savremenog sveta [11]. Više od 30% celokupne populacije je iskusilo neki oblik nesanice. Prema trajanju ona može biti intermitentna (povremena), kratkotrajna ili hronična (bar 3 dana nedeljno, duže od 6 meseci). Oko 6–11% osoba ima dijagnozu hronične nesanice (od toga 59% imaju nesanicu i posle 5 godina). Prevalencija nesanice se povećava sa starenjem, češća je kod žena i kod bolesnika sa neurološkim komorbiditetima, psihijatrijskim bolestima, hroničnim somatskim oboljenjima ili različitim egzogenim činiocima. Ipak, kod oko 50% ljudi sa hroničnom nesanicom, u pitanju je primarna bolest (psihofiziološka nesanica) [12]. Kod njih je nesanica, na prvom mestu, posledica poremećaja aktivnosti centara u mozgu koji su odgo-

low-voltage, irregular, and rapid brain activity (paradoxical sleep), accompanied by atonia of the striated muscles and rapid eye movements. Most dreaming is thought to occur during this stage of sleep [4].

The NREM–REM cycle typically repeats four to six times during a normal night of sleep. In the morning, awakening most commonly occurs from the REM phase [5].

Function of sleep

Although there is no broad consensus regarding the importance of sleep, it is clear that sleep deprivation (chronically insufficient sleep) leads to increased sleepiness and impaired functioning [6]. Several hypotheses have been proposed regarding the function of sleep, with particular emphasis on the preservation of metabolic energy and the cognitive function. During slow-wave sleep, adenosine is cleared from the brain through activation of the glymphatic system. Slow-wave sleep also contributes to the elimination of unnecessary neural connections and information, while playing an important role in the consolidation of newly acquired memories [7,8]. During the REM phase, procedural, perceptual, and emotional memories are consolidated. Newly acquired information is integrated with previously established knowledge, resulting in a qualitatively new form of experiential memory and associative thinking [9].

Sleep is particularly important for the restoration of physiological control of cardiovascular system, especially following physical exertion. During slow-wave sleep, sympathetic activity is stabilized at levels comparable to those observed during relaxed wakefulness, while parasympathetic activity is enhanced and heart rate variability (HRV) increases. These changes facilitate greater adaptability of the heart to different levels of workload. Consequently, blood pressure, heart rate, and peripheral vascular resistance decrease, collectively reducing cardiac workload and promoting autonomic stability. During REM sleep, there is a phasic increase in sympathetic activity (transient increases in blood pressure), while parasympathetic activity and HRV decrease (there is a risk of cardiac arrhythmias) [10].

Do we sleep enough?

Insomnia can reasonably be considered the most common sleep disorder today and, arguably, one of the most prevalent diseases in the modern world [11]. More than 30% of the general population has experienced some form of insomnia. Depending on its duration, insomnia may be classified as intermittent (occasional), short-term, or chronic (occurring at least three days per week for more than six months). Approximately 6–11% of the population meets the criteria for chronic insomnia, of

vorni za promociju budnosti (prednji hipotalamus koji aktivira retikularnu formaciju) i centara koji promovišu spavanje (ventrolateralna preoptička jedra) i inhibiraju delove mozga odgovorne za budnost. Sistem za kontrolu budnosti (orexin) ne smanjuje svoju aktivnost što onemogućava ovim pacijentima da započnu spavanje. Dodatni doprinoseći faktori su poremećaj cirkadijalnog ritma i emocionalni (stresogeni) faktori koji mogu narušiti homeostazu spavanja. Tako dolazimo da zaključka da je hronična nesanica rezultat konstelacije (sinergizma) genetskih (epigenetskih), faktora okruženja i neurokognitivih/bihevioralnih uticaja na delove mozga odgovornih za smenu budnosti i spavanja [13].

Pacijenti sa hroničnom insomnijom imaju narušen kvalitet života i mnoge zdravstvene posledice u oblasti mentalnog zdravlja (veći rizik od anksioznosti, depresije i suicidalnosti), somatskog zdravlja (hipertenzija, gojaznost, infarkt miokarda, DM tip 2), narušenu radnu sposobnost, veći rizik od saobraćajnih nezgoda i povreda na radu, itd [14].

U daljem tekstu, posebno će biti prikazan negativan uticaj nesanice na funkciju autonomnog, posebno kradiovaskularnog sistema i posledice koje takvo stanje može imati.

Negativan uticaj nesanice na autonomni i neuroendokrini sistem

Nesanica ne predstavlja isključivo subjektivni poremećaj sna, već se definiše kao stanje perzistentne fiziološke hiperbudnosti [15,16]. Karakteriše se pojačanom aktivnošću centralnog nervnog sistema, hipotalamo-hipofizno-adrenalne (HHA) osovine, simpatoadrenalnog sistema i pro-inflamatornih signalnih puteva [17,18]. Naime, nesanica se definiše kao stabilan obrazac povišene pobuđenosti tokom čitavog 24-časovnog ciklusa, sa posledičnim porastom lučenja kortizola i katecholamina, poremećajem autonomne ravnoteže sa dominacijom simpatičkog nad parasimpatičkim tonusom [16–18]. Na ovaj način se u toku noći narušava period neurovegetativnog smirivanja i hemodinamskog rasterećenja, dok se produžava trajanje biološkog stresa, što predstavlja jednu od glavnih spona između nesanice i razvoja kradiovaskularnih bolesti [15,16].

Jedan od najvažnijih patofizioloških mehanizama ove povezanosti jeste disfunkcija autonomnog nervnog sistema. U fiziološkim uslovima, tokom sna, naročito u dubljim stadijumima NREM faza, dolazi do smanjenja simpatičke aktivnosti i relativne dominacije parasimpatičkog tonusa, te posledičnog usporenja srčane frekvence, smanjenja perifernog vaskularnog otpora i arterijskog krvnog pritiska [16,18]. Ovaj period „kradiovaskularne restauracije” u toku sna ima zaštitnu ulogu za srce i krvne sudove, jer omogućava privremeno smanjenje hemodinamskog opterećenja [17,18]. Nasuprot tome, kod

whom 59% continue to experience insomnia five years later. The prevalence of insomnia increases with age and is higher among women and patients with neurological comorbidities, psychiatric disorders, chronic somatic diseases, or various exogenous factors. However, in approximately 50% of individuals with chronic insomnia, the condition is considered a primary disorder, referred to as psychophysiological insomnia [12]. In these individuals, insomnia is primarily a consequence of disturbances in the activity of brain centers responsible for promoting wakefulness (the anterior hypothalamus which activates the reticular formation), and centers that promote sleep (the ventrolateral preoptic nuclei) which inhibit brain regions responsible for wakefulness. The wakefulness-promoting system (orexin) fails to adequately reduce its activity, making it difficult for these patients to initiate sleep. Additional contributing factors include circadian rhythm disturbances and emotional (stress-related) factors that may disrupt sleep homeostasis. Thus, chronic insomnia can be understood as the result of a constellation, or synergy, of genetic (epigenetic) and environmental factors, together with neurocognitive and behavioral influences on the brain regions responsible for the transition between wakefulness and sleep [13].

Patients with chronic insomnia experience impaired quality of life and a range of adverse health consequences affecting mental health (an increased risk of anxiety, depression, and suicidality), somatic health (hypertension, obesity, myocardial infarction, and type 2 diabetes mellitus), impaired work performance, and an increased risk of traffic accidents and occupational injuries, among other adverse outcomes [14].

The following section will specifically examine the negative impact of insomnia on autonomic function, particularly cardiovascular function, as well as the potential consequences of these disturbances.

The negative impact of insomnia on the autonomic and neuroendocrine systems

Insomnia is not exclusively a subjective sleep disorder; rather, it is defined as a state of persistent physiological hypervigilance [15,16]. It is characterized by increased activity of the central nervous system, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathoadrenal system, and pro-inflammatory signaling pathways [17,18]. Namely, insomnia is defined as a stable pattern of heightened arousal throughout the entire 24-hour cycle, resulting in increased secretion of cortisol and catecholamines and a disruption of autonomic balance, characterized by a predominance of sympathetic over parasympathetic tone [16–18]. In this way, the period of neurovegetative relaxation and hemodynamic relief that normally occurs during the night is disrupted,

osoba sa insomnijom, fragmentacijom sna ili generalno skraćenim trajanjem sna, ovaj fiziološki period oporavka biva narušen ili čak izostaje u potpunosti [16,19]. Kumulativno, takve promene povećavaju ukupno 24-časovno opterećenje srca i krvnih sudova, te značajno doprinose razvoju arterijske hipertenzije [20–24].

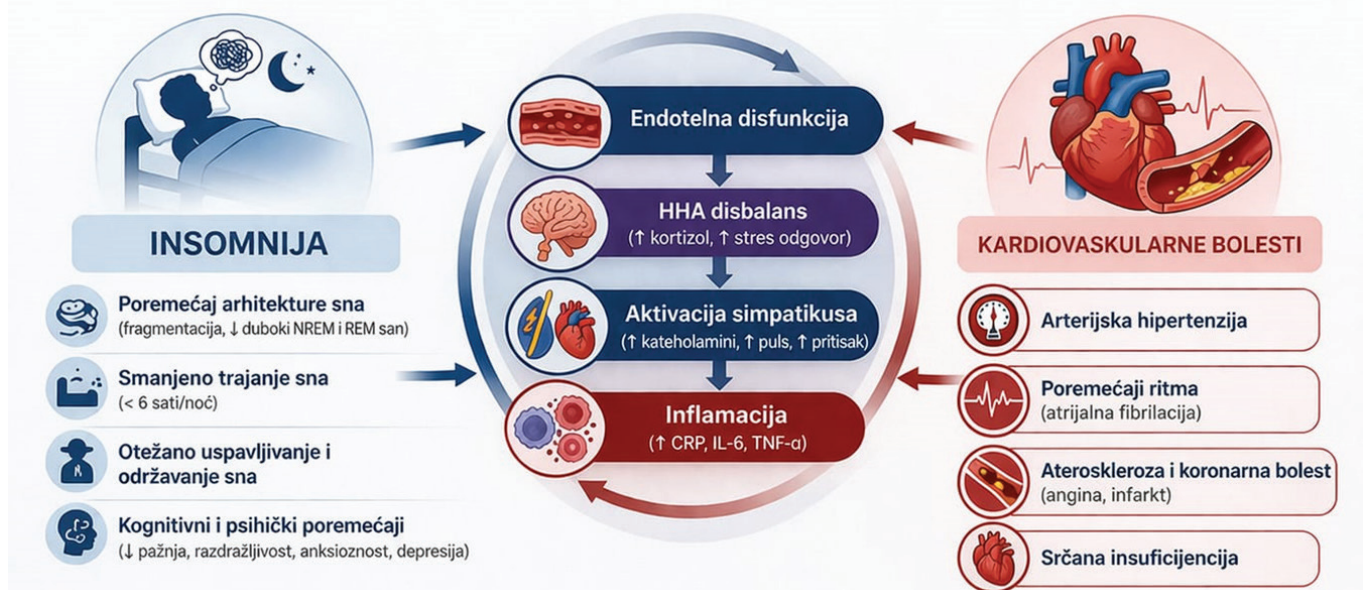
Hronična nesanica je u korelaciji sa neuroendokrinom disfunkcijom, pojačanim lučenjem kortikotropin-oslobađajućeg hormona, adrenokortikotropnog hormona i kortizola, čime se narušava normalni cirkadijalni obrazac neuroendokrine sekrecije [17,18]. Povišene noćne i jutarnje vrednosti kortizola doprinose perzistenciji budnosti, i uz povišen simpatički tonus, stvaraju niz štetnih kardiometaboličkih efekata [17,18]. Hronično narušen san praćen je povišenim koncentracijama proinflammatoryh citokina, C-reaktivnog proteina i drugih medijatora sistemske inflamacije, pri čemu inflamatorni medijatori dodatno remete arhitekturu sna, stvarajući začarani krug u kome inflamacija pogoršava nesanicu, a nesanica dalje pojačava inflamatorni odgovor [15,17,18] (Slika 2).

Povećani simpatički tonus i neuroendokrina aktivacija doprinose endotelnoj disfunkciji, oksidativnom stresu, proinflammatoryh aktivnosti i poremećaju metaboličke homeostaze, uključujući insulinsku rezistenciju i poremećaj metabolizma glukoze i lipida [17,18,25,26]. Na nivou krvnih sudova, kombinacija simpatičke prenadraženosti, povišenog kortizola i inflamacije smanjuje biodostupnost azot-monoksida, povećava vaskularnu reaktivnost i arterijsku rigidnost, čime se stvaraju uslovi za razvoj hipertenzije, ateroskleroze i progresivnog vaskularnog remodelovanja [17,18]. Razvoj nesanice kod bolesnika sa već postojećim kardiovaskularnim oboljenjima, bilo da je u pitanju arterijska hipertenzija, koronarna bolest ili srčana insuficijencija, upravo može doprineti progresiji osnovne bolesti i nepovoljnijim kliničkim ishodima [27,28].

while the duration of biological stress is prolonged, representing one of the principal links between insomnia and the development of cardiovascular disease [15,16].

One of the most important pathophysiological mechanisms underlying this association is dysfunction of the autonomic nervous system. Under physiological conditions, sleep, particularly during the deeper stages of NREM sleep, is characterized by a reduction in sympathetic activity and a relative predominance of parasympathetic tone, accompanied by a consequent slowing of the heart rate, a reduction in peripheral vascular resistance, and a decrease in arterial blood pressure [16,18]. This period of "cardiovascular restoration" during sleep plays a protective role for the heart and blood vessels by enabling a temporary reduction in hemodynamic load [17,18]. In contrast, in individuals with insomnia characterized by sleep fragmentation or a generally shortened sleep duration, this physiological recovery period is impaired or may be entirely absent [16,19]. Cumulatively, these changes increase the total 24-hour workload imposed on the heart and blood vessels and significantly contribute to the development of arterial hypertension [20–24].

Chronic insomnia is associated with neuroendocrine dysfunction and increased secretion of corticotropin-releasing hormone, adrenocorticotrophic hormone, and cortisol, thereby disrupting the normal circadian pattern of neuroendocrine secretion [17,18]. Elevated nocturnal and morning cortisol levels contribute to the persistence of wakefulness and, together with increased sympathetic tone, give rise to a range of adverse cardiometabolic effects [17,18]. Chronically disrupted sleep is accompanied by elevated concentrations of pro-inflammatory cytokines, C-reactive protein, and other mediators of systemic inflammation,



Slika 2. Patofiziološka povezanost nesanice i kardiovaskularnih bolesti

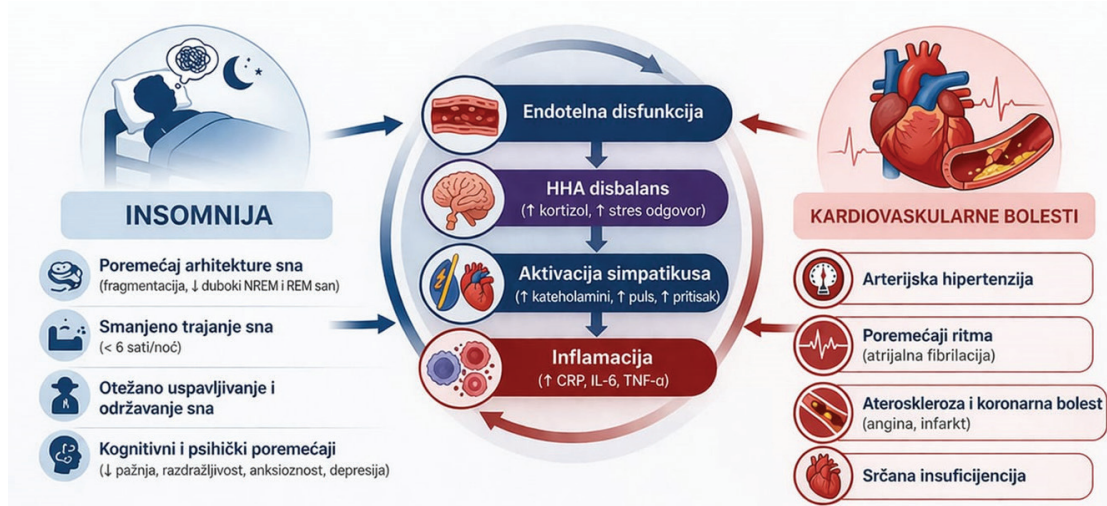


Figure 2. Pathophysiological relationship between insomnia and cardiovascular diseases

Pored hipertenzije i aterosklerotske bolesti, nesanica može doprineti i aritmogenezi [29,30]. Poremećaji sna povećavaju električnu nestabilnost miokarda kroz kombinaciju autonomne labilnosti, inflamacije, oksidativnog stresa i dugoročnog strukturnog remodelovanja [17,26] (Tabela 1).

Nesanica i kardiovaskularne bolesti

Sve je više podataka koji ukazuju da nesanica može predstavljati faktor rizika za razvoj kardiovaskularnih oboljenja, kao i doprineti nepovoljnijim ishodima i smanjenim kvalitetom života kod već obolelih bolesnika [15,28,31,32]. Najkonzistentniji i klinički najrelevantniji podaci o povezanosti nesanice i kardiovaskularnih bolesti odnose se na arterijsku hipertenziju [16,20–22]. Brojne prospektivne kohortne studije, sistematski pregledi i meta-analize pokazali su da nesanica nije povezana samo sa prolaznim porastom vrednosti krvnog pritiska, već i sa većim rizikom za razvoj incidentne hipertenzije i drugih kardiovaskularnih ishoda [20,22,31]. Posebno se izdvaja fenotip nesanice

while these inflammatory mediators further disrupt sleep architecture, thereby creating a vicious cycle in which inflammation exacerbates insomnia, and insomnia, in turn, further amplifies the inflammatory response [15,17,18] (Figure 2).

Increased sympathetic tone and neuroendocrine activation contribute to endothelial dysfunction, oxidative stress, pro-inflammatory activity, and disruption of metabolic homeostasis, including insulin resistance and disturbances in glucose and lipid metabolism [17,18,25,26]. At the vascular level, the combination of sympathetic overstimulation, elevated cortisol levels, and inflammation reduces the bioavailability of nitric oxide, increases vascular reactivity and arterial stiffness, and thereby creates conditions conducive to the development of hypertension, atherosclerosis, and progressive vascular remodeling [17,18]. The development of insomnia in patients with pre-existing cardiovascular disease, including arterial hypertension, coronary artery disease, or heart failure, may contribute to

Tabela 1. Patofiziologija povezanosti nesanice i kardiovaskularnih bolesti

Table 1. Pathophysiology of the relationship between insomnia and cardiovascular diseases

Autori / Authors	Časopis / Journal	Godina / Year	Broj ispitanika / Participants (n)	Tip studije / Study type	Primarni cilj rada / Primary study objective	Zaključak rada / Conclusion
Fernández-Mendoza i sar. / Fernández-Mendoza et al.	<i>Hypertension</i>	2012	~1741	Prospektivna kohorta / Prospective cohort	Incidentna HTA / Incidental HTN	Kratko trajanje sna ↑ HTA rizik / Short sleep duration ↑ HTN risk
Laugsand i sar. / Laugsand et al.	<i>Eur Heart J</i>	2014	~54000	Prospektivna kohorta / Prospective cohort	Incidentna HF / Incident HF	Nesanica povezana sa HF / Insomnia associated with HF
Liu i sar. / Liu et al.	<i>Int J Hypertens</i>	2022	>200000	Meta-analiza / Meta-analysis	Insomija i HTA / Insomnia and HTN	Dvosmerna povezanost / Bidirectional connectivity
Berger i sar. / Berger et al.	<i>J Am Heart Assoc</i>	2022	~2000+	Kohortna / Cohort	Arhitektura sna / Sleep architecture	Fragmentacija sna ↑ HTA / Sleep fragmentation ↑ HTN
Dai i sar. / Dai et al.	<i>Sleep Med Rev</i>	2024	Meta-analiza	Meta-analiza / Meta-analysis	Nesanica + kratak san / Insomnia + short sleep	↑ HTA rizik / ↑ HTN risk

HTA – hipertenzija, HF – srčana slabost

HTN – hypertension, HF – heart failure

ce sa objektivno kratkim trajanjem sna koji je povezan sa značajno većim rizikom od razvoja hipertenzije u odnosu na subjektivno loš san bez objektivnog skraćenja sna [21]. U prilog tome govore i nalazi sistematskih pregleda koji pokazuju da su hipertenzija i nepovoljna arhitektura sna usko povezane, naročito kroz veću fragmentaciju sna i redukciju dubljih stadijuma NREM spavanja, što dodatno naglašava značaj objektivnih parametara sna u stratifikaciji rizika [19]. Nadalje, noviji longitudinalni podaci ukazuju na to da sa porastom broja simptoma nesanice raste i rizik od incidentnih kardiovaskularnih događaja, dok perzistentni ili progresivno nepovoljan tok simptoma nosi dodatno kardiovaskularno opterećenje [32].

Značaj zdravih obrazaca spavanja u kardiovaskularnoj prevenciji potvrđen je i u savremenim velikim kohortnim studijama [33–35]. Yan i saradnici su pokazali da je kod osoba sa prehipertenzijom pridržavanje zdravog obrasca spavanja povezano sa značajno manjim rizikom od razvoja novonastale arterijske hipertenzije i kardiovaskularnih bolesti, pri čemu je uočen i jasan gradijent smanjenja rizika sa porastom skora zdravog spavanja [33]. Slično tome, Nambiema i saradnici su u velikim evropskim prospektivnim kohortama pokazali da su viši skor zdravog spavanja, ali i njegovo poboljšanje tokom vremena, povezani sa manjim rizikom od koronarne bolesti i moždanog udara [34]. Ovi nalazi zajedno ukazuju na to da zdravlje sna ne predstavlja samo pokazatelj, već i potencijalno modifikabilnu komponentu kardiovaskularnog rizika, zbog čega procena i optimizacija spavanja mogu imati značajno mesto u strategijama primarne prevencije kardiovaskularnih bolesti [33–35].

Pored arterijske hipertenzije, sve je više podataka koji govore u prilog tome da poremećaji sna predstavljaju dodatni faktor rizika u nastanku i održavanju poremećaja ritma po tipu atrijske fibrilacije. Samim tim, narušena arhitektura spavanja, učestala noćna buđenja, duža latencija uspjavanja, kao i kraće trajanje spavanja povezani su sa većim rizikom za nastanak atrijske fibrilacije [29,30].

Srčana slabost predstavlja poseban entitet u okviru povezanosti nesanice i kardiovaskularnih bolesti, jer odražava kumulativne posledice dugotrajnog hemodinamskog, neurohumoralnog i metaboličkog opterećenja. U velikoj norveškoj populacionoj kohorti pokazana je jasna povezanost između broja simptoma nesanice i rizika od incidentne srčane slabosti. Ovi podaci ukazuju na to da teža i kompleksnija simptomatologija nesanice može implicirati veće kardiovaskularno opterećenje, posredstvom hronične simpatičke aktivacije, poremećaja HHA osovine i perzistentne inflamacije, iako opservaciona priroda dostupnih studija i dalje zahteva oprez u tumačenju uzročnosti [15,28].

Metabolički sindrom predstavlja važan klinički domen u kojem se prepliću nesanica i rizik od razvoja kardiovaskularnih oboljenja, s obzirom na to da postoje

progression of the underlying disease and result in less favorable clinical outcomes [27,28].

In addition to hypertension and atherosclerotic disease, insomnia may also contribute to arrhythmogenesis [29,30]. Sleep disturbances increase myocardial electrical instability through a combination of autonomic lability, inflammation, oxidative stress, and long-term structural remodeling [17,26] (Table 1).

Insomnia and cardiovascular diseases

There is increasing evidence that insomnia may represent a risk factor for the development of cardiovascular diseases, as well as contribute to less favorable clinical outcomes and reduced quality of life in patients who already have cardiovascular disease [15,28,31,32]. The most consistent and clinically relevant evidence regarding the association between insomnia and cardiovascular diseases concerns arterial hypertension [16,20–22]. Numerous prospective cohort studies, systematic reviews, and meta-analyses have demonstrated that insomnia is associated not only with transient increases in blood pressure but also with an increased risk of incident hypertension and other cardiovascular outcomes [20,22,31]. In particular, the insomnia phenotype characterized by objectively short sleep duration has been highlighted as being associated with a significantly higher risk of developing hypertension compared with subjectively poor sleep without objectively shortened sleep duration [21]. Supporting this association, systematic reviews have demonstrated that hypertension and unfavorable sleep architecture are closely related, particularly through greater sleep fragmentation and a reduction in the deeper stages of NREM sleep, further emphasizing the importance of objective sleep parameters in risk stratification [19]. Furthermore, recent longitudinal data indicate that an increase in the number of insomnia symptoms is associated with a corresponding increase in the risk of incident cardiovascular events, while a persistent or progressively worsening course of symptoms imposes an additional cardiovascular burden [32].

The importance of healthy sleep patterns in cardiovascular prevention has also been confirmed in recent large-scale cohort studies [33–35]. Yan et al. demonstrated that, among individuals with prehypertension, adherence to a healthy sleep pattern was associated with a significantly lower risk of developing new-onset arterial hypertension and cardiovascular disease, with a clear gradient of risk reduction with increasing healthy sleep scores [33]. Similarly, Nambiema et al. demonstrated in large European prospective cohorts that a higher healthy sleep score, as well as improvement in the score over time, was associated with a lower risk of coronary

dokazi koji ukazuju na to da poremećaji sna mogu doprineti insulinskoj rezistenciji, poremećenoj glikoregulaciji, promenama telesne mase i razvoju dislipidemije [18,25] (Tabela 2).

Kako lečiti nesanicu?

S obzirom na to da nesanica može imati bidirekcionu odnos sa mnogim psihijatrijskim i somatskim komorbiditetima, prvi korak je upravo dijagnostikovanje ovih bolesti i njihovo lečenje. Uz to, svakom pacijentu treba predložiti važne elemente adekvatne higijene spavanja: a) odlazak na spavanje uvek u isto vreme; b) izbegavanje popodnevno spavanja („popodnevna dremka”); c) neuzimanje kofeinskih napitaka 5–6 sati pre odlaska u krevet; d) tuširanje toplom vodom pre odlaska na spavanje; e) nekorišćenje mobilnog telefona (plavo svetlo) po leganju u krevet; f) privremeno ustajanje pola sata ranije od uobičajnog („da se mozak zaželi spavanja”) [36].

Kognitivno-bihevioralna terapija predstavlja najvažniji postupak u lečenju hronične nesanice (CBT-I). Ona se sastoji od nekoliko elemenata: i) kontrole stimulusa (leći tek kada se oseti pospanost, ako pacijent ne zaspi za 15–20 min treba da ustane, pređe u drugu prostoriju i radi nešto opuštajuće...); ii) restrikcije vremena provedenog u krevetu (ne kraće od 5 sati, sa postepenim produžavanjem za 15–20 min nedeljno); iii) izbegavanja nerealnih očekivanja u cilju smanjenja anksioznosti; iv) sprovođenja tehnika relaksacije (vežbe opuštanja, meditacija, itd) [37].

Ipak, kod mnogih pacijenata koji se žale na nesanicu, farmakoterapija u vidu primene hipnosedativnih lekova predstavlja najrasprostranjeniji vid lečenja uprkos činjenici da nijedan lek na tržištu koji se koristi u tu svrhu, ne

heart disease and stroke [34]. Together, these findings indicate that sleep health is not only an indicator of cardiovascular risk but also a potentially modifiable component of such risk, suggesting that sleep assessment and optimization may have an important role in primary prevention strategies for cardiovascular disease [33–35].

In addition to arterial hypertension, increasing evidence supports the notion that sleep disorders represent an additional risk factor for the development and persistence of cardiac rhythm disorders of the type of atrial fibrillation. Accordingly, disturbed sleep architecture, frequent nocturnal awakenings, prolonged sleep onset latency, and shorter sleep duration are associated with an increased risk of atrial fibrillation [29,30].

Heart failure represents a distinct entity within the association between insomnia and cardiovascular diseases, as it reflects the cumulative consequences of long-term hemodynamic, neurohumoral, and metabolic burden. A clear association between the number of insomnia symptoms and the risk of incident heart failure has been demonstrated in a large Norwegian population-based cohort. These findings suggest that more severe and complex insomnia symptomatology may be associated with a greater cardiovascular burden through chronic sympathetic activation, disruption of the HPA axis, and persistent inflammation, although the observational nature of the available studies warrants caution in interpreting causality [15,28].

Metabolic syndrome represents an important clinical domain in which insomnia and the risk of developing cardiovascular disease are closely intertwined, given evidence that sleep disturbances may contrib-

Tabela 2. Nesanica i kardiovaskularne bolesti

Autori / Authors	Časopis / Journal	Godina / Year	Broj ispitanika / Participants (n)	Tip studije / Study type	Primarni cilj rada / Primary study objective	Zaključak rada / Conclusion
Laugsand i sar. / Laugsand et al.	<i>Eur Heart J</i>	2014	~54000	Prospektivna kohorta / Prospective cohort	Incidentna HF / Incident HF	Doza-odgovor veza sa HF / Dose-response relationship with HF
Hu i sar. / Hu et al.	<i>Front Psychiatry</i>	2021	>1,000,000	Meta-analiza / Meta-analysis	Kardiovaskularni događaji / Cardiovascular events	Nesanica ↑ rizik KVB / Insomnia ↑ CVD risk
Liu i sar. / Liu et al.	<i>Int J Hypertens</i>	2022	>200000	Meta-analiza / Meta-analysis	Hipertenzija / Hypertension	Dvosmerna povezanost / Bidirectional connectivity
Nambiema i sar. / Nambiema et al.	<i>Eur Heart J</i>	2023	~380000	Prospektivna kohorta / Prospective cohort	KVB / CVD	Bolji skor sna ↓ KVB rizik / Better sleep score ↓ CVD risk
Zhong i sar. / Zhong et al.	<i>Sleep Med</i>	2023	~50000	Prospektivna kohorta / Prospective cohort	KVB / CVD	Zdrav obrazac sna protektivan / A healthy sleep pattern is protective
Yan i sar. / Yan et al.	<i>Prev Med Rep</i>	2025	~300000	Kohortna / Cohort	HTA/KVB / HTN/CVD	Zdrav san ↓ incidence KVB / Healthy sleep ↓ CVD incidence
Huang i sar. / Huang et al.	<i>Heart</i>	2026	~10000+	Longitudinalna kohorta / Longitudinal cohort	Incidentna KVB / Incident CVD	Trajektorije nesanice prediktuju KVB / Insomnia trajectories are predictive of CVD

KVB – kardiovaskularni, HTA – hipertenzija, HF – srčana slabost, DM2 – dijabetes melitus tip 2, KVB – kardiovaskularne bolesti

Table 2. Insomnia and cardiovascular disease

KVB – kardiovaskularni, HTN – hypertension, HF – heart failure, DM2 – Type 2 diabetes

izaziva u potpunosti prirodan san. U našoj kliničkoj praksi najčešće prepisivani lekovi u tu svrhu pripadaju benzodijazepinskim anksioliticima (diazepam, lorazepam, bromazepam, klonazepam) i/ili sedativnim antidepresivima (trazodon, mirtazapin) (Slika 3). Nezavisno od efikasnosti ovih lekova, problemi koje oni izazivaju (tolerancija, zavisnost, apsitnencijalni sindrom, *rebound* nesanica), naročito u slučaju hronične primene, prevazilaze korist u lečenju nesanice. Ovo se posebno odnosi na bolesnike sa hroničnim kardiovaskularnim bolestima [38].

Benzodijazepini i kardiovaskularni ishodi kod bolesnika sa kardiovaskularnim bolestima

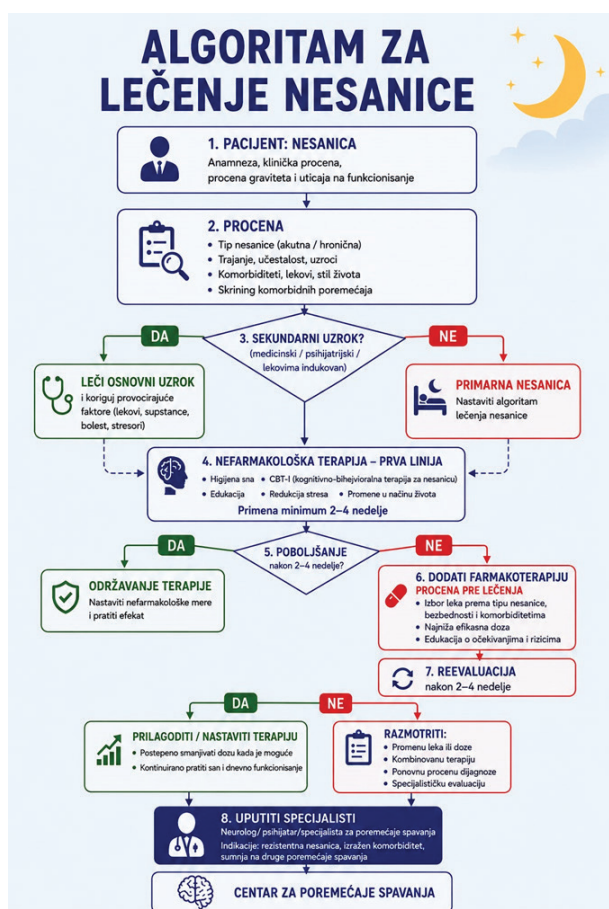
Rezultati novijih studija sugerišu da primena benzodijazepina kod bolesnika sa srčanom insuficijencijom može biti povezana sa višom stopom morbiditeta, mortaliteta i lošijim kvalitetom života. U velikoj kohorti bolesnika sa srčanom insuficijencijom i redukovanom ejekcijom frakcijom, benzodijazepini su bili udruženi sa većim rizikom kompozitnog ishoda kardiovaskularne smrti i ponavljanih hospitalizacija zbog srčane slabosti, i istovremeno sa većim rizikom nefatalnog moždanog udara i nefatalnog infarkta miokarda [39]. Ovakve nalaze podržava i studija sprovedena kod bolesnika hospitalizovanih zbog srčane slabosti i lečenih

ute to insulin resistance, impaired glycemic regulation, changes in body weight, and the development of dyslipidemia [18,25] (Table 2).

How to treat insomnia?

Given the bidirectional relationship between insomnia and many psychiatric and somatic comorbidities, the first step is to identify and appropriately treat these underlying conditions. In addition, the key principles of good sleep hygiene should be explained to each patient: a) maintaining a consistent bedtime; b) avoiding daytime sleep ("afternoon naps"); c) avoiding caffeinated beverages for 5–6 hours before bedtime; d) taking a warm shower before going to bed; e) avoiding the use of mobile phones (blue light) after going to bed; and f) temporarily waking approximately half an hour earlier than usual ("to make the brain long for sleep") [36].

Cognitive-behavioral therapy for insomnia (CBT-I) is the most important therapeutic approach in the treatment of chronic insomnia. It consists of several components: i) stimulus control (going to bed only when drowsiness is felt; if the patient does not fall asleep within 15–20 minutes, they should get up, move to another room, and engage in a relaxing activity); ii) restriction of time spent in bed (not less than 5 hours, with a gradual



Slika 3. Algoritam lečenja nesanice

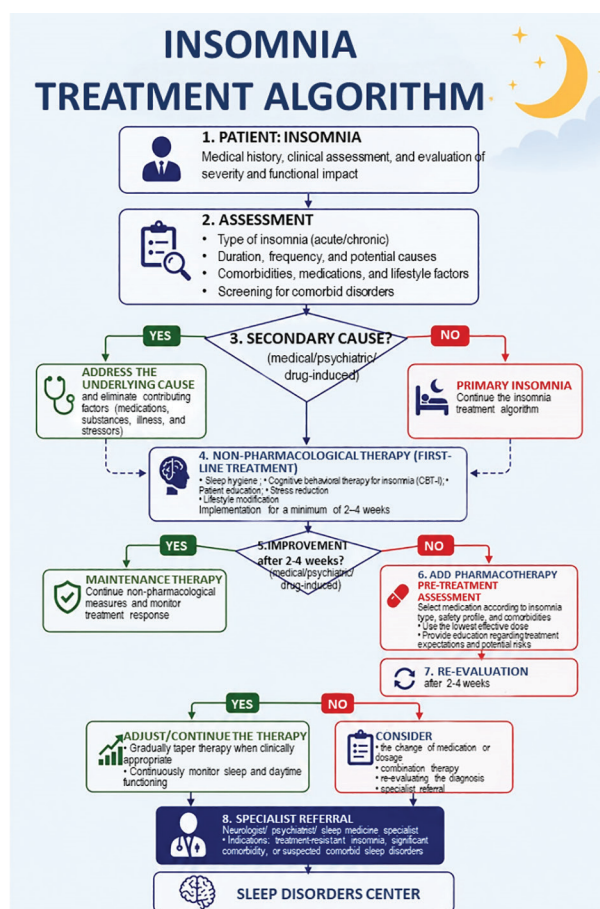


Figure 3. Algorithm for the treatment of insomnia

zbog nesanice, u kojoj su benzodiazepini, u poređenju sa Z-lekovima, bili nezavisno povezani sa većim rizikom od rehospitalizacije zbog srčane slabosti, zbog čega su autori sugerisali da bi nebenzodiazepinski hipnotici mogli imati povoljniji profil u ovoj populaciji [40].

U velikoj retrospektivnoj kohortnoj studiji iz Kine, koja je uključila približno 74.000 pacijenata sa novodijagnostikovanom kardiovaskularnom bolešću kao primarnim razlogom hospitalizacije, analizirana je povezanost započinjanja terapije benzodiazepinima sa kasnijim kardiovaskularnim ishodima. Pokazano je da je njihova primena povezana sa približno dvostruko većim rizikom od iznenadnog srčanog zastoja tokom 12 meseci praćenja, uz jasno izražen doza–odgovor odnos [41]. Hipoteza o različitim uticajima pojedinih hipnotika na kardiovaskularne ishode potvrđena je i u opservacionoj studiji koju su sprovedi Xie i saradnici 2025. godine. Dobijeni rezultati ukazali su na to da je primena benzodiazepina bila statistički značajno povezana sa većim rizikom od koronarne bolesti, srčane slabosti i kardiovaskularnog mortaliteta. Nasuprot tome, autori nisu našli čvrste dokaze za to da je primena Z-lekova u opštoj populaciji bolesnika sa insomnijom povezana sa nepovoljnim kardiovaskularnim ishodima [42].

Meta-analiza koja je obuhvatila više od 2,3 miliona ispitanika pokazala je da je primena anksiolitika i hipnotika povezana sa 43% većim rizikom od ukupnog mortaliteta, pri čemu je za benzodiazepine rizik bio još izraženiji [43]. U skladu s tim, rezultati dve velike kohortne studije iz Francuske i Ujedinjenog Kraljevstva pokazali su značajno, mada umereno, povećanje jednogodišnjeg ukupnog mortaliteta kod novih korisnika benzodiazepina, čak i nakon prilagođavanja za brojne kliničke faktore i psihijatrijske komorbiditete [44]. Rezultati kohortne studije sa preko 1.320.000 učesnika potvrdili su da je primena benzodiazepina povezana sa većim rizikom od mortaliteta [45].

Većina dostupnih studija, iako retrospektivnih opservacionih, ukazuje na povezanost primene benzodiazepina sa nepovoljnijim kardiovaskularnim ishodima, uključujući veći rizik od kardiovaskularnih događaja, rehospitalizacija zbog srčane insuficijencije i mortaliteta u pojedinim populacijama bolesnika (Tabela 3). Zbog toga, primena ovih lekova u cilju lečenja nesanice zahteva strogu individualizaciju i primenu u najmanjoj mogućoj dozi ne duže od dve nedelje.

Z-lekovi (zopiklon)

Sa pojavom nebenzodijazepinskih agonista benzodiazepinskih receptora (NBBRA), mnogi od potencijalnih problema su prevaziđeni uz postizanje zadovoljavajuće efikasnosti. Ovi lekovi (zaleplon, zolpidem, zopiklon – Z lekovi) imaju selektivnije dejstvo na GABA receptore vezu-

increase of 15–20 minutes per week); iii) avoidance of unrealistic expectations in order to reduce anxiety; and iv) implementation of relaxation techniques, including relaxation exercises, meditation, etc.[37].

However, for many patients who complain of insomnia, pharmacotherapy with hypnotic drugs remains the most common form of treatment, despite the fact that no currently available medication used for this purpose can completely reproduce natural sleep. In our clinical practice, the most frequently prescribed drugs for this purpose include benzodiazepine anxiolytics (diazepam, lorazepam, bromazepam, and clonazepam) and/or sedative antidepressants (trazodone and mirtazapine) (Figure 3). Regardless of their effectiveness, the adverse consequences associated with these drugs, including tolerance, dependence, withdrawal syndrome, and rebound insomnia, particularly with chronic use, may outweigh their benefits in the treatment of insomnia. This is especially relevant in patients with chronic cardiovascular diseases [38].

Benzodiazepines and cardiovascular outcomes in patients with cardiovascular disease

The results of recent studies suggest that benzodiazepine use in patients with heart failure may be associated with higher morbidity and mortality rates, as well as poorer quality of life. In a large cohort of patients with heart failure with reduced ejection fraction, benzodiazepine use was associated with a higher risk of the composite outcome of cardiovascular death and recurrent hospitalizations for heart failure, as well as with a higher risk of nonfatal stroke and nonfatal myocardial infarction [39]. These findings are supported by a study conducted in patients hospitalized for heart failure who were receiving treatment for insomnia, in which benzodiazepines, compared with Z-drugs, were independently associated with a higher risk of rehospitalization for heart failure. Consequently, the authors suggested that non-benzodiazepine hypnotics may have a more favorable safety profile in this population [40].

In a large retrospective cohort study from China, which included approximately 74,000 patients with newly diagnosed cardiovascular disease as the primary reason for hospitalization, the association between initiation of benzodiazepine therapy and subsequent cardiovascular outcomes was analyzed. The study demonstrated that benzodiazepine use was associated with approximately twice the risk of sudden cardiac arrest during the 12-month follow-up period, with a clear dose–response relationship [41]. The hypothesis that different hypnotic agents may have differential effects on cardiovascular outcomes was also supported by an observational study conducted by Xie et al.

Tabela 3. Povezanost upotrebe benzodiazepina i kardiovaskularnih događaja kod pacijenata sa kardiovaskularnim bolestima

Autori / Authors	Časopis / Journal	Godina / Year	Broj ispitanika / Participants (n)	Tip studije / Study type	Primarni cilj rada / Primary study objective	Zaključak rada / Conclusion
Lan i sar. / Lan et al.	<i>PLoS One</i>	2015	~1,300,000	Prospektivna kohorta / Retrospective cohort	Mortalitet / Mortality	Zolpidem niži rizik u poređenju sa BZD / Zolpidem associated with lower risk than BZD
Palmaro i sar. / Palmaro et al.	<i>Eur Neuropsychopharmacol</i>	2015	~200,000	Kohortna / Cohort	Mortalitet / Mortality	BZD ↑ mortalitet / BZD ↑ mortality
Parsaik i sar. / Parsaik et al.	<i>Aust N Z J Psychiatry</i>	2016	>2,300,000	Meta-analiza / Meta-analysis	Mortalitet / Mortality	Hipnotici ↑ mortalitet (BZD najviše) / Hypnotics ↑ mortality (highest with BZD)
Sato i sar. / Sato et al.	<i>J Am Heart Assoc</i>	2020	~1,000	Kohortna / Cohort	HF rehospitalizacija / HF rehospitalization	BZD lošiji od Z-lekova / BZD worse than Z-drugs
Chuang i sar. / Chuang et al.	<i>Acta Cardiol Sin</i>	2022	~6,000	Kohortna / Cohort	CVD mortality + HF hospitalizations	BZD ↑ loši ishodi / BZD ↑ poor outcomes
Mo i sar. / Mo et al.	<i>Sci Prog</i>	2024	~74,000	Prospektivna kohorta / Retrospective cohort	Sudden cardiac arrest	BZD ~2x ↑ rizik / BZD → ~2-fold higher risk
Xie i sar. / Xie et al.	<i>Eur J Prev Cardiol</i>	2025	>100,000	Kohortna / Cohort	CVD + mortality	BZD ↑ KVB; Z-lekovi neutralniji / BZD ↑ CVD; Z-drugs are more neutral

KVB – kardiovaskularne bolesti, HF – srčana slabost, KVB – kardiovaskularni, BZD – benzodiazepini, CBT-I – kognitivno bihevioralna terapija

Table 3. Association between benzodiazepine use and cardiovascular events in patients with cardiovascular diseases

CVD – cardiovascular disease, HF – heart failure, CV – cardiovascular, BZD – benzodiazepines, CBT-I – cognitive-behavioral therapy

jući se isključivo za alfa 1 podjedinicu (selektivni antagonisti GABA receptora). Pored dobre podnošljivosti, svi imaju dobru efikasnost, visok stepen bioraspoloživosti i nastupanje dejstva unutar 15–20 min od oralne upotrebe [46].

Među ovim lekovima, posebno se izdvaja zopiklon po sledećim farmakološkim osobinama: i) ima duže poluvreme eliminacije u odnosu na zolpidem (5 vs. 2,6 sati) čime je ukupno vreme spavanja produženo, a broj buđenja tokom noći smanjen; ii) nema potencijal za razvoj tolerancije čak ni kod hronične upotrebe; iii) pojava *rebound* nesanice je izuzetno retka. Prema polisomnografskim nalazima zopiklon takođe poboljšava strukturu spavanja i približava je spavanju kod zdravih kontrola. On povećava udeo sporotalasne faze spavanja u ukupnom spavanju, bez uticaja na REM fazu. Na ovaj način, zopiklon kod bolesnika sa nesanicom povećava restorativnu ulogu spavanja uz efikasnije uklanjanje adenoza, konsolidaciju memorije i stabilizaciju vegetativnog nervnog sistema [47,48].

ZAKLJUČAK

Savremeni pristup lečenju hronične nesanice zasniva se na razumevanju da ovaj poremećaj predstavlja trajno stanje poremećene regulacije sna koje zahteva dugoročnu terapijsku strategiju, a ne isključivo simptomatsko ublažavanje tegoba, posebno u osetljivim podgrupama bolesnika kakvi su kardiovaskularni. Dostupni podaci podržavaju oprez pri primeni benzodiazepina kod kardioloških bolesnika, dok se izbor Z-lekova, uključujući zopiklon, mora tumačiti u kontekstu ograničenog broja direktnih uporednih studija i individualnog kliničkog

in 2025. The results indicated that benzodiazepine use was statistically significantly associated with a higher risk of coronary artery disease, heart failure, and cardiovascular mortality. In contrast, the authors found no strong evidence that the use of Z-drugs in the general population of patients with insomnia was associated with adverse cardiovascular outcomes [42].

A meta-analysis including more than 2.3 million subjects showed that the use of anxiolytics and hypnotics was associated with a 43% higher risk of all-cause mortality, with benzodiazepines being associated with an even greater risk [43]. Similarly, the results of two large cohort studies from France and the United Kingdom demonstrated a significant, albeit moderate, increase in 1-year all-cause mortality among new benzodiazepine users, even after adjustment for numerous clinical factors and psychiatric comorbidities [44]. The results of a cohort study involving more than 1,320,000 participants further confirmed that benzodiazepine use is associated with a higher risk of mortality [45].

Most of the available studies, although retrospective and observational in design, indicate an association between benzodiazepine use and less favorable cardiovascular outcomes, including a higher risk of cardiovascular events, rehospitalization due to heart failure, and mortality in certain patient populations (Table 3). Therefore, the use of these drugs for the treatment of insomnia requires strict individualization and administration at the lowest possible dose for no longer than two weeks.

profila bolesnika. Nasuprot tome, kognitivno-bihevioralna terapija za nesanicu (CBT-I) predstavlja terapiju prvog izbora zbog dokazane dugoročne efikasnosti, održivosti terapijskog efekta i odsustva rizika od zavisnosti.

Najkraće rečeno, budući razvoj lečenja hronične nesanice usmeren je ka individualizovanom pristupu koji integriše nefarmakološke intervencije sa selektivnom primenom farmakoterapije kod odgovarajućih bolesnika.

Sukob interesa: Nije prijavljen.

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Z-drugs (zopiclone)

With the advent of non-benzodiazepine benzodiazepine receptor agonists (NBBRAs), many of the potential limitations associated with conventional benzodiazepines have been addressed while maintaining satisfactory efficacy. These drugs (zaleplon, zolpidem, and zopiclone, collectively referred to as Z-drugs) exert a more selective effect on GABA receptors by preferentially binding to the $\alpha 1$ subunit. In addition to good tolerability, they demonstrate good efficacy, a high degree of bioavailability, and a rapid onset of action, typically within 15–20 minutes of oral administration [46].

Among these drugs, zopiclone is distinguished by the following pharmacological properties: i) it has a longer half-life than zolpidem (5 vs. 2.6 hours), which increases total sleep time and reduces the number of nocturnal awakenings; ii) it has no significant potential for the development of tolerance, even with chronic use; and iii) the occurrence of rebound insomnia is extremely rare. According to polysomnographic findings, zopiclone also improves sleep architecture and brings it closer to that observed in healthy controls. It increases the proportion of slow-wave sleep in total sleep time without affecting the REM phase. In this way, zopiclone may enhance the restorative function of sleep in patients with insomnia by promoting more efficient clearance of adenosine, memory consolidation, and stabilization of autonomic nervous system function [47,48].

CONCLUSION

The modern approach to the treatment of chronic insomnia is based on the understanding that this disorder represents a persistent state of disrupted sleep regulation requiring a long-term therapeutic strategy rather than merely symptomatic relief, particularly in vulnerable subgroups of patients, such as those with cardiovascular disease. Available data support caution in the use of benzodiazepines in cardiac patients, while the use of Z-drugs, including zopiclone, should be considered in the context of the limited number of direct comparative studies and the individual clinical profile of each patient. In contrast, cognitive-behavioral therapy for insomnia (CBT-I) is considered the treatment of first choice because of its demonstrated long-term efficacy, sustained therapeutic effects, and absence of a risk of dependence.

In short, the future development of chronic insomnia treatment is directed toward an individualized approach that integrates non-pharmacological interventions with the selective use of pharmacotherapy in appropriate patients.

Conflict of interest: None declared

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POREMEĆAJ IZ SPEKTRA AUTIZMA I VAKCINACIJA: RAZBIJANJE MITOVA I PREDSTAVLJANJE ČINJENICA

PREGLEDNI RAD

REVIEW ARTICLE

AUTISM SPECTRUM DISORDER AND VACCINATION: DISPELLING MYTHS AND PRESENTING EVIDENCE

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SAŽETAK

Uvod/Cilj: Poremećaj iz spektra autizma (PAS) predstavlja složen neurorazvojni poremećaj čija etiologija nije u potpunosti razjašnjena. Nakon objavljivanja rada Endrua Vejkfilda 1998. godine, kojim je sugerisana moguća povezanost MMR vakcine i PAS-a, došlo je do značajnog pada poverenja u vakcinaciju i porasta zabrinutosti javnosti. Cilj ovog rada bio je pregled i analiza dostupnih naučnih dokaza o povezanosti MMR vakcine i poremećaja iz spektra autizma.

Metode: Izvršen je pregled dostupne naučne literature koja se odnosi na MMR vakcinu i poremećaj iz spektra autizma, sa posebnim osvrtom na epidemiološke studije, kohortne studije, sistematske preglede i metaanalize koje su ispitivale moguću povezanost između vakcinacije i razvoja PAS-a.

Rezultati: Analizirana istraživanja dosledno pokazuju da ne postoji uzročno-posledična povezanost između primene MMR vakcine i razvoja poremećaja iz spektra autizma. Istovremeno, pad obuhvata vakcinacijom povezan je sa ponovnom pojavom epidemija malih boginja u brojnim zemljama. Savremeni naučni dokazi potvrđuju bezbednost i efikasnost MMR vakcine.

Zaključak: Dostupni naučni dokazi jasno pokazuju da MMR vakcina ne povećava rizik za nastanak poremećaja iz spektra autizma. Kontinuirana edukacija zdravstvenih radnika i roditelja, zasnovana na naučnim dokazima, od ključnog je značaja za suzbijanje dezinformacija, jačanje poverenja u vakcinaciju i održavanje visokog obuhvata imunizacijom.

Ključne reči: MMR vakcina, poremećaj iz spektra autizma, vakcinacija

ABSTRACT

Introduction/Objective: Autism spectrum disorder (ASD) is a complex neuro-developmental condition with a multifactorial and not yet fully understood etiology. Following the publication of Andrew Wakefield's 1998 paper suggesting a possible association between the measles, mumps and rubella (MMR) vaccine and ASD, public confidence in vaccination declined substantially. This review aimed to examine and summarise the current scientific evidence on the association between MMR vaccination and ASD.

Methods: A narrative review of the available scientific literature was conducted, focusing on epidemiological studies, cohort studies, systematic reviews, and meta-analyses evaluating the potential association between MMR vaccination and ASD.

Results: The reviewed evidence consistently shows no causal association between MMR vaccination and ASD development. Conversely, declining vaccination coverage has contributed to the re-emergence of measles outbreaks in several countries. Current evidence strongly supports the safety, effectiveness, and favourable benefit-risk profile of the MMR vaccine.

Conclusion: Available scientific evidence confirms that the MMR vaccine does not increase the risk of ASD. Promoting evidence-based communication and maintaining high vaccination coverage remain essential to prevent vaccine-preventable diseases and address vaccine hesitancy.

Keywords: MMR vaccine, autism spectrum disorder, vaccination

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UVOD

Imunizacija predstavlja jedno od najvećih dostignuća medicine i i dalje je najefikasniji način prevencije zaraznih bolesti [1]. Zahvaljujući imunizaciji, milioni dece i odraslih zaštićeni su od teških bolesti i smrtnog ishoda [1]. Međutim, uprkos uspehu imunizacije, sumnje, nepoverenje i strah od neželjenih događaja doprineli su oklevanju u vezi sa vakcinacijom i ponovnoj pojavi bolesti koje se mogu sprečiti vakcinacijom, naročito morbila, u nekoliko zemalja [2].

U pojedinim slučajevima, strah od potencijalnih neželjenih efekata čak je prevazišao strah od komplikacija koje izazivaju same bolesti [3]. Jedan od najupornijih izvora nepoverenja u vezi sa vakcinacijom bila je kombinovana vakcina protiv morbila, zaušaka i rubeole (MMR) [3]. MMR vakcina, koja štiti od morbila, zaušaka i rubeole, primenjuje se već decenijama [1]. Ovo nepoverenje potiče iz 1998. godine, kada je Andrew Wakefield objavio članak u časopisu *The Lancet*, u kojem je izneo tvrdnju o navodnoj povezanosti između MMR vakcine i pojave poremećaja iz spektra autizma (PSA) [3–5].

Wakefieldov članak, koji je kasnije povučen iz publikacije i čiji rezultati nikada nisu naučno potvrđeni, privukao je značajnu pažnju medija i izazvao strah među roditeljima [3–5]. Od tada su sprovedena brojna epidemiološka istraživanja, od kojih nijedno nije pokazalo povezanost između MMR vakcine i poremećaja iz spektra autizma, čak ni kod dece sa visokim rizikom, čija braća ili sestre imaju dijagnostikovan PSA. Pored toga, određeni simptomi PSA mogu se uočiti i pre primene prve doze MMR vakcine [3,6,7]. Ovo oklevanje i dalje doprinosi pojavi epidemija bolesti koje se mogu sprečiti vakcinacijom, posebno morbila [2].

Epidemiološka Situacija Morbila

Srbija je poslednju veliku epidemiju morbila doživela tokom 2017–2018. godine, kada je prijavljeno 5.798 slučajeva, uz 15 smrtnih ishoda, uključujući odojčad i druge vulnerabilne osobe [8,9]. Komplikacije su bile česte, naročito kod male dece, a poznato je da morbili mogu izazvati ozbiljne ishode, kao što su pneumonija, koja predstavlja najčešću komplikaciju, i encefalitis, koji je redak, ali težak oblik komplikacije. Epidemija je prvenstveno zahvatila nevakcinisane osobe ili osobe sa nepoznatim vakcinalnim statusom [10].

Glavni uzrok epidemije u Srbiji, kao i u drugim evropskim zemljama, bio je pad obuhvata vakcinacijom. Tokom ovog perioda obuhvat MMR vakcinacijom pao je na približno 70–75%, što je značajno ispod nivoa potrebnog za održavanje kolektivnog imuniteta [11]. Za sprečavanje budućih epidemija morbila neophodan je obuhvat vakcinacijom od najmanje 95% kako bi se održao kolektivni imunitet [12].

INTRODUCTION

Immunization is one of medicine's greatest achievements and remains the most effective way to prevent infectious diseases [1]. Thanks to immunization, millions of children and adults have been protected from severe illness and death [1]. However, alongside immunization's success, doubts, mistrust, and fear of adverse events have contributed to vaccine hesitancy and the re-emergence of vaccine-preventable diseases, particularly measles, in several countries [2].

In some cases, the fear of potential adverse effects has even surpassed the fear of the complications caused by the diseases themselves [3]. One of the most persistent sources of vaccine-related mistrust has been the combined measles, mumps, and rubella (MMR) vaccine [3]. The MMR vaccine, which protects against measles, mumps, and rubella, has been administered for decades [1]. This mistrust originated in 1998 when Andrew Wakefield published an article in *The Lancet*, claiming a supposed link between the MMR vaccine and the onset of autism spectrum disorder (ASD) [3–5].

Wakefield's article, which was later retracted and whose findings were never scientifically validated, garnered significant media attention and instilled fear among parents [3–5]. Since then, numerous epidemiological studies have been conducted, all of which have demonstrated no association between the MMR vaccine and autism spectrum disorder, even in high-risk children who have siblings diagnosed with ASD. Moreover, certain symptoms of ASD can be observed even before the first dose of the MMR vaccine is administered [3,6,7]. This hesitancy continues to contribute to outbreaks of vaccine-preventable diseases, particularly measles [2].

Epidemiological situation of measles

Serbia experienced its most recent major measles outbreak during 2017–2018, when 5,798 cases were reported, with 15 deaths recorded, including infants and other vulnerable individuals [8,9]. Complications were frequent, particularly among young children, and measles is known to cause serious outcomes such as pneumonia (the most common complication) and encephalitis (a rare but severe complication). The outbreak primarily affected unvaccinated individuals or those with unknown vaccination status [10].

The main cause of the epidemic in Serbia, as well as in other European countries, was a decline in vaccination coverage. During this period, MMR vaccine coverage dropped to approximately 70–75%, which is significantly below the level required for herd immunity [11]. To prevent future outbreaks, measles requires at least 95% vaccination coverage to maintain herd immunity [12].

Pre uvođenja široko rasprostranjene vakcinacije, morbili su širom sveta uzrokovali milione smrtnih ishoda svake godine. Programi vakcinacije su od tada sprečili procenjenih nekoliko desetina miliona smrtnih ishoda širom sveta [13]. Zbog nedovoljnog obuhvata vakcinacijom i ciklične prirode epidemija morbila, Srbija i dalje ostaje u riziku od budućih epidemija ukoliko ne bude održavala visok nivo imunizacije [11].

Pregled poremećaja iz spektra autizma

Poremećaj iz spektra autizma (PSA) predstavlja neuorazvojni poremećaj koji karakterišu trajni deficiti u socijalnoj komunikaciji i socijalnoj interakciji, zajedno sa ograničenim i repetitivnim obrascima ponašanja, interesovanja ili aktivnosti. Simptomi počinju u ranom detinjstvu, ometaju svakodnevno funkcionisanje i značajno variraju po težini. Simptomi su obično evidentni u ranom detinjstvu, a PSA se često može pouzdano dijagnostikovati između 18. i 24. meseca života [14].

Etiologija PSA je složena i multifaktorijalna. Dosađajni dokazi ukazuju na to da genetski faktori imaju dominantnu ulogu, dok faktori sredine, naročito prenatalni i perinatalni faktori, mogu doprineti riziku za razvoj PSA kroz interakciju sa genetskom predispozicijom [15].

Prijavljena prevalencija poremećaja iz spektra autizma značajno je porasla tokom poslednjih nekoliko decenija [16]. Rana epidemiološka istraživanja sprovedena tokom 1960-ih i 1970-ih godina procenjivala su prevalenciju PSA na 0,5–0,7 na 10.000 dece. Do početka 1990-ih, prijavljena prevalencija porasla je na približno 3,3–16 na 10.000, što je odražavalo poboljšanje identifikacije slučajeva i promene dijagnostičkih koncepta, a ne stvarnu epidemiju ovog poremećaja [16].

Nakon toga, izmene dijagnostičkih kriterijuma, povećana informisanost javnosti i stručnjaka, širi programi skrininga i bolja dostupnost dijagnostičkih usluga doprineli su značajnom porastu prijavljene prevalencije širom sveta [17,18]. Prema ažuriranom sistematskom pregledu koji su sprovedli Zeidan i sar., a koji je obuhvatio istraživanja iz 34 zemlje objavljena između 2012. i 2021. godine, medijana globalne prevalencije PSA iznosi približno 100 na 10.000 dece (1%). Međutim, prijavljene procene značajno variraju, od 1,09 do 436 na 10.000, u zavisnosti od metodologije istraživanja, geografskog regiona i zdravstvene infrastrukture [17].

Slično tome, Talantseva i sar. pokazali su zbirnu globalnu prevalenciju od približno 0,72%, pri čemu su najviše procene zabeležene u zemljama sa visokim prihodima i Severnoj Americi [18]. Nedavni podaci sistema nadzora iz Sjedinjenih Američkih Država dodatno ilustruju povećanje broja identifikovanih slučajeva PSA. Prema podacima CDC Autism and Developmental

Before widespread vaccination, measles caused millions of deaths globally each year. Vaccination programs have since prevented an estimated tens of millions of deaths worldwide [13]. Because of insufficient vaccination coverage and the cyclical nature of measles outbreaks, Serbia remains at risk of future epidemics unless it maintains high immunization rates [11].

Overview of autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterised by persistent deficits in social communication and social interaction, together with restricted and repetitive patterns of behaviour, interests, or activities. Symptoms begin in early childhood, interfere with everyday functioning, and vary considerably in severity. Symptoms are typically evident in early childhood, and ASD can often be reliably diagnosed between 18 and 24 months of age [14].

The etiology of ASD is complex and multifactorial. Current evidence suggests that genetic factors play the predominant role, while environmental influences, particularly prenatal and perinatal factors, may contribute to ASD risk through interaction with genetic susceptibility [15].

The reported prevalence of autism spectrum disorder has increased substantially over the past several decades [16]. Early epidemiological studies conducted during the 1960s and 1970s estimated ASD prevalence to range between 0.5 and 0.7 per 10,000 children. By the early 1990s, reported prevalence had increased to approximately 3.3–16 per 10,000, reflecting improvements in case identification and evolving diagnostic concepts rather than a true epidemic of the disorder [16].

Subsequently, revisions of diagnostic criteria, increased public and professional awareness, broader screening programs, and improved access to diagnostic services have contributed to a marked rise in reported prevalence worldwide [17,18]. According to the updated systematic review by Zeidan et al., which included studies from 34 countries published between 2012 and 2021, the median global prevalence of ASD is approximately 100 per 10,000 children (1%). However, reported estimates vary considerably, ranging from 1.09 to 436 per 10,000 depending on study methodology, geographic region, and healthcare infrastructure [17].

Similarly, Talantseva et al. demonstrated a pooled global prevalence of approximately 0.72%, with the highest estimates reported in high-income countries and North America [18]. Recent surveillance data from the United States further illustrate the increasing number of identified ASD cases. According to the Centers for Disease Control and Prevention (CDC) Autism and Developmental Disabilities Monitoring (ADDM) Net-

Disabilities Monitoring (ADDM) Network, kod približno jednog od 31 deteta uzrasta od 8 godina identifikovan je PSA u 2022. godini. Međutim, ove procene odražavaju podatke nadzora iz odabranih zajednica u SAD i ne treba ih tumačiti kao globalnu prevalenciju.

Razlike u procenama prevalencije uglavnom se pripisuju razlikama u dijagnostičkoj praksi, identifikaciji slučajeva, nivou informisanosti i dostupnosti zdravstvenih usluga [19]. Aktuelni dokazi ukazuju na to da je veliki deo uočenog porasta prevalencije PSA posledica promena u dijagnostičkoj praksi, veće informisanosti i bolje identifikacije slučajeva, a ne jednog jedinstvenog uzročnog faktora. Ipak, istraživači i dalje ispituju doprinos faktora sredine i demografskih faktora [18].

Imunizacija

Imunizacija je jedna od najefikasnijih javnozdravstvenih intervencija u prevenciji zaraznih bolesti putem primene vakcina, koje stimulišu imunski sistem da razvije dugotrajni zaštitni imunitet. Visok obuhvat vakcinacijom obezbeđuje kako individualnu zaštitu, tako i kolektivni imunitet, čime se smanjuje prenošenje bolesti i sprečava pojava epidemija [1,20]. Vakcinacija predstavlja jednu od najstarijih medicinskih praksi u prevenciji bolesti [21].

Prvu uspešnu vakcinu razvio je Edward Jenner 1796. godine protiv velikih boginja. Ubrizgavanjem virusa kravljih boginja zdravim osobama, Jenner je uočio razvoj imuniteta protiv velikih boginja. Budući da je prva vakcina bila dobijena od virusa kravljih boginja, termin *vakcina* potiče od latinske reči *vacca*, što znači „krava“ [22].

Vakcinacija je značajno doprinela smanjenju smrtnosti na globalnom nivou od bolesti koje se mogu sprečiti vakcinacijom, naročito među decom. Vakcinacijom velikog dela populacije razvija se kolektivni imunitet. Ovaj mehanizam prekida prenošenje mikroorganizma odgovornog za nastanak bolesti. Budući da mnogi infektivni uzročnici zavise od osetljivih domaćina za nastavak prenosa, visok nivo imuniteta populacije smanjuje njihovu cirkulaciju i štiti vulnerabilne osobe koje iz medicinskih razloga ne mogu biti vakcinisane [22,23].

U Republici Srbiji, Zakon o zaštiti stanovništva od zaraznih bolesti reguliše obaveznu i preporučenu aktivnu imunizaciju [24].

MMR Vakcina

MMR vakcina je kombinovana živa atenuisana vakcina koja štiti od morbila, zaušaka i rubeole indukovanjem trajnog imunskog odgovora. Pokazala je visoku efikasnost, dugotrajnu imunogenost i odličan bezbednosni profil, zbog čega predstavlja osnovu rutinskih programa imunizacije dece širom sveta [1,25,26].

work, approximately 1 in 31 children aged 8 years were identified with ASD in 2022. However, these estimates reflect surveillance data from selected U.S. communities and should not be interpreted as global prevalence.

Differences in prevalence estimates are largely attributed to variations in diagnostic practices, case ascertainment, awareness, and access to healthcare services [19]. Current evidence suggests that much of the observed increase in ASD prevalence is attributable to changes in diagnostic practices, greater awareness, and improved ascertainment rather than a single causal factor. However, researchers continue to investigate the contribution of environmental and demographic influences [18].

Immunization

Immunization is one of the most effective public health interventions for preventing infectious diseases through vaccine administration, which stimulates the immune system to develop long-lasting protective immunity. High vaccination coverage provides both individual protection and herd immunity, thereby reducing disease transmission and preventing outbreaks [1,20]. Vaccination represents one of the oldest medical practices for disease prevention [21].

The first successful vaccine was developed by Edward Jenner in 1796 against smallpox. By injecting healthy individuals with the cowpox virus, Jenner observed the development of immunity to smallpox. Because the first vaccine was derived from the cowpox virus, the term *vaccine* originates from the Latin word *vacca*, meaning *cow* [22].

Vaccination has contributed substantially to the global reduction in mortality from vaccine-preventable diseases, particularly among children. By vaccinating a large portion of the population, herd immunity develops. This mechanism disrupts the transmission of the microorganism responsible for the disease. Because many infectious agents rely on susceptible hosts for continued transmission, high population immunity reduces their circulation and protects vulnerable individuals who cannot be vaccinated for medical reasons [22,23].

In the Republic of Serbia, the Law on the Protection of the Population from Infectious Diseases regulates mandatory and recommended active immunization [24].

MMR Vaccine

The MMR vaccine is a combined live-attenuated vaccine that protects against measles, mumps and rubella by inducing a durable immune response. It has demonstrated high effectiveness, long-term immunogenicity and an excellent safety profile, making it a cornerstone of routine childhood immunization programs worldwide [1,25,26].

Zauške mogu dovesti do muške neplodnosti, dok rubeola predstavlja ozbiljan rizik za trudnice i fetus u razvoju. Vakcinacija značajno smanjuje učestalost ovih bolesti i težinu njihovih komplikacija, od kojih neke mogu ugroziti život [27,28].

U Srbiji se MMR vakcina primenjuje u dve doze. Prema nacionalnom kalendaru imunizacije, prva doza se daje između 12. i 15. meseca života, iako pojedini izvori dozvoljavaju njenu primenu do 18. meseca. Iako se prva doza još uvek može primeniti tokom druge godine života, nije preporučljivo odlagati vakcinaciju, jer se time povećava rizik od obolevanja od neke od ovih bolesti pre imunizacije.

Druga doza, odnosno revakcinacija, daje se pre polaska u školu (prvi razred) kako bi se obezbedio potpun imunitet. Brojna istraživanja potvrdila su efikasnost, značaj i bezbednost MMR vakcine, zbog čega je ona deo obaveznog kalendara imunizacije [24].

Roditelji i vakcinacija

Oklevanje u vezi sa vakcinacijom postoji još od uvođenja prvih vakcina, ali je poslednjih godina sve više pod uticajem dezinformacija, društvenih mreža i opadanja poverenja u naučne i javnozdravstvene institucije [1,2].

Objavljivanje Wakefeldove studije iz 1998. godine, koja je iznela nepotkrepljenu tvrdnju o povezanosti između MMR vakcine i autizma, značajno je pojačalo zabrinutost javnosti i doprinelo smanjenju poverenja u imunizaciju dece, uprkos njenom kasnijem povlačenju iz publikacije i naučnoj diskreditaciji [4,5].

Roditelji su često izloženi protivrečnim informacijama o bezbednosti vakcina, neželjenim događajima i rasporedu vakcinacije, što može uticati na odluke o imunizaciji [1,2]. Međutim, brojna epidemiološka istraživanja sprovedena tokom prethodne dve decenije dosledno su pokazala da ne postoji povezanost između MMR vakcinacije i poremećaja iz spektra autizma [6,7,29].

Javnozdravstvene institucije i dalje naglašavaju da je visok obuhvat vakcinacijom od suštinskog značaja za sprečavanje epidemija bolesti koje se mogu sprečiti vakcinacijom i zaštitu vulnerabilnih populacija [1,2].

MMR vakcina i poremećaj iz spektra autizma (PSA)

Zabrinutost zbog moguće povezanosti između MMR vakcine i poremećaja iz spektra autizma (PSA) potekla je od sada diskreditovane studije koju su 1998. godine objavili Andrew Wakefield i saradnici. Studija je obuhvatila samo dvanaestoro dece, od kojih je osmoro imalo dijagnostikovan PSA.

Autori su pretpostavili da MMR vakcina može izazvati inflamaciju creva, omogućavajući štetnim supstancama da dospeju u krvotok i deluju na centralni nervni sistem, čime bi potencijalno doprinele razvoju autizma [4,5]. Međutim, studija je imala ozbiljna meto-

Mumps can lead to male infertility, while rubella poses a serious risk to pregnant women and the developing fetus. Vaccination significantly reduces both the incidence of these diseases and the severity of their complications, some of which can be life-threatening [27,28].

In Serbia, the MMR vaccine is administered in two doses. According to the national immunization schedule, the first dose is given between 12 and 15 months of age, although some sources allow administration up to 18 months. While the first dose can still be given during the second year of life, it is not advisable to delay, as this increases the risk of contracting one of these diseases before immunization.

The second dose, or booster, is given before school entry (first grade) to ensure full immunity. Numerous studies have confirmed the efficacy, importance, and safety of the MMR vaccine, which is why it is part of the mandatory immunization schedule [24].

Parents and Vaccination

Vaccine hesitancy has existed since the introduction of the first vaccines but has become increasingly influenced by misinformation, social media, and declining trust in scientific and public health institutions [1,2].

The publication of Wakefield's 1998 study, which proposed an unsupported association between the MMR vaccine and autism, substantially amplified public concern and contributed to declining confidence in childhood immunization despite its subsequent retraction and scientific discrediting [4,5].

Parents are often exposed to conflicting information about vaccine safety, adverse events, and vaccination schedules, which may influence immunization decisions [1,2]. However, extensive epidemiological studies conducted over the past two decades have consistently demonstrated no association between MMR vaccination and autism spectrum disorder [6,7,29].

Public health authorities continue to emphasize that high vaccination coverage is essential to prevent outbreaks of vaccine-preventable diseases and protect vulnerable populations [1,2].

MMR Vaccine and Autism Spectrum Disorder (ASD)

Concerns regarding a potential association between the MMR vaccine and autism spectrum disorder (ASD) originated from a now-discredited study published in 1998 by Andrew Wakefield and colleagues. The study included only twelve children, eight of whom were diagnosed with ASD.

The authors hypothesized that the MMR vaccine could cause intestinal inflammation, allowing harmful substances to enter the bloodstream and affect the central nervous system, ultimately contributing to the

določka ograničenja, uključujući izuzetno mali uzorak, odsustvo kontrolne grupe i nepostojanje dokaza koji bi utvrdili vremensku povezanost između gastrointestinalnih nalaza i pojave PSA.

Naknadna istraživanja otkrila su ozbiljna kršenja etičkih principa i neprijavljene finansijske sukobe interesa, uključujući Wakefieldovo učešće u razvoju alternativne vakcine protiv morbila. Članak je 2010. godine formalno povučen iz publikacije, a Wakefield je zbog profesionalnog nedoličnog postupanja brisan iz registra lekara Ujedinjenog Kraljevstva [5,30,31].

Uprkos povlačenju rada, njegova publikacija imala je dubok i dugotrajan globalni uticaj, značajno narušavajući poverenje javnosti u MMR vakcinu i doprinoseći dugotrajnom oklevanju u vezi sa vakcinacijom u mnogim zemljama [1,29].

Hipoteza je privukla pažnju javnosti delimično zbog toga što se rani simptomi PSA često javljaju između 18. i 24. meseca života, što se vremenski podudara sa periodom kada se MMR vakcina rutinski primenjuje. Ova vremenska povezanost doprinela je zabrinutosti roditelja, uprkos odsustvu naučnih dokaza koji bi podržali uzročnu povezanost.

Tokom prethodne dve decenije brojna velika epidemiološka istraživanja sprovedena u različitim zemljama i populacijama dosledno su pokazala da MMR vakcinacija ne povećava rizik od PSA. Jedno od prvih epidemioloških istraživanja, sprovedeno u Ujedinjenom Kraljevstvu, nije pronašlo dokaze o uzročnoj povezanosti između MMR vakcinacije i autizma [29].

Nakon toga, Madsen i saradnici sprovedli su veliku populacionu kohortnu studiju u Danskoj koja je obuhvatila 537.303 dece. Studija nije pokazala statistički značajnu razliku u incidenciji PSA između vakcinisane i nevakcinisane dece [32].

Dodatne kohortne studije i studije tipa slučaj-kontrola sprovedene u Ujedinjenom Kraljevstvu, Sjedinjenim Američkim Državama, Finskoj i Japanu dodatno su potvrdile ove nalaze, pri čemu nijedna od njih nije pokazala povezanost između MMR vakcinacije i PSA [33–35]. Nadalje, nacionalna kohortna studija sprovedena u Danskoj i objavljena 2019. godine, koja je obuhvatila 657.461 dete, potvrdila je da MMR vakcinacija ne povećava rizik od autizma, čak ni među decom koja se smatraju rizičnijom zbog porodičnih ili faktora sredine [7].

Prirodni populacioni eksperiment sproveden u Japanu dodatno je doveo u pitanje pretpostavljenu povezanost između MMR vakcinacije i PSA. Nakon povlačenja MMR vakcine iz nacionalnog programa imunizacije, istraživači su ispitivali da li se incidencija PSA smanjila uporedo sa smanjenjem stope vakcinacije. Međutim, uprkos smanjenom obuhvatu MMR vakcinacijom, prevalencija PSA je nastavila da raste, što je bilo u suprotnosti sa hipotezom o uzročnoj povezanosti [36,37].

development of autism [4,5]. However, the study had major methodological limitations, including an extremely small sample size, no control group, and no evidence establishing a temporal relationship between gastrointestinal findings and ASD onset.

Subsequent investigations revealed serious ethical violations and undisclosed financial conflicts of interest, including Wakefield's involvement in developing an alternative measles vaccine. In 2010, the article was formally retracted, and Wakefield was removed from the UK medical register due to professional misconduct [5,30,31].

Despite its retraction, the publication had a profound and long-lasting global impact, substantially undermining public confidence in the MMR vaccine and contributing to persistent vaccine hesitancy in many countries [1,29].

The hypothesis gained public attention partly because early symptoms of ASD commonly emerge between 18 and 24 months of age, which coincides with the period when the MMR vaccine is routinely administered. This temporal association contributed to parental concern despite the absence of scientific evidence supporting causation.

Over the past two decades, numerous large-scale epidemiological studies conducted in different countries and populations have consistently demonstrated that MMR vaccination does not increase the risk of ASD. One of the earliest epidemiological investigations, conducted in the United Kingdom, found no evidence of a causal association between MMR vaccination and autism [29].

Subsequently, Madsen et al. conducted a large population-based cohort study in Denmark that included 537,303 children. The study demonstrated no statistically significant difference in ASD incidence between vaccinated and unvaccinated children [32].

Additional cohort and case-control studies in the United Kingdom, the United States, Finland, and Japan reinforced these findings, consistently failing to show an association between MMR vaccination and ASD [33–35]. Furthermore, a nationwide Danish cohort study published in 2019 involving 657,461 children confirmed that MMR vaccination does not increase the risk of autism, even among children considered at higher risk due to familial or environmental factors [7].

A natural population-based experiment conducted in Japan further challenged the proposed association between MMR vaccination and ASD. After the MMR vaccine was withdrawn from the national immunization program, researchers examined whether ASD incidence declined alongside reduced vaccination rates. However, despite decreased MMR uptake, ASD prevalence continued to increase, contradicting the hypothesis of a causal relationship [36,37].

Slično tome, istraživanje sprovedeno u Kaliforniji analiziralo je trendove u obuhvatu MMR vakcinacijom i dijagnozama autizma u periodu od 1980. do 1994. godine. Iako su stope MMR vakcinacije tokom ovog perioda porasle, nije uočeno odgovarajuće povećanje prevalencije PSA koje bi se moglo pripisati vakcinaciji [38].

Naknadna zabrinutost bila je usmerena na komponente vakcina, naročito na tiomersal, konzervans koji sadrži živu i koji se ranije koristio u nekim vakcinama radi sprečavanja bakterijske kontaminacije u višedoznim bočicama. Iako nijedan dokaz nije podržao povezanost između izloženosti tiomersalu i autizma, ovo jedinjenje je iz predostrožnosti uklonjeno iz većine vakcina namenjenih deci u Sjedinjenim Američkim Državama. Naknadne studije pokazale su da je prevalencija PSA nastavila da raste i nakon uklanjanja tiomersala, pružajući dodatne dokaze protiv uzročne povezanosti [39].

Istraživači su takođe ispitivali da li kumulativna izloženost antigenima iz vakcina tokom ranog detinjstva može doprineti razvoju PSA. Studija tipa slučaj-kontrola, koja je procenjivala izloženost antigenima tokom prve dve godine života, nije pokazala povećan rizik od PSA kod dece izložene većem broju antigena iz vakcina u poređenju sa kontrolnom grupom [40].

Naučni dokazi nisu potvrdili zabrinutost da primena više vakcina u skladu sa preporučenim kalendarom imunizacije može negativno uticati na neurorazvoj. Studije koje su upoređivale decu vakcinisanu prema preporučenom kalendaru sa decom kod koje je vakcinacija odložena nisu pokazale razlike u neuropsihološkim ili razvojnim ishodima, dok je odlaganje vakcinacije povećalo osetljivost na bolesti koje se mogu sprečiti vakcinacijom [41].

Pored ovih ključnih epidemioloških istraživanja, noviji dokazi dodatno su ojačali zaključak da MMR vakcinacija nije povezana sa PSA. Jain i sar. pokazali su da MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA čak ni kod dece čija su starija braća ili sestre imali dijagnostikovani autizam, odnosno kod populacije koja se smatra populacijom sa povećanim porodičnim rizikom [6].

Slično tome, Goin-Kochel i saradnici nisu pronašli razlike u obrascima vakcinacije između dece sa PSA i kontrolne grupe koje bi podržale uzročnu povezanost između vakcinacije i autizma [42]. Eksperimentalni dokazi takođe su dodatno potvrdili ove nalaze. Gadad i sar. izvestili su da primena vakcina koje sadrže tiomersal kod mladunaca rhesus makakija nije dovela do ponašanja sličnog autizmu niti do neuropatoloških abnormalnosti [43].

Nadalje, sveobuhvatni sistematski pregled koji su sproveli Modabbernia i sar. zaključio je da PSA nastaje kao rezultat složene interakcije genetskih faktora i faktora sredine. Istovremeno, nema dokaza koji podržavaju vakcinaciju kao faktor rizika za autizam [15] (Tabela 1).

Similarly, a study conducted in California analyzed trends in MMR vaccination coverage and autism diagnoses between 1980 and 1994. Although MMR vaccination rates increased during this period, no corresponding increase in ASD prevalence attributable to vaccination was observed [38].

Additional concerns later focused on vaccine components, particularly thimerosal, a mercury-containing preservative previously used in some vaccines to prevent bacterial contamination in multidose vials. Although no evidence supported an association between thimerosal exposure and autism, the compound was removed from most childhood vaccines in the United States as a precautionary measure. Subsequent studies demonstrated that ASD prevalence continued to rise even after thimerosal removal, providing further evidence against a causal association [39].

Researchers have also investigated whether cumulative exposure to vaccine antigens during early childhood could contribute to ASD development. A case-control study evaluating antigen exposure during the first two years of life found no increased risk of ASD among children exposed to more vaccine antigens than controls [40].

Scientific evidence has not supported concerns that administering multiple vaccines according to the recommended immunization schedule could negatively affect neurodevelopment. Studies comparing children vaccinated according to the recommended schedule with those receiving delayed vaccinations found no differences in neuropsychological or developmental outcomes, while delayed vaccination increased susceptibility to vaccine-preventable diseases [41].

In addition to these landmark epidemiological studies, more recent evidence has further strengthened the conclusion that MMR vaccination is not associated with ASD. Jain et al. demonstrated that MMR vaccination was not associated with an increased risk of ASD even among children with older siblings diagnosed with autism, a population considered to be at increased familial risk [6].

Similarly, Goin-Kochel et al. found no differences in vaccination patterns between children with ASD and controls that would support a causal relationship between vaccination and autism [42]. Experimental evidence has also reinforced these findings. Gadad et al. reported that administering thimerosal-containing vaccines to infant rhesus macaques did not result in autism-like behavior or neuropathological abnormalities [43].

Furthermore, a comprehensive systematic review by Modabbernia et al. concluded that ASD arises from a complex interaction between genetic and environmental factors. At the same time, no evidence supports vaccination as a risk factor for autism [15] (Table 1).

Tabela 1. Najznačajnije epidemiološke studije koje su ispitivale povezanost između MMR vakcinacije i poremećaja iz spektra autizma (PSA)

Studija / Study	Zemlja / Country	Dizajn studije / Veličina uzorka / Study design / Sample size	Glavni nalazi / Main findings
Taylor et al., 2014 [29]	United Kingdom	Epidemiological study	Nije utvrđena uzročna povezanost između MMR vakcinacije i autizma / No causal association between MMR vaccination and autism
Madsen et al., 2002 [32]	Denmark	Cohort study, 537,303 children	Nije utvrđen povećan rizik od PSA kod vakcinisane dece / No increased risk of ASD among vaccinated children
Smeeth et al., 2004 [34]	United Kingdom	Case-control study	Nije utvrđena povezanost između MMR vakcinacije i pervazivnih razvojnih poremećaja / No association between MMR vaccination and pervasive developmental disorders
Honda et al., 2005 [36]	Japan	Population-based study	Incidencija PSA nastavila je da raste nakon povlačenja MMR vakcine / ASD incidence continued to rise after MMR withdrawal
Hviid et al., 2019 [7]	Denmark	Nationwide cohort study, 657,461 children	MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA / MMR vaccination not associated with increased ASD risk
Jain et al., 2015 [6]	United States	Retrospective cohort study, 95,727 children	MMR vakcinacija nije bila povezana sa povećanim rizikom od PSA, uključujući i decu čiji je stariji brat ili sestra imao/la PSA / MMR vaccination was not associated with increased ASD risk, including among children with an older sibling with ASD

Sveukupno, dokazi dobijeni iz velikih epidemioloških studija, sistematskih pregleda, meta-analiza, eksperimentalnih istraživanja i nacionalnih kohortnih studija sprovedenih tokom više od dve decenije dosledno pokazuju da MMR vakcinacija nije povezana sa povećanim rizikom od PSA. Velike međunarodne zdravstvene organizacije, uključujući Svetsku zdravstvenu organizaciju (SZO) i Centre za kontrolu i prevenciju bolesti (CDC), i dalje podržavaju ove nalaze i potvrđuju da je MMR vakcina bezbedna i da ne izaziva autizam [24].

ZAKLJUČAK

Pad stope MMR vakcinacije i povećanje prevalencije poremećaja iz spektra autizma (PSA) jasno pokazuju da između ova dva fenomena ne postoji uzročna povezanost. Brojna epidemiološka istraživanja, kliničke studije i literatura zasnovana na dokazima detaljno su opovrgli ovu široko rasprostranjenu zabludu.

MMR vakcina, kao i druge vakcine, ne utiče na neuropsihološki razvoj dece i ostaje veoma efikasna u prevenciji zaraznih bolesti. Sa smanjenjem stope imunizacije povećava se rizik od nove epidemije morbila, a istraživači predviđaju da bi do nje moglo doći u bliskoj budućnosti.

Stav Svetske zdravstvene organizacije (SZO) je jasan: vakcinacija ne štiti samo pojedinca, već i čitavu zajednicu, doprinoseći eliminaciji i iskorenjivanju mnogih smrtonosnih bolesti jednom zauvek.

Sukob interesa: Nije prijavljen.

Table 1. Major epidemiological studies investigating the association between MMR vaccination and ASD

Collectively, evidence from large epidemiological studies, systematic reviews, meta-analyses, experimental investigations and nationwide cohort studies conducted over more than two decades consistently demonstrates that MMR vaccination is not associated with an increased risk of ASD. Major international health organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), continue to endorse these findings and affirm that the MMR vaccine is safe and does not cause autism [24].

CONCLUSION

The declining MMR vaccination rate and the increasing prevalence of autism spectrum disorder (ASD) clearly demonstrate that there is no causal link between the two. Numerous epidemiological studies, clinical research, and evidence-based literature have thoroughly disproven this widespread misconception.

The MMR vaccine, like all other vaccines, does not affect children's neuropsychological development and remains highly effective at preventing infectious diseases. As immunization rates decline, the risk of a new measles outbreak is rising, and researchers predict one may occur in the near future.

The World Health Organization (WHO) position is clear: vaccination not only protects the individual but also safeguards the entire community, helping eliminate and eradicate many deadly diseases once and for all.

Conflict of interest: None declared

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HIDDEN HEARING LOSS – COCHLEAR SYNAPTOPATHY

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SAŽETAK

Uvod/Cilj: Kohlearna sinaptopatija, u literaturi poznata i kao „skriveni gubitak sluha“ (engl. *hidden hearing loss*), predstavlja primarni gubitak sinapsi između unutrašnjih trepljastih ćelija i kohlearnih nervnih vlakana, dok same senzorne ćelije ostaju očuvane. Glavni etiološki faktori uključuju izloženost buci, proces starenja i upotrebu ototoksičnih lekova. Cilj ovog preglednog rada je sveobuhvatna analiza patofizioloških mehanizama kohlearne sinaptopatije i evaluacija savremenih dijagnostičkih pristupa za detekciju skrivenog gubitka sluha.

Metode: U ovom preglednom radu izvršena je analiza relevantne savremene literature i naučnih radova indeksiranih u bazama *PubMed* i *SCIndex*. Pretraga je obuhvatila radove koji se bave anatomskim i patofiziološkim mehanizmima oštećenja, kao i validacijom novih kliničkih i elektrofizioloških protokola za identifikaciju sinaptičkih disfunkcija.

Rezultati: Kliničku sliku karakteriše očuvan prag sluha na standardnoj tonalnoj liminarnoj audiometriji u tišini, ali uz izražen deficit u razumevanju govora u bučnom okruženju, praćen tinitusom i hiperakuzijom. S obzirom na to da konvencionalni testovi ne detektuju ovo oštećenje, dijagnostika se oslanja na napredne elektrofiziološke metode, prvenstveno na analizu amplitude talasa I auditivnih evociranih potencijala moždanog stabla (ABR), kao i na psihoakustičke testove govora u buci. Trenutne terapijske opcije obuhvataju upotrebu slušnih aparata sa naprednim algoritmima za redukciju šuma i audiološku rehabilitaciju, dok su savremena pretklinička istraživanja usmerena ka neurotrofičkoj regeneraciji sinaptičkih veza.

Zaključak: Konvencionalni audiološki pristup nije dovoljan za detekciju kohlearne sinaptopatije, te je u kliničku praksu neophodno uvesti napredne elektrofiziološke i psihoakustičke testove. Pravovremeno razumevanje ovog entiteta ključno je za rano prepoznavanje i prevenciju trajnih auditivnih disfunkcija.

Ključne reči: skriveni gubitak sluha, kohlearna sinaptopatija, auditivni evocirani potencijali moždanog stabla, percepcija govora, tinitus

ABSTRACT

Introduction/Objective: Cochlear synaptopathy, also known in the literature as “hidden hearing loss”, represents a primary loss of synapses between inner hair cells and cochlear nerve fibers, while the sensory cells themselves remain preserved. The main etiological factors include noise exposure, aging, and ototoxic drug use. This review aims to provide a comprehensive analysis of the pathophysiological mechanisms of cochlear synaptopathy and evaluate current diagnostic approaches for detecting hidden hearing loss.

Methods: This review paper analyzes relevant literature and scientific papers indexed in the PubMed and SCIndex databases. The search included studies on the anatomical and pathophysiological mechanisms of impairment, as well as the validation of new clinical and electrophysiological protocols for identifying synaptic dysfunction.

Results: The clinical presentation is characterized by a preserved hearing threshold on standard pure-tone audiometry in quiet, but with a pronounced deficit in speech understanding in noisy environments, accompanied by tinnitus and hyperacusis. Since conventional tests do not detect this impairment, diagnosis relies on advanced electrophysiological methods, primarily the amplitude analysis of wave I of auditory brainstem responses (ABR), as well as psychoacoustic speech-in-noise tests. Current therapeutic options include hearing aids with advanced noise-reduction algorithms and audiological rehabilitation, while contemporary preclinical research focuses on neurotrophic regeneration of synaptic connections.

Conclusion: The conventional audiological approach is insufficient for detecting cochlear synaptopathy; therefore, it is essential to introduce advanced electrophysiological and psychoacoustic tests into clinical practice. Timely understanding of this entity is crucial for early identification and prevention of permanent auditory dysfunctions.

Keywords: hidden hearing loss, cochlear synaptopathy, auditory brainstem responses, speech perception, tinnitus

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UVOD

Skriveni gubitak sluha je termin koji se od nedavno koristi kako bi se opisao slušni poremećaj koji se pretpostavlja da utiče na slušno – neuralnu obradu zvučnog signala i oštrinu sluha kod osoba sa urednim nalazima tonalne liminarne audiometrije [1]. Kod klasičnog senzorneuralnog oštećenja sluha koje je uzrokovano disfunkcijom ili degenerativnim promenama na unutrašnjim i spoljašnjim redovima ćelija Kortijevog organa i/ili spiralnog gangliona dolazi do trajno povišenih pragova na audiometrijskom nalazu. Međutim, u praksi se neretko srećemo sa pacijentima koji pokazuju urednu slušnu osetljivost, ali imaju značajne perceptivne poteškoće uključujući razumevanje govora u bučnim sredinama. Takva perceptivna disfunkcija se često naziva „poremećaj obrade slušnih informacija” i smatra se da defekti u centralnim slušnim putevima igraju ključnu ulogu.

Iako se kohlearna sinaptopatija često poistovećuje sa skrivenim gubitkom sluha, ona predstavlja njegov primarni patofiziološki mehanizam, dok je skriveni gubitak sluha širi klinički entitet koji može biti uzrokovan i drugim procesima. Novija istraživanja pokazuju da do skrivenog gubitka sluha može doći i usled demijelinizacije slušnog nerva [2], degenerativnih promena slušnog nerva [3] ili neuralnog pojačanja kada mozak dobija slabije signale sa periferije pa pokušava da pojača svoju osetljivost kako bi nadoknadio gubitak [4]. Prema ovom autoru to može dovesti do pojave tinitusa i hiperakuzije.

Kohlearna sinaptopatija predstavlja rani znak gubitka sluha koji pogađa jednu od 4 osobe starije od 45 godina sa još većom prevalencom kod pacijenata sa hroničnim bolestima [5]. Predstavlja oštećenje sinapsi između unutrašnjih trepljastih ćelija i vlakana slušnog nerva tako da sinaptopatija nastaje kada se prekine veza koja prenosi zvučne signale do mozga iako su senzorne ćelije u uhu ostale neoštećene. Prema izveštaju Svetske zdravstvene organizacije od 3. marta 2026. godine predikcija je da će do 2050. godine blizu 2.5 biliona ljudi imati neki stepen oštećenja sluha, a da će preko 700 miliona zahtevati neki vid slušne rehabilitacije [6]. Na osnovu nedavnih istraživanja prevalenca skrivenog gubitka sluha, kako je opisana od strane ispitanika sa prijavljenim teškoćama u razumevanju uprkos urednom pragu sluha, procenjena je na 12% – 15% [7,8].

Veliki broj istraživanja potvrdio je da gubitak sluha i nerazumevanje govora negativno utiče na mentalno zdravlje, ponašanje i kvalitet života i da povećava rizik od socijalne izolacije, anksioznosti i depresije [9,10]. Osobe sa ovim problemom potvrđuju da nedostatak informacija u razgovorima izaziva frustraciju i anksioznost koju povezuju sa potencijalno pogrešnim tumačenjem onoga što je rečeno [11]. Autori navode i izveštaje kli-

INTRODUCTION

Hidden hearing loss is a term recently used to describe an auditory disorder presumed to affect auditory-neural processing of sound signals and hearing acuity in individuals with normal pure-tone audiometry findings [1]. In classical sensorineural hearing loss caused by dysfunction or degenerative changes affecting the inner and outer rows of hair cells of the organ of Corti and/or the spiral ganglion, permanently elevated thresholds are observed on audiometric testing. However, in clinical practice, we frequently encounter patients who have normal auditory sensitivity but significant perceptual difficulties, including difficulty understanding speech in noisy environments. Such perceptual dysfunction is often referred to as an “auditory information processing disorder,” and defects in the central auditory pathways are considered to play a key role.

Although cochlear synaptopathy is often equated with hidden hearing loss, it is its primary pathophysiological mechanism, whereas hidden hearing loss is a broader clinical entity that may also result from other processes. Recent studies have shown that hidden hearing loss may also result from demyelination of the auditory nerve [2], degenerative changes in the auditory nerve [3], or neural gain, whereby the brain receives weaker signals from the periphery and attempts to increase its sensitivity in order to compensate for the loss [4]. According to this author, this may lead to tinnitus and hyperacusis.

Cochlear synaptopathy represents an early sign of hearing loss that affects one in four individuals over 45 years of age, with an even higher prevalence among patients with chronic diseases [5]. Synaptopathy involves damage to the synapses between inner hair cells and auditory nerve fibers; it occurs when the connection that transmits sound signals to the brain is disrupted, even though the sensory cells in the ear remain intact. According to a World Health Organization report dated March 3, 2026, by 2050 nearly 2.5 billion people will have some degree of hearing impairment, while more than 700 million will require some form of hearing rehabilitation [6]. Based on recent studies, the prevalence of hidden hearing loss, as described by participants reporting difficulties understanding speech despite normal hearing thresholds, has been estimated at 12%–15% [7,8].

A large number of studies have confirmed that hearing loss and difficulties understanding speech negatively affect mental health, behavior, and quality of life and increase the risk of social isolation, anxiety, and depression [9,10]. Individuals with this problem report that a lack of information during conversations causes frustration and anxiety, which they associate with the

ničara da nemaju dovoljno obuke i resursa za podršku ovim pacijentima, a kao glavni nedostatak navode nedostatak jedinstvenog i standardizovanog protokola za dijagnostiku i plan lečenja osoba sa ovim problemom.

U cilju obezbeđivanja sveobuhvatnog uvida u predmetnu materiju, sproveden je strukturirani pregled literature indeksirane u bazama *PubMed* i *SCIndeks*. Strategija pretraživanja obuhvatila je selekciju naučnih članaka primenom ključnih reči u korelaciji sa kohlearnom sinaptopatijom i kliničkim entitetom skrivenog gubitka sluha (npr. *“cochlear synaptopathy”*, *“hidden hearing loss”*). Kriterijumi za uključivanje literature obuhvatili su originalne naučne radove i pregledne članke publikovane na engleskom i srpskom jeziku koji primarno istražuju etiologiju, dijagnostiku i patofiziološke mehanizme ovih stanja. Sa druge strane, kriterijumi za isključenje odnosili su se na radove u obliku sažetaka sa konferencija, prikaze slučajeva (case reports), kao i studije sa neadekvatnom ili nejasnom metodologijom procene auditivne funkcije.

Polazeći od navedenog, cilj ovog preglednog rada je da na osnovu relevantne savremene literature pruži integrativni prikaz kohlearne sinaptopatije. Rad je fokusiran na tri ključna aspekta: analizu etiologije i molekularne patogeneze poremećaja, evaluaciju njegovog uticaja na centralno procesuiranje auditivnih informacija, kao i na kritički prikaz savremenih, objektivnih dijagnostičkih metoda namenjenih detekciji skrivenog gubitka sluha.

ANATOMIJA I FIZIOLOGIJA UHA – ČULO SLUHA

Čulo sluha spada u mehanoreceptore, što znači da se mehanička draž, u ovom slučaju zvuk, u receptoru kodira akcionim potencijalima nervnih vlakana [12] i predstavlja jedno od pet osnovnih ljudskih čula koje nam omogućava da primamo i interpretiramo zvučne talase iz okoline. Osnovna uloga sluha je da sve zvukove iz okoline prikupi, sprovede, dekodira i sistematizuje te tako ovaj proces rezultira obiljem informacija koje predstavljaju osnov za razvoj komunikacijskog sistema koji izdvaja čoveka kao posebnu vrstu [13].

Čulo sluha deli se na spoljašnje, srednje i unutrašnje uvo odakle se slušnim putem informacije prenose do centara u kori velikog mozga.

Spoljašnje uvo sastoji se od ušne školjke i spoljašnjeg slušnog hodnika na čijem kraju se nalazi bubna opna. Osnovna funkcija spoljašnjeg uva odnosi se na lokalizaciju zvuka u prostoru, zatim povećava zvučni pritisak za 12dB u frekventnom opsegu od 3000Hz do 4000Hz i štiti srednje uvo od traumatskih oštećenja [14].

Srednje uvo čini sistem šupljina ispunjenih vazduhom koje su povezane Eustahijevom tubom sa gornjim spratom ždrele – epifarinksom. Srednje uvo čini bubna duplja, lanac slušnih košćica, mastoidni nastavak i

potential misinterpretation of what has been said [11]. The authors also report that clinicians lack sufficient training and resources to support these patients, identifying the absence of a unified, standardized protocol for diagnosis and treatment planning as a major deficiency.

To provide a comprehensive overview, we conducted a structured review of the literature indexed in the PubMed and SCIndeks databases. The search strategy included selecting scientific articles using keywords related to cochlear synaptopathy and the clinical entity of hidden hearing loss (e.g., *“cochlear synaptopathy”*, *“hidden hearing loss”*). The inclusion criteria comprised original research articles and review articles published in English and Serbian that primarily investigated the etiology, diagnosis, and pathophysiological mechanisms of these conditions. The exclusion criteria included conference abstracts, case reports, and studies with inadequate or unclear methodology for assessing auditory function.

Based on the above, this review aims to provide an integrative overview of cochlear synaptopathy based on relevant contemporary literature. The paper focuses on three key aspects: an analysis of the disorder's etiology and molecular pathogenesis, an evaluation of its impact on central auditory processing, and a critical review of contemporary objective diagnostic methods for detecting hidden hearing loss.

ANATOMY AND PHYSIOLOGY OF THE EAR – THE SENSE OF HEARING

The sense of hearing belongs to the mechanoreceptors, meaning that a mechanical stimulus, in this case sound, is encoded in the receptor as action potentials of nerve fibers [12]. It represents one of the five basic human senses, enabling us to receive and interpret sound waves from the environment. Hearing's fundamental role is to collect, transmit, decode, and organize environmental sounds, producing an abundance of information that forms the basis of the communication system that distinguishes humans as a unique species [13].

The sense of hearing is divided into the external, middle, and inner ear, from which auditory information is transmitted via the auditory pathway to the centers in the cerebral cortex.

The external ear consists of the auricle and the external auditory canal, at the end of which is the tympanic membrane. The external ear's primary function is to localize sound in space; it also increases sound pressure by 12 dB within the frequency range of 3000 Hz to 4000 Hz and protects the middle ear from traumatic injury [14].

The middle ear consists of a system of air-filled cavities that are connected via the Eustachian tube

Eustahijeva tuba. Bubna opna i lanac slušnih koščica vrše funkciju akustičkog transformatora koji prenosi mehaničku energiju zvučnih talasa koji se prostiru kroz vazduh u mehaničku energiju zvučnih talasa koji se prostiru kroz tečnost kohlee sa najmanjim mogućim energetskim gubicima.

Unutrašnje uvo se sastoji od koštanog labirinta i membranoznog labirinta unutar koštanog. Koštani labirint se može podeliti na tri dela. Centralna struktura se naziva vestibulum (predvorje). Na njega se sa prednje strane nastavlja kohlea dok sa zadnje strane vestibuluma polaze tri polukružna kanala. S obzirom na temu naše interesovanje se usredsređuje na kohleu, kohlearni nerv i centralne slušne puteve.

Kohlea je 2,5 puta savijeni koštani kanal u obliku kućice puža po čemu i nosi ime. Sam kohlearni kanal je delimično pregrađen spiralnom laminom po sredini lumena celom dužinom kanala gde se pripajaju dve membrane– bazilarna i Rajsnerova membrana. Međuprostor između ivice spiralne lamine i lateralnog zida kohlearnog kanala premošćen je bazilarnom membranom dok ga Rajsnerova premošćuje koso naviše. Bazilarna i Rajsnerova membrana dele lumen kanala na tri skale – skalu vestibuli, skalu mediju i skalu timpani. Skala vestibuli i skala timpani su ispunjene perilimfom dok je skala medija ispunjena endolimfom. Skala vestibuli i skala timpani spojene su preko helikotrema na vrhu kohlee dok je skala medija zatvoren sistem i ne komunicira ni sa jednim drugim prostorom. U skali mediji, celom dužinom bazilarne membrane, smešten je Kortijev organ.

Senzorne ćelije Kortijevog organa su potpornim ćelijama pričvršćene za bazilarnu membranu i postavljene u jedan unutrašnji red ćelija kojih ima oko 3500 i tri reda spoljašnjih ćelija kojih ima oko 13000. Na vrhu senzornih ćelija nalaze se cilije poredane po visini koje su spojene postraničnim i vršnim vezama tako da prate pokrete jedna druge. Iznad senzornih ćelija nalazi se tekotorijalna membrana koja gradi krov Kortijevog organa. Pri pomeranju bazilarne membrane dolazi do smicajućih pokreta tekotorijalne membrane i stereocilija tj. najviše stereocilije – kinocilije ćelija spoljašnjih redova što rezultira otvaranjem kanala na vrhu stereocilija. Stereocilije unutrašnjih senzornih ćelija dopiru skoro do tekotorijalne membrane, ali nisu u direktnom kontaktu sa njom već se savijaju usled kretanja endolimfe koju pokreće tekotorijalna membrana [15].

Perilimfa je tipična ekstracelularna tečnost bogata jonima natrijuma (Na⁺) dok ima nizak sadržaj jona kalijuma (K⁺). Sa druge strane endolimfa je jedinstvena među ekstracelularnim tečnostima po tome što je njena koncentracija kalijumovih jona veća od koncentracije natrijumovih jona. Proces formiranja endolimfe i održavanje u jonskom sastavu između nje i perilimfe

to the upper part of the pharynx–the epipharynx. The middle ear comprises the tympanic cavity, the chain of auditory ossicles, the mastoid process, and the Eustachian tube. The tympanic membrane and the chain of auditory ossicles function as an acoustic transformer that transmits the mechanical energy of sound waves propagating through air into the mechanical energy of sound waves propagating through the fluid of the cochlea, with minimal energy loss.

The inner ear consists of the bony labyrinth and the membranous labyrinth located within it. The bony labyrinth can be divided into three parts. The central structure is called the vestibule. The cochlea extends from its anterior aspect, while three semicircular canals arise from its posterior aspect. Given our subject of interest, we focus on the cochlea, the cochlear nerve, and the central auditory pathways.

The cochlea is a bony canal coiled 2.5 turns in the shape of a snail shell, from which it derives its name. The cochlear canal is partially divided by the spiral lamina along the middle of the lumen throughout the entire length of the canal, where two membranes–the basilar membrane and Reissner's membrane–are attached. The space between the edge of the spiral lamina and the lateral wall of the cochlear canal is bridged by the basilar membrane, while Reissner's membrane bridges it obliquely upward. The basilar and Reissner's membranes divide the lumen of the canal into three scales–the scala vestibuli, scala media, and scala tympani. The scala vestibuli and scala tympani are filled with perilymph, whereas the scala media is filled with endolymph. The scala vestibuli and scala tympani are connected through the helicotrema at the apex of the cochlea, while the scala media is a closed system and does not communicate with any other space. The organ of Corti is located within the scala media along the entire length of the basilar membrane.

The sensory cells of the organ of Corti are attached to the basilar membrane by supporting cells and are arranged in a single inner row containing approximately 3,500 cells and three rows of outer cells containing approximately 13,000 cells. At the apical surface of the sensory cells are cilia arranged according to height and connected by lateral and tip links, allowing them to follow one another's movements. Above the sensory cells is the tectorial membrane, which forms the roof of the organ of Corti. When the basilar membrane moves, shearing movements occur between the tectorial membrane and the stereocilia, i.e., the tallest stereocilia–the kinocilia–of the outer rows of cells, resulting in the opening of channels at the tips of the stereocilia. The stereocilia of the inner sensory cells extend almost to the tectorial membrane but are not in direct contact with it; instead, they

još uvek nisu u potpunosti objašnjeni. Rajsnerova membrana formira selektivnu barijeru između dve tečnosti i dokazi ukazuju na to da se endolimfa proizvodi iz perilimfe kao rezultat selektivnog transporta jona kroz epitelne ćelije Rajsnerove membrane, a ne direktno iz krvi [16]. U mirovanju unutar senzornih ćelija potencijal je negativan: oko -45 mV kod unutrašnjih i -70 mV kod spoljašnjih senzornih ćelija dok je u endolimfi pozitivan potencijal od oko $+80$ mV. Razlika u potencijalu između endolimfe i intracelularnog prostora je 125 mV ili 150 mV što predstavlja veliku razliku u potencijalu i od velikog je značaja za hemijske procese u senzornim ćelijama [15]. Prilikom otvaranja kanala na vrhu stereocilija dolazi do ulaska pozitivnih jona kalijuma, ćelija se depolarise, luči neurotransmiter u sinaptičku pukotinu i dolazi do okidanja akcionog potencijala. Na taj način odvija se proces transdukcije – pretvaranje mehaničke energije u akcioni potencijal [17].

Kohlearni kanal je savijen oko koštanog stuba koji se naziva mediolus ili stožer. U mediolusu se nalazi sistem kanala u kojima su smeštena tela bipolarnih nervnih ćelija koje čine spiralni ganglion. To je zapravo početna tačka kohlearnog nerva. Kohlearni nerv sadrži oko 30000 vlakana, od kojih su skoro sva aferentna i skoro sva polaze sa unutrašnjih senzornih ćelija. Pored aferentnih postoji i mali broj eferentnih vlakana kohlearnog nerva što znači da oni sprovode informacije od mozga do kohlee. Njih ima samo nekoliko stotina i završavaju na senzornim ćelijama spoljašnjih redova [12]. Čak 95% aferentnih vlakana slušnog nerva povezano je sa unutrašnjim senzornim ćelijama pri čemu svaka ćelija ostvaruje 10 – 30 sinaptičkih veza zavisno od lokacije [18]. Prema ovim autorima najveći broj sinapsi nalazi se u regiji unutrašnjih senzornih ćelija najosetljivijih na zvuk (kod ljudi je to oblast srednjih frekvencija) dok ćelije koje detektuju veoma visoke i veoma niske frekvencije često imaju manji broj sinapsi od onih u sredini. Sa spoljašnjih ćelija polazi preostalih 5% aferentnih vlakana i ovde je situacija suprotna. Naime, senzorne ćelije spoljašnjih redova ostvaruju znatno manji broj sinapsi 2 – 3 i jedno nervno vlakno se grana i prikuplja informacije sa više senzornih ćelija.

Još davne 1978. godine Čarls Liberman je objavio rezultate istraživanja na slušnom nervu mačaka [19]. Ovo je pionirski rad koji je definisao tri grupe vlakana na osnovu spontanog ritma (niski, srednji i visoki) i povezao ih sa pragovima osetljivosti. Naime, vlakna visokog spontanog ritma čine 60% aferentnih vlakana koja polaze sa unutrašnjih senzornih ćelija i omogućavaju detekciju zvuka u tišini. Vlakna niskog spontanog ritma čine 15% aferentnih vlakana i ključna su za razumevanje govora u buci dok vlakna srednjeg spontanog ritma (preostalih 25%) omogućavaju mozgu da razlikuje

bend as a result of the movement of the endolymph induced by the tectorial membrane [15].

Perilymph is a typical extracellular fluid rich in sodium ions (Na^+), while it has a low concentration of potassium ions (K^+). In contrast, endolymph is unique among extracellular fluids because its potassium ion concentration is higher than its sodium ion concentration. The process of endolymph formation and maintenance of its ionic composition relative to perilymph has not yet been fully elucidated. Reissner's membrane forms a selective barrier between the two fluids, and evidence indicates that endolymph is produced from perilymph as a result of selective ion transport through the epithelial cells of Reissner's membrane, rather than directly from the blood [16]. At rest, the potential within the sensory cells is negative: approximately -45 mV in inner sensory cells and -70 mV in outer sensory cells, whereas the endolymph potential is positive, at approximately $+80$ mV. The potential difference between the endolymph and the intracellular space is 125 mV or 150 mV, a large difference that is important for the chemical processes occurring in sensory cells [15]. When channels at the tips of the stereocilia open, positively charged potassium ions enter the cell, causing depolarization, the release of neurotransmitters into the synaptic cleft, and the generation of an action potential. This is the process of transduction—the conversion of mechanical energy into an action potential [17].

The cochlear canal coils around a bony core called the modiolus, or central pillar. The modiolus contains a system of canals in which the cell bodies of bipolar nerve cells forming the spiral ganglion are located. This is essentially the starting point of the cochlear nerve. The cochlear nerve contains approximately $30,000$ fibers, almost all of which are afferent and originate from the inner sensory cells. In addition to afferent fibers, there is also a small number of efferent fibers in the cochlear nerve, meaning that they transmit information from the brain to the cochlea. There are only several hundred of them, and they terminate on the sensory cells of the outer rows [12]. As many as 95% of the afferent fibers of the auditory nerve are connected to inner sensory cells, with each cell forming 10 – 30 synaptic connections depending on its location [18]. According to these authors, the greatest number of synapses is found in the region of the inner sensory cells most sensitive to sound (in humans, this is the middle-frequency region), whereas cells detecting very high and very low frequencies often have fewer synapses than those in the middle. The remaining 5% of afferent fibers originate from the outer cells, where the situation is reversed. Namely, the sensory cells of the outer rows form significantly fewer synapses (2 – 3),

nijanse između umereno tihih i umereno glasnih zvukova. Bez njih prelaz sa tihih na glasne zvukove bio bi nagao i neprecizan.

U godinama koje su usledile Liberman je sa saradnicima vršio istraživanja različitih uticaja na senzorne ćelije i ćelije spiralnog gangliona došavši do zaključka da izloženost buci, prirodan proces starenja i ototoksični lekovi dovode do trajnih oštećenja prvenstveno sinapsi između unutrašnjih senzornih ćelija i vlakana niskog spontanog ritma, a zatim i srednjeg spontanog ritma [20–22]. Iz tog razloga vlakna visokog spontanog ritma detektuju tihe zvuke, a oštećenje sinapsi ostaje sakriveno iza urednih vrednosti na audiometrijskom nalazu. Tako su 2009. godine Kujawa i Liberman dokazali da buka koja izaziva privremeni gubitak sluha zapravo trajno uništava sinapse. Termin koji su koristili je primarna neuralna degeneracija dok je sam termin kohlearna sinaptopatija tek 2013. godine upotrebljen kako bi se preciznije definisao skriveni gubitak sluha [23]. Od tada ovaj termin je opšte prihvaćen i postaje standard u literaturi.

DIJAGNOSTIČKE METODE

U Srbiji je zvanično u upotrebi MKB-10 (Međunarodna klasifikacija bolesti 10. revizije) kao važeći sistem šifriranja u zdravstvenom sistemu. Najnovija verzija MKB-11, usvojena je na 72. Svetskoj zdravstvenoj skupštini 2019. godine i stupila je na snagu 1. januara 2022. godine [24]. Iako je ova revizija zvanično stupila na snagu, države članice se nalaze u različitim fazama implementacije jer prelazak zahteva korenite izmene u informacionim sistemima i obuku osoblja. U 11. reviziji Svetska zdravstvena organizacija je uvela znatno preciznije kategorije pa tako MKB-11 sadrži zvaničnu šifru AB57: auditivna sinaptopatija ili neuropatija (Auditory synaptopathy or neuropathy). Kako se navodi u klasifikaciji ova šifra se odnosi na nedostatak sinhronizacije neuralnog prenosa slušnih informacija zbog oštećenja unutrašnjih senzornih ćelija i njihovih sinapsi ili ćelija spiralnog gangliona i kohleranog živca uz očuvanu funkciju spoljašnjih redova senzornih ćelija.

U svetu još uvek ne postoji jedinstveni dijagnostički zlatni standard za definitivnu potvrdu kohlearne sinaptopatije kod ljudi, zbog čega se dijagnoza postavlja indirektno, kombinacijom različitih elektrofizioloških i bihevioralnih testova. Tokom inicijalnog pregleda izvodi se tonalna liminarna audiometrija koja uglavnom pokazuje urednu slušnu osetljivost bez povišenih pragova na audiometrijskom nalazu. S obzirom da se pacijenti najčešće žale na nerazumevanje govora u bučnim sredinama veliki broj istraživanja kao ključni funkcionalni test navode govornu audiometriju u buci, zatim evocirane potencijale moždanog stabla, elektrokohleografi-

and a single nerve fiber branches and collects information from multiple sensory cells.

As early as 1978, Charles Liberman published the results of research on the auditory nerve of cats [19]. This pioneering study defined three fiber groups based on spontaneous firing rate (low, medium, and high) and associated them with sensitivity thresholds. Specifically, high-spontaneous-rate fibers account for 60% of afferent fibers originating from inner sensory cells and enable sound detection in silence. Low-spontaneous-rate fibers account for 15% of afferent fibers and are essential for understanding speech in noise, whereas medium-spontaneous-rate fibers (the remaining 25%) enable the brain to distinguish nuances between moderately quiet and moderately loud sounds. Without them, the transition from quiet to loud sounds would be abrupt and imprecise.

In the years that followed, Liberman and his colleagues investigated various effects on sensory cells and spiral ganglion cells and concluded that exposure to noise, the natural aging process, and ototoxic drugs cause permanent damage, primarily to the synapses between inner sensory cells and low-spontaneous-rate fibers, followed by damage to medium-spontaneous-rate fibers [20–22]. For this reason, high-spontaneous-rate fibers detect quiet sounds, while synaptic damage remains hidden behind normal values on audiometric testing. Thus, in 2009, Kujawa and Liberman demonstrated that noise exposure causing temporary hearing loss actually permanently destroys synapses. They used the term primary neural degeneration, whereas cochlear synaptopathy was not used until 2013, when it was introduced to more precisely define hidden hearing loss [23]. Since then, this term has been widely accepted and has become standard in the literature.

DIAGNOSTIC METHODS

In Serbia, the ICD-10 (International Classification of Diseases, 10th Revision) is officially in use as the valid coding system in the healthcare system. The latest version, ICD-11, was adopted at the 72nd World Health Assembly in 2019 and came into effect on January 1, 2022 [24]. Although this revision officially came into effect, Member States are at different stages of implementation because the transition requires fundamental changes to information systems and staff training. In the 11th revision, the World Health Organization introduced considerably more precise categories; thus, ICD-11 contains the official code AB57: auditory synaptopathy or neuropathy (Auditory synaptopathy or neuropathy). As stated in the classification, this code refers to a lack of synchronization of the neural transmission of auditory information due to damage to the

ju i u poslednje vreme koristi se testiranje amplitude i praga akustičkog refleksa mišića srednjeg uva [25,26].

Govorna audiometrija predstavlja metodu ispitivanja sluha, odnosno sposobnost razumevanja reči van konteksta neke rečenice, tj. izolovano izgovorenih reči. Razumevanje govora podrazumeva percepciju zvučnog stimulusa, kao i prepoznavanje i razumevanje govorne poruke. Da bi se postiglo razumevanje govorne poruke potrebna je očuvanost svih struktura koje učestvuju u prijemu, prenosu i razumevanju sagovornika, a to su očuvanost čula sluha, auditivnog puta, primarnih i sekundarnih kortikalnih centara, tercijarnih asocijativnih kortikalnih oblasti, kao i kognitivnih sposobnosti. Ukoliko postoje lezije na nekim od ovih struktura doći će do teškoća u razumevanju govorne poruke [27].

Tokom izvođenja govorne audiometrije u buci ključan je odnos jačine stimulusa (govora) i pozadinskog šuma – SNR (signal/noise ratio). Matematički to je jednostavna razlika između jačine govora i jačine buke i izračunava se po formuli: $SNR = \text{jačina govora (dB)} - \text{jačina buke (dB)}$. Nulti SNR (0 dB) predstavlja odnos gde su govor i buka iste jačine. Kod testiranja kohlearne sinaptopatije ključno je koristiti niske ili negativne SNR uslove npr. (0 dB ili -5 dB). Osobe sa sinaptopatijom prikazaće drastičan pad u razumevanju reči čim se SNR smanji, iako im je prag sluha urednih vrednosti [28].

Za kompletnu kliničku evaluaciju kohlearne sinaptopatije od izuzetnog značaja je primena i drugih specifičnih metoda. U tom kontekstu, bihevioralni testovi vremenske rezolucije, poput *Gaps-in-Noise (GIN)* testa, omogućavaju preciznu procenu sposobnosti procesiranja vremenskog aspekta zvuka koji je često narušen kod skrivenog gubitka sluha. Sa druge strane, psihoakustičko ispitivanje u vidu proširene visokofrekventne audiometrije (iznad 8 kHz) predstavlja izuzetno senzitivnu metodu za detekciju ranih faza oštećenja sinapsi pre nego što se jave promene na standardnim audiometrijskim frekvencijama.

Auditivni evocirani potencijali. Postoji veći broj termina koji se odnose na ispitivanje auditivnih odgovora moždanog stabla, a svi oni proističu iz različitih skraćenica na engleskom jeziku [14]. Tako se u literaturi mogu sresti različite skraćenice: ABR – Auditory Brainstem Response (auditivni odgovor moždanog stabla), BERA – Brainstem Evoked Response Audiometry (audiometrija evociranih odgovora moždanog stabla), BAEP – Brainstem Auditory Evoked Potentials (auditivni evocirani potencijali moždanog stabla) koje, u stvari, znače isto, a predstavljaju objektivnu metodu za ispitivanje sluha koja beleži nervnu aktivnost od kohlee duž slušnog puta do vrha moždanog stabla [12].

Test podrazumeva postavljanje elektroda na čelo i mastoidni nastavak kako bi se zabeležila električna ak-

inner sensory cells and their synapses or to the cells of the spiral ganglion and cochlear nerve, with preserved function of the outer rows of sensory cells.

No single diagnostic gold standard exists worldwide for definitive confirmation of cochlear synaptopathy in humans; therefore, clinicians establish the diagnosis indirectly through a combination of electrophysiological and behavioral tests. During the initial examination, pure-tone audiometry is performed, which generally shows normal auditory sensitivity without elevated thresholds on the audiometric findings. Given that patients most commonly complain of difficulty understanding speech in noisy environments, a large number of studies identify speech audiometry in noise as a key functional test, followed by auditory brainstem responses, electrocochleography, and, more recently, assessment of the amplitude and threshold of the acoustic reflex of the middle-ear muscles [25,26].

Speech audiometry is a method of hearing assessment, i.e., the ability to understand words outside the context of a sentence, namely, individually spoken words. Speech understanding involves perceiving an auditory stimulus and recognizing and comprehending a spoken message. In order to achieve comprehension of a spoken message, the integrity of all structures involved in the reception, transmission, and comprehension of the speaker must be preserved. These include the sense of hearing, the auditory pathway, the primary and secondary cortical centers, the tertiary associative cortical areas, and cognitive abilities. If lesions are present in any of these structures, difficulties in understanding a spoken message will occur [27].

During speech audiometry in noise, the key parameter is the relationship between stimulus (speech) intensity and background noise–SNR (signal-to-noise ratio). Mathematically, this is the simple difference between speech intensity and noise intensity and is calculated using the formula: $SNR = \text{speech intensity (dB)} - \text{noise intensity (dB)}$. A zero SNR (0 dB) represents a ratio in which speech and noise are of equal intensity. When testing for cochlear synaptopathy, it is essential to use low or negative SNR conditions, e.g., 0 dB or -5 dB. Individuals with synaptopathy will show a drastic decline in word recognition as SNR decreases, even though their hearing thresholds are within normal limits [28].

For a complete clinical evaluation of cochlear synaptopathy, the application of other specific methods is also of great importance. In this context, behavioral tests of temporal resolution, such as the *Gaps-in-Noise (GIN)* test, enable precise assessment of the ability to process the temporal aspects of sound, which is often impaired in hidden hearing loss. On the other hand, psychoacoustic testing in the form of extended high-frequency audiom-

tivnost mozga kao odgovor na slušne stimuluse, često predstavljene kao klikovi ili tonovi. Ovaj snimljeni neuronski odgovor se pažljivo analizira kako bi se identifikovali različiti talasi koji odgovaraju različitim fazama slušne obrade u moždanom stablu. Ispitivanjem latencija i amplituda ovih talasa, lekari mogu da utvrde prisustvo i lokaciju abnormalnosti, bacajući svetlo na prirodu i obim oštećenja sluha, nervne disfunkcije, pa čak i suptilne lezije moždanog stabla [29].

Istraživanja su pokazala da se na ovaj način kod urednog sluha u prvih 10ms dobija sedam karakterističnih talasa koji se obeležavaju rimskim brojevima. Posebno stabilni i zato klinički značajni su prvih pet talasa i među njima se izdvajaju prvi – I, treći – III i peti – V talas [12]. Prvi talas je odraz aktivnosti u kohlearnom živcu u nivou kohlee i latenca – vremenski interval od klika do vrha talasa je oko 2 ms. S obzirom na temu naše istraživanje se usredsređuje na amplitudu i latencu samo prvog talasa.

Talas I predstavlja elektro-fiziološki korelat sumiranog akcionog potencijala distalnog segmenta slušnog nerva [30]. Formiranje ovog talasa inicirano je mehanoreceptorskom aktivacijom unutrašnjih trepljastih ćelija, koje usled akustičke stimulacije oslobađaju neurotransmitter – glutamat u sinaptičku pukotinu. Vezivanjem neurotransmitera za postsinaptičke receptore aferentnih vlakana spiralnog gangliona dolazi do sinhrona depolarizacije neurona i okidanja akcionog potencijala na slušnom nervu [31]. Tokom testa koristi se klik stimulus koji je kratak i nagao što tera veliki broj neurona na istovremenu reakciju. Pri niskim intenzitetima zvuka talas I je jedva uočljiv jer reaguju samo vlakna visokog spontanog ritma [19]. Kako se zvuk pojačava (preko 70–80 dB HL) aktiviraju se i vlakna niskog spontanog ritma. Tek kada se aktiviraju oba tipa vlakana zajedno dobijamo maksimalnu amplitudu talasa I [23,32].

Pokazatelj kohlearne sinaptopatije na ABR testu jeste pad amplitude talasa I pri visokim intenzitetima stimulacije, dok latenca ovog talasa ostaje nepromenjena [22]. Autori navode da vlakna visokog spontanog ritma ostaju neoštećena te i dalje uredno provode impuls tako da informacija stiže do elektrode tačno na vreme. Brzina provođenja impulsa kroz preostala vlakna nije usporena pa samim tim nema ni produženja latence.

U osnovi kohlearne sinaptopatije leži glutamatergična eksitotoksičnost; usled nemogućnosti brzog uklanjanja viška glutamata pri glasnim zvucima (preko 80–90 dB HL), dolazi do patološkog priliva jona u postsinaptičke terminale. Sinaptopatija selektivno uništava sinapse na vlaknima niskog spontanog ritma koja imaju visok prag aktivacije i reaguju tek na glasne zvuke. Zbog toga izostaje njihov doprinos pa je ukupni sumirani akcioni potencijal, odnosno amplituda talasa I znatno manja nego kod zdravog uva [23].

etry (above 8 kHz) represents a highly sensitive method for detecting early stages of synaptic damage before changes occur at standard audiometric frequencies.

Auditory evoked potentials. Several terms refer to the assessment of auditory brainstem responses, each derived from different English abbreviations [14]. Thus, various abbreviations can be found in the literature: ABR – Auditory Brainstem Response, BERA – Brainstem Evoked Response Audiometry, BAEP – Brainstem Auditory Evoked Potentials, etc., which, in fact, mean the same thing and represent an objective method for hearing assessment that records neural activity from the cochlea along the auditory pathway to the upper part of the brainstem [12].

The test involves placing electrodes on the forehead and mastoid process to record the brain's electrical activity in response to auditory stimuli, often presented as clicks or tones. This recorded neural response is carefully analyzed in order to identify different waves corresponding to different stages of auditory processing in the brainstem. By examining the latencies and amplitudes of these waves, physicians can determine the presence and location of abnormalities, shedding light on the nature and extent of hearing impairment, neural dysfunction, and even subtle brainstem lesions [29].

Studies have shown that, in individuals with normal hearing, seven characteristic waves are obtained within the first 10 ms, designated by Roman numerals. The first five waves are particularly stable and therefore clinically significant, among which waves I, III, and V are distinguished [12]. Wave I reflects activity in the cochlear nerve at the level of the cochlea, and its latency—the time interval from the click to the peak of the wave—is approximately 2 ms. Given the focus of our study, we focus only on the amplitude and latency of wave I.

Wave I represents the electrophysiological correlate of the summed action potential of the distal segment of the auditory nerve [30]. The formation of this wave is initiated by mechanoreceptor activation of the inner hair cells, which, in response to acoustic stimulation, release the neurotransmitter glutamate into the synaptic cleft. Binding of the neurotransmitter to postsynaptic receptors of the afferent fibers of the spiral ganglion leads to synchronous depolarization of the neurons and the generation of an action potential in the auditory nerve [31]. During the test, a brief, abrupt click stimulus causes many neurons to respond simultaneously. At low sound intensities, wave I is barely detectable because only high-spontaneous-rate fibers respond [19]. As the sound intensity increases (above 70–80 dB HL), low-spontaneous-rate fibers are also activated. Only when both fiber types are activated together is the maximum amplitude of wave I obtained [23,32].

Karakteristike talasa I, prvenstveno njegova amplituda pri visokim intenzitetima stimulacije, direktno odražavaju gustinu i funkcionalni integritet ovih bazičnih sinaptičkih spojeva, čineći ga primarnim biomarkerom u istraživanju kohlearne sinaptopatije [33].

Elektrokohleografija (ECoG) predstavlja objektivnu elektrofiziološku metodu koja registruje najranije električne potencijale kohlee i inicijalnog segmenta slušnog živca, što direktno odgovara talasu I auditivnih potencijala moždanog stabla [22]. Ključna prednost ove metode u kontekstu istraživanja kohlearne sinaptopatije, odnosno skrivenog gubitka sluha, ogleda se u njenoj sposobnosti da izoluje funkcionalni status unutrašnjih senzornih ćelija i njihovih pripadajućih sinaptičkih veza sa aferentnim vlaknima slušnog živca [33]. ECoG signal se sastoji od tri komponente: kohlearnog mikrofonizma (CM), sumacionog potencijala (SP) i akcionog potencijala (AP). Dok su generatori CM i SP locirani u receptorima – unutrašnjim i spoljašnjim senzornim ćelijama, AP direktno odražava sinhronu depolarizaciju vlakana slušnog nerva. Kod kohlearne sinaptopatije uočava se specifičan patofiziološki profil: pošto su same unutrašnje senzorne ćelije očuvane, amplituda sumacionog potencijala ostaje u granicama normale. Međutim, usled selektivnog propadanja sinapsi i gubitka vlakana niskog spontanog ritma, dolazi do drastičnog smanjenja amplitude akcionog potencijala pri visokim intenzitetima stimulacije [23]. Posledično, ovaj selektivni pad amplitude dovodi dospecifičnog rasta matematičkog odnosa SP/AP [34]. Klinički i istraživački značaj ECoG-a leži upravo u prepoznavanju ovog specifičnog šablona – normalan SP uz redukovan AP – što u praksi omogućava diferenciranje sinaptopatije od Menijerove bolesti kod kojeg povišen SP/AP odnos nastaje primarno zbog patološkog rasta same SP komponente [35].

Stapedijalni refleksi je nevoljna kontrakcija mišića srednjeg uva m. stapedijusa (*m. stapedius*) koja se javlja kao zaštitni mehanizam pri izlaganju glasnim zvucima. Zvuk jačine 70-80 dB refleksno ukružuje lanac slušnih košćica prigušujući prenos zvučnih talasa ka unutrašnjem uvu [36].

Stapedijalni refleks se prvenstveno aktivira preko vlakana niskog spontanog ritma koja imaju visok prag aktivacije i reaguju tek na glasne zvuke. Upravo ova vlakna, kako je već naglašeno, su najosetljivija na oštećenja izazvana bukom ili starenjem i prva stradaju u procesu sinaptopatije. Kod osoba sa ovim stanjem, pragovi za izazivanje stapedijalnog refleksa mogu biti povišeni, dok amplituda i rast snage refleksa slabe [37].

Iako je u eksperimentalnim studijama na životinjama dokazano da je refleks mišića srednjeg uva visoko osetljiv marker za rano prepoznavanje oštećenja sinapsi slušnog živca [38] njegova primena kod ljudi još uvek je u fazi istraživanja.

An indicator of cochlear synaptopathy on the ABR test is a decrease in the amplitude of wave I at high stimulus intensities, while its latency remains unchanged [22]. The authors state that high-spontaneous-rate fibers remain undamaged and therefore continue to conduct impulses normally, so that the information reaches the electrode at the expected time. The conduction velocity of impulses through the remaining fibers is not reduced and, consequently, there is no prolongation of latency.

The underlying mechanism of cochlear synaptopathy is glutamatergic excitotoxicity; because the cochlea cannot rapidly remove excess glutamate during exposure to loud sounds (above 80–90 dB HL), ions pathologically influx into the postsynaptic terminals. Synaptopathy selectively destroys synapses on low-spontaneous-rate fibers, which have a high activation threshold and respond only to loud sounds. Consequently, their contribution is absent, and the total summed action potential, i.e., the amplitude of wave I, is significantly lower than in a healthy ear [23].

The characteristics of wave I, particularly its amplitude at high stimulus intensities, directly reflect the density and functional integrity of these fundamental synaptic connections, making it a primary biomarker for investigating cochlear synaptopathy [33].

Electrococleography (ECoG) is an objective electrophysiological method that records the earliest electrical potentials of the cochlea and the initial segment of the auditory nerve, which directly corresponds to wave I of the auditory brainstem potentials [22]. The key advantage of this method for investigating cochlear synaptopathy, i.e., hidden hearing loss, is its ability to isolate the functional status of the inner sensory cells and their associated synaptic connections with the afferent fibers of the auditory nerve [33]. The ECoG signal consists of three components: the cochlear microphonic (CM), the summing potential (SP), and the action potential (AP). While the generators of CM and SP are located in the receptors – the inner and outer sensory cells – the AP directly reflects the synchronous depolarization of auditory nerve fibers. In cochlear synaptopathy, a specific pathophysiological profile is observed: because the inner sensory cells themselves are preserved, the amplitude of the summing potential remains within the normal range. However, because synapses selectively degenerate and low-spontaneous-rate fibers are lost, the action-potential amplitude drops drastically at high stimulus intensities [23]. Consequently, this selective amplitude decrease leads to a specific increase in the mathematical SP/AP ratio [34]. The clinical and research significance of ECoG lies precisely in the identification of this specific pattern – normal SP with reduced AP –

Tabela 1. Usporedni prikaz očekivanih dijagnostičkih nalaza kod zdravog uva i uva sa kohlearnom sinaptopatijom

Dijagnostička metoda	Nalaz kod zdravog uva	Nalaz kod uva sa kohlearnom sinaptopatijom
Tonalna liminarna audiometrija (ADG)	Uredan prag sluha (0–20 dB) na svim standardnim frekvencijama	Uredan prag sluha (0–20 dB) na svim standardnim frekvencijama
Proširena visokofrekventna audiometrija	Očuvani pragovi čujnosti na visokim frekvencijama	Povišenje pragova čujnosti iznad 8kHz
Govorna audiometrija u buci	Visok procenat razumevanja reči; stabilan i uredan SNR prag	Drastičan pad u razumevanju reči sa smanjenjem ili negativnim vrednostima SNR-a
Auditivni evocirani potencijali (ABR)	Uredne amplitude i latencije svih talasa (I–V) pri visokim intenzitetima (80–90 dB HL)	Selektivno smanjenje amplitude talasa I pri visokim intenzitetima stimulusa uz očuvane latencije
Elektrokohleografija (EcochG)	Uredan odnos amplituda sumacionog i akcionog potencijala (SP/AP)	Značajno povišen odnos amplituda SP/AP usled redukcije amplitude akcionog potencijala
Akustički (stapedijalni) refleksi	Uredan prag izazivanja refleksa na standardnim intenzitetima	Povišeni pragovi ili potpuno odsustvo refleksa, praćeno bržim zamorom (<i>decay</i>) refleksa
Testovi vremenske rezolucije (GIN test)	Uredan (nizak) prag detekcije pauze u šumu	Povišen prag detekcije pauze

Table 1. Comparison of expected diagnostic findings in a healthy ear and an ear with cochlear synaptopathy

Diagnostic method	Findings in a healthy ear	Findings in an ear with cochlear synaptopathy
Pure-tone audiometry (ADG)	Normal hearing thresholds (0–20 dB) at all standard frequencies	Normal hearing thresholds (0–20 dB) at all standard frequencies
Extended high-frequency audiometry	Preserved hearing thresholds at high frequencies	Elevated hearing thresholds above 8 kHz
Speech audiometry in noise	High percentage of word recognition; stable and normal SNR threshold	Drastic decline in word recognition with decreasing or negative SNR values
Auditory evoked potentials (ABR)	Normal amplitudes and latencies of all waves (I–V) at high intensities (80–90 dB HL)	Selective reduction in the amplitude of wave I at high stimulus intensities with preserved latencies
Electrocochleography (ECoG)	Normal amplitude ratio of the summing potential to the action potential (SP/AP)	Significantly elevated SP/AP amplitude ratio due to a reduction in action potential amplitude
Acoustic (stapedial) reflex	Normal reflex elicitation threshold at standard intensities	Elevated thresholds or complete absence of the reflex, accompanied by more rapid reflex decay
Temporal resolution tests (GIN test)	Normal (low) gap-detection threshold in noise	Elevated gap-detection threshold

SAVREMENI TERAPIJSKI PRISTUPI

Tehnološka i amplifikaciona rešenja

S obzirom da u trenutnoj kliničkoj praksi ne postoje odobreni farmakološki protokoli za kauzalno lečenje, odnosno za direktnu strukturnu obnovu oštećenih sinapsi, savremeni tretman kohlearne sinaptopatije primarno je usmeren na ublažavanje pratećih simptoma. Kako je audiogram kod ovih pacijenata po pravilu uredan, terapijska paradigma se ne fokusira na pojačavanje pragova čujnosti, već na poboljšanje funkcionalnog sluha u nepovoljnim akustičkim uslovima.

Primarni problem pacijenata sa sinaptopatijom nije nemogućnost detekcije zvuka, već nemogućnost izdvajanja korisnog signala (govora) iz pozadinske buke. U ovakvim situacijama od velike pomoći mogu biti slušni aparati sa uskopojasnim direkcionim mikrofona i digitalnom redukcijom šuma. Pored slušnih aparata mogu se koristiti i bežični FM sistemi. Ovi uređaji detektuju glas govornika putem mikrofona koji je

which in practice enables differentiation of synaptopathy from Ménière's disease, in which an elevated SP/AP ratio occurs primarily due to a pathological increase in the SP component itself [35].

The stapedius reflex is an involuntary contraction of the middle-ear muscle *m. stapedius* that occurs as a protective mechanism during exposure to loud sounds. A sound intensity of 70–80 dB reflexively stiffens the chain of auditory ossicles, attenuating the transmission of sound waves to the inner ear [36].

The stapedius reflex is primarily activated through low-spontaneous-rate fibers, which have a high activation threshold and respond only to loud sounds. As noted, these fibers are most susceptible to damage from noise or aging and are the first to be affected in synaptopathy. In individuals with this condition, the thresholds for eliciting the stapedius reflex may be elevated, while the amplitude and growth of reflex strength are reduced [37].

postavljen u blizini ili pričvršćen na govorniku i prenosi signal direktno u uvo pacijenta putem zvučnika ili preko bežične veze sa slušnim aparatom [39].

Klinička primarna prevencija i otoprotekcija

U kontekstu prevencije trajnih auditivnih disfunkcija, važnu ulogu za lekare praktičare ima primarna prevencija neposredno pre ili nakon akustičke traume. Kliničke studije ukazuju na to da primena farmakološke antioksidativne zaštite – prvenstveno visokih doza vitamina A, C i E, kao i N-acetilcisteina (NAC) – može ublažiti oksidativni stres i eksitotoksičnost u unutrašnjem uhu. Ovi antioksidativni protokoli pokazali su potencijal u očuvanju integriteta trakastih (*ribbon*) sinapsi ukoliko se primene unutar ranog terapijskog prozora nakon izloženosti buci [40].

Eksperimentalni farmakološki pristupi (Klinička ispitivanja)

Trenutno se u svetu dve farmaceutske kompanije nalaze u različitim fazama razvoja potencijalnih terapijskih rešenja koja ciljaju direktnu obnovu oštećenih sinapsi između unutrašnjih senzornih ćelija i vlakana slušnog nerva. Međutim, važno je naglasiti da su ovi farmakološki pristupi još uvek u eksperimentalnoj fazi i da njihova klinička efikasnost kod ljudi tek treba da bude potvrđena kroz dalja detaljna istraživanja.

Nemačka farmaceutska kompanija AudioCure vrši testiranje leka pod nazivom AC 102 i trenutno se čeka objava rezultata završene Faze 2. U ovoj fazi vršena je ocena efikasnosti, bezbednosti i podnošljivosti pojedinačne intratimpanične doze leka u poređenju sa oralnim kortikosteroidima – sadašnjim standardom lečenja iznenadnog idiopatskog sensorineuralnog gubitka sluha [41].

U pretkliničkim studijama na životinjama, molekul AC102 je pokazao izuzetne rezultate. Istraživanje je sprovedeno na mongolskim gerbilima (pustinjским miševima) i potvrdilo je da je jedna doza leka ubrizgana u srednje uvo dovela do regeneracije trakastih (*ribbon*) sinapsi. Nakon 5 nedelja od primene leka, ponašanje koje ukazuje na prisustvo tinitusa je kod testiranih subjekata skoro u potpunosti nestalo. Registrovano je ponašanje povezano sa tinitusom samo kod jednog od ukupno petnaest testiranih subjekata za razliku od kontrolne grupe kod koje je ovo ponašanje registrovano kod jedanaest od trinaest subjekata [42].

Francusko – američka biotehnološka kompanija Cilcare trenutno radi na razvoju eksperimentalnog neurotrofnog leka pod nazivom CIL001. Aktivni molekul u leku CIL001, paliroden, prvobitno je razvila velika farmaceutska kuća Sanofi Aventis za neurodegenerativne bolesti. Cilcare je 2020.godine otkupio licencu od

Although experimental studies in animals have shown that the middle-ear muscle reflex is a highly sensitive marker for early detection of damage to auditory nerve synapses [38], its application in humans remains in the research phase.

CONTEMPORARY THERAPEUTIC APPROACHES Technological and Amplification Solutions

Given that there are currently no approved pharmacological protocols for the causal treatment of cochlear synaptopathy, i.e., for the direct structural restoration of damaged synapses, contemporary treatment of cochlear synaptopathy is primarily aimed at alleviating associated symptoms. Because the audiogram in these patients is generally within normal limits, the therapeutic paradigm focuses not on amplifying hearing thresholds, but on improving functional hearing under unfavorable acoustic conditions.

The primary problem in patients with synaptopathy is not the inability to detect sound, but the inability to extract the useful signal (speech) from background noise. In such situations, hearing aids with narrowband directional microphones and digital noise reduction can be highly beneficial. In addition to hearing aids, wireless FM systems can also be used. These devices detect the speaker's voice through a nearby microphone or one attached to the speaker and transmit the signal directly to the patient's ear via a loudspeaker or through a wireless connection with the hearing aid [39].

Clinical Primary Prevention and Otoprotection

To prevent permanent auditory dysfunction, primary prevention immediately before or after acoustic trauma plays an important role for practicing physicians. Clinical studies indicate that the use of pharmacological antioxidant protection – primarily high doses of vitamins A, C, and E, as well as N-acetylcysteine (NAC) – may attenuate oxidative stress and excitotoxicity in the inner ear. These antioxidant protocols have shown potential to preserve the integrity of ribbon synapses when administered within the early therapeutic window after noise exposure [40].

Experimental Pharmacological Approaches (Clinical Trials)

Currently, two pharmaceutical companies worldwide are at different stages of developing potential therapeutic solutions aimed at directly restoring damaged synapses between inner sensory cells and auditory nerve fibers. However, it is important to emphasize that these pharmacological approaches are still in the experimental phase and that their clinical efficacy in

kompanije Sanofi kako bi ovaj molekul preusmerio isključivo na lečenje unutrašnjeg uva i sinaptopatije. S obzirom da je lek još uvek u fazi kliničkih ispitivanja (faza 1b/2a) podaci o njegovoj uspešnosti se još uvek prikupljaju i nisu dostupni javnosti. Sama kompanija je izuzetno optimistična i promovise ovo jedinjenje kao mogući lek za sinaptopatiju i tinitus. Na dodeli nagrada Hearing Technology Innovator Awards 2024. godine ovo jedinjenje je proglašeno pobednikom u kategoriji terapija [43].

ZAKLJUČAK

Uvođenje prvih farmakoloških rešenja za regeneraciju kohlearnih sinapsi, praćeno formalnom implementacijom specifične šifre unutar Međunarodne klasifikacije bolesti, označice istorijsku promenu u audiologiji. Međutim, uspeh ove terapijske revolucije neće zavisiti samo od efikasnosti samog leka, već od spremnosti zdravstvenog sistema da prepozna i adekvatno selektuje pacijente. Kako bismo spremni dočekali trenutak kada ovi lekovi pređu iz kliničkih studija u apoteke neophodno je paralelno sprovesti pripreme u dva ključna pravca:

- **standardizacija dijagnostičkih protokola** - trenutni skrining sluha i dalje se primarno oslanja na tonalnu liminarnu audiometriju koja je slepa za kohlearnu sinaptopatiju. Zdravstveni sistemi moraju u redovnu praksu uvrstiti govornu audiometriju u buci kao i napredne elektrofiziološke testove. Bez ove dijagnostičke tranzicije, pacijenti sa skrivenim gubitkom sluha ostaće neprepoznati i uskraćeni za pravo na novu terapiju.
- **stratifikacija pacijenata i dugoročno praćenje podataka.** Klinička implementacija šifre bolesti u MKB omogućice precizno epidemiološko praćenje. Ovaj fond podataka postaje temelj za izgradnju oštih indikacionih kriterijuma i stratifikaciju pacijenata na osnovu stepena i reverzibilnosti oštećenja.

Kohlearna sinaptopatija više nije teorijski koncept sa životinjskih modela, već klinička realnost na pragu farmakološkog rešenja. Pravovremena priprema dijagnostičkog aparata, zakonodavstva u zdravstvu (kroz MKB) i edukacija stručne javnosti predstavljaju imperativ. Samo tako se može osigurati da, u trenutku kada regenerativni lekovi postanu komercijalno dostupni, tranzicija od „skrivenog gubitka sluha” do efektivnog terapijskog odgovora i neuroregenerativne restauracije slušnog puta bude brza, bezbedna i klinički efikasna.

Sukob interesa: Nije prijavljen.

humans has yet to be confirmed through further detailed research.

The German pharmaceutical company AudioCure is testing a drug known as AC102, and the results of the completed Phase 2 trial are currently awaiting publication. In this phase, researchers evaluated the efficacy, safety, and tolerability of a single intratympanic dose of the drug compared with oral corticosteroids—the current standard treatment for sudden idiopathic sensorineural hearing loss [41].

In preclinical animal studies, the AC102 molecule demonstrated remarkable results. The study was conducted in Mongolian gerbils (desert mice) and confirmed that a single dose of the drug administered into the middle ear resulted in regeneration of ribbon synapses. Five weeks after drug administration, tinnitus-related behavior had almost completely disappeared in the tested subjects. Tinnitus-related behavior was recorded in only one of the fifteen tested subjects, compared with the control group, in which this behavior was recorded in eleven of thirteen subjects [42].

The French-American biotechnology company Cilcare is currently developing an experimental neurotrophic drug known as CIL001. The active molecule in CIL001, paliroden was originally developed by the major pharmaceutical company Sanofi Aventis for neurodegenerative diseases. In 2020, Cilcare acquired a license from Sanofi to redirect the molecule exclusively toward treating the inner ear and synaptopathy. Because the drug is still in the clinical trial phase (Phase 1b/2a), efficacy data are still being collected and are not publicly available. The company itself is highly optimistic and promotes this compound as a potential treatment for synaptopathy and tinnitus. At the 2024 Hearing Technology Innovator Awards, this compound won the therapeutics category [43].

CONCLUSION

The introduction of the first pharmacological solutions for regenerating cochlear synapses, accompanied by the formal implementation of a specific code within the International Classification of Diseases, will mark a historic change in audiology. However, the success of this therapeutic revolution will depend not only on the drug's efficacy, but also on the healthcare system's readiness to recognize and select patients appropriately. In order to be prepared for the moment when these drugs move from clinical trials to pharmacies, preparations must be undertaken simultaneously in two key directions:

- **Standardization of diagnostic protocols** – current hearing screening still primarily relies on pure-tone audiometry, which is insensitive to cochlear synaptopathy. Healthcare systems must incorporate

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speech audiometry in noise as well as advanced electrophysiological tests into routine practice. Without this diagnostic transition, patients with hidden hearing loss will remain undiagnosed and deprived of access to the new therapy.

- **Patient stratification and long-term data monitoring.** The clinical implementation of the disease code in the ICD will enable precise epidemiological monitoring. This data will form the basis for establishing precise indication criteria and stratifying patients by the severity and reversibility of the damage.

Cochlear synaptopathy is no longer merely a theoretical concept derived from animal models, but a clinical reality on the threshold of a pharmacological solution. Timely preparation of diagnostic infrastructure, healthcare legislation (through the ICD), and education of the professional community are imperative. Only then can we ensure that, once regenerative drugs become commercially available, the transition from “hidden hearing loss” to an effective therapeutic response and neuroregenerative restoration of the auditory pathway will be rapid, safe, and clinically effective.

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PRIMENA PENG I LFCN BLOKA ZA HIRURŠKU KOREKCIJU KONGENITALNE DISLOKACIJE KUKA KOD DETETA – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

PENG AND LFCN BLOCK FOR SURGICAL CORRECTION OF CONGENITAL HIP DYSPLASIA IN A CHILD – A CASE REPORT

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SAŽETAK

Uvod/Cilj: Kongenitalna dislokacija kuka (KDK) predstavlja najčešći muskulo-skeletni deformitet ranog detinjstva. PENG (engl. *Pericapsular nerve group*) blok predstavlja relativno novu tehniku regionalne anestezije čiji je benefit u hirurgiji kuka kod odraslih definitivno dokazan, dok se kod dece i dalje ispituje. Slučajevi primene PENG bloka bez neuraksijalne anestezije su kod dece mlađe od 5 godina izuzetno retki, dok je kombinovana primena sa LFCN (engl. *lateral femoral cutaneous nerve*) blokom gotovo potpuno neispitana.

Prikaz slučaja: Pacijentkinja stara 5 godina primljena je radi operativnog lečenja KDK. Po uvodu u opštu anesteziju pod kontrolom ultrazvuka izvedeni su PENG i LFCN blok. Ukupna doza lokalnih anestetika iznosila je 1,5 mg/kg levobupivakaina i 3 mg/kg lidokaina, dok je ukupna doza opioda uvodnih 40 µg intravenoskog fentanila. Tokom intervencije od 240 minuta pacijentkinja je bila potpuno hemodinamski i respiratorno stabilna. Po buđenju prevedena je na odeljenje gde je postoperativno bol praćen putem WBFPS (engl. *Wong-Baker Faces Pain Scale*), a metamizol u dozi od 50 mg/kg je ordiniran u slučaju uočenog izraza lica koji odgovara intenzitetu bola 4 ili više. U prvih 24 časa data je jedna doza metamizola. Ukupna perioperativna doza opioda svedena je na uvodnih 2 µg/kg fentanila.

Zaključak: PENG i LFCN blok mogu obezbediti adekvatnu intraoperativnu i postoperativnu analgeziju kod dece do 5 godina starosti podvrgnute hirurškoj korekciji KDK. Njihova primena može značajno smanjiti perioperativnu potrošnju opioda.

Ključne reči: regionalna anestezija, periferni nervni blok, pedijatrija, kongenitalna dislokacija kuka, ortopedija

ABSTRACT

Introduction/Objective: Congenital hip dysplasia is the most common musculoskeletal disorder in early childhood. The pericapsular nerve group (PENG) block is a relatively novel regional anesthesia technique, proven useful for hip surgery in adults but still being evaluated in children. Cases of pure PENG block without neuraxial anesthesia in children under 5 years of age are very rare, while cases of combined use with lateral femoral cutaneous nerve (LFCN) block are virtually unexamined.

Case report: A 5-year-old girl was scheduled for corrective hip surgery. After induction of general anesthesia, an ultrasound-guided PENG and lateral femoral cutaneous nerve (LFCN) block were performed. The total local anesthetic dose was 1.5 mg/kg of levobupivacaine and 3 mg/kg of lidocaine, while the total opioid dose was 40 µg of intravenous fentanyl on induction. Throughout the 240-minute procedure, she maintained perfect hemodynamic and respiratory stability. Following awakening, she was referred back to the ward where pain was monitored via the Wong-Baker Faces Pain Scale, and 50 mg/kg of metamizole was administered if pain was reported at a 4 or higher. In the first 24 hours, patients received only one dose. The total dose of perioperative opioids was limited to the 2 µg/kg induction dose of fentanyl.

Conclusion: PENG and LFCN block may provide adequate analgesia intraoperatively and postoperatively for children under the age of 5 years scheduled for complex congenital hip dislocation surgery. Their use may significantly reduce the perioperative use of opioids.

Keywords: regional anesthesia, peripheral nerve block, pediatrics, congenital hip dysplasia, orthopedics

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UVOD

Kongenitalna dislokacija kuka (KDK) je najčešći muskuloskeletni poremećaj u ranom dečjem uzrastu [1]. Hirurško zbrinjavanje najčešće se izvodi do 4. godine života, u zavisnosti od uzrasta pacijenta i opsežnosti deformiteta, ali se može izvesti čak i do 8. godine [2]. PENG (engl. *pericapsular nerve group* – PENG) blok je relativno nova tehnika regionalne anestezije koja se uspešno primenjuje u hirurgiji kuka kod odraslih a sve češće i kod dece [3–5]. Pod kontrolom ultrazvuka prikazujemo iliopektinealnu eminenciju i tetivu mišića psoasa koja prelazi preko nje (Slika 1). Cilj nam je da usmerimo vrh igle između kosti i tetive psoasa što zahteva strm ugao pristupa, kako ne bismo akcidentalno povredili femoralnu arteriju smeštenu medijalno. Obično se upotrebljava niskofrekventna konveksna ultrazvučna sonda. Primenljivost PENG bloka kod dece i dalje se aktivno ispituje [6].

Operativno lečenje KDK uglavnom podrazumeva pristup kroz rez na spoljašnjoj strani natkolenice u predelu velikog trohantera, što je inervaciono područje LFCN (engl. *lateral femoral cutaneous nerve* – LFCN). Postavljanjem ultrazvučne sonde, obično linearne visokofrekventne, neposredno ispod prednje-godnje bedrene bodlje prikazuje se terzijski mišić (lat. *m. sartorius*), na čijoj se prednjoj površini LFCN uočava u vidu hiperehogene ovoidne formacije (Slika 2).

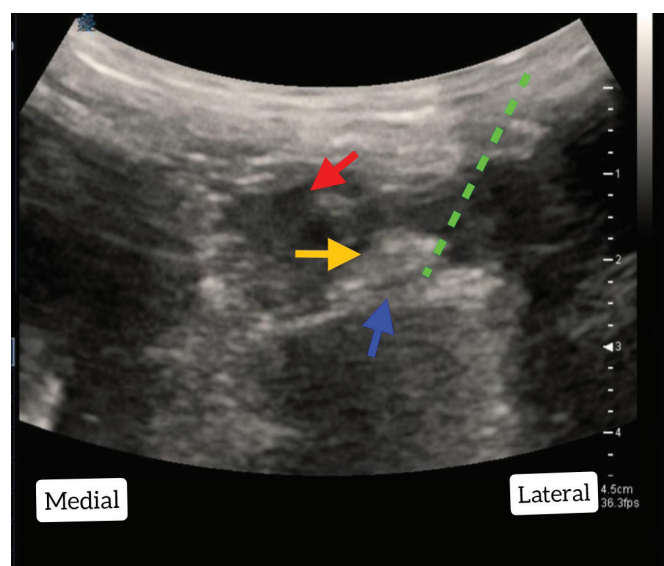
Prema dostupnoj literaturi, u trenutku pripreme ovog prikaza, objavljeno je manje od 10 slučajeva primene PENG bloka kod dece mlađe od 5 godina bez istovremene primene spinalne anestezije [7]. Od tih 10

INTRODUCTION

Congenital dislocation of the hip (CDH) is the most common musculoskeletal disorder in early childhood [1]. Surgical management is most commonly performed by the age of 4, depending on the patient's age and the extent of the deformity, but it can be performed as late as 8 years of age [2]. The PENG (pericapsular nerve group) block is a relatively new regional anesthesia technique that has been successfully applied in adult hip surgery and increasingly in children [3–5]. Under ultrasound guidance, the iliopectineal eminence and the psoas tendon crossing over it are visualized (Figure 1). We aim to direct the needle tip between the bone and the psoas tendon, which requires a steep approach angle to avoid accidental injury to the medial femoral artery. A low-frequency convex ultrasound probe is usually used. The applicability of the PENG block in children is still being actively investigated [6].

Surgical treatment of CDH generally involves an approach through an incision on the lateral aspect of the thigh in the region of the greater trochanter, which corresponds to the innervation territory of the LFCN (lateral femoral cutaneous nerve). By positioning an ultrasound probe, usually a high-frequency linear probe, immediately inferior to the anterior superior iliac spine, the sartorius muscle (lat. *m. sartorius*) is visualized, with the LFCN identified on its anterior surface as a hyperechoic ovoid structure (Figure 2).

According to the available literature, at the time of preparation of this report, fewer than 10 cases of PENG

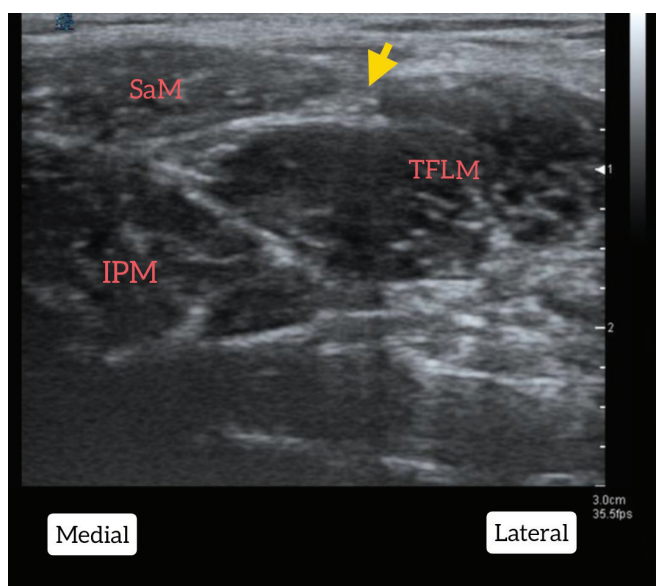


Slika 1. Ultrazvučni prikaz anatomije PENG bloka.

Crvena strelica – femoralna arterija, žuta strelica – tetiva psoasa, plava strelica – iliopektinealna eminencija, isprekidana bela linija – putanja igle.

Figure 1. Ultrasound visualization of the anatomy for the PENG block.

Red arrow – femoral artery; yellow arrow – psoas tendon; blue arrow – iliopectineal eminence; dashed white line – needle trajectory



Slika 2. Ultrazvučni prikaz anatomije LFCN bloka.

SaM – m. sartorius, TFLM – m. tensor fasciae latae, IPM – m. iliopsoas, žuta strelica – n. cutaneus femoris lateralis.

Figure 2. Ultrasound visualization of the anatomy for the PENG block.

Red arrow – femoral artery; yellow arrow – psoas tendon; blue arrow – iliopectineal eminence; dashed white line – needle trajectory

slučajeva, samo 2 slučaja podrazumevaju istovremenu primenu LFCN bloka, te procenu efekta njihove kombinovane primene na intraoperativnu i postoperativnu analgeziju u hirurgiji KDK [7,8].

Izvođenje PENG i LFCN bloka takođe može biti praćeno komplikacijama poput neuspelog bloka, oštećenja nerava, akcidentalne intravaskularne primene lokalnog anestetika i sledstvene sistemske toksičnosti [9]. Primena PENG bloka u pedijatrijskoj populaciji ima jasan opioidno-pošteđan efekat [10], dok bi istovremena primena LFCN bloka mogla u potpunosti da eliminiše postoperativnu upotrebu opioida nakon hirurške korekcije kongenitalne dislokacije kuka.

PRIKAZ SLUČAJA

Petogodišnja devojčica teška 20 kg primljena je na Odeljenje ortopedске hirurgije i traumatologije Univerzitetske dečje klinike radi operativnog lečenja desnostrane KDK. Hirurški zahvat podrazumevao je subtrohanteričnu osteotomiju femura, fiksaciju pločom, kapsulotomiju zgloba kuka i njegovu repoziciju, ekstrakciju grafta ilijačne kosti i njenu fiksaciju sa dve igle (Slika 3). Pacijentkinja nije imala druge komorbiditete od značaja, te je klasifikovana kao ASA (engl. *American Society of Anesthesiology*) status 1.

Primenjen je osnovni monitoring vitalnih funkcija (EKG, pulsna oksimetrija, neinvazivno merenje krvnog pritiska, kapnografija). Pacijentkinja je premedicirana intravenskom primenom 0,2 mg atropina i 2 mg deksametazona, a potom uvedena u opštu anesteziju intravenskom primenom 40 mg propofola, 20 mg rokuronijuma, i 40 µg fentanila. Po endotrahealnoj intubaciji, u leđnom položaju je u uslovima asepse i pod kontrolom ultrazvuka (aparatus eZono 4000, igla 22G/10mm, konveksna niskofrekventna sonda, *in-plane* tehnika) izveden PENG blok (0,25% levobupivakain, 10 ml, i 2% lidokain, 2 ml) i LFCN blok (0,25% levobupivakaina, 2ml, i 2% lidokaina, 1 ml). Ukupna doza lokalnih anestetika iznosila je 1,5 mg/kg levobupivakaina i 3 mg/kg lidokaina. Sedacija je održavana kontinuiranom primenom propofola u dozi od 8 mg/kg/h.

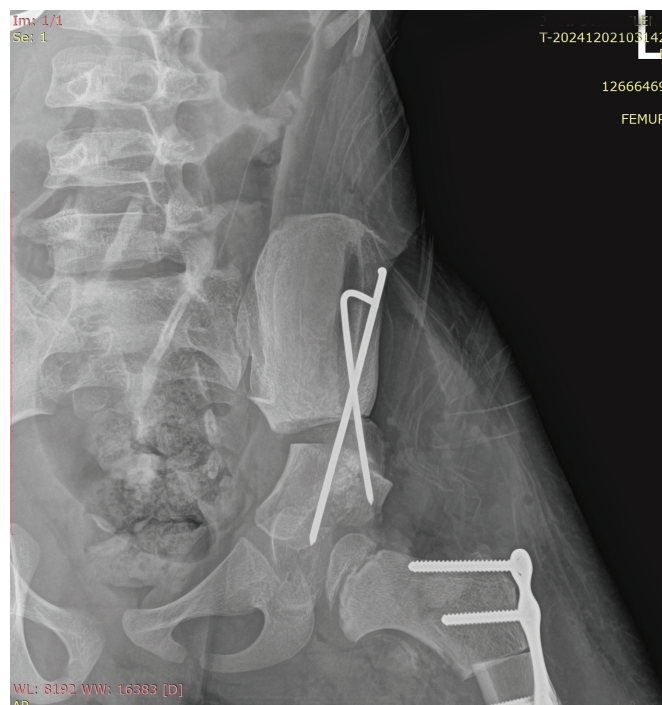
Tokom intervencije koja je trajala 240 minuta pacijentkinja je bila u potpunosti hemodinamski i respiratorno stabilna, održavajući srednji arterijski pritisak između 70–75 mmHg, srčanu frekvencu 80–90 otkucaja u minuti, kao i saturaciju hemoglobina kiseonikom od 97–99%. Sledstveno tokom intervencije nije bilo ponavljanih doza opioida niti mišićnog relaksanta. Prilikom buđenja nije bilo uočljivih komplikacija, te je pacijentkinja prevedena na odeljenje. Odlukom nadležnog anesteziologa postoperativno bol je praćen primenom WBFPs (engl. *Wong-Baker Faces Pain Scale – WBFPs*)

block application in children younger than 5 years of age without concomitant spinal anesthesia had been published [7]. Of these 10 cases, only 2 involved the concomitant use of an LFCN block, with an assessment of the effect of their combined application on intraoperative and postoperative analgesia in CDH surgery [7,8].

Performance of PENG and LFCN blocks may also be associated with complications such as block failure, nerve injury, accidental intravascular administration of the local anesthetic, and consequent systemic toxicity [9]. The use of the PENG block in the pediatric population has a clear opioid-sparing effect [10], while the concomitant use of an LFCN block could eliminate the need for postoperative opioid administration following surgical correction of congenital dislocation of the hip.

CASE REPORT

A five-year-old girl weighing 20 kg was admitted to the Department of Orthopedic Surgery and Traumatology of the University Children's Hospital for surgical treatment of right-sided CDH. The surgical procedure consisted of subtrochanteric femoral osteotomy, plate fixation, hip joint capsulotomy and reduction, iliac bone graft harvesting and fixation with two pins (Figure 3). The patient had no other significant comorbidities and was classified as ASA (American Society of Anesthesiologists) physical status 1.



Slika 3. Radiografija kuka.

- A. Pre operacije.
- B. Posle operacije

Figure 3. Hip radiograph.

- A. Preoperative.
- B. Postoperative.

[11], a parenteralni metamizol u dozi od 50 mg/kg propisan je u slučaju uočenog izraza lica koji odgovara intenzitetu bola 4 ili više. U toku prvih 24 časa postoperativno primenjena je jedna doza metamizola, i to 16 sati posle operacije. U postoperativnom toku nisu uočene komplikacije po tipu oštećenja nerava, infekcije ubodnog mesta, kao ni toksičnih efekata lokalnih anestetika. Ukupna perioperativna potrošnja opioda svedena je na uvodnu dozu fentanila od 2 µg/kg.

DISKUSIJA

Iako značajno dobija na popularnosti, primena PENG bloka i dalje se ne smatra široko rasprostranjenom u pedijatrijskoj populaciji, a naročito kod dece mlađe od 5 godina. Donedavno nije bilo nikakvih većih studija koje su se bavile efektima ovog bloka kod dece, sve dok *Reysner i sar.* nisu objavili rezultate svoje randomizovane dvostruko slepe kliničke studije 2025. godine [12]. Treba naglasiti da su u ovoj studiji poredili efekat PENG bloka i ESP (engl. *Erector spinae plane* – ESP) bloka na analgeziju posle operacije kuka kod dece koja su po uvodu u opštu anesteziju, a pred intervenciju, dobila spinalnu anesteziju. Samim tim rezultati ove studije ne mogu govoriti o samostalnom analgetskom efektu ovih blokova tokom i nakon datog hirurškog zahvata. Tehnike neuraksijalne anestezije, konkretno kaudalni blok, kod dece ovog uzrasta predstavljaju klinički smislenu i proverenu alternativu. Ipak, dosadašnjim ispitivanjima utvrđeno je da je PENG blok u hirurgiji kuka kod dece pruža bolju postoperativnu analgeziju i manju potrošnju opioda u odnosu na kaudalni blok [10].

Pregledom ranijih slučajeva primene PENG bloka u uslovima opšte anestezije kod dece može se doći do zaključka da ona obezbeđuje značajno bolju intraoperativnu i postoperativnu analgeziju u odnosu na slučajeve kada blok nije primenjen [7,13]. Samim tim smanjuje perioperativnu potrošnju opioda i njene komplikacije (produženo buđenje, respiratorne komplikacije na buđenju, postoperativna mučnina i povraćanje, odložen postoperativni unos vode i hrane, postoperativni hipomotilitet creva, itd.), ali je prema dostupnoj literaturi ne eliminiše u potpunosti. Činjenica koja tome može doprineti jeste da, kao u našem slučaju, hirurški pristup podrazumeva rez i u spoljašnjem aspektu proksimalne trećine natkolenice, što je upravo inervaciono područje LFCN. Cilj ovog prikaza jeste da skrene pažnju na moguću analgetsku efikasnost kombinovane primene PENG i LFCN bloka u hirurgiji KDK. Na osnovu dostupne literature do sada su objavljena samo dva takva slučaja kod dece mlađe od 5 godina [7,8], pri čemu oba slučaja jasno ukazuju na benefit primene ovih blokova. Jedna kadaverična studija koju su sprovedi *Ciftci i sar.* [14] pokazala je da primenom veće

Standard vital-function monitoring was used (ECG, pulse oximetry, non-invasive blood pressure measurement, and capnography). The patient was premedicated with intravenous administration of 0.2 mg of atropine and 2 mg of dexamethasone, followed by induction of general anesthesia with intravenous administration of 40 mg of propofol, 20 mg of rocuronium, and 40 µg of fentanyl. Following endotracheal intubation, with the patient in the supine position, under aseptic conditions and ultrasound guidance (eZono 4000, 22G/10 mm needle, low-frequency convex probe, *in-plane* technique), a PENG block (0.25% levobupivacaine, 10 mL, and 2% lidocaine, 2 mL) and an LFCN block (0.25% levobupivacaine, 2 mL, and 2% lidocaine, 1 mL) were performed. The total dose of local anesthetics was 1.5 mg/kg of levobupivacaine and 3 mg/kg of lidocaine. Sedation was maintained with continuous propofol at 8 mg/kg/h.

During the 240-minute procedure, the patient remained hemodynamically and respiratorily stable, with a mean arterial pressure of 70–75 mmHg, a heart rate of 80–90 beats per minute, and an oxygen saturation of 97–99%. Consequently, no additional doses of opioids or muscle relaxants were administered during the procedure. No complications were observed during emergence from anesthesia, and the patient was subsequently transferred to the ward. At the discretion of the attending anesthesiologist, postoperative pain was assessed using the WBFPs (Wong-Baker Faces Pain Scale – WBFPs) [11], and parenteral metamizole at a dose of 50 mg/kg was prescribed in the event of an observed facial expression corresponding to a pain intensity score of 4 or higher. During the first 24 postoperative hours, a single dose of metamizole was administered 16 hours after surgery. No postoperative complications were observed, including nerve injury, infection at the injection site, or toxic effects of local anesthetics. Total perioperative opioid consumption was limited to the induction dose of fentanyl, 2 µg/kg.

DISCUSSION

Although the PENG block is gaining popularity, it is still not widely used in the pediatric population, particularly in children younger than 5 years. Until recently, no major studies had addressed the effects of this block in children, until Reysner et al. published the results of their randomized, double-masked clinical trial in 2025 [12]. This study compared the effects of the PENG block and ESP (Erector Spinae Plane) block on analgesia following hip surgery in children who received spinal anesthesia after induction of general anesthesia and before surgery. Therefore, the results of this study cannot provide information on the independent anal-

zapremine lokalnog anestetika kod PENG bloka i LFCN može da bude zahvaćen, ali bi to podrazumevalo istovremeno zahvatanje femoralnog nerva i sledstvenu motornu slabost natkolenice. Iako ovo konkretno područje zahteva dodatna ispitivanja, kliničko iskustvo sa primenom ovog bloka u našoj ustanovi upućuje na primenu zapremine od 0,5 ml/kg a najviše 20 ml lokalnog anestetika za PENG blok uz zasebnu injekciju za blok LFCN. Dekametazon, ukoliko ne postoje kontraindikacije, može se primeniti intravenski zbog dokazanog efekta produženja trajanja perifernog nervnog bloka kao i prevencije postoperativnog povratnog bola [15].

Zaključujemo da je moguća bezbedna i efikasna kominovana primena PENG i LFCN bloka kod dece uzrasta 5 godina za hirurško lečenje KDK. Potrebne su dalje studije u ovoj uzrasnoj grupi radi poređenja analgetskog efekta ove kombinacije blokova u odnosu na druge tehnike regionalne anestezije i multimodalne analgezije.

Sukob interesa: Nije prijavljen.

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gesic effect of these blocks during and after the given surgical procedure. Neuraxial anesthesia techniques, specifically the caudal block, represent a clinically reasonable and established alternative in children of this age. Nevertheless, previous studies have demonstrated that the PENG block in pediatric hip surgery provides better postoperative analgesia and lower opioid consumption compared with the caudal block [10].

A review of previous cases involving the PENG block under general anesthesia in children suggests it provides significantly better intraoperative and postoperative analgesia than cases in which the block was not performed [7,13]. Consequently, it reduces perioperative opioid consumption and opioid-related complications (prolonged emergence, respiratory complications during emergence, postoperative nausea and vomiting, delayed postoperative intake of fluids and food, postoperative intestinal hypomotility, etc.). However, according to the available literature, it does not eliminate opioid use. One factor that may contribute to this is that, as in our case, the surgical approach involves an incision on the lateral aspect of the proximal third of the thigh, which corresponds precisely to the LFCN innervation territory. This case report highlights the potential analgesic efficacy of combining PENG and LFCN blocks in CDH surgery. Based on the available literature, only two such cases have been published to date in children younger than 5 years of age [7,8], with both cases clearly demonstrating the benefit of using these blocks. A cadaveric study conducted by *Ciftci et al.* [14] demonstrated that the LFCN may also be affected when a larger volume of local anesthetic is used for the PENG block; however, this would imply simultaneous involvement of the femoral nerve and consequent motor weakness of the thigh. Although this area requires further investigation, clinical experience with this block at our institution supports administering 0.5 mL/kg of local anesthetic for the PENG block, up to a maximum of 20 mL, with a separate injection for the LFCN block. If there are no contraindications, dexamethasone may be administered intravenously because it prolongs peripheral nerve blockade and helps prevent rebound postoperative pain [15].

We conclude that combined PENG and LFCN blocks in a 5-year-old child undergoing surgical treatment of CDH are potentially safe and effective. Further studies in this age group are required to compare the analgesic effect of this combination of blocks with other regional anesthesia techniques and multimodal analgesia.

Conflict of interest: None declared

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„LUPUS IN FABULA”: SISTEMSKI ERITEMSKI LUPUS KOMPLIKOVAN SINDROMOM AKTIVACIJE MAKROFAGA SA FATALNIM ISHODOM

PRIKAZ SLUČAJA

CASE REPORT

"LUPUS IN FABULA": SYSTEMIC LUPUS ERYTHEMATOSUS COMPLICATED BY MACROPHAGE ACTIVATION SYNDROME WITH A FATAL OUTCOME

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SAŽETAK

Uvod/Cilj: Sindrom aktivacije makrofaga (engl. *macrophage activation syndrome – MAS*) predstavlja hiperinflamatorni sindrom i izuzetno retku, ali potencijalno životno ugrožavajuću komplikaciju sistemskog eritemskog lupusa (SEL), drugih sistemskih autoimunskih i autoinflamatornih bolesti, infekcija i maligniteta.

Prikaz slučaja: Pacijentkinja starosti 33 godine, sa istorijom ponavljanih holangitisa od detinjstva i perzistentno pozitivnim antinuklearnim antitelima (ANA) tokom više godina, simptomatski je lečena, u decembru 2022. godine, zbog febrilnosti i gastroenteroloških tegoba shvaćenih kao ponovni atak holangitisa, uprkos prisutnoj pancitopeniji, potrošnoj koagulopatiji i oštećenju bubrežne funkcije. U januaru 2023. godine dolazi do ponovne febrilnosti uz perifernu limfadenopatiju, splenomegaliju, progresiju pancitopenije i hipokomplementemiju, kada je postavljena dijagnoza SEL i započeto lečenje metilprednizolonom. Zbog novonastalih promena mentalnog statusa sa halucinacijama i izraženim kožnim promenama, razmatran je neurolupus, koji nije potvrđen usled odsustva adekvatnog neuroradiološkog korelata. Potom dolazi do progresivnog pogoršanja funkcije jetre i bubrega, produbljivanja pancitopenije, uz ekstremnu hiperferritinemiju ($> 33511 \mu\text{g/L}$), hipofibrinogenemiju i hipertrigliceridemiju, na osnovu čega je postavljena dijagnoza sindroma aktivacije makrofaga, kao komplikacije aktivnog, prethodno neprepoznatog sistemskog eritemskog lupusa (*H-score* 266). Uvođenje ciklosporina dovelo je do prolaznog poboljšanja. Međutim, uprkos primeni imunomodulatornih doza intravenskih imunoglobulina uz svu ostalu terapiju, razvijaju se anasarka, respiratorna, srčana i bubrežna slabost. Terapijske izmene plazme i intenzivne ultrafiltracije dovode do kratkotrajnog kliničkog, laboratorijskog i ehokardiografskog poboljšanja, iza čega dolazi do produbljivanja sindroma multiorganske disfunkcije. Uprkos svim primenjenim modalitetima lečenja, došlo je do fatalnog ishoda.

Zaključak: Preklapanje kliničkih i laboratorijskih manifestacija aktivnog sistemskog eritemskog lupusa i sindroma aktivacije makrofaga značajno otežava pravovremeno postavljanje dijagnoze. Poseban dijagnostički značaj ima praćenje koncentracija feritina, pri čemu se vrednosti $> 10.000 \mu\text{g/L}$ smatraju visoko sugestivnim za MAS.

Ključne reči: feritin, H-skor, sindrom multiorganske disfunkcije

ABSTRACT

Introduction/Objective: Macrophage activation syndrome (MAS) is a hyperinflammatory syndrome and an extremely rare but potentially life-threatening complication of systemic lupus erythematosus (SLE), other systemic autoimmune and autoinflammatory diseases, infections, and malignancies.

Case report: A 33-year-old female patient with a history of recurrent cholangitis since childhood and persistently positive antinuclear antibodies (ANA) for several years was treated symptomatically in December 2022 for fever and gastrointestinal symptoms interpreted as a recurrent episode of cholangitis, despite the presence of pancytopenia, consumptive coagulopathy, and impaired renal function. In January 2023, she developed recurrent fever accompanied by peripheral lymphadenopathy, splenomegaly, progression of pancytopenia, and hypocomplementemia, at which point a diagnosis of SLE was established and treatment with methylprednisolone was initiated. Due to newly developed changes in mental status with hallucinations and prominent nightmare content, neuropsychiatric lupus was considered; however, it was not confirmed because of the absence of an adequate neuroradiological correlate. Subsequently, progressive deterioration of liver and kidney function and worsening pancytopenia occurred, accompanied by extreme hyperferritinemia ($> 33,511 \mu\text{g/L}$), hypofibrinogenemia, and hypertriglyceridemia, leading to the diagnosis of macrophage activation syndrome as a complication of active, previously unrecognized systemic lupus erythematosus (*H-score* 266). Cyclosporine was introduced, resulting in transient improvement; however, despite immunomodulatory doses of intravenous immunoglobulins along with the other therapy, anasarca, respiratory, cardiac, and renal failure developed. Therapeutic plasma exchange and intensive ultrafiltration resulted in short-term clinical, laboratory, and echocardiographic improvement, followed by worsening of the multiple organ dysfunction syndrome. Despite all treatment modalities employed, the patient had a fatal outcome.

Conclusion: The overlap of the clinical and laboratory manifestations of active systemic lupus erythematosus and macrophage activation syndrome significantly complicates timely diagnosis. Monitoring ferritin concentrations is of particular diagnostic importance, with values $> 10,000 \mu\text{g/L}$ considered highly suggestive of MAS.

Keywords: ferritin, H-score, multiple organ dysfunction syndrome

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UVOD

Sindrom aktivacije makrofaga (engl. *macrophage activation syndrome* – MAS) ili reaktivna hemofagocitna limfocitocitoza (rHLH) je životno ugrožavajuće hiperinflamatorno stanje koje karakteriše nekontrolisana aktivacija T-limfocita i makrofaga, uz masivno oslobađanje citokina. Kašnjenje u dijagnostici i lečenju dovodi do razvoju sindroma multiorganske disfunkcije (engl. *multiorgan dysfunction syndrome* – MODS) [1]. Karakterišu ga febrilnost, splenomegalija, citopenija u dve ili više krvnih loza (citopenija ≥ 2 krvne loze), (hemoglobin < 90 g/l, trombociti $< 100 \times 10^9$ /l, neutrofili $< 1,0 \times 10^9$ /l), hipofibrinogenemija ($\leq 1,5$ g/l) i/ili hipertrigliceridemija ($\geq 3,5$ mmol/l), hiperferitinemija (≥ 500 μ g/l) uz nalaz hemofagocita u koštanoj srži, sniženu aktivnost NK ćelija (engl. *natural killer cells*) i povišene vrednosti α -subjedinice solubilnog interleukin (IL)-2 receptora (≥ 2400 U/ml). Za postavljanje dijagnoze sindroma aktivacije makrofaga, neophodno je prisustvo bar 5 od navedenih 8 kriterijuma [2].

Razlikuju se tri kategorije faktora koji doprinose razvoju sindroma aktivacije makrofaga: genetski (npr. urođeni poremećaji imunskog sistema), predisponirajuća stanja (sistemske autoimunske bolesti, limfoproliferativna oboljenja) i akutni okidači (infekcije, imunoterapija). U patogenezi često učestvuje više faktora istovremeno, npr. infekcije su najčešći pokretač sindroma aktivacije makrofaga kod pacijenata sa sistemskim autoimunskim bolestima i urođenim poremećajima imunskog sistema [1,3].

Iako izuzetno retka, MAS je životno ugrožavajuća komplikacija pacijenata sa sistemskim autoimunskim bolestima. Najčešće se opisuje kod pedijatrijskih pacijenata sa sistemskim juvenilnim idiopatskim artritism (sJIA) i odraslih sa Stilovom bolešću [4]. Javlja se kod 0,9%–4,6% pacijenata sa sistemskim eritemskim lupusom (SEL) [5,6].

Proгноza i ishod sindroma aktivacije makrofaga zavise od uzroka, trajanja bolesti, zahvaćenosti pojedinih organskih sistema, razvoja sindroma multiorganske disfunkcije. MAS koji je nastao kao komplikacija neke od sistemskih autoimunskih bolesti ima bolju prognozu od onog koji je nastao kao komplikacija hematoloških maligniteta. Takođe, razvoj insuficijencije jetre i bubrega je povezan sa lošijom prognozom [1]. Mortalitet kod pacijenata sa SEL varira i iznosi 5%–35% [4,6]. Nelečen, MAS ima progresivan tok zbog čega je pravovremeno prepoznavanje i uvođenje adekvatne terapije od vitalnog značaja za pacijenta.

Cilj ovog rada je da prikaže slučaj pacijentkinje sa kasno prepoznatim sistemskim eritemskim lupusom, koji se komplikovao razvojem sindroma aktivacije makrofaga sa fatalnim ishodom i da ukaže na značaj brzog

INTRODUCTION

Macrophage activation syndrome (MAS), or reactive hemophagocytic lymphohistiocytosis (rHLH), is a life-threatening hyperinflammatory condition characterized by uncontrolled activation of T-lymphocytes and macrophages, accompanied by massive cytokine release. Delayed diagnosis and treatment lead to the development of multiple organ dysfunction syndrome (MODS) [1]. It is characterized by fever, splenomegaly, cytopenia affecting two or more blood cell lineages (cytopenia in ≥ 2 blood cell lineages), (hemoglobin < 90 g/l, platelet count $< 100 \times 10^9$ /l, neutrophils $< 1.0 \times 10^9$ /l), hypofibrinogenemia (≤ 1.5 g/l) and/or hypertriglyceridemia (≥ 3.5 mmol/l), hyperferritinemia (≥ 500 μ g/l), along with the presence of hemophagocytes in the bone marrow, decreased natural killer (NK) cell activity, and elevated levels of the soluble α -subunit of the interleukin (IL)-2 receptor (≥ 2400 U/ml). For the diagnosis of macrophage activation syndrome, at least 5 of the 8 aforementioned criteria must be present [2].

Three categories of factors contribute to the development of macrophage activation syndrome: genetic factors (e.g., congenital disorders of the immune system), predisposing conditions (systemic autoimmune diseases, lymphoproliferative disorders), and acute triggers (infections, immunotherapy). Multiple factors often contribute simultaneously to MAS pathogenesis; for example, infections are the most common trigger of MAS in patients with systemic autoimmune diseases and congenital disorders of the immune system [1,3].

Although extremely rare, MAS is a life-threatening complication in patients with systemic autoimmune diseases. It is most commonly described in pediatric patients with systemic juvenile idiopathic arthritis (sJIA) and in adults with Still's disease [4]. It occurs in 0.9%–4.6% of patients with systemic lupus erythematosus (SLE) [5,6].

The prognosis and outcome of macrophage activation syndrome depend on its cause, disease duration, involvement of individual organ systems, and development of multiple organ dysfunction syndrome. MAS occurring as a complication of a systemic autoimmune disease has a better prognosis than MAS developing as a complication of hematological malignancies. In addition, the development of liver and renal failure is associated with a poorer prognosis [1]. Mortality among patients with SLE varies and ranges from 5% to 35% [4,6]. Untreated MAS follows a progressive course; therefore, timely recognition and initiation of appropriate therapy are of vital importance for the patient.

This paper aims to present the case of a patient with late-diagnosed systemic lupus erythematosus complicated by the development of macrophage activation

prepoznavanja i adekvatnog lečenja ove životno ugrožavajuće komplikacije sistemskog eritemskog lupusa.

PRIKAZ SLUČAJA

Pacijentkinja starosti 33 godine, imala je od detinjstva, a nakon operisane atrezije žučnih puteva u drugom mesecu života, ponavljane holangitise. U imunološkoj obradi su utvrđena pozitivna antinuklearna antitela (ANA) koja su perzistirala godinama unazad, uz prisutna antitela protiv Sjögrenovog sindroma (engl. *anti-Sjögren's syndrome A antibodies – ASSA*), antiglatkomišićna antitela (AGMA) i antimito hondrijalna antitela (AMA). Uprkos višegodišnjoj pozitivnosti antitela, u diferencijalnoj dijagnostičkoj obradi nije razmatrana sistemska autoimunska bolest, kao ni organ-specifična autoimunska bolest jetre i žučnih puteva. Lična i porodična anamneza su bile neupadljive.

Dominantno opšte i gastroenterološke tegobe (bolovi ispod desnog rebarnog luka, mučnina, povraćanje, tečne stolice) praćene febrilnošću do 39 °C u decembru 2022. godine shvaćene su kao samo još jedan napad holangitisa. Uz poremećaj analiza funkcije jetre i leziju bubrega, detektovana je pancitopenija (leukociti $2,87 \times 10^9/l$; eritrociti $3,05 \times 10^{12}/l$; hemoglobin 94 g/l; trombocitopenija) i poremećaj koagulacije po tipu potrošne koagulopatije (D-dimer 5,23 mg/l; fibrinogen 1,23 g/l). Ultrazvučno su opisani hepatosplenomegalija i ascites, a magnetnom rezonantnom holangiopankreatografijom isključena je opstruktivna bolest žučnih puteva. Pacijentkinja je u nadležnoj zdravstvenoj ustanovi lečena antibioticima, transfuzijama eritrocita, faktorima stimulacije granulocitne loze, ursodeoksiholnom kiselinom, uz simptomatsku terapiju što je dovelo do kratkotrajnog kliničkog poboljšanja.

U januaru 2023. godine, pacijentkinja ponovo postaje febrilna uz produktivan kašalj, perifernu limfadenopatiju, hepatosplenomegaliju i pogoršanje pancitopenije (leukociti $1,0 \times 10^9/l$; eritrociti $2,34 \times 10^{12}/l$; hemoglobin 79 g/l; trombociti $81 \times 10^9/l$). Biopsija kosti ukazala je na reaktivnu koštanu srž uz megakariocitnu trombocitopeniju. Hipoalbuminemija je bila klinički praćena otokom mekih tkiva, pleuralnim izlivima i ascitesom.

Pri inicijalnom fizikalnom pregledu, u Univerzitet-skom kliničkom centru Srbije, viđen je malarni osip uz bezbolne ulceracije u usnoj duplji. Pacijentkinja je negirala artralgijske, a klinički nije bilo znakova artritisa. U pristiglim imunološkim analizama je registrovana visokopozitivna ANA na HEp2 supstratu, homogenog bojenja nukleoplazme u titru $>> 1:640$ deobne ćelije $>> 1:640$, kao i antitela usmerena protiv dvolančane dezoksiribonukleinske kiseline (engl. *double-stranded deoxyribonucleic acid – dsDNA*) $>> 1:640$, uz potrošnju obe komponente komplementa (C3 0,16 g/l; C4 0,02 g/l).

syndrome with a fatal outcome, and to highlight the importance of rapid recognition and appropriate treatment of this life-threatening complication of systemic lupus erythematosus.

CASE REPORT

A 33-year-old female patient had been experiencing recurrent episodes of cholangitis since childhood, following surgical treatment of biliary atresia at the age of two months. Immunological evaluation revealed positive antinuclear antibodies (ANA), which had persisted for several years, along with anti-Sjögren's syndrome A antibodies (ASSA), anti-smooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA). Despite the persistent antibody positivity over several years, neither a systemic autoimmune disease nor an organ-specific autoimmune disease of the liver and biliary tract had been considered in the differential diagnosis. Her personal and family medical histories were unremarkable.

Predominantly general and gastrointestinal symptoms (right upper quadrant pain, nausea, vomiting, and loose stools) accompanied by fever up to 39 °C in December 2022 were interpreted as yet another episode of cholangitis. In addition to abnormal liver function tests and renal injury, pancytopenia was also detected (WBC $2.87 \times 10^9/l$; RBC $3.05 \times 10^{12}/l$; hemoglobin 94 g/l; thrombocytopenia), together with a coagulation disorder consistent with consumptive coagulopathy (D-dimer 5.23 mg/l; fibrinogen 1.23 g/l). Ultrasonography revealed hepatosplenomegaly and ascites, while magnetic resonance cholangiopancreatography ruled out obstructive disease of the biliary tract. At the healthcare institution in charge of her treatment, the patient received antibiotics, red blood cell transfusions, granulocyte colony-stimulating factors, ursodeoxycholic acid, and symptomatic therapy, resulting in short-term clinical improvement.

In January 2023, the patient again developed fever accompanied by a productive cough, peripheral lymphadenopathy, hepatosplenomegaly, and worsening pancytopenia (WBC $1.0 \times 10^9/l$; RBC $2.34 \times 10^{12}/l$; hemoglobin 79 g/l; platelet count $81 \times 10^9/l$). Bone marrow biopsy indicated reactive bone marrow with megakaryocytic thrombocytopenia. Hypoalbuminemia clinically manifested as soft-tissue edema, pleural effusions, and ascites.

At her initial physical examination at the University Clinical Center of Serbia, a malar rash and painless oral ulcerations were observed. The patient denied arthralgia, and there were no clinical signs of arthritis. The available immunological analyses showed strongly positive ANA on a HEp-2 substrate, with homogeneous nucleoplasmic staining at a titer of $> 1:640$, as

Na osnovu febrilnosti, malarnog osipa, oralnih ulceracija, poliserozitisa (pleuralni izliv, ascites), pozitivnih ANA, pozitivnih dsDNA, potrošnje obe komponente komplementa, leuko/limfopenije, autoimunske hemolizne anemije, trombocitopenije i lezije bubrega sa eritrociturijom i proteinurijom do 1,13 g/dan, zaključeno je da se kod pacijentkinje radi o sistemskom eritemskom lupusu sa elementima akutne lezije bubrega i jetre.

Ubrzo dolazi do promene mentalnog statusa sa halucinacijama i izraženim košmarnim sadržajima. Razmatran je neurolupus, koji nije potvrđen usled odsustva adekvatnog neuroradiološkog korelata na magnetnoj rezonanci (MR) endokranijuma. Lečenje je započeto metilprednizolonom u pulsним dozama od po 250 mg (ukupno tri pulsa), a potom nastavljeno u dozi od 1 mg/kg telesne mase (TM).

Sprovedene su detaljne mikrobiološke analize. Isključene su bakterijske, virusne i gljivične infekcije – uredni nalazi briseva nosa i ždrela, pregleda sputuma na bakterije i gljivice, urinokulture, hemokulture na aerobe, anaerobe i gljivice uzorkovane u više navrata, serologije na *Leishmania infantum*; virus teškog akutnog respiratornog sindroma 2 (SARS-CoV-2), virusi hepatitisa B i C, virus humane imunodeficijencije, Epštajn-Bar virus – EBV i citomegalovirus; *Aspergillus* i *Candida spp.*, negativni galatkomanan i *Candida mannan* antigen.

Uprkos započetoj kortikosteroidnoj terapiji, dolazi do pogoršanja pancitopenije, uz ekstremnu hiperferitinemiju ($> 33511 \mu\text{g/l}$), hipofibrinogenemiju i hipertrigliceridemiju, kao i uz održavanje hepatosplenomegalije i periferne limfadenopatije. Primenom kriterijuma definisanih preporukama za dijagnostiku i lečenje hemofagocitne limfohistiocitoze iz 2004. godine (HLH-2004), zaključeno je da se radi o sindromu aktivacije makrofaga (H-skor 266; referentna vrednost > 250 upućuje na MAS sa verovatnoćom od preko 99%) kao komplikaciji aktivnog, više godina neprepoznatog sistemskog eritemskog lupusa. Povećava se 24 h-proteinurija na 2,48 g/dan.

Nastavljena je primena pulsних doza metilprednizolona od po 500 mg (primila kumulativno ukupno 2,25 g) i započeta primena ciklosporina 3mg/kg TM. Nakon inicijalno kratkotrajnog kliničkog i diskretnog laboratorijskog poboljšanja, opšte stanje pacijentkinje se ponovo pogoršava u vidu febrilnosti, kašlja, tahidispnee. Primenjene su imunomodulatorne doze intravenskih imunoglobulina (IVIG) u ukupnoj dozi od 2 g/kg TM, uz nastavak terapije metilprednizolonom i ciklosporinom. Uprkos primenjenoj terapiji ne dolazi do zadovoljavajućeg kliničkog odgovora i stanje se komplikuje razvojem anasarke, sa znacima parcijalne respiratorne, srčane (EF 10–15%) i bubrežne insuficijencije (najpre kao posledica sindroma sistemskog kapilarnog curenja).

Pacijentkinja je dodatno lečena terapijskim izmenama plazme i intenzivnim ultrafiltracijama. Razmatrana je i mogućnost primene dodatnih lekova poput

well as antibodies directed against double-stranded deoxyribonucleic acid (dsDNA) at a titer of $> 1:640$, accompanied by consumption of both complement components (C3 0.16 g/l; C4 0.02 g/l).

Based on fever, malar rash, oral ulcerations, polyserositis (pleural effusion, ascites), positive ANA, positive dsDNA antibodies, consumption of both complement components, leukopenia/lymphopenia, autoimmune hemolytic anemia, thrombocytopenia, and renal involvement with erythrocyturia and proteinuria of up to 1.13 g/day, it was concluded that the patient had systemic lupus erythematosus presenting with acute kidney and liver injury.

The patient's mental status soon changed, and she experienced hallucinations and vivid nightmares. Neuropsychiatric lupus was considered but was not confirmed due to the absence of an adequate neuroradiological correlate on magnetic resonance imaging (MRI) scans of the brain. Treatment was initiated with methylprednisolone at pulse doses of 250 mg each (three pulses in total), which was continued at a dose of 1 mg/kg body weight (BW).

Detailed microbiological analyses were performed. Bacterial, viral, and fungal infections were excluded, specifically – unremarkable findings from nasal and pharyngeal swabs, sputum examination for bacteria and fungi, urine cultures, and blood cultures for aerobic and anaerobic bacteria and fungi obtained on multiple occasions, serology for *Leishmania infantum*; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hepatitis B and C viruses, human immunodeficiency virus, Epstein–Barr virus (EBV), and cytomegalovirus; *Aspergillus* and *Candida spp.*, negative galactomannan and *Candida mannan* antigen tests.

Although corticosteroid therapy was introduced, pancytopenia worsened, accompanied by extreme hyperferritinemia ($> 33,511 \mu\text{g/l}$), hypofibrinogenemia, and hypertriglyceridemia, with persistent hepatosplenomegaly and peripheral lymphadenopathy. Applying the criteria defined in the 2004 recommendations for the diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH-2004), the condition was diagnosed as macrophage activation syndrome (H-score 266; a reference value > 250 indicates MAS with a probability of more than 99%) as a complication of active systemic lupus erythematosus that had remained unrecognized for several years. Twenty-four-hour proteinuria increased to 2.48 g/day.

Treatment with methylprednisolone pulse doses of 500 mg each was continued (a cumulative total dose of 2.25 g was administered), and cyclosporine was initiated at 3 mg/kg BW. Following an initially brief clinical and modest laboratory improvement, the pa-

Tabela 1. Laboratorijske i imunološke analize tokom lečenja pacijentkinje: po postavljanju dijagnoze SEL, uspostavljanju dijagnoze SEL sa MAS, i po razvoju sindroma multiorganske disfunkcije**Table 1.** Laboratory and immunological analyses during the patient's treatment: at the time of SLE diagnosis, upon establishment of the diagnosis of SLE with MAS, and following the development of multiple organ dysfunction syndrome

Parametri (referentne vrednosti) / Parameters (reference values)	Dijagnoza SEL (07.01.2023) / SLE diagnosis (January 7, 2023)	Dijagnoza SEL/MAS (17.01.2023) / SLE/MAS diagnosis (January 17, 2023)	MODS (06.02.2023) / MODS (February 6, 2023)
Leukociti (3,4–9,7x10 ⁹ /l) / WBC (3.4–9.7x10 ⁹ /l)	1.0	2.1	6.4
Hemoglobin (119–157 g/l) / Hemoglobin (119–157 g/l)	79	74	82
Trombociti (158–424x10 ⁹ /l) / Platelet count (158–424x10 ⁹ /l)	81	59	35
C reaktivni protein (0–5 mg/l) / C-reactive protein (0–5 mg/l)	1.1	23.1	119.7
Sedimentacija eritrocita (0–10 mm/h) / ESR (0–10 mm/h)	12	34	10
Interleukin 6 (0–7 pg/ml) / Interleukin 6 (0–7 pg/ml)	5.7	148.5	3,549
Feritin (4,6–204 µg/l) / Ferritin (4.6–204 µg/l)	> 33,511	12,236	1,798
Fibrinogen (2–4 g/l) / Fibrinogen (2–4 g/l)	2.5	2.2	2.6
D-dimer (< 0,5 mg/l) / D-dimer (< 0.5 mg/l)	1.72	2.87	8.32
Trigliceridi (0–1,7 mmol/l) / Triglycerides (0–1.7 mmol/l)	6.82	3.44	2.3
Urea (2,5–7,5 mmol/l) / Urea (2.5–7.5 mmol/l)	11.8	9.8	29.1
Kreatinin (45–84 µmol/l) / Creatinine (45–84 µmol/l)	189	50	143
eGFR (> 60 ml/min/1,73 m ²) / eGFR (> 60 ml/min/1.73 m ²)	51	60	37
Sediment urina / Urine sediment	eritrociturija, proteinurija (+++) / erythrocyturia, proteinuria (+++)		
24h proteinurija (0–0,15 g/24 h) / 24-hour proteinuria (0–0.15 g/24 h)	1.92	2.49	/
Ukupni proteini (62–81 g/l) / Total protein (62–81 g/l)	43	47	50
Albumini (34–55 g/l) / Albumins (34–55 g/l)	22	27	24
Aspartat transaminaza (0–37 U/l) / Aspartate transaminase (0–37 U/l)	1,011	82	49
Alanin transaminaza (0–41 U/l) / Alanine transaminase (0–41 U/l)	319	98	45
Gama-glutamil transferaza (0–38 U/l) / Gamma-glutamyl transferase (0–38 U/l)	621	694	198
Laktat dehidrogenaza (220–460 u/l) / Lactate dehydrogenase (220–460 u/l)	1,254	343	657
Imunološke analize / Immunological analyses	ANA HEp2 nukleoplazma homogena >> 1:640, deobne ćelije >> 1:640; anti-dsDNA >> 1:640 ENA screen ++ / ANA HEp2 homogeneous nucleoplasm >> 1:640, proliferating cells >> 1:640; anti-dsDNA >> 1:640 ENA screen ++		
C3 (0,65–1,8 g/l) / C3 (0.65–1.8 g/l)	0.18	0.23	0.27
C4 (0,1–0,4 g/l) / C4 (0.1–0.4 g/l)	0.03	< 0.027	0.03
H skor (< 169) / H score (< 169)	205	266 (> 99% verovatnoće za MAS / probability of MAS)	143

etopozida i rekombinantnog inhibitora interleukina-1 (anakinra). Zbog razvoja globalne respiratorne insuficijencije pacijentkinja je priključena na neinvazivnu, a potom na invazivnu mehaničku ventilaciju.

Nakon inicijalnog, kratkotrajnog, kliničkog, laboratorijskog i ehokardiografskog poboljšanja, u daljem toku dolazi do produbljivanja sindroma multiorganske disfunkcije koji se, uprkos svim primenjenim modalitetima lečenja, završava fatalnim ishodom 34 dana po postavljanju dijagnoze sistemskog eritemskog lupusa.

Laboratorijske i imunološke analize tokom lečenja pacijentkinje su prikazane u Tabeli 1.

tient's general condition deteriorated again, with fever, cough, and tachypnea. Immunomodulatory doses of intravenous immunoglobulins (IVIG) were administered at a total dose of 2 g/kg BW, with continuation of methylprednisolone and cyclosporine therapy. Despite the treatment administered, there was no satisfactory clinical response, and the condition became further complicated by the development of anasarca, with signs of partial respiratory, cardiac (EF 10–15%), and renal insufficiency (primarily due to systemic capillary leak syndrome).

The patient was additionally treated with thera-

DISKUSIJA

Aktivan SEL i MAS se preklapaju u određenim kliničkim i laboratorijskim karakteristikama kao što su febrilnost, psihijatrijske tegobe, pancitopenija, znaci insuficijencije više organskih sistema. Kako i SEL i MAS mogu da obuhvate različite sisteme organa, ne postoji patognomoničan nalaz koji ih razlikuje. Mnoge od navedenih manifestacija se mogu videti i u teškim infekcijama, zbog čega diferencijalna dijagnoza između ova tri entiteta predstavlja izazov.

Postojeći dijagnostički kriterijumi za MAS su nedovoljne senzitivnosti i specifičnosti, posebno kad kod pacijenta postoje koegzistirajuća stanja (infekcije, inflamacije, maligniteti) [1]. Imajući u vidu fulminantan tok sindroma aktivacije makrofaga i veliku smrtnost, postojanje specifičnog i senzitivnog biomarkera bi bilo od izuzetnog kliničkog značaja. Evropski savez udruženja za reumatologiju (engl. *European Alliance of Associations for Rheumatology – EULAR*) i Američki koledž za reumatologiju (engl. *American College of Rheumatology – ACR*) u svojim preporukama za rano prepoznavanje MAS, ističu značaj određivanja i serijskog praćenja koncentracije feritina [1]. Feritin vezuje slobodno gvožđe smanjujući oksidativni stres i inhibirajući apoptozu endotelih ćelija, te je porast njegove koncentracije najpre kompenzatorni mehanizam u uslovima hiperinflamacije [7]. Ukoliko se isključe alternativni uzroci hiperferitinemije, kao što su preopterećenost gvožđem, hepatitis i maligniteti, koncentracije feritina > 10 000 µg/l kod odraslih pacijenata se smatraju visoko sugestivnim za MAS [1,5,8]. Kod dece se značajnim smatraju i niže koncentracije feritina (500–2000 µg/l) [1]. Visoka koncentracija feritina, zabeležena u slučaju naše pacijentkinje – inicijalno pripisana leziji jetre, svakako je daljim porastom usmerila diferencijalnu dijagnozu ka razmatranju MAS.

Laktat dehidrogenaza (LDH) bi, uz koncentraciju feritina, mogla da bude značajan marker u prepoznavanju sindroma aktivacije makrofaga [4], ali treba imati na umu da povišen nivo LDH može da upućuje i na druge i/ili paralelne inflamatorne procese [9]. Povišene vrednosti LDH kod naše pacijentkinje su shvaćene kao posledica aktivne hemolize i lezije jetre (Tabela 1). Kako je u daljem toku došlo do normalizacije hepatograma, održavanje izuzetno povišenih koncentracija feritina je, uz produbljivanje pancitopenije, hipofibrinogemiju i hipertrigliceridemiju, primenom HLH-2004 kriterijuma dovelo do zaključka da se radi o MAS kao komplikaciji aktivnog sistemskog eritemskog lupusa [2]. Drugi biomarkeri za MAS su merenje aktivnosti T-ćelija (solubilni IL-2 receptor-α, ekspresija DR izotipa humanog leukocitnog antigena), makrofaga (npr. CD163,

peutic plasma exchange and intensive ultrafiltration. The possibility of administering additional drugs, such as etoposide and the recombinant interleukin-1 inhibitor anakinra, was also considered. Due to the development of global respiratory failure, the patient was placed first on noninvasive and subsequently on invasive mechanical ventilation.

Following an initial, short-term clinical, laboratory, and echocardiographic improvement, the subsequent course was characterized by worsening of multiple organ dysfunction syndrome which, despite all treatment modalities employed, resulted in a fatal outcome 34 days after the diagnosis of systemic lupus erythematosus was established.

Laboratory and immunological analyses obtained during the patient's treatment are presented in Table 1.

DISCUSSION

Active SLE and MAS overlap in certain clinical and laboratory characteristics, such as fever, psychiatric symptoms, pancytopenia, and signs of multiple organ dysfunction. Since both SLE and MAS can involve different organ systems, there is no pathognomonic finding that can distinguish between them. Many of the aforementioned manifestations may also occur in severe infections, making the differential diagnosis among these three entities challenging.

The existing diagnostic criteria for MAS have insufficient sensitivity and specificity, particularly when patients have coexisting conditions such as infections, inflammatory disorders, or malignancies [1]. Given the fulminant course of macrophage activation syndrome and its high mortality, the availability of a specific and sensitive biomarker would be of exceptional clinical importance.

The European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), in their recommendations for the early recognition of MAS, emphasize the importance of determining and serially monitoring ferritin concentrations [1]. Ferritin binds free iron, thereby reducing oxidative stress and inhibiting endothelial cell apoptosis; thus, an increase in its concentration initially represents a compensatory mechanism under conditions of hyperinflammation [7]. After excluding alternative causes of hyperferritinemia, such as iron overload, hepatitis, and malignancies, ferritin concentrations >10,000 µg/l in adult patients are considered highly suggestive of MAS [1,5,8]. In children, lower ferritin concentrations (500–2,000 µg/l) are also considered clinically significant [1]. The high ferritin concentration recorded in our patient, initially attributed to liver injury, subsequently increased further and consequently directed the differential diagnosis toward MAS.

neopterin), inflamazoma (interleukin (IL)-18) i puta interferona gama (IFN γ). Iako specifičniji, ovi biomarkeri često nisu rutinski dostupni u kliničkoj praksi [1,9].

U nedostatku jedinstvenog kliničkog, laboratorijskog i/ili patološkog nalaza za MAS, razvijen je tzv. H-skor (engl. *H-score*) koji procenjuje rizik za razvoj sindroma aktivacije makrofaga. Sistem bodovanja obuhvata kombinaciju devet kliničkih, laboratorijskih i citoloških parametara: prethodna imunosuprimiranost, febrilnost, organomegalija, citopenije, koncentracija feritina, triglicerida, fibrinogena, vrednosti aspartat transaminaze, te prisustvo hemofagocita u aspiratu koštane srži. Granična (engl. *cutoff*) vrednost H-skora iznosi 169, što odgovara senzitivnosti od 93% i specifičnosti od 86%, dok vrednosti H-skora preko 250 govore sa > 99% verovatnoće da se radi o MAS [8,10].

Naknadnom evaluacijom kliničko-laboratorijskih parametara u trenutku postavljanja dijagnoze sistemskog eritemskog lupusa, kod naše pacijentkinje je utvrđen H-skor 205 koji govori sa 88-93% verovatnoće da je došlo do razvoja MAS [10]. Međutim, niža vrednost H-skora (143) u trenutku razvoja sindroma multiorganske disfunkcije bi mogla da upućuje na iscrpljenost kompenzatornih mehanizama pacijentkinje i smanjene produkcije proinflamatornih citokina. Značaj ovog sistema bodovanja se ogleda u tome što omogućava kliničarima da, na osnovu kliničke slike i rutinskih laboratorijskih analiza, brzo procene verovatnoću da je kod pacijenta došlo do razvoja MAS i blagovremeno započnu lečenje. Navedene parametre treba pratiti longitudinalno kroz vreme uz reevaluaciju H-skora, nekada i više puta dnevno, ukoliko kliničko stanje pacijenta tako nalaže.

Manifestacije centralnog nervnog sistema (CNS) nisu uključene u HLH-2004 dijagnostičke kriterijume [2], što u kliničkoj praksi može biti razlog da se ne uoče blagovremeno. Iako se češće javljaju u pedijatrijskom uzrastu, ni kod odraslih ne smeju biti zanemarene. Poremećaj mentalnog statusa ili stanja svesti, pojava konvulzija, encefalopatije, meningizma, znakovi zahvaćenosti kranijalnih nerava, zahtevaju dopunsku neurološku obradu – MR endokranijuma sa/bez angiografije, lumbalnu punkciju sa pregledom cerebrospinalne tečnosti i elektroencefalografiju (EEG) [1,11]. Kako je MR endokranijuma naše pacijentkinje isključila parenhimske promene u sklopu SEL, njene neuropsihijatrijske tegobe su shvaćene kao manifestacije sindroma aktivacije makrofaga.

Patofiziologija sindroma aktivacije makrofaga je izuzetno kompleksna i zasniva se na disfunkciji citotoksičnih ćelija (NK ćelija i CD8⁺ T-limfocita) koje u uslovima adekvatnog imunskog odgovora zaustavljaju inflamaciju eliminacijom aktiviranih antigen-prezentujućih

Lactate dehydrogenase (LDH), together with ferritin concentration, may be an important marker for the recognition of macrophage activation syndrome [4], but it should be kept in mind that an elevated LDH level may also indicate other and/or concomitant inflammatory processes [9]. The elevated LDH levels in our patient were interpreted as a consequence of active hemolysis and liver injury (Table 1). As liver function tests subsequently normalized, the persistence of extremely elevated ferritin concentrations, together with worsening pancytopenia, hypofibrinogenemia, and hypertriglyceridemia, led, upon application of the HLH-2004 criteria, to the conclusion that the patient had MAS as a complication of active systemic lupus erythematosus [2]. Other biomarkers for MAS include assessment of T-cell activity (soluble IL-2 receptor- α , expression of the DR isotype of human leukocyte antigen), macrophage activity (e.g., CD163, neopterin), the inflammasome (interleukin [IL]-18), and the interferon-gamma (IFN γ) pathway. Although more specific, these biomarkers are often not routinely available in clinical practice [1,9].

In the absence of a single clinical, laboratory, and/or pathological finding to diagnose MAS, the so-called H-score was developed to assess the risk of developing macrophage activation syndrome. The scoring system incorporates a combination of nine clinical, laboratory, and cytological parameters: previous immunosuppression, fever, organomegaly, cytopenias, ferritin concentration, triglyceride concentration, fibrinogen concentration, aspartate transaminase levels, and the presence of hemophagocytes in a bone marrow aspirate. The H-score cutoff value is 169, corresponding to a sensitivity of 93% and specificity of 86%, whereas H-score values above 250 indicate a >99% probability of MAS [8,10].

Retrospective evaluation of the clinical and laboratory parameters at the time of SLE diagnosis revealed an H-score of 205 in our patient, corresponding to an 88%–93% probability of MAS development [10]. However, the lower H-score (143) at the time of development of multiple organ dysfunction syndrome could indicate exhaustion of the patient's compensatory mechanisms and reduced production of proinflammatory cytokines. The significance of this scoring system lies in its ability to enable clinicians, based on the clinical presentation and routine laboratory analyses, to rapidly assess the probability that a patient has developed MAS and to initiate treatment promptly. These parameters should be monitored longitudinally over time, with reassessment of the H-score, sometimes several times a day, if warranted by the patient's clinical condition.

ćelija, na prvom mestu makrofaga. Kada takav imunski odgovor izostane, T-limfociti i makrofagi ostaju stalno aktivni. Makrofagi dovode do fagocitoze krvnih ćelija (hemofagocitoza) i amplifikacije inflamatornog odgovora koji kroz tzv. citokinsku oluju sam sebe održava. Pored faktora nekroze tumora (engl. *tumor necrosis factor* – *TNF*) koji je odgovoran za oštećenje tkiva, aktivirani makrofagi proizvode i brojne interleukine. IL-18 stimuliše CD8⁺ T-limfocite koje proizvode IFN γ i aktivirajući makrofage amplifikuju ovu citokinsku kaskadu. Smatra se da su IL-1 i IL-6 odgovorni za sistemsku inflamaciju u sindromu aktivacije makrofaga [3,7]. Navedeni citokini i/ili njihovi receptori mogu biti meta terapijskog delovanja (npr. anakinra je monoklonsko antitelo koje se vezuje za alfa subjedinicu IL-1 receptora). Ograničena dostupnost ciljanih bioloških lekova je glavni razlog za izostanak njihove češće primene u kliničkoj praksi.

EULAR/ACR preporučuju visoke doze glukokortikoida uz anakinru i/ili IVIG kao prvu terapijsku opciju za lečenje MAS kod odraslih, čak i pre definitivnog otkrivanja uzroka [1]. Izbor glukokortikoida je individualan i prilagođen specifičnostima sindroma aktivacije makrofaga kod pacijenta. Pulsne doze metilprednizolona (10–30 mg/kg telesne mase/dan, do 1 g dnevno) su prvi izbor u situacijama kad je potreban brži terapijski efekat. Zbog prolaska krvno-moždane barijere, deksametazon (10 mg/m²/dan) je pogodan za pacijente sa CNS manifestacijama. Naša pacijentkinja je inicijalno imala dobar klinički odgovor na pulsne doze metilprednizolona, a deksametazon je aplikovan nešto kasnije, u skladu sa kliničkim stanjem. Psihijatrijske tegobe se nisu ponavljale.

Glukokortikoide treba davati sa oprezom kad postoji sumnja da je MAS pokrenut/održavan infekcijom ili malignitetom. U tim situacijama su pogodniji IVIG ili anakinra koji omogućavaju imunomodulaciju bez imunosupresije. Oni omogućavaju veću bezbednost bez uticaja na eventualno naknadno ispitivanje etiologije MAS [1,12]. Imunomodulatorne doze IVIG su, uz metilprednizolon i ciklosporin A, kod naše pacijentkinje samo tranzitorno dovele do povoljnog terapijskog efekta. Brz početak dejstva i kratak polужivot anakinre je čini pogodnom za MAS pokrenut sistemskim autoimunskim bolestima [7,13], ali u konkretnom slučaju nije bio dostupan za brzu primenu kod naše pacijentkinje. Etoposid je takođe razmatran, ali je u kontekstu brzo napredujuće slike sindroma multiorganske disfunkcije, zaključeno da bi njegova primena pogoršala postojeću tešku srčanu insuficijenciju [14].

Ciklosporin A je, zbog svog efekta na smanjenje produkcije IL-1, IL-6 i TNF α , koji igraju ključnu ulogu u patogenezi sindroma aktivacije makrofaga, zauzeo

Central nervous system (CNS) manifestations are not included in the HLH-2004 diagnostic criteria [2], which in clinical practice may be a reason why they are not recognized on time. Although they occur more frequently in the pediatric population, they should not be overlooked in adults either. Altered mental status or level of consciousness, seizures, encephalopathy, meningism, and signs of cranial nerve involvement require additional neurological evaluation, including brain MRI with or without angiography, lumbar puncture with cerebrospinal fluid analysis, and electroencephalography (EEG) [1,11]. Since brain MRI scans in our patient excluded parenchymal changes associated with SLE, her neuropsychiatric symptoms were interpreted as manifestations of macrophage activation syndrome.

The pathophysiology of macrophage activation syndrome is extremely complex and is based on dysfunction of cytotoxic cells (NK cells and CD8⁺ T lymphocytes), which, under conditions of an adequate immune response, terminate inflammation by eliminating activated antigen-presenting cells, primarily macrophages. When such an immune response is absent, T lymphocytes and macrophages remain continuously activated. Macrophages cause phagocytosis of blood cells (hemophagocytosis) and amplify the inflammatory response, which sustains itself through the so-called cytokine storm. In addition to tumor necrosis factor (TNF), which is responsible for tissue damage, activated macrophages produce numerous interleukins. IL-18 stimulates CD8⁺ T lymphocytes, which produce IFN γ and, by activating macrophages, amplify this cytokine cascade. IL-1 and IL-6 are considered responsible for systemic inflammation in MAS [3,7]. These cytokines and/or their receptors may represent therapeutic targets (e.g., anakinra is a monoclonal antibody that binds to the alpha subunit of the IL-1 receptor). Limited availability of targeted biological agents is the main reason for their infrequent use in clinical practice.

EULAR/ACR recommend high-dose glucocorticoids with anakinra and/or IVIG as the first therapeutic option for the treatment of MAS in adults, even before the underlying cause has been definitively identified [1]. The choice of glucocorticoid is individualized and tailored to the specific characteristics of MAS in each patient. Methylprednisolone pulse doses (10–30 mg/kg body weight/day, up to 1 g/day) are the first choice when a rapid therapeutic effect is required. Because of its ability to cross the blood–brain barrier, dexamethasone (10 mg/m²/day) is suitable for patients with CNS manifestations. Our patient initially showed a good clinical response to methylprednisolone pulse doses, while dexamethasone was administered a bit later,

značajno mesto u terapijskom algoritmu. Iako to nije bio slučaj kod naše pacijentkinje, u dozi od 3 mg/kg telesne mase/dan u kombinaciji sa visokim dozama glukokortikoida i IVIG može dovesti ne samo do indukcije već i do održavanja remisije sindroma aktivacije makrofaga indukovanog sistemskim eritemskim lupusom [15].

Terapijske izmene plazme (TIP) su se pokazale kao efikasna *add-on* terapija u MAS (uz glukokortikoidnu i imunosupresivnu terapiju) dovodeći do redukcije proinflammatoryh citokina [16]. Iako postoje podaci da su TIP dovodile i do redukcije mortaliteta kod pacijenata sa MAS, ishod je u slučaju naše pacijentkinje bio nepovoljan, što je verovatno bilo uslovljeno već odmaklim stadijumom bolesti sa posledičnim sindromom multiorganske disfunkcije unutar mesec dana od započinjanja lečenja.

Prema pregledu literature o aktuelnim terapijskim modalitetima MAS u pedijatrijskom uzrastu iz 2025. godine, visoke doze glukokortikoida uz inhibitore IL-1 (anakinra) i IFN γ (emapalumab) efikasne su u terapiji sindroma aktivacije makrofaga koji je povezan sa sJIA. Podaci o eventualnoj terapijskoj efikasnosti ove kombinacije kod drugih sistemskih autoimunskih bolesti, kao što je SEL, još uvek su oskudni [17].

Emapalumab, humanizovano monoklonsko antitelo usmereno na IFN γ , pokazao je veliku efikasnost za indukciju remisije kod dece sa rekurentnim i refraktarnim primarnim HLH [18]. De Benedetti i saradnici su pokazali da je emapalumab efikasan i kod pacijenata sa sekundarnim MAS, kod kojih visoke doze glukokortikoida, kao monoterapija ili konkomitantno uz anakinru i/ili ciklosporin, nisu pokazale zadovoljavajući efekat [19]. Iako dokazano efikasna terapijska metoda, nedostupnost emapalumaba u određenim zemljama, uključujući i Srbiju, jeste razlog što se još uvek nije započelo sa njegovom primenom.

Ruksolitinib (inhibitor Janus kinaze, JAK1 i JAK2) takođe je pokazao izvesnu efikasnost kod maligniteta i MAS za koji je okidač EBV infekcija kod odraslih [1,20], ali se i dalje savetuje oprez kod MAS pokrenutog sistemskim autoimunskim bolestima [6]. Iako IL-6 ima svoju ulogu u nastanku i održavanju citokinske oluje, blokada njegovog receptora tocilizumabom, nije se pokazala kao dovoljno efikasna opcija u lečenju MAS [7].

Velika studija slučaj-kontrola u Bostonu na preko 2.000 odraslih pacijenata sa sistemskim eritemskim lupusom, pokazala je da upotreba hidroksihlorokina smanjuje šansu za razvojem MAS, najverovatnije zbog njegovog efekta na produkciju proinflammatoryh citokina koji učestvuju u patogenezi MAS. Takođe, pacijenti sa artritisa u sklopu sistemskog eritemskog lupusa su ređe imali klinički tok komplikovan sindromom ak-

in keeping with her clinical condition. The psychiatric symptoms did not recur.

Glucocorticoids should be administered with caution when MAS is suspected to have been triggered or sustained by infection or malignancy. In such situations, IVIG or anakinra are more appropriate because they enable immunomodulation without immunosuppression. They provide greater safety without interfering with subsequent investigation of the etiology of MAS [1,12].

In our patient, immunomodulatory doses of IVIG, together with methylprednisolone and cyclosporine A, resulted in only a transient favorable therapeutic effect. The rapid onset of action and short half-life of anakinra make it suitable for MAS triggered by systemic autoimmune diseases [7,13]. However, it was not available for rapid administration to our patient. Etoposide was also considered; however, in the context of the rapidly progressive picture of multiple organ dysfunction syndrome, it was concluded that its administration would worsen the existing severe cardiac insufficiency [14].

Cyclosporine A, owing to its effect on reducing the production of IL-1, IL-6, and TNF α , which play a key role in the pathogenesis of macrophage activation syndrome, has assumed an important place in the therapeutic algorithm. Although this was not the case in our patient, at a dose of 3 mg/kg body weight/day in combination with high-dose glucocorticoids and IVIG, it may lead not only to induction but also to maintenance of remission of systemic lupus erythematosus-induced macrophage activation syndrome [15].

Therapeutic plasma exchange (TPE) has been shown to be an effective *add-on* therapy in MAS (in addition to glucocorticoid and immunosuppressive therapy), resulting in a reduction in proinflammatory cytokines [16]. Although there are data indicating that TPE may also reduce mortality in patients with MAS, the outcome in our patient was unfavorable, probably owing to the already advanced stage of the disease, with consequent multiple organ dysfunction syndrome developing within one month of starting treatment.

According to a 2025 review of current therapeutic modalities for MAS in the pediatric population, high-dose glucocorticoids combined with IL-1 inhibitors (anakinra) and IFN γ inhibitors (emapalumab) are effective in the treatment of MAS associated with sJIA. Data on the potential therapeutic efficacy of this combination in other systemic autoimmune diseases, such as SLE, remain scarce [17].

Emapalumab, a humanized monoclonal antibody directed against IFN γ , has demonstrated high efficacy in inducing remission in children with recurrent and refractory primary HLH [18]. De Benedetti et al. demonstrated that emapalumab is also effective in

tivacije makrofaga [21]. Zbog fulminantnog toka SEL i MAS i rapidnog pogoršanja opšteg stanja naše pacijentkinje, hidroksihlorokin u kratkotrajnoj primeni nije mogao postići željeni klinički efekat.

Iako genetsko testiranje nije rutinski indikovano kod svih bolesnika sa sindromom aktivacije makrofaga u sklopu sistemskog eritemskog lupusa, treba ga razmotriti u selektovanim slučajevima, posebno kod pacijenata sa ranom pojavom bolesti, rekurentnim i/ili refraktornim MAS, pozitivnom porodičnom anamnezom ili funkcionalnim poremećajima citotoksičnosti NK i T ćelija. U ovim situacijama identifikacija genetske predispozicije može imati značajan uticaj na dijagnostiku, procenu prognoze i izbor terapije [1].

Pacijenti sa sumnjom ili već razvijenim MAS se, bez obzira na uzrok, moraju lečiti u jedinicama intenzivne nege uz kontinuirano praćenje vitalnih parametara i redovno praćenje laboratorijskih analiza. Bitno je što pre identifikovati osnovnu bolest, ali i doprinoseće faktore i lečiti ih paralelno. Individualizovan pristup pacijentima sa MAS omogućava bolje prevazilaženje izazova u kontekstu prepoznavanja osnovne bolesti, procene faktora rizika i odluke o terapiji. Formiranje multidisciplinarnog tima sačinjenog od lekara različitih specijalnosti, u zavisnosti od prezentacije i kliničkog toka bolesti, od presudnog je značaja za pravovremeno prepoznavanje i lečenje komplikacija sindroma aktivacije makrofaga [1].

ZAKLJUČAK

Preklapanje kliničkih i laboratorijskih manifestacija aktivnog sistemskog eritemskog lupusa, sindroma aktivacije makrofaga i teških infekcija značajno otežava pravovremeno postavljanje dijagnoze. Na MAS se mora misliti kod pacijenata sa aktivnim SEL i/ili znacima multiorganske disfunkcije. Praćenje specifičnih biomarkera je od presudnog značaja za pravovremeno postavljanje dijagnoze, pri čemu se koncentracije feritina > 10 000 µg/l smatraju visoko sugestivnim za MAS. Rano prepoznavanje ovog sindroma i primena adekvatne imunomodulatorne terapije su ključni za poboljšanje kliničkog ishoda i smanjenje mortaliteta ovih kompleksnih pacijenata.

Sukob interesa: Nije prijavljen.

patients with secondary MAS in whom high-dose glucocorticoids, either as monotherapy or concomitantly with anakinra and/or cyclosporine, failed to produce a satisfactory response [19]. Although this is a proven effective therapeutic modality, the unavailability of emapalumab in certain countries, including Serbia, is the reason why its use has not yet been initiated.

Ruxolitinib (a Janus kinase inhibitor, JAK1 and JAK2) has also demonstrated some efficacy in malignancies and MAS triggered by EBV infection in adults [1,20], but caution is still advised in MAS triggered by systemic autoimmune diseases [6]. Although IL-6 plays a role in the development and maintenance of the cytokine storm, blockade of its receptor with tocilizumab has not proven to be a sufficiently effective option for the treatment of MAS [7].

A large case-control study conducted in Boston involving more than 2,000 adult patients with systemic lupus erythematosus showed that hydroxychloroquine use reduced the likelihood of developing MAS, most likely because of its effect on the production of proinflammatory cytokines involved in the pathogenesis of MAS. In addition, patients with arthritis associated with systemic lupus erythematosus were less likely to have a clinical course complicated by macrophage activation syndrome [21]. Owing to the fulminant course of SLE and MAS and the rapid deterioration of our patient's general condition, short-term administration of hydroxychloroquine could not achieve the desired clinical effect.

Although genetic testing is not routinely indicated in all patients with macrophage activation syndrome associated with systemic lupus erythematosus, it should be considered in selected cases, particularly in patients with early disease onset, recurrent and/or refractory MAS, a positive family history, or functional abnormalities of NK and T-cell cytotoxicity. In these situations, identification of a genetic predisposition may have a significant impact on diagnosis, prognostic assessment, and treatment selection [1].

Patients with suspected or confirmed MAS, regardless of the underlying cause, must be treated in intensive care units with continuous monitoring of vital parameters and regular monitoring of laboratory analyses. It is important to identify the underlying disease as soon as possible, as well as the contributing factors, and to treat them concurrently. An individualized approach to patients with MAS facilitates better management of the challenges associated with identifying the underlying disease, assessing risk factors, and making treatment decisions. Establishing a multidisciplinary team comprising physicians from different specialties, depending on the presentation and clinical course

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- of the disease, is of crucial importance for the timely recognition and treatment of complications of macrophage activation syndrome [1].

CONCLUSION

The overlap of the clinical and laboratory manifestations of active systemic lupus erythematosus, macrophage activation syndrome, and severe infections significantly complicates timely diagnosis. MAS should be considered in patients with active SLE and/or signs of multiple organ dysfunction. Monitoring specific biomarkers is of crucial importance for timely diagnosis, with ferritin concentrations >10,000 µg/l considered highly suggestive of MAS. Early recognition of this syndrome and the administration of appropriate immunomodulatory therapy are essential for improving clinical outcomes and reducing mortality in these complex patients.

Conflict of interest: None declared

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PRIKAZ SLUČAJA JEDNOSTRANOG ODSUSTVA PLUĆNE ARTERIJE – RADIOLOŠKA DIJAGNOZA RETKOG UZROKA HEMOPTIZIJA

PRIKAZ SLUČAJA

CASE REPORT

CASE REPORT OF UNILATERAL ABSENCE OF PULMONARY ARTERY – RADIOLOGICAL DIAGNOSIS OF A RARE CAUSE OF HAEMOPTYSIS

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SAŽETAK

Uvod/Cilj: Jednostrano odsustvo plućne arterije ili UAPA (Unilateral Absence of Pulmonary Artery) predstavlja retku kongenitalnu kardiovaskularnu anomaliju koju karakteriše plućno stablo sa samo jednom završnom granom. Nastaje usled involucije ventralnog dela VI aortnog luka tokom embriogeneze. Pacijenti u dečijem uzrastu su najčešće bez simptoma, dok se kasnije u životu mogu javiti životno ugrožavajuće komplikacije kao što su plućna hipertenzija i masivne hemoptizije. U ovom članku ćemo prikazati slučaj pacijentkinje sa desnostranom UAPA-om, udruženom sa atrijalnim septalnim defektom (ASD) i ventrikularnim septalnim defektom (VSD).

Prikaz slučaja: Pacijentkinja se javila lekaru zbog hemoptizija. Na prijemu sa izraženom hipoksemijom (Sat. 69% O₂) i perifernom cijanozom. Na multidetektorskoj kompjuterizovanoj tomografskoj angiografiji (MDCTA) torakalne aorte viđena je agenezija ekstrapulmonalnog dela desne glavne grane plućnog stabla.

Zaključak: Pacijenti sa UAPA-om često mogu biti bez simptoma i dijagnoza se postavlja slučajno. S obzirom na ozbiljne komplikacije koje mogu nastati, od značaja je da lekari imaju UAPA-u na umu, pogotovo kod pacijenata sa hemoptizijama.

Ključne reči: plućna arterija, kardiovaskularne anomalije, hemoptizije, multidetektorska kompjuterizovana tomografija, angiografija

ABSTRACT

Introduction/Objective: Unilateral absence of the pulmonary artery (UAPA) is a rare congenital cardiovascular anomaly characterized by a pulmonary trunk with only one terminal branch. It occurs due to the involution of the ventral portion of the sixth aortic arch during embryogenesis. Pediatric patients are usually asymptomatic, whereas life-threatening complications, such as pulmonary hypertension and massive hemoptysis, may develop later in life. In this article, we present a case of a female patient with right-sided UAPA associated with an atrial septal defect (ASD) and a ventricular septal defect (VSD).

Case report: The patient presented to the physician due to hemoptysis. At admission, the patient exhibited severe hypoxemia (O₂ saturation of 69%) and peripheral cyanosis. Multidetector computed tomography angiography (MDCTA) of the thoracic aorta revealed agenesis of the extrapulmonary segment of the right main branch of the pulmonary trunk.

Conclusion: Patients with UAPA are frequently asymptomatic, and the diagnosis is often established incidentally. Given the potential for severe complications, it is crucial for clinicians to keep UAPA in mind in the differential diagnosis, particularly in patients presenting with hemoptysis.

Keywords: pulmonary artery, cardiovascular abnormalities, hemoptysis, multidetector computed tomography, angiography

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UVOD

Jednostrano odsustvo plućne arterije ili UAPA (Unilateral Absence of Pulmonary Artery) predstavlja retku kongenitalnu kardiovaskularnu anomaliju koju karakteriše odsustvo jedne od dve završne grane plućne arterije. Razvija se samo sa jednom granom koja ishranjuje istostrano plućno krilo, dok u drugo plućno krilo krv dovode kolateralni krvni sudovi [1,2]. Javlja se usled involucije proksimalnog dela VI aortnog luka sa leve ili desne strane tokom embriogeneze [1,2]. Prvi put je opisana 1868. godine i smatra se da ima prevalencu od 1:200.000 ljudi [1,2]. Najčešće se javlja udružena sa drugim kongenitalnim srčanim anomalijama, kao što su tetralogija Fallot, perzistentni duktus arteriozus, atrijalni septalni defekt (ASD), ventrikularni septalni defekt (VSD) i drugo, iako se može javiti i kao izolovana UAPA [3]. Pacijenti u dečijem uzrastu često mogu biti bez simptoma, pogotovo ako nema udruženih kongenitalnih anomalija, i javiti se lekaru kasnije kao adulti [4]. Klinički simptomi uključuju lako zamaranje, hemoptizije, bolove u grudima, dispneju i učestale respiratorne infekcije [1]. Kasnije u životu se mogu javiti i komplikacije kao što su plućna hipertenzija, bronhiektazije i fibroza pluća [2].

Smatra se da je ukupna smrtnost kod pacijenata sa UAPA-om oko 7%, gde plućna hipertenzija i hemoptizije predstavljaju negativne prediktivne faktore [1,2]. Ne postoji jasno definisan terapijski plan kod pacijenata sa UAPA-om, već se lečenje zasniva na uklanjanju simptoma, udruženih anomalija i na anatomiji plućne arterije. [5,6]. Kod asimptomatskih pacijenata kojima je postavljena dijagnoza UAPA-e se savetuje redovno praćenje u cilju rane detekcije plućne hipertenzije [3,5]. Ukoliko pacijent ima hemoptizije, u opticaj dolaze okluzija kolateralnih krvnih sudova i pneumektomija, dok u izuzetnim slučajevima treba uzeti u obzir i transplantaciju srca ili pluća [3].

U ovom članku ćemo, sa aspekta radiološke dijagnostike, predstaviti slučaj 37-godišnje žene sa desnostranom UAPA-om, udruženu sa ASD-om i sa VSD-om, koja se javila lekaru zbog hemoptizija.

PRIKAZ SLUČAJA

Pacijentkinja stara 37 godina se javlja lekaru Urgentnog centra Univerzitetskog kliničkog centra Srbije zbog iskašljavanja svetlocrvene krvi, povremeno i sa koagulimumima, koje je počelo dan pre pregleda. Navodi da desetak dana unazad ima tegobe u vidu povišene telesne temperature (do 37,4 °C), malaksalosti, bolova u leđima, kašlja i iskašljavanja, i da otežano diše. Saznaje se da pacijentkinja ima urođenu srčanu manu u vidu ASD-a i VSD-a, srčanu insuficijenciju (NYHA II-III), sekundarnu plućnu hipertenziju, sekundarnu policitemiju

INTRODUCTION

Unilateral absence of the pulmonary artery (UAPA) is a rare congenital cardiovascular anomaly characterized by the absence of one of the two terminal branches of the pulmonary artery. It develops with only one branch supplying the ipsilateral lung, while the contralateral lung receives its blood supply through collateral vessels [1,2]. It occurs as a result of involution of the proximal portion of the sixth aortic arch on either the left or right side during embryogenesis [1,2]. It was first described in 1868 and is estimated to affect 1:200,000 individuals [1,2]. It most commonly occurs in association with other congenital cardiac anomalies, such as tetralogy of Fallot, patent ductus arteriosus, atrial septal defect (ASD), ventricular septal defect (VSD), and others. However, it may also occur as an isolated form of UAPA [3]. Pediatric patients are often asymptomatic, particularly without associated congenital anomalies, and may present to a physician later in adulthood [4]. Clinical symptoms include easy fatigability, hemoptysis, chest pain, dyspnea, and recurrent respiratory infections [1]. Later in life, complications such as pulmonary hypertension, bronchiectasis, and pulmonary fibrosis may develop [2].

The overall mortality rate among patients with UAPA is estimated at approximately 7%, with pulmonary hypertension and hemoptysis representing adverse prognostic factors [1,2]. No clearly defined therapeutic strategy exists for patients with UAPA; treatment is based on managing symptoms and associated anomalies, as well as the anatomy of the pulmonary artery [5,6]. In asymptomatic patients diagnosed with UAPA, regular follow-up is recommended for the early detection of pulmonary hypertension [3,5]. In patients presenting with hemoptysis, occlusion of collateral vessels and pneumonectomy may be considered, while in exceptional cases, heart or lung transplantation should also be taken into consideration [3].

In this article, from the perspective of radiological diagnosis, we present the case of a 37-year-old woman with right-sided UAPA associated with ASD and VSD who presented with hemoptysis.

CASE REPORT

A 37-year-old female patient presented to the Emergency Department of the University Clinical Center of Serbia due to expectoration of bright-red blood, occasionally containing clots, which had begun one day before examination. She reported a 10-day history of symptoms including elevated body temperature (up to 37.4 °C), malaise, back pain, cough, and sputum production, accompanied by dyspnea. It was established that the patient had congenital heart disease

ju, hroničnu bubrežnu insuficijenciju, i da se redovno kontroliše kod interniste.

Po prijemu u bolnicu pacijentkinja je lako dispnoična, cijanotična (periferna cijanoza), blede i suve kože, plavičasto prebojenih usana, sa batičastim prstima, bačvastog grudnog koša. Nad plućima difuzno obostrano oslabljen disajni šum bez propratnog nalaza. Srčana radnja ritmična, sa ejakcionim šumom nad pulmonalnim ušćem. Vitalni parametri pacijentkinje su bili sledeći: TA: 90/60 mmHg, Fr 75/min, Sat. 69%, podignuta na 72% nakon primene 2L O₂/min.

Na transtorakalnoj ehokardiografiji koja je bila suboptimalnog kvaliteta usled loše vidljivosti, pokazano je da pacijentkinja ima VSD, uvećanu desnu komoru sa zadebljalim zidom i granično očuvanom funkcijom dok je leva komora urednih ultrazvučnih karakteristika.

Na multidetektorskoj kompjuterizovanoj tomografskoj angiografiji (MDCTA) torakalne aorte je agenezija ekstrapulmonalnog dela desne glavne grane plućnog stabla, dok intrapulmonalni deo krv dobija kroz vezu sa desnom potključnom arterijom. Takođe je primećena sinistropozicionirana gornja šuplja vena, zona alveolitisa apikalno u desnom plućnom krilu koje je manje zapremine u odnosu na levo plućno krilo, kao i devijacija medijastinalnih struktura udesno, što je prikazano na Slikama 1 i 2.

in the form of ASD and VSD, heart failure (NYHA II–III), secondary pulmonary hypertension, secondary polycythemia, and chronic renal insufficiency, and that she was undergoing regular follow-up by an internist.

Upon admission to the hospital, the patient was mildly dyspneic and cyanotic (peripheral cyanosis), with pale, dry skin, bluish discoloration of the lips, clubbing of the fingers, and a barrel-shaped chest. On lung auscultation, breath sounds were diffusely diminished bilaterally, without additional pathological findings. Cardiac rhythm was regular, with an ejection murmur over the pulmonary valve area. The patient's vital parameters were as follows: BP 90/60 mmHg, HR 75/min, SpO₂ 69%, increasing to 72% after administration of O₂ at 2 L/min.

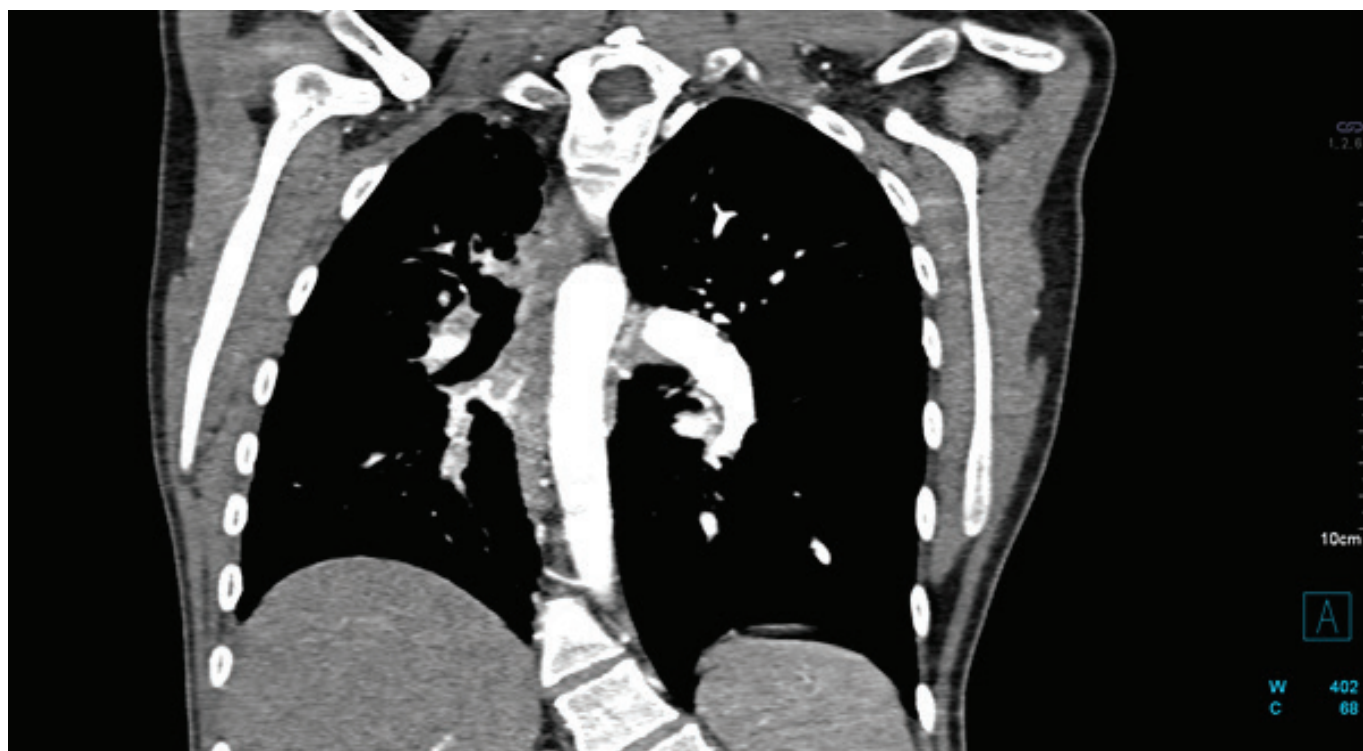
Transthoracic echocardiography, suboptimal due to poor visualization, showed a VSD and an enlarged right ventricle with wall thickening and borderline preserved function. In contrast, the left ventricle showed normal echocardiographic characteristics.

Multidetector computed tomography angiography (MDCTA) of the thoracic aorta demonstrated agenesis of the extrapulmonary portion of the right main pulmonary artery. In contrast, the intrapulmonary portion received its blood supply through a connection with the right subclavian artery. A left-sided superior vena cava was also noted, along with an area of alveolitis in the apical region of the right lung, which was smaller



Slika 1. MDCTA torakalne aorte, aksijalni presek. Uočavaju se odsustvo ekstrapulmonalnog dela desne plućne arterije, sinistropozicionirana gornja šuplja vena, devijacija medijastinalnih struktura udesno i desno plućno krilo koje je manje zapremine u odnosu na levo.

Figure 1. MDCTA of the thoracic aorta, axial view. The image shows the absence of the extrapulmonary segment of the right pulmonary artery, sinistroposition of the superior vena cava, right mediastinal shift, and volume loss of the right lung compared with the left.



Slika 2. MDCTA torakalne aorte, koronalni presek. Uočava se odsustvo ekstrapulmonalnog dela desne plućne arterije

Figure 2. MDCTA of the thoracic aorta, coronal view. The image reveals the absence of the extrapulmonary segment of the right pulmonary artery.

DISKUSIJA

Tokom embriogeneze proksimalni tj. ventralni deo VI aortnog luka sa leve i desne strane postaje proksimalni tj. ekstrapulmonalni deo plućnih arterija [7,8]. Distalni tj. dorzalni deo VI aortnog luka sa desne strane involui- ra, dok će sa leve strane formirati duktus arteriozus [7]. Od kapilarnih pleksusa odgovarajućih plućnih pupolja- ka će se razviti distalni tj. intrapulmonalni deo plućnih arterija [7].

Kod UAPA-e dolazi do involucije ventralnog dela VI aortnog luka, u oko dve trećine slučajeva desnostrano, što dovodi do odsustva proksimalnog dela odgovara- juće plućne arterije [2,7,8].

Važno je naznačiti da termin „Odsustvo plućne ar- terije“ ili „Agenezija plućne arterije“, koji su generalno prihvaćeni, zapravo nisu adekvatni jer plućna arterija postoji u njenom distalnom tj. intrapulmonalnom delu dok je odsutan ekstrapulmonalni deo [9].

Kao što smo prethodno pomenuli, UAPA je često bez simptoma u ranom detinjstvu [7], smatra se da je srednja vrednost starosti pacijenata, kada se prvi put pojave simptomi, 14 godina [2]. Najčešći simptomi su dispneja, brzo umaranje, hemoptizije, rekurentne res- piratorne infekcije i bolovi u grudima [10].

Na radiografiji će se tipično videti hipoplazija pluć- nog krila na strani gde izostaje ekstrapulmonalna plućna arterija, pomeranje mediastinalnih struktura u ipsilateralnu stranu, kompenzatorna hiperinflacija kon-

in volume than the left lung, as well as rightward devi- ation of the mediastinal structures, as shown in **Figures 1 and 2**.

DISCUSSION

During embryogenesis, the proximal, i.e., ventral, por- tion of the sixth aortic arch on both the left and right sides develops into the proximal, i.e., extrapulmonary, portions of the pulmonary arteries [7,8]. The distal, i.e., dorsal, portion of the sixth aortic arch on the right side undergoes involution, whereas on the left side it forms the ductus arteriosus [7]. The distal, i.e., intrapulmo- nary, portions of the pulmonary arteries develop from the capillary plexuses of the corresponding pulmonary buds [7].

In UAPA, involution of the ventral portion of the sixth aortic arch occurs, in approximately two-thirds of cases on the right side, resulting in the absence of the proximal portion of the corresponding pulmonary artery [2,7,8].

It is important to note that the terms “absence of the pulmonary artery” or “pulmonary artery agenesis,” which are generally accepted, are not entirely accurate, because the pulmonary artery is present in its distal, i.e., intrapulmonary, portion. In contrast, the extrapul- monary portion is absent [9].

As previously mentioned, UAPA is often asymp- tomatic during early childhood [7], and the mean age

tralateralnog plućnog krila, prominentne vaskularne strukture kontralateralnog hilusa i uvećana srčano-sudovna senka [1,7]. Nekada, usled nepravilne pozicije pacijenta prilikom snimanja radiografije, može biti teško sa sigurnošću detektovati sve navedene patološke znakove pa samim tim i posumnjati da se radi o UAPA-i.

MDCT grudnog koša sa kontrastom pruža nedvosmisleno rešenje jer se jasno uočava da iz plućnog stabla izlazi samo jedna grana koja je šireg lumena, plućno krilo koje ona ishranjuje je u hiperinflaciji sa naglašenim krvnim sudovima, dok je kontralateralno plućno krilo hipoplastično, često sa ožiljnim promenama usled rekurentnih respiratornih infekcija ili zonama *Ground glass* opacifikacije (GGO) koje predstavljaju fokuse krvarenja [7,11]. Mogu se uočiti i udružene kardiovaskularne anomalije, što je viđeno i kod naše pacijentkinje [7].

ZAKLJUČAK

UAPA predstavlja retku kongenitalnu kardiovaskularnu malformaciju koja je često asimptomatska, te njeno prepoznavanje predstavlja klinički izazov. Radiološke metode, poput radiografije grudnog koša, ehokardiografije i kompjuterizovane tomografije (MDCT), imaju ključnu ulogu u postavljanju tačne dijagnoze. Klinički lekari radiolozi bi trebalo da imaju na umu ovu retku anomaliju u diferencijalnoj dijagnozi, pogotovo kod pacijenata sa nejasnim hemoptizijama.

Sukob interesa:

Autori izjavljuju da nemaju finansijski niti bilo koji drugi sukob interesa koji bi mogao da utiče na rezultate ili tumačenje rezultata ovog rada.

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at which patients first develop symptoms is considered to be 14 years [2]. The most common symptoms are dyspnea, easy fatigability, hemoptysis, recurrent respiratory infections, and chest pain [10].

Chest radiography typically demonstrates hypoplasia of the lung on the side where the extrapulmonary pulmonary artery is absent, displacement of the mediastinal structures toward the ipsilateral side, compensatory hyperinflation of the contralateral lung, prominent vascular structures of the contralateral hilum, and an enlarged cardiomeastinal silhouette [1,7]. Occasionally, improper patient positioning during radiographic imaging makes it difficult to reliably detect all of the aforementioned pathological findings and, consequently, to suspect UAPA.

Contrast-enhanced MDCT of the chest provides a definitive diagnosis, clearly demonstrating that only one branch, with a larger lumen, arises from the pulmonary trunk. The lung supplied by this branch is hyperinflated with prominent vascular structures. In contrast, the contralateral lung is hypoplastic, often with scarring from recurrent respiratory infections or areas of ground-glass opacity (GGO) representing foci of hemorrhage [7,11]. Associated cardiovascular anomalies may also be identified, as in our patient [7].

CONCLUSION

UAPA is a rare congenital cardiovascular malformation that is frequently asymptomatic, making its recognition a clinical challenge. Radiological modalities, such as chest radiography, echocardiography, and computed tomography (MDCT), play a key role in establishing an accurate diagnosis. Clinicians and radiologists should consider this rare anomaly in the differential diagnosis, particularly in patients presenting with unexplained hemoptysis.

Conflict of interest

The authors declare no financial or other conflicts of interest that could influence the results or interpretation of this study.

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ABSTRACT should be up to 250 words, including acronyms (third page). For original papers, preliminary and short communications, meta-analyses and review papers, the abstract should have the following structure: Introduction, Aim, Methods, Results, Conclusion. Each of these segments should be written as a separate paragraph. For case report, the summary should have the following sections: Introduction, Case Report, Conclusion; each part should be written as a separate paragraph. For other types of papers, the abstract does not have a special structure. List three to six key words or phrases below the abstract. Words from the

ba da se ponavljaju reči iz naslova, a ključne reči treba da budu relevantne i opisne. U izboru ključnih reči koristiti *Medical Subject Headings* – MeSH (<http://www.nlm.nih.gov/mesh>). Sažetak treba da bude napisan na srpskom i engleskom jeziku.

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Od pete strane broji se broj strana predviđen za odgovarajuću strukturu rada.

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Ukoliko je moguće, sve numeričke vrednosti zaokružiti na jedno decimalno mesto. Ne duplirati prikaz rezultata u tabelama i grafikonima. Za prikaz rezultata u tabelama i tekstu preporuka je da se: numerički podaci sa normalnom raspodelom i bez ekstremnih vrednosti prikazuju kao aritmetička sredina $\pm$ standardna devijacija; numerički podaci čija raspodela odstupa od normalnosti ili kada postoje ekstremne vrednosti, i ordinalni podaci prikazuju kao medijana i opseg (minimalna – maksimalna vrednost); nominalni podaci i ordinalni podaci sa malim brojem kategorija prikazuju kao n (%).

Prilikom opisa primenjenih statističkih metoda, prikaza i interpretacije rezultata u radu pridržavati se *SAMPL Guidelines* (Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines*. *Int J Nurs Stud* 2015;52(1):5-9.). Primenjene statističke metode treba opisati dovoljno detaljno da ih čitalac može ponoviti na svojim podacima. Navesti korišćeni statistički test i nivo značajnosti. Saopštiti tačnu *p*-vrednost na 3 decimalna mesta.

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(mol), a pritisak krvi u milimetrima živinog stuba (mm Hg). Sve rezultate hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).

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