



ISSN 2737-971X
eISSN 2737-9752

SERBIAN JOURNAL OF THE MEDICAL CHAMBER

SRPSKI MEDICINSKI ČASOPIS LEKARSKE KOMORE

VOLUMEN 7 • BROJ 1 • MART 2026.

VOLUME 7 • NUMBER 1 • MARCH 2026

ISSN 2737-971X
eISSN 2737-9752

SRPSKI MEDICINSKI ČASOPIS LEKARSKE KOMORE



SERBIAN JOURNAL OF THE MEDICAL CHAMBER

VOLUMEN 7 • BROJ 1 • MART 2026.
VOLUME 7 • NUMBER 1 • MARCH 2026

OSNIVAČ, VLASNIK, IZDAVAČ

Lekarska komora Srbije
Kraljice Natalije 1-3, 11000 Beograd, Srbija

SUIZDAVAČ

Institut za medicinska istraživanja, Univerzitet u Beogradu
Dr Subotića 4, p.p. 102, 11129 Beograd, Srbija

FOUNDER, OWNER & PUBLISHER

Serbian Medical Chamber
1-3 Kraljice Natalije Street, 11000 Belgrade, Serbia

CO-PUBLISHER

Institute for Medical Research, University of Belgrade
4 Dr Subotića Street, P.O. Box 102, 11129 Belgrade, Serbia

UREDNIŠTVO

Glavni i odgovorni urednik

Prof. dr Milena Šantrić-Milićević
*Univerzitet u Beogradu, Medicinski fakultet, Institut za
socijalnu medicinu, Beograd, Srbija*

Zamenik glavnog urednika

Prof. dr Goran Tulić
*Univerzitetski klinički centar Srbije, Klinika za ortopedsku
hirurgiju i traumatologiju; Univerzitet u Beogradu,
Medicinski fakultet, Beograd, Srbija*

Pomoćnici glavnog i odgovornog urednika

Prof. dr Predrag Đurđević
*Univerzitetski klinički centar Kragujevac, Klinika za
hematologiju; Univerzitet u Kragujevcu, Fakultet
medicinskih nauka, Kragujevac, Srbija*

Prof. dr Milena Todorović Balint
*Univerzitetski klinički centar Srbije, Klinika za
hematologiju; Univerzitet u Beogradu, Medicinski
fakultet, Beograd, Srbija*

Prof. dr Bojan Zarić
*Univerzitet u Novom Sadu, Medicinski fakultet; Institut
za plućne bolesti Vojvodine, Klinika za pulmološku
onkologiju, Sremska Kamenica, Srbija*

Dr Saša Radovanović, naučni savetnik
*Univerzitet u Beogradu, Institut za medicinska
istraživanja, Beograd, Srbija*

Prof. dr Aleksandra Ilić
*Univerzitet u Prištini – Kosovska Mitrovica, Medicinski
fakultet, Centar za biostatistiku i informacione
tehnologije, Kosovska Mitrovica, Srbija*

Doc. dr Mlađan Golubović
*Univerzitetski klinički centar Niš, Klinika za
kardiohirurgiju; Univerzitet u Nišu, Medicinski fakultet,
Niš, Srbija*

EDITORIAL OFFICE

Editor-in-Chief

Prof. Milena Šantrić-Milićević, MD, PhD
*University of Belgrade, Faculty of Medicine, Institute of
Social Medicine, Belgrade, Serbia*

Deputy Editor-in-Chief

Prof. Goran Tulić, MD, PhD
*University Clinical Center of Serbia, Clinic for Orthopedic
Surgery and Traumatology; University of Belgrade, Faculty
of Medicine, Belgrade, Serbia*

Assistant Editor-in-Chief

Prof. Predrag Đurđević, MD, PhD
*University Clinical Center Kragujevac, Clinic for
Hematology; University of Kragujevac, Faculty of Medical
Sciences, Kragujevac, Serbia*

Prof. Milena Todorović Balint, MD, PhD
*University Clinical Center of Serbia, Clinic for
Hematology; University of Belgrade, Faculty of Medicine,
Belgrade, Serbia*

Prof. Bojan Zarić, MD, PhD
*University of Novi Sad, Faculty of Medicine; Institute for
Pulmonary Diseases of Vojvodina, Clinic for Thoracic
Oncology, Sremska Kamenica, Serbia*

Res. Prof. Saša Radovanović, MD, PhD
*University of Belgrade, Institute for Medical Research,
Belgrade, Serbia*

Prof. Aleksandra Ilić, MD, PhD
*University of Pristina – Kosovska Mitrovica, Faculty
of Medicine, Center for Biostatistics and Information
Technology, Kosovska Mitrovica, Serbia*

Asst. Prof. Mlađan Golubović, MD, PhD
*University Clinical Center Niš, Cardiovascular and
Transplant Surgery Clinic; University of Niš, Faculty of
Medicine, Niš, Serbia*

Tehnički urednik

Prof. dr Zoran Bukumirić
Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku statistiku i informatiku, Beograd, Srbija

Sekretar

Doc. dr Aleksandra Radovanović Spurnić, *Univerzitetski klinički centar Srbije, Klinika za infektivne i tropske bolesti; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Lektori i prevodioci za srpski i engleski jezik

Biljana Vukčević Lacković, prof. engleskog jezika
Danka Sinadinović, prof. engleskog jezika
Danijela Bulatović, prof. engleskog jezika

Technical Editor

Prof. Zoran Bukumirić, MD, PhD
University of Belgrade, Faculty of Medicine, Institute for Medical Statistics and Informatics, Belgrade, Serbia

Secretary

Asst. Prof. Aleksandra Radovanović Spurnić, MD, PhD
University Clinical Center of Serbia, Clinic for Infectious and Tropical Diseases; University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Serbian and English Language Editors

Biljana Vukčević Lacković, English language teacher
Danka Sinadinović, English language teacher
Danijela Bulatović, English language teacher

IZDAVAČKI SAVET

Predsednik

Asist. dr sci. med. Danilo Jeremić

Članovi

Spec. dr med. Miodrag Stanić
Dr med. Milan Dinić
Prof. dr Boris Đinđić
Prof. dr Dejan Sakač
Mr sci. med. Slađana Ilić
Spec. dr med. Ksenija Turković

PUBLISHER'S ADVISORY BOARD

President

TA Danilo Jeremić, MD, PhD

Members

Miodrag Stanić, MD
Milan Dinić, MD
Prof. Boris Đinđić, MD, PhD
Prof. Dejan Sakač, MD, PhD
Slađana Ilić, MD, MSc
Ksenija Turković, MD

UREĐIVAČKI ODBOR

Predsednik

Akademik prof. dr Bela Balint, *Srpska akademija nauka i umetnosti, Odeljenje za medicinske nauke, Beograd, Srbija*

Članovi

Akademik prof. dr Vladimir Kostić, *Srpska akademija nauka i umetnosti, Odeljenje za medicinske nauke, Beograd, Srbija*

Akademik prof. dr Nebojša Lalić, *Srpska akademija nauka i umetnosti, Odeljenje za medicinske nauke, Beograd, Srbija*

Akademik prof. dr Predrag Peško, *Srpska akademija nauka i umetnosti, Odeljenje za medicinske nauke, Beograd, Srbija*

Prof. dr Milena Šantrić-Milićević, *Univerzitet u Beogradu, Medicinski fakultet, Institut za socijalnu medicinu, Beograd, Srbija*

Prof. dr Ivan Paunović, *Naučno društvo Srbije, Odeljenje medicinsko-bioloških nauka, Beograd, Srbija*

Prof. dr Zoran Bašćarević, *Institut za ortopediju „Banjica”; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Prof. dr Eleonora Gvozdenović, *Opšta bolnica MediGroup, Beograd, Srbija*

Prof. dr Goran Tulić, *Univerzitetski klinički centar Srbije, Klinika za ortopedsku hirurgiju i traumatologiju; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Prof. dr Dejan Nešić, *Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku fiziologiju, Beograd, Srbija*

Prof. dr Mirjana Šumarac-Dumanović, *Univerzitetski klinički centar, Klinika za endokrinologiju, dijabetes i bolesti metabolizma; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Prof. dr Milena Todorović Balint, *Univerzitetski klinički centar Srbije, Klinika za hematologiju; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Prof. dr Nemanja Slavković, *Institut za ortopediju „Banjica”; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

EDITORIAL BOARD

President

Academician Prof. Bela Balint, MD, PhD, *Serbian Academy of Sciences and Arts, Department of Medical Sciences, Belgrade, Serbia*

Members

Academician Prof. Vladimir Kostić, MD, PhD, *Serbian Academy of Sciences and Arts, Department of Medical Sciences, Belgrade, Serbia*

Academician Prof. Nebojša Lalić, MD, PhD, *Serbian Academy of Sciences and Arts, Department of Medical Sciences, Belgrade, Serbia*

Academician Prof. Predrag Peško, MD, PhD, *Serbian Academy of Sciences and Arts, Department of Medical Sciences, Belgrade, Serbia*

Prof. Milena Šantrić-Milićević, MD, PhD, *University of Belgrade, Faculty of Medicine, Institute of Social Medicine, Belgrade, Serbia*

Prof. Ivan Paunović, MD, PhD, *Serbian Scientific Society, Department of Biomedical Sciences, Belgrade, Serbia*

Prof. Zoran Bašćarević, MD, PhD, *Institute for Orthopedic Surgery “Banjica”; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Prof. Eleonora Gvozdenović, MD, PhD, *General Hospital MediGroup, Belgrade, Serbia*

Prof. Goran Tulić, MD, PhD, *University Clinical Center of Serbia, Clinic for Orthopedic Surgery and Traumatology; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Prof. Dejan Nešić, MD, PhD, *University of Belgrade, Faculty of Medicine, Institute of Medical Physiology, Belgrade, Serbia*

Prof. Mirjana Šumarac-Dumanović, MD, PhD, *University Clinical Center of Serbia, Clinic for Endocrinology, Diabetes and Metabolic Diseases; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Prof. Milena Todorović Balint, MD, PhD, *University Clinical Center of Serbia, Clinic for Hematology; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Prof. Nemanja Slavković, MD, PhD, *Institute for Orthopedic Surgery “Banjica”; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Prof. dr Zoran Bukumirić, *Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku statistiku i informatiku, Beograd, Srbija*

Prof. dr Marija Zdravković, *Kliničko-bolnički centar Bežanijska kosa; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Dr Saša Radovanović, naučni savetnik, *Univerzitet u Beogradu, Institut za medicinska istraživanja, Beograd, Srbija*

Dr Irina Maslovarić, viši naučni saradnik, *Univerzitet u Beogradu, Institut za medicinska istraživanja, Beograd, Srbija*

Prof. dr Aleksandar Pavlović, *Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Kosovska Mitrovica, Srbija*

Prof. dr Milica Mijović, *Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Institut za patološku anatomiju, Kosovska Mitrovica, Srbija*

Prof. dr Aleksandra Ilić, *Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Centar za biostatistiku i informacione tehnologije, Kosovska Mitrovica, Srbija*

Prof. dr Dobrila Stanković-Đorđević, *Lekarska komora Srbije, Niš, Srbija*

Prof. dr Jelena Milenković, *Univerzitet u Nišu, Medicinski fakultet, Katedra za patološku fiziologiju, Niš, Srbija*

Prof. dr Predrag Đurđević, *Univerzitetski klinički centar Kragujevac, Klinika za hematologiju; Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija*

Prof. dr Svetlana Radević, *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za socijalnu medicinu, Kragujevac, Srbija*

Prof. dr Slobodanka Mitrović, *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za patološku anatomiju, Kragujevac, Srbija*

Prof. dr Vojin Kovačević, *Univerzitetski klinički centar Kragujevac, Centar za neurohirurgiju; Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za hirurgiju, Kragujevac, Srbija*

Prof. dr Dejana Ružić Zečević, *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmakologiju i toksikologiju, Kragujevac, Srbija*

Prof. Zoran Bukumirić, MD, PhD, *University of Belgrade, Faculty of Medicine, Institute for Medical Statistics and Informatics, Belgrade, Serbia*

Prof. Marija Zdravković, MD, PhD, *University Hospital Medical Center Bezanijska kosa; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Res. Prof. Saša Radovanović, MD, PhD, *University of Belgrade, Institute for Medical Research, Belgrade, Serbia*

Sr. Res. Assoc. Irina Maslovarić, MD, PhD, *University of Belgrade, Institute for Medical Research, Belgrade, Serbia*

Prof. Aleksandar Pavlović, MD, PhD, *University of Pristina – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia*

Prof. Milica Mijović, MD, PhD, *University of Pristina – Kosovska Mitrovica, Faculty of Medicine, Institute of Pathology, Kosovska Mitrovica, Serbia*

Prof. Aleksandra Ilić, MD, PhD, *University of Pristina – Kosovska Mitrovica, Faculty of Medicine, Centre for Biostatistics and Information Technology, Kosovska Mitrovica, Serbia*

Prof. Dobrila Stanković-Đorđević, MD, PhD, *Serbian Medical Chamber, Niš, Serbia*

Prof. Jelena Milenković, MD, PhD, *University of Niš, Faculty of Medicine, Department of Pathophysiology, Niš, Serbia*

Prof. Predrag Đurđević, MD, PhD, *University Clinical Center Kragujevac, Clinic for Hematology; University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia*

Prof. Svetlana Radević, MD, PhD, *University of Kragujevac, Faculty of Medical Sciences, Department of Social Medicine, Kragujevac, Serbia*

Prof. Slobodanka Mitrović, MD, PhD, *University of Kragujevac, Faculty of Medical Sciences, Department of Pathology, Kragujevac, Serbia*

Prof. Vojin Kovačević, MD, PhD, *University Clinical Center Kragujevac, Center for Neurosurgery; University of Kragujevac, Faculty of Medical Sciences, Department of Surgery, Kragujevac, Serbia*

Prof. Dejana Ružić Zečević, MD, PhD, *University of Kragujevac, Faculty of Medical Sciences, Clinical Pharmacology Department, Kragujevac, Serbia*

Doc. dr Aleksandra Radovanović Spurnić, *Univerzitetski klinički centar Srbije, Klinika za infektivne i tropske bolesti; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Doc. dr Darko Laketić, *Univerzitet u Beogradu, Medicinski fakultet, Institut za anatomiju, Beograd, Srbija*

Doc. dr Mihailo Stjepanović, *Univerzitetski klinički centar Srbije, Klinika za pulmologiju; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Doc. dr Kristina Davidović, *Univerzitetski klinički centar Srbije, Centar za radiologiju; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Doc. dr Marija Milić, *Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Katedra za epidemiologiju, Kosovska Mitrovica, Srbija*

Doc. dr Mlađan Golubović, *Univerzitetski klinički centar Niš, Klinika za kardiohirurgiju; Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija*

Doc. dr Jagoš Golubović, *Univerzitetski klinički centar Vojvodine, Klinika za neurohirurgiju; Univerzitet u Novom Sadu, Medicinski fakultet, Novi Sad, Srbija*

Doc. dr Tomi Kovačević, *Univerzitet u Novom Sadu, Medicinski fakultet; Institut za plućne bolesti Vojvodine, Sremska Kamenica, Srbija*

Doc. dr Andrej Preveden, *Univerzitet u Novom Sadu, Medicinski fakultet; Institut za kardiovaskularne bolesti Vojvodine, Sremska Kamenica, Srbija*

Asist. dr sci. med. Nina Rajović, *Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku statistiku i informatiku, Beograd, Srbija*

Asist. dr Igor Spurnić, *Institut za onkologiju i radiologiju Srbije; Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*

Internacionalni članovi

Prof. dr Marija Vavlukis, *Univerzitet „Sv. Ćirila i Metodija“, Medicinski fakultet, Skoplje, Severna Makedonija*

Prof. dr Oleg Lozan, *Državni univerzitet za medicinu i farmaciju „Nicolae Testemitanu“, Škola menadžmenta javnog zdravlja, Kišinjev, Moldavija*

Prof. dr Natalya Glushkova, *Kazahstanski nacionalni univerzitet Al-Farabi, Fakultet medicinskih i zdravstvenih studija, Katedra za epidemiologiju, medicinu baziranu na dokazima i biostatistiku, Almati, Kazahstan*

Asst. Prof. Aleksandra Radovanović Spurnić, MD, PhD, *University Clinical Center of Serbia, Clinic for Infectious and Tropical Diseases; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Asst. Prof. Darko Laketić, MD, PhD, *University of Belgrade, Faculty of Medicine, Institute of Anatomy, Belgrade, Serbia*

Asst. Prof. Mihailo Stjepanović, MD, PhD, *University Clinical Centre of Serbia, Clinic for Pulmonology; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Asst. Prof. Kristina Davidović, MD, *University Clinical Centre of Serbia, Center for Radiology; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

Asst. Prof. Marija Milić, MD, PhD, *University of Pristina – Kosovska Mitrovica, Faculty of Medicine, Department of Epidemiology, Kosovska Mitrovica, Serbia*

Asst. Prof. Mlađan Golubović, MD, PhD, *University Clinical Center Niš, Cardiovascular and Transplant Surgery Clinic; University of Niš, Faculty of Medicine, Niš, Serbia*

Asst. Prof. Jagoš Golubović, MD, PhD, *University Clinical Centre of Vojvodina, Department of Neurosurgery; University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia*

Asst. Prof. Tomi Kovačević, MD, PhD, *University of Novi Sad, Faculty of Medicine; Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia*

Asst. Prof. Andrej Preveden, MD, *University of Novi Sad, Faculty of Medicine; Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia*

TA Nina Rajović, MD, PhD, *University of Belgrade, Faculty of Medicine, Institute for Medical Statistics and Informatics, Belgrade, Serbia*

TA Igor Spurnić, MD, *Institute for Oncology and Radiology of Serbia; University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

International members

Prof. Marija Vavlukis, MD, PhD, *University “Ss. Cyril and Methodius”, Faculty of Medicine, Skopje, North Macedonia*

Prof. Oleg Lozan, MD, MPH, PhD, *Nicolae Testemitanu State University of Medicine and Pharmacy, School of Public Health Management, Chisinau, Republic of Moldova*

Prof. Natalya Glushkova, MD, PhD, *Al-Farabi Kazakh National University, Faculty of Medicine and Health Care, Epidemiology, Evidence Based, Medicine and Biostatistics Department, Almaty, Kazakhstan*

Prof. dr Marius Ungureanu, *Univerzitet Babeş-Boljaj, Fakultet za političke, administrativne i komunikacione nauke, Kluž-Napoka, Rumunija*

Prof. dr Mihajlo (Michael) Jakovljević, *Tehnološki univerzitet Šensi, Handžong, Kina; UNESCO – TWAS, Trst, Italija; Univerzitet u Kragujevcu; Fakultet medicinskih nauka, Katedra za globalno zdravlje, zdravstvenu ekonomiju i politiku, Kragujevac, Srbija*

Prof. dr Kalina Grivcheva Stardelova, *Univerzitet „Sv. Ćirila i Metodija“, Medicinski fakultet, Univerzitetska klinika za gastroenterohepatologiju, Skopje, Severna Makedonija*

Prof. dr Artem N. Kuzovlev, *Federalni istraživački i klinički centar za intenzivnu negu i rehabilitaciju, Istraživački institut za opštu reanimatologiju „V. A. Negovski“, Moskva, Rusija*

Prof. dr Zoran Ivanović, *Francuska ustanova za krv, region Nova Akvitanija, Bordo, Francuska*

Prof. dr Srđan Mašić, *Univerzitet u Istočnom Sarajevu, Medicinski fakultet, Katedra za primarnu zdravstvenu zaštitu i javno zdravlje, Foča, Bosna i Hercegovina*

Doc. dr Saša Rajšić, *Medicinski univerzitet u Inzbruku, Klinika za anesteziologiju i intenzivnu negu, Inzbruk, Austrija*

Dr sci. med. Jelena Jeličić, *Odense univerzitetska bolnica, Odeljenje za hematologiju, Odense, Danska; Sygehus Lillebaelt, Vejle bolnica, Odeljenje za hematologiju, Vejle, Danska*

Prof. Marius Ungureanu, MD, PhD, MHA, *Babeş-Bolyai University, Faculty of Political, Administrative and Communication Sciences, Cluj-Napoca, Romania*

Prof. Mihajlo (Michael) Jakovljevic, MD, PhD, MAE, *Shaanxi University of Technology, Hanzhong, China; UNESCO – TWAS, Trieste, Italy; University of Kragujevac, Faculty of Medical Sciences, Department of Global Health Economics and Policy, Kragujevac, Serbia*

Prof. Kalina Grivcheva Stardelova, MD, PhD, *University “Ss. Cyril and Methodius”, Faculty of Medicine, University Clinic of Gastroenterohepatology, Skopje, North Macedonia*

Prof. Artem N. Kuzovlev, MD, PhD, *Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Negovsky Research Institute of General Reanimatology, Moscow, Russia*

Prof. Zoran Ivanovic, MD, PhD, *French Blood Institute, Nouvelle Aquitaine Branch, Bordeaux, France*

Prof. Srdjan Masic, MBI, MPH, PhD, *University of East Sarajevo, Faculty of Medicine, Department of Primary Health Care and Public Health, Foca, Bosnia and Herzegovina*

Asst. Prof. Sasa Rajsic, MD, PhD, *Medical University of Innsbruck, Department of Anaesthesiology and Critical Care Medicine, Innsbruck, Austria*

Jelena Jelacic, MD, PhD, *Odense University Hospital, Department of Hematology, Odense, Denmark; Sygehus Lillebaelt, Vejle Hospital, Department of Hematology, Vejle, Denmark*

ADRESA UREDNIŠTVA

Trg Nikole Pašića 7
11000 Beograd, Srbija

Telefoni:
(+381 11) 362 6196; (+381 11) 362 6197;
(+381 11) 362 6198

Elektronska adresa: info@smj.rs
Internet sajt: <https://smj.rs>

Časopis izlazi 4 puta godišnje

EDITORIAL OFFICE

7 Nikola Pašić Square
11000 Belgrade, Serbia

Telephone:
(+381 11) 362 6196; (+381 11) 362 6197;
(+381 11) 362 6198

E-mail: info@smj.rs
Website: <https://smj.rs>

The Journal is published quarterly

EDITORIJAL



„Ko ne čini ništa za druge, ne čini ništa ni za sebe.”
Johan Volfgang Gete

Uvažene kolegice i kolege,

Pripala mi je čast da vam se obratim u prvom broju Srpskog medicinskog časopisa Lekarske komore u 2026. godini, časopisa čiji kvalitet kontinuirano raste i koji je u ovoj godini postavio velike izazove pred buduće autore, recenzente, uredništvo i izdavače. Dosadašnjim zajedničkim radom uspeli smo da utemeljimo prepoznatljivi kvalitet objavljenih radova, uz uverenje da će ta plodonosna saradnja jačati sa svakim narednim brojem. Potvrda tom kvalitetu je i stalni rast kategorije časopisa koji je u prethodnoj godini dostigao rang M52, što pripada kategoriji nacionalnog časopisa u oblasti medicinskih nauka. Ovaj uspeh dodatno obavezuje sve nas da težimo još većoj odgovornosti i posvećenosti na putu ka kategoriji međunarodnog časopisa. Časopis je od 2025. god indeksiran u DOAJ (*Directory of Open Access Journals*) bazi podataka, što će učiniti da radovi objavljeni u njemu budu vidljivi i dostupni široj međunarodnoj naučnoj zajednici. Uticajnost našeg časopisa je postala prepoznatljiva među autorima van granica naše zemlje i okruženja, što nam daje jasne putokaze i usmerenje. Zahvaljujem se svim autorima koji su nam ukazali poverenje u ovom broju i svojim istraživanjima dodatno proširili raznolikost tema i oblasti koje pokriva naš časopis.

Rad po pozivu, autora Kristofera A. Rajsa i Roberta M. Jakobsona, prikazuje pristupe u rešavanju problema kolebljivosti prema vakcinaciji. Autori izводе zaključak da snažnije preporuke zdravstvenih radnika imaju jači efekat u povećanju prihvatanja vakcina.

Na poziv uredništva, autorke Žansaja Nurgalijeva i Natalija Glušкова predstavljaju kvalitativno istraživanje na temu KOVID-19 infekcije u trudnoći, sprovedeno u Kazahstanu. Rad jasno naglašava potrebu za unapređenjem bezbednosti zdravstvenih usluga za trudnice i porodilje tokom izbijanja epidemija zaraznih bolesti, oslanjajući se na poboljšanje kontinuiteta zdravstvene zaštite i smanjenje kašnjenja u eskaliranju zdravstvene zaštite žena tokom trudnoće.

Originalni rad Nikole Gavrilovića daje uvid u ispoljavanje depresivnih smetnji kod porodičnih negovatelja pacijenata koji su uključeni u kućno lečenje. Rezultati studije preseka ukazuju da su depresivni simptomi prisutni kod značajnog dela porodičnih negovatelja, a intenzitet simptoma je povezan sa većom narušenošću svakodnevnog funkcionisanja.

Dejan Munjiza i saradnici su u svom originalnom radu potvrdili postavljenu hipotezu da sa porastom dijametra interventrikularnog septuma i/ili zadnjeg zida leve komore raste i mogućnost lošijeg ishoda neuroangioloških oboljenja.

EDITORIAL

"Those who do nothing for others do nothing for themselves."

Johann Wolfgang von Goethe

Dear Colleagues,

It is an honor to be the one to address you in the first issue of *the Serbian Journal of the Medical Chamber* for 2026, a journal whose quality is continuously improving and which, in this year, has set significant challenges before future authors, reviewers, the Editorial Board, and publishers. Through our joint efforts to date, we have succeeded in establishing a recognizable standard of quality in the published papers, with the conviction that this fruitful collaboration will continue to strengthen with each subsequent issue. The confirmation of this quality is reflected in the steady rise of the journal ranking, which, in the previous year, reached category M52, corresponding to the status of a national journal in the field of medical sciences. This achievement further obliges all of us to strive for even greater responsibility and dedication on the path toward attaining the status of an international journal. Since 2025, the journal has been indexed in the DOAJ (Directory of Open Access Journals) database, thereby ensuring that the papers published in it are visible and accessible to the broader international scientific community. The impact of our journal has become increasingly recognized among authors beyond the borders of our country and region, thus providing us with clear direction and guidance towards our future goals. I would like to express my gratitude to all the authors who have placed their trust in us by submitting their articles for publication in this issue and who, through their research, have further expanded the diversity of topics and fields covered by our journal.

An invited paper by Christopher A. Reis and Robert M. Jacobson presents the approaches to addressing vaccine hesitancy. The authors conclude that stronger recommendations by healthcare professionals have a greater effect on increasing vaccine acceptance.

At the invitation of the editorial board, Zhansaya Nurgaliyeva and Nataliya Glushkova present a qualitative study on COVID-19 infection in pregnancy, conducted in Kazakhstan. The article clearly emphasizes the need to improve the safety of healthcare services for pregnant women and postpartum mothers during infectious disease outbreaks, relying on the enhancement of continuity of care and the reduction of delays in the escalation of healthcare for women during pregnancy.

The original article by Nikola Gavrilović provides insight into the manifestation of depressive symptoms among family members providing care to patients receiving home-based treatment. The results of this cross-sectional study indicate that depressive symptoms are present in a significant proportion of family caregivers, and that symptom intensity is associated with greater impairment in daily functioning.

U originalnom radu Sonje Smiljić i saradnika prikazana je učestalost metaboličkih poremećaja i hipertenzije kod žena pre menopauze i u menopauzi. Žene u menopauzi su bile značajno opterećenije hipertenzijom, gojaznošću, dislipidemijom i dijabetesom melitusom 2, što upućuje na potrebu preventivnih pregleda žena i ranog prepoznavanja i lečenja kardiometaboličkih poremećaja.

Petogodišnje iskustvo postavljanja dijagnoze, toka bolesti, terapijskog odgovora i preživljavanja pacijenata sa ne-Hoćkinovim folikularnim limfomom, predstavila je grupa autora predvođena Danijelom Jovanović. U svom originalnom radu oni prikazuju značajnu korelaciju parametara hemostaze – fibrinogena i D-dimera sa tokom bolesti.

Starenje, kao modulator patofiziologije multiple skleroze, predmet je preglednog rada Jasmine Đuretić. U radu je istaknut značaj razumevanja interakcija starenja i patofizioloških mehanizama multiple skleroze, što je ključno za razvoj ciljanih terapijskih strategija za sve brojniju populaciju starijih pacijenata sa multiplom sklerozom.

Stevan Čičić i saradnici, kroz prikaz slučaja, ukazuju na važnost pojave radijacijom indukovano os-teosarkoma, kao retke, ali ozbiljne kasne komplikacije radioterapije karcinoma dojke, te ističu složenost i specifičnost hirurškog lečenja i rekonstrukcije, neophodnih za optimalne ishode.

Prikaz slučaja pacijenta sa frakturom penisa udruženom sa povredom uretre opisali su Nebojša Prijović i saradnici. Autori navode da je u pitanju retko urgentno urološko stanje, te da pravovremeno prepoznavanje i hirurško lečenje daje odlične funkcionalne rezultate.

Formiranje arteriovenske fistule u aksilarnom bloku i sedaciji kod deteta sa terminalnom bubrežnom insuficijencijom, prikazali su Lazar Jakšić i saradnici opisom procedure kojom je obezbeđena adekvatna analgezija uz minimalnu upotrebu opioda prilikom formiranja AV fistule uz izbegavanje očekivane otežane intubacije.

Autorke Margita Lučić i Dolika Vasović su dale pregled literature koji pokazuje da peribulbarna anestezija u kombinaciji sa ciljanom intravenskom analgo-sedacijom esketaminom predstavlja bezbedan i efikasan savremeni anesteziološki pristup za izvođenje enukleacije, naročito kod starijih i pacijenata sa komorbiditetima.

Na kraju obraćanja, pozivam vas da podelite svoje istraživačke ideje sa nama kako bi naš časopis bio vaš put do čitalačke publike.

S poštovanjem,
Prof. dr Aleksandra Ilić
Pomoćnik glavnog i odgovornog urednika

In their original article, Dejan Munjiza et al. confirmed the proposed hypothesis that an increase in the diameter of the interventricular septum and/or the posterior wall of the left ventricle is associated with a higher likelihood of poorer outcomes in neuroangiological diseases.

The original article by Sonja Smiljić et al. reports on the prevalence of metabolic disorders and hypertension in premenopausal and menopausal women. Women in menopause were found to have a significantly higher burden of hypertension, obesity, dyslipidemia, and type 2 diabetes mellitus, indicating the need for preventive examinations and the early detection and treatment of cardiometabolic disorders in women.

A group of authors led by Danijela Jovanović presented five years of experience in diagnosing, monitoring the disease course, therapeutic response, and survival in patients with non-Hodgkin follicular lymphoma. In their original article, they demonstrate a significant correlation between hemostatic parameters – fibrinogen and D-dimer, and disease progression.

A review article by Jasmina Đuretić addresses aging as a modulator of the pathophysiology of multiple sclerosis. The paper highlights the importance of understanding the interaction between aging and the pathophysiological mechanisms of multiple sclerosis, which is essential for the development of targeted therapeutic strategies for the growing population of older patients with multiple sclerosis.

In their case report, Stevan Čičić et al. emphasize the importance of recognizing radiation-induced osteosarcoma as a rare but serious late complication of breast cancer radiotherapy, highlighting the complexity and specificity of surgical treatment and reconstruction necessary for optimal outcomes.

A case report of a patient with penile fracture associated with urethral injury was presented by Nebojša Prijović et al. The authors note that this is a rare urological emergency and that timely recognition and surgical management yield excellent functional outcomes.

The formation of an arteriovenous fistula under axillary block and sedation in a child with end-stage renal disease was presented by Lazar Jakšić et al., describing a procedure that ensured adequate analgesia with minimal opioid use during AV fistula formation, while avoiding anticipated difficult intubation.

Margita Lučić and Dolika Vasović provided a literature review demonstrating that peribulbar anesthesia combined with targeted intravenous analgosedation using esketamine represents a safe and effective contemporary anesthesiological approach for performing enucleation, particularly in elderly patients and those with comorbidities.

In closing, I invite you to share your research ideas with us, so that our journal may serve as a platform for disseminating your findings to a wide readership.

Sincerely,

Prof. Aleksandra Ilić, MD, PhD

Assistant-Editor-in-Chief

SADRŽAJ

RAD PO POZIVU

INVITED PAPER

Christopher A. Reis, Robert M. Jacobson

PREVENCIJA I PRISTUP REŠAVANJU PROBLEMA KOLEBLJIVOSTI PREMA VAKVINACIJI
PREVENTION AND MANAGEMENT OF VACCINE HESITANCY 15

Zhansaya Nurgaliyeva, Nataliya Glushkova

KOVID-19 U TRUDNOĆI: PUTEVI ZDRAVSTVENE ZAŠTITE I IZAZOVI ZDRAVSTVENOG SISTEMA
U KAZAHSTANU – KVALITATIVNA STUDIJA
NAVIGATING COVID-19 IN PREGNANCY: CARE PATHWAYS AND SYSTEM CHALLENGES
IN KAZAKHSTAN – A QUALITATIVE STUDY 23

ORIGINALNI RADOVI

ORIGINAL ARTICLES

Nikola Gavrilović

DEPRESIVNE SMETNJE MEĐU ČLANOVIMA PORODICE KOJI BRINU O PACIJENTIMA
U KUĆNOM LEČENJU: PHQ-9 STUDIJA PRESEKA
DEPRESSIVE SYMPTOMS AMONG FAMILY MEMBERS PROVIDING INFORMAL CARE FOR
PATIENTS RECEIVING HOME-BASED CARE: A PHQ-9 CROSS-SECTIONAL STUDY..... 43

Dejan Munjiza, Biljana Georgievski-Brkić, Filip Vitošević, Ljubica Dimitrijević, Marjana Vukićević

UTICAJ GEOMETRIJE LEVE KOMORE, ISKAZANE DEBLJINOM INTERVENTRIKULARNOG SEPTUMA
I ZADNJEG ZIDA KOMORE, NA ISHOD AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA
IMPACT OF LEFT VENTRICULAR GEOMETRY, EXPRESSED AS INTERVENTRICULAR SEPTAL
AND POSTERIOR WALL THICKNESS, ON THE OUTCOME OF ACUTE ISCHEMIC STROKE..... 53

Sonja Smiljić, Srna Šapić, Vojkan Nestorović, Zvezdan Milanović, Mirjana Dejanović, Andrijana Karanović

UČESTALOST METABOLIČKIH POREMEĆAJA I HIPERTENZIJE KOD ŽENA PRE MENOPAUZE I U MENOPAUI
THE PREVALENCE OF METABOLIC DISORDERS AND HYPERTENSION IN WOMEN DURING
PERIMENOPAUSE AND MENOPAUSE..... 61

Danijela Jovanović, Snežana Sretenović, Sanja Aleksić, Ana Dragović, Ivana Andrejević

POVEZANOST LABORATORIJSKIH PARAMETARA SA TOKOM BOLESTI KOD PACIJENATA
SA FOLIKULARNIM LIMFOMOM – PETOGODIŠNJE ISKUSTVO JEDNOG CENTRA
LABORATORY PARAMETERS AND THEIR RELATIONS WITH DISEASE OUTCOME IN PATIENTS
WITH NON-HODGKIN FOLLICULAR LYMPHOMA – SINGLE CENTRE FIVE-YEAR FOLLOW-UP 72

CONTENTS

PREGLEDNI RADOVI

REVIEW ARTICLES

Jasmina Đuretić

STARENJE KAO MODULATOR PATOFIZIOLOGIJE MULTIPLE SKLEROZE

AGING AS A MODULATOR OF MULTIPLE SCLEROSIS PATHOPHYSIOLOGY 79

PRIKAZI SLUČAJEVA

CASE REPORTS

Stevan Čičić, Aleksandar Ristanović, Mladen Prcović, Nebojša Marić, Mlađana Savić

HIRURŠKI TRETMAN RADIJACIJOM INDUKOVANOG OSTEOSARKOMA

PREDNJEG ZIDA GRUDNOG KOŠA NAKON KARCINOMA DOJKE: PRIKAZ SLUČAJA

SURGICAL TREATMENT OF RADIATION-INDUCED ANTERIOR CHEST WALL OSTEOSARCOMA

AFTER BREAST CARCINOMA: A CASE REPORT 88

Nebojša Prijović, Branko Stanković, Milan Radovanović, Veljko Šantrić, Uroš Babić

FRAKTURA PENISA UDRUŽENA SA POVREDOM URETRE – PRIKAZ SLUČAJA

PENILE FRACTURE ASSOCIATED WITH URETHRAL INJURY – CASE REPORT 96

Lazar Jakšić, Emil Bosinci, Velja Milačić

FORMIRANJE ARTERIOVENSKE FISTULE U AKSILARNOM BLOKU I SEDACIJI KOD DETETA

SA TERMINALNOM BUBREŽNOM INSUFICIJENCIJOM – PRIKAZ SLUČAJA

AXILLARY BRACHIAL PLEXUS BLOCK UNDER PROCEDURAL SEDATION FOR ARTERIOVENOUS

FISTULA FORMATION IN A CHILD WITH END-STAGE RENAL DISEASE – A CASE REPORT 104

OSTALI ČLANCI

OTHER ARTICLES

Margita Lučić, Dolika D. Vasović

PERIBULBARNA ANESTEZIJA UZ CILJANU INTRAVENSKU ANALGOSEDACIJU

ESKETAMINOM TOKOM ENUKLEACIJE: SAVREMENI REVIJALNI PRIKAZ

PERIBULBAR ANESTHESIA WITH TARGETED INTRAVENOUS ESKETAMINE

ANALGOSEDATION DURING ENUCLEATION: A CONTEMPORARY NARRATIVE REVIEW 110

UPUTSTVO AUTORIMA

INSTRUCTIONS FOR AUTHORS

PREVENCIJA I PRISTUP REŠAVANJU PROBLEMA KOLEBLJIVOSTI PREMA VAKCINACIJI

RAD PO POZIVU: PERSPEKTIVA

INVITED PAPER: PERSPECTIVE

PREVENTION AND MANAGEMENT OF VACCINE HESITANCY

Christopher A. Reis¹, Robert M. Jacobson^{1,2}

¹ Mejo klinika, Odeljenje opšte i adolescentne pedijatrije, Ročester, Minesota, SAD

² Mejo klinika, Odeljenje kvantitativnih zdravstvenih nauka, Ročester, Minesota, SAD

¹ Mayo Clinic, Department of Pediatric and Adolescent Medicine, Rochester, Minnesota, USA

² Mayo Clinic, Department of Quantitative Health Sciences, Rochester, Minnesota, USA

SAŽETAK

Kolebljivost prema vakcinaciji odnosi se na odlaganje prihvatanja ili odbijanje vakcina uprkos dostupnosti usluga vakcinacije. Kvalitetno sprovedene studije i klinička ispitivanja koja se razmatraju u ovom radu podržavaju metode kako za prevenciju, tako i za pristup rešavanju problema kolebljivosti prema vakcinaciji. Kliničari bi trebalo da znaju koje su vakcine predviđene za njihove pacijente i da svaki kontakt iskoriste za bavljenje ovim pitanjem. Istraživanja pokazuju da preporuke zdravstvenih radnika povećavaju obuhvat vakcinacijom. Preporuke koje pacijenti doživljavaju kao snažnije imaju jači efekat u povećanju prihvatanja vakcina. Formulisanje preporuka u vidu podrazumevanih pretpostavki pokazalo se efikasnijim nego predstavljanje vakcine razgovorno, kao jedne od opcija za pacijenta. Kada pacijent na snažnu preporuku odgovori kolebanjem, lekar bi trebalo da pacijenta motiviše putem motivacionog razgovora, po mogućstvu primenom procesa poznatog kao „Četiri P“ (engl. four A's), koji se sastoji iz četiri koraka.

Ključne reči: vakcinacija, kolebljivost prema vakcinaciji, odbijanje vakcinacije

ABSTRACT

Vaccine hesitancy refers to the delay in accepting or refusing vaccines despite the availability of vaccination services. Well-conducted studies and trials reviewed in this article support methods both to prevent and manage vaccine hesitancy. Clinicians should know which vaccines their patients are due to receive and should use every encounter to address this issue. Research shows clinicians' recommendations increase vaccine uptake. Recommendations that patients perceive as stronger have a greater effect in increasing vaccine uptake. Using presumptive language to phrase the recommendation is more effective than presenting the vaccine conversationally as an option for the patient. When the patient counters the strong recommendation with hesitancy, the clinician should engage the patient with motivational interviewing, perhaps using a four-step process called the "Four A's".

Keywords: vaccination, vaccination hesitancy, vaccination refusal

Autor za korespondenciju:
Robert M. Jacobson
Odsek Ba3b, Mejo klinika
200 First Street Southwest, Rochester, Minnesota 55905-0001
Elektronska adresa: jacobson.robert@mayo.edu

Corresponding author:
Robert M. Jacobson
Desk Ba3b, Mayo Clinic
200 First Street Southwest, Rochester, Minnesota 55905-0001
E-mail: jacobson.robert@mayo.edu

Primljeno • Received: November 3, 2025; **Revidirano • Revised:** December 22, 2025; **Prihvaćeno • Accepted:** December 25, 2025; **Online first:** March 25, 2026

DOI: 10.5937/smcl7-62537

UVOD

Kolebljivost prema vakcinaciji predstavlja odlaganje prihvatanja ili odbijanje vakcina uprkos dostupnosti usluga vakcinacije. Reč je o složenom i kontekstualno uslovljenom fenomenu koji varira u zavisnosti od vremena i mesta. Pored toga, kolebljivost prema vakcinaciji nije ujednačena: roditelji mogu prihvatiti neke vakcine, ali odlagati ili odbijati druge. Faktori koji utiču na ovu pojavu uključuju: sumnju u neophodnost vakcinacije (engl. *complacency*), odnosno malu percipiranu opasnost od bolesti, komfor (engl. *convenience*), odnosno pristup imunizaciji, i poverenje (engl. *confidence*), odnosno poverenje u vakcine, zdravstvene radnike i kreatore politika. Motivi se kreću od zabrinutosti za bezbednost i nepoverenja u institucije, do dezinformacija i ličnih uverenja. Ovaj pregledni rad prikazuje pristup zasnovan na dokazima za prevenciju i rešavanje pitanja kolebljivosti prema vakcinaciji.

MATERIJALI I METODE

Izvršili smo fokusirani pregled literature kako bismo identifikovali aktuelne trendove u kolebljivosti prema vakcinaciji na globalnom nivou, analizirajući istraživačke studije o metodama za unapređenje prihvatanja vakcina u kliničkom okruženju.

Kolebljivost prema vakcinaciji u 21. veku

Imunizacija je učinila da bolesti koje se mogu sprečiti vakcinacijom postanu znatno ređe. Ovaj uspeh je, paradoksalno, doveo do toga da se potreba za vakcinacijom dovede u pitanje. Nadalje, kalendari imunizacije su složeni i podložni promenama, te se razlikuju među organizacijama i zdravstvenim ustanovama. Roditelji često dovode u pitanje potrebu za vakcinama, vreme njihovog davanja i broj imunizacija koje se preporučuju njihovoj deci. Ova pitanja mogu dovesti do nesporazuma, uz upliv nepotpunih i netačnih „činjenica“ iz neproverenih izvora, koje dodatno doprinose kolebljivosti prema vakcinaciji.

Svetska zdravstvena organizacija je 2019. godine označila kolebljivost prema vakcinaciji kao globalni problem [1]. Ova organizacija je istakla vakcinaciju kao jedno od najuspešnijih i najisplativijih sredstava javnog zdravlja, koje svake godine sprečava milione smrtnih ishoda. Kolebljivost prema vakcinaciji prepoznata je ne samo kao lokalni ili ideološki problem, već kao pojava koja može da ugrozi decenije napretka u kontroli bolesti koje se mogu sprečiti vakcinacijom. Kao ključne razloge koji leže u osnovi kolebljivosti, savetodavna grupa organizacije za vakcine navela je sumnju u neophodnost vakcinacije, otežan pristup imunizaciji i nedostatak poverenja. Kako je u pojedinim zajednicama došlo do opadanja obuhvata vakcinacijom, prago-

INTRODUCTION

Vaccine hesitancy is the delay in accepting or refusing vaccines despite the availability of vaccination services. It is a complex and context-specific issue varying across time and location. Additionally, vaccine hesitancy is not uniform: parents may accept some vaccines but delay or refuse others. Factors that influence this phenomenon include complacency (a low perceived risk of the disease), convenience (access to immunizations), and confidence (trust in vaccines, healthcare providers, and policymakers). Motivations range from safety concerns and distrust in institutions to misinformation and personal beliefs. This review presents an evidence-based approach for preventing and managing vaccine hesitancy.

MATERIALS AND METHODS

We conducted a focused literature review to identify current trends in global vaccine hesitancy, analyzing research studies on methods to improve vaccine uptake in clinical settings.

Vaccine hesitancy in the 21st century

Immunization has made vaccine-preventable diseases far less common. This success paradoxically eliminated their own apparent need. Furthermore, immunization schedules are complicated and evolving, varying between organizations and medical authorities. Parents often question the need for vaccines, the timing, and the number of immunizations recommended to their children. These questions can lead to misunderstandings, with incomplete and untrue “facts” from unverified sources, further increasing the hesitancy.

The World Health Organization called vaccine hesitancy a global problem in 2019 [1]. The organization highlighted vaccination as one of the most successful and cost-effective public health tools, preventing millions of deaths each year. Vaccine hesitancy was identified as not just a local or ideological problem, but one that could undermine decades of progress in controlling preventable diseases. Vaccine complacency, inconvenience in access, and lack of confidence were the key reasons underlying hesitancy, as found by the organization’s vaccine advisory group. Because vaccination coverage in some communities waned, herd immunity thresholds were not being met, leading to outbreaks of vaccine-preventable illnesses such as measles, which had a 30% rise in cases globally the previous year.

The World Health Organization’s call predated the COVID pandemic [1]. Unfortunately, the pandemic

kolektivnog imuniteta nisu dostizani, što je dovelo do pojave epidemija bolesti koje se mogu sprečiti vakcinacijom, poput morbila, kod kojih je u godini koja je prethodila objavljivanju ovih nalaza zabeležen porast broja slučajeva od 30% na globalnom nivou.

Navedeno upozorenje Svetske zdravstvene organizacije prethodilo je pandemiji KOVID-19 oboljenja [1]. Nažalost, pandemija je dodatno pogoršala probleme poverenja u vakcine i medicinske organizacije. Dezinformacije tokom perioda pandemije KOVID-19 oboljenja pojačale su skepticizam prema vakcinama – platforme društvenih mreža i tzv. „eho-komore“ umnožavale su lažne narative, podrivajući poverenje u rutinsku imunizaciju. Na globalnom nivou, dobiti od vakcinacije stagniraju: jedno istraživanje objavljeno u časopisu *Lancet* ukazalo je na stagnaciju ili čak nazadovanje po pitanju rutinske imunizacije, čak i u zemljama sa visokim dohodkom, usled kolebljivosti prema vakcinaciji, dezinformacija i poremećaja izazvanih pandemijom KOVID-19 [2]. Istraživanja sprovedena među roditeljima i starateljima pokazala su da se, iako se ukupni nivo kolebljivosti nije dramatično promenio, poverenje u informacije o vakcinama tokom pandemije dodatno poljuljalo, a stavovi roditelja polarizovali: jedni su postali skloniji prihvatanju vakcinacije, dok su drugi postali još kolebljiviji [3]. Sami kliničari su prijavili i „prenosni“ efekat pandemije: skepticizam prema vakcinama protiv KOVID-19 oboljenja proširio se i na rutinske vakcine, što je ponovo bilo oblikovano uticajem medija, dezinformacijama i različitim nivoima poverenja u zdravstvene sisteme [4].

Klinička strategija za povećanje obuhvata vakcinacijom

Lekari bi trebalo da koriste svaki klinički susret da svojim pacijentima obezbede imunizaciju, a ne samo preventivne, odnosno rutinske preglede. Zauzete porodice često mogu da zapostave rutinsku preventivnu zdravstvenu zaštitu i da se jave lekaru isključivo zbog akutnih stanja ili kada se pojave neki konkretni zdravstveni problemi kod njih samih ili članova porodice. I posete zbog akutnih stanja i kontrole hroničnih bolesti ključne su za održavanje ažurnog vakcinalnog statusa. Čak i ako data specijalistička ambulanta ne sprovodi vakcinaciju, ove posete mogu predstavljati važnu priliku da se razmotri i razreši eventualna kolebljivost prema vakcinaciji kod pacijenta.

Da bi se svaki klinički susret iskoristio za vakcinaciju, lekar treba da ima pristup vakcinalnoj dokumentaciji svakog pacijenta i da je pažljivo pregleda. Temeljan uvid u vakcinalni status pacijenata pretvara pasivni sistem u proaktivni. Time se obezbeđuje da svaki kontakt sa pacijentom bude prilika za zaštitu od bolesti koje se mogu sprečiti vakcinacijom i smanjuje

aggravated the issues regarding trust in vaccines and medical organizations. COVID-era misinformation heightened vaccine skepticism – social media platforms and echo chambers amplified false narratives, undermining confidence in routine immunizations. Globally, vaccination gains are stalling: one *Lancet* study reported stagnation or reversal of routine immunization, even in high-income countries, because of hesitancy, misinformation, and COVID-19 disruptions [2]. Surveys of parents and caregivers found that while overall hesitancy did not dramatically change, trust in vaccine information grew more uncertain during the pandemic, and parental attitudes polarized: some became more accepting, while others became more hesitant [3]. Clinicians themselves reported a “spillover” effect from the pandemic: COVID-19 vaccine skepticism extended to routine vaccines, which again was shaped by media, misinformation, and differing trust in health systems [4].

A clinical strategy to improve vaccine uptake

Physicians should use every clinical encounter to provide immunizations to their patients, not just well visits. Busy families may falter in routine preventive care and may only present for acute visits or when specific health concerns arise with themselves or their family members. Both acute-care and chronic-condition visits are key to maintaining an up-to-date vaccination status. Even if a specialty clinic does not carry vaccines, these visits can be a key opportunity to address any hesitancy the patient may have.

To use any and every clinical encounter for vaccination, the clinician will need to access and review the vaccine records for each patient. Careful review of patient vaccination records transforms a passive system into a proactive one. It ensures each patient encounter is an opportunity to protect against vaccine-preventable diseases and reduces missed opportunities. This also provides a foundation for effective communication and trust-building with patients.

Vaccines have very few contraindications [5]. Furthermore, most contraindications are temporary. Parents will often highlight their child's acute illness as a barrier to vaccination. Adult patients will question getting a vaccine on top of their presenting concern. In reality, illness is only a precaution, not a contraindication to vaccination, and this only if the illness is acute and moderate to severe. More specifically, acute and not chronic, and moderate or severe and not mild. Moderate illness means that the symptoms interfere with daily activities of living, while the symptoms of severe illness prevent daily activities of living.

broj propuštenih prilika. Ovakav pristup istovremeno predstavlja osnovu za efikasnu komunikaciju i izgradnju poverenja sa pacijentima.

Vakcine imaju vrlo malo kontraindikacija [5]. Štaviše, većina kontraindikacija je privremena. Roditelji često ističu akutnu bolest svog deteta kao prepreku za vakcinaciju. Odrasli pacijenti mogu dovoditi u pitanje primanje vakcine u isto vreme kada imaju zdravstveni problem zbog kojeg su se javili lekaru. Zapravo, bolest predstavlja samo meru opreza, a ne kontraindikaciju za vakcinaciju, i to samo ako je bolest akutna i umerenog do teškog intenziteta. Preciznije, bolest mora biti akutna, a ne hronična, i umerena ili teška, a ne blaga. Umerena bolest znači da simptomi ometaju obavljanje svakodnevni životnih aktivnosti, dok teška bolest onemogućava obavljanje svakodnevni životnih aktivnosti.

Preporuke lekara imaju svoju težinu [6–10], a jače preporuke su efikasnije [11]. Istraživanja su pokazala da formulacije u obliku podrazumevanih pretpostavki (engl. *presumptive language*) šalju signal snažne preporuke kliničara [12]. Ovo potkrepljuju i opservacione studije [12–16] i klinička ispitivanja [17–21]. Konverzacijski, neutralni jezik, poput: „Šta mislite o vakcinaciji danas?“ ili „Da li želite da vaše dete primi vakcinu danas?“ se ne preporučuje. Umesto toga, preporučuje se formulisanje podrazumevanih pretpostavki, kao na primer: „Danas su vam po redu vakcine.“ ili „Preporučujem da vaše dete danas primi predviđene vakcine.“

Navedene studije i randomizovana kontrolisana ispitivanja su pokazala dramatično poboljšanje u obuhvatu vakcinacijom kada se koristi ovakav način izražavanja. Zašto to funkcioniše? Davanje snažne preporuke signalizira pacijentu šta treba da učini i da alternative nisu razborite opcije. Snažna preporuka koristi činjenicu da je pacijent potražio susret sa lekarom. Pacijent veruje proceni i preporukama lekara u vezi sa njegovom akutnom bolešću ili hroničnim zdravstvenim problemom. Lekar bi trebalo da iskoristi ovo poverenje kao osnovu za razgovor o vakcinaciji.

Ako se roditelj koleba uprkos snažnoj preporuci lekara, lekar ne bi trebalo da ulazi u raspravu, grdi ili pokušava da „obrazuje“ roditelja. Studije su pokazale da ovakvi pristupi obično ne uspevaju [22–24], pa čak mogu imati suprotan efekat [25–28]. Takođe, ove studije su pokazale da edukativne intervencije, same za sebe – bilo da su to objave javnih servisa, bilbordi, informacije u čekaonicama, distribuirane brošure ili ponuđeni linkovi ka informativnim veb-stranicama – ne poboljšavaju obuhvat vakcinacijom [22–24]. Nekoliko kliničkih studija je pokazalo da naponi ka edukaciji ponekad mogu imati kontraefekat i povećati rešenost primaoca da se NE vakciniše [25–28]. Preporučuje se umesto toga primena motivacionog razgovora zasnovanog na doka-

Clinicians' recommendations matter [6–10], and stronger recommendations are more effective [11]. Studies have found that presumptive language signals a clinician's strong recommendation [12]. Observational studies [12–16] and interventional trials [17–21] support this. Conversational, neutral language, such as: "What are your thoughts about vaccination today?" or "Would you like your child to get vaccines today?" is not recommended. Using presumptive language is recommended instead, such as: "You are due for vaccines today." or "I recommend your child get the vaccines due today."

The above-mentioned studies and randomized controlled trials demonstrated a dramatic improvement in vaccine uptake when this type of language is used. Why does it work? Voicing a strong recommendation signals to the patient what should be done and that the alternatives are not prudent options. A strong recommendation utilizes the reason why the patient has sought out an encounter with a physician. The patient is trusting the physician's assessment and recommendations regarding their acute illness or management of a chronic issue. The physician should build on this trust.

If the parent hesitates despite the physician's strong recommendation, the doctor should not argue, scold, or attempt to educate. Studies have shown that these approaches usually fail [22–24] and even backfire [25–28]. These studies have also shown that educational interventions alone – whether they be public service announcements, billboards, waiting room communications, distributed pamphlets, or proffered links to informational web pages – fail to improve vaccine uptake [22–24]. Several interventional trials have shown that educational efforts can even backfire and increase the recipients' resolve NOT to vaccinate [25–28]. The recommendation is to use evidence-based motivational interviewing instead. Randomized trials have shown that this approach in clinical encounters works in improving vaccine uptake [18,29–32]. The same trials indicate that this effort takes even less time than trying to educate the family or using other tactics. Studies support the finding that this interviewing technique can give patients and caregivers more confidence in vaccines overall. Participants in these studies have notably highlighted that motivational interviewing improved their understanding of the need for vaccination and even alleviated doubts and concerns.

Motivational interviewing requires the creation of a safe space where everyone feels comfortable being honest. The physician should be empathetic towards the parent or caregiver, avoid conflict, and be an active listener. They should start by asking the parent to name

„Četiri P“ u pristupu rešavanju problema kolebljivosti prema vakcinaciji
putem motivacionog razgovora

PITANJE

“Šta vas najviše brine u pogledu ove vakcine?”

PRIHVATANJE

“Jasno je da ste zaista promislili o ovome. Razumem zašto vas to toliko zabrinjava.”

POTVRDA

“I ja sam se oko toga pitao kada je objavljena preporuka, pa sam to dalje samostalno istražio.”

PRUŽANJE ODGOVORA

“Želite li da čujete šta sam ja saznao o tome?” ili “Želite li da dalje ispitam to što vas brine i da vas kontaktiram sa novim informacijama?”

Preuzeto od: Voices for Vaccines. Becoming Trusted Messengers. Ažurirano: 2025.
Pristupljeno: 15. 9. 2025. Dostupno: <https://www.voicesforvaccines.org/course/becoming-trusted-messengers/>.

Slika 1. „Četiri P“ u pristupu rešavanju problema kolebljivosti prema vakcinaciji
putem motivacionog razgovora

zima. Randomizovana klinička istraživanja su pokazala da ovaj pristup u kliničkim susretima poboljšava obuhvat vakcinacijom [18,29–32]. Iste studije ukazuju da ova metoda zahteva čak manje vremena od pokušaja da se porodica edukuje ili drugih taktika. Studije podržavaju nalaz da ova tehnika razgovora povećava poverenje pacijenata i staratelja u vakcine uopšte. Učesnici ovih studija posebno su istakli da im je motivacioni razgovor unapredio razumevanje potrebe za vakcinacijom, pa čak i ublažio sumnje i razloge za brigu.

Motivacioni razgovor zahteva stvaranje bezbednog prostora gde svi imaju slobodu da budu iskreni. Lekar treba da bude empatičan prema roditelju ili staratelju, da izbegava sukobe i da bude aktivan slušalac. Trebalo bi da počne tako što će zamoliti roditelja da navede najveću brigu ili strah koji ima u vezi sa preporučenom vakcinom. Brige ili strahovi roditelja treba da budu uzeti u obzir kao stvarni, a ne da roditelji zbog njih budu kritikovani. Dalje se preporučuje postavljanje otvorenih pitanja, traženje dozvole pre davanja informacija i strpljenje. Lekar takođe treba da naglasi da je svestan da roditelj već ima određeno znanje i da donosi dobre odluke po pitanju dobrobiti svog deteta.

Koristan način za rešavanje problema kolebljivosti prema vakcinaciji putem motivacionog razgovora u kliničkom okruženju jeste takozvani pristup „Četiri P“ (engl. *four A's*)¹ [33]. Kao što je prikazano na **Slici 1**, ova tehnika se odnosi na četiri zadatka koja treba obaviti određenim redosledom.

Prvim „P“ kliničar pita. Na ovaj način, lekar podstiče roditelja/pacijenta da bude precizan kada je u pitanju ono što ga brine u vezi sa vakcinom i da navede oko čega se najviše koleba.

npr. “Šta vas najviše brine u pogledu ove vakcine?”

The “Four A’s” of addressing vaccine hesitancy through motivational interviewing

ASK

“What is your main concern with this vaccine?”

ACKNOWLEDGE

“It’s clear you’ve really thought about this. I can imagine why this would be so concerning to you.”

AFFIRM

“I had that concern myself when the recommendation came out, and so I did my own investigation.”

ANSWER

“May I tell you what I learned?” or “May I investigate your concern and contact you with what I find?”

From Voices for Vaccines. Becoming Trusted Messengers. Updated: 2025.
Accessed: September 15, 2025. Available from:
<https://www.voicesforvaccines.org/course/becoming-trusted-messengers/>.

Figure 1. The “Four A’s” of addressing vaccine hesitancy through motivational interviewing

the single greatest concern or fear they have regarding the recommended vaccine. The parents’ concerns or fears should be validated, rather than berated. It is further recommended to ask open-ended questions, to ask permission before giving information, and to be patient. The physician should also reinforce that they are aware that the parent already has certain knowledge and makes good decisions for the well-being of their child.

A helpful way to address vaccine hesitancy through motivational interviewing in the clinical setting is the “Four A’s” approach [33]. As shown in **Figure 1**, the “Four A’s” mnemonic refers to four tasks that should be accomplished in a specific order.

With the first A, the clinician asks. In this way, the clinician encourages the parent/patient to be specific about their concerns regarding the vaccine and name what they are most hesitant about.

e.g., “What is your main concern regarding the vaccine?”

With the second A, the clinician acknowledges. The clinician recognizes that the patient/parent is concerned and ultimately is the decision-maker for their own, i.e., their child’s healthcare, including whether to vaccinate.

e.g., “In the end, it is your decision. You need to want to do this. I am not going to make you do this.”

The clinician should acknowledge that the patient wants to do the right thing.

e.g., “It’s clear you’ve really thought about this. I can imagine why this would be so concerning to you.”

With the third A, the clinician affirms. The clinician affirms that it is okay to have questions.

e.g., “That’s a great question. I heard that as well, so I investigated that.”

1 prim. prev.

engl. The four A’s: ask, acknowledge, affirm, answer
sr. „Četiri P“: pitati, prihvatiti, potvrditi, pružiti odgovor

Drugim „P“, kliničar prihvata. Lekar prihvata da je pacijent/roditelj zabrinut i da je na kraju krajeva on donosilac odluka o sopstvenoj, tj. zdravstvenoj zaštiti svog deteta, uključujući i odluku o tome da li će se vakcinisati.

npr., „Na kraju krajeva, to je vaša odluka. Potrebno je da sami želite da ovo uradite. Neću vas terati da to uradite.“

Lekar treba da potvrdi da razume da pacijent želi da uradi pravu stvar.

npr., „Jasno je da ste zaista promislili o ovome. Razumem zašto vas to toliko zabrinjava.“

Trećim „P“ kliničar potvrđuje. Lekar potvrđuje da je u redu da pacijent ima pitanja.

npr., „To je odlično pitanje. I ja sam to čuo, pa sam istražio tu stvar.“

Najzad, četvrtim „P“, kliničar pruža odgovore, ali samo nakon što dobije dozvolu da odgovori. Lekar treba da pita da li pacijent želi da mu on saopšti šta su saznali o datoj temi.

npr., „Želite li da čujete šta sam ja saznao o tome?“

Druga opcija, kada je kliničar trenutno bez odgovora po pitanju nekog novog uzroka za brigu, treba to i da otvoreno kaže, te da ponudi da se na tu temu podrobnije informiše.

npr., „Želite li da dalje ispitam to što vas brine i da vas kontaktiram sa novim informacijama?“

Primenom ovih strategija, lekar se fokusira na svoj odnos sa pacijentom. Izbegava se debata ili konfrontacija, a pacijentu se ukazuje poštovanje. Da, može se desiti da pacijent zaustavi lekara već na prvom „P“. Ako se to dogodi, tj. ako pacijent odbije razgovor na tu temu, lekar bi to trebalo da to poštuje i da stane. Biće budućih susreta, a poverenje i vera pacijenta u lekara važniji su od ispunjavanja preostalih „P“ koraka u okviru jedne posete. Bitno je samo da lekar uloži trud. Pacijent će to osetiti i poštovati lekara zbog toga.

ZAKLJUČAK

Iako smo postigli veliki napredak u razvoju vakcina i uspeali da kontrolišemo mnoge bolesti koje se mogu sprečiti vakcinacijom, kolebljivost prema vakcinaciji i dalje predstavlja značajnu pretnju – pretnju koja se dodatno pogoršala načinom na koji se pristupilo pandemiji KOVID-19 oboljenja. Pandemija je poremetila rutinske tokove vakcinacije, pojačala nepoverenje i polarizovala stavove roditelja prema imunizaciji. Teret i odgovornost je na lekarima da i dalje štite pacijente od bolesti koje se mogu sprečiti vakcinacijom. Dobro utemeljene strategije podržavaju davanje snažnih preporuka uz korišćenje formulacija u vidu podrazumevanih pretpostavki kako bi se poboljšao obuhvat vakcinacijom. Dok dokazi jasno pokazuju da aktivnosti edukacije same po sebi ne uspevaju da reše problem ko-

Finally, with the fourth A, the clinician answers, but only after obtaining permission to answer. The clinician should ask whether they might share what they have learned.

e.g., “May I tell you what I learned?”

Alternatively, when the clinician is momentarily stumped with a novel concern, they should acknowledge this and offer to investigate it further.

e.g., “May I investigate your concern and contact you with what I find?”

In using these strategies, the clinician focuses on their relationship with the patient. A debate or confrontation is avoided, and respect for the patient is shown. Yes, the individual may stop the clinician at the first A. If this happens, i.e., if after permission is asked the patient declines, the clinician should respect this and stop. There will be future encounters, and the patient's trust and confidence in the doctor should matter more than completing the remaining A's at a particular visit. It is just important that the clinician makes the effort. The patient will sense this and respect the clinician for that.

CONCLUSION

While we have made great progress with the development of vaccines and succeeded in controlling many vaccine-preventable diseases, vaccine hesitancy remains a significant threat – one that has been exacerbated through the management of the COVID-19 pandemic. The pandemic disrupted routine vaccination pathways, amplified distrust, and polarized parental attitudes about immunization. It is the burden and responsibility of clinicians to continue protecting patients from vaccine-preventable diseases. Well-evidenced strategies support making strong recommendations with presumptive language to improve vaccine uptake. While evidence clearly shows that educational efforts fail to resolve vaccine hesitancy, data clearly demonstrate that motivational interviewing directed toward vaccine hesitancy improves vaccine uptake.

The “Four A's” approach to motivational interviewing provides a helpful framework to guide clinicians during a patient encounter efficiently and effectively. Clinicians are critical in preventing and managing vaccine hesitancy because of their relationship with the patient. Through thoughtful, empathetic, and evidence-based communication, we can rebuild trust in vaccines and continue reducing the global burden of preventable illnesses.

lebljivosti prema vakcinaciji, podaci takođe jasno ukazuju da motivacioni razgovori usmereni na kolebljivost prema vakcinaciji poboljšavaju obuhvat vakcinacijom.

Pristup „Četiri P“ motivacionom razgovoru pruža koristan okvir koji usmerava kliničare tokom susreta sa pacijentom na efikasan i delotvoran način. Kliničari imaju ključnu ulogu u prevenciji i pristupu rešavanja problema kolebljivosti prema vakcinaciji zbog njihovog odnosa sa pacijentom. Kroz promišljenu i empatičnu komunikaciju utemeljenu na dokazima možemo ponovo izgraditi poverenje u vakcine i nastaviti sa smanjenjem globalnog opterećenja bolestima koje se mogu sprečiti.

AUTORSTVO

Dr Jakobson je predstavio glavne nalaze iznete u ovom radu na 15. Medicinskoj konferenciji srpske dijaspe, održanoj 12. juna 2025. godine. Dr Rajs je dodatno razradio detalje, izradio ilustrativnu sliku (Slika 1) i obezbedio reference iz objavljenog spiska literature.

IZJAVE O SUKOBU INTERESA:

Robert M. Jakobson daje sledeću izjavu: član Eksterne komisije za praćenje podataka u Merck & Co.; vlasnik nasleđenih akcija – Zimvie, Baxter, Eli Lilly, Johnson & Johnson, Abbot, Zimmer, Medtronics, AbbVie, Becton Dickinson, 3M, Hubbell, Takeda, & Embecta

AUTHORSHIP

Dr. Jacobson presented the major findings reported in this paper at the 15th Serbian Diaspora Medical Conference on June 12, 2025. Dr. Reis expanded on the details, created the illustrative figure (Figure 1), and provided citations of the published literature.

CONFLICT OF INTEREST DISCLOSURES:

Robert M. Jacobson declares the following: External data monitoring committee member at Merck & Co.; owner of inherited stock – Zimvie, Baxter, Eli Lilly, Johnson & Johnson, Abbot, Zimmer, Medtronics, AbbVie, Becton Dickinson, 3M, Hubbell, Takeda, & Embecta

LITERATURA / REFERENCES

1. World Health Organization. Ten Threats to Global Health in 2019. [Internet]. Pristupljeno: 15. 9. 2025. Dostupno: <https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019>
2. Shet A, Carr K, Danovaro-Holliday MC, Sodha SV, Prosperi C, Wunderlich J, et al. Impact of the SARS-CoV-2 pandemic on routine immunisation services: evidence of disruption and recovery from 170 countries and territories. *Lancet Glob Health*. 2022 Feb;10(2):e186-e194. doi: 10.1016/S2214-109X(21)00512-X.
3. Higgins DM, Moss A, Blackwell S, O'Leary ST. The COVID-19 Pandemic and Parental Attitudes Toward Routine Childhood Vaccines. *Pediatrics*. 2023 Nov 1;152(5):e2023062927. doi: 10.1542/peds.2023-062927.
4. Gurfinkel D, Tietbohl C, Clark E, Saville A, Albertin C, O'Leary ST, et al. Perceived Effects of COVID-19 on Vaccine Hesitancy and Clinician Discussion: A Qualitative Study. *Pediatrics*. 2024 Oct 1;154(4):e2024066819. doi: 10.1542/peds.2024-066819.
5. Centers for Disease Control and Prevention. Contraindications and Precautions. [Internet]. Pristupljeno: 9. 9. 2025. Dostupno: <https://www.cdc.gov/vaccines/hcp/immunization-best-practices/contraindications-precautions.html>
6. Nowalk MP, Lin CJ, Zimmerman RK, Ko FS, Hoberman A, Zoffel L, et al. Changes in parents' perceptions of infant influenza vaccination over two years. *J Natl Med Assoc*. 2007 Jun;99(6):636-41.
7. Guerry SL, De Rosa CJ, Markowitz LE, Walker S, Liddon N, Kerndt PR, et al. Human papillomavirus vaccine initiation among adolescent girls in high-risk communities. *Vaccine*. 2011 Mar 9;29(12):2235-41. doi: 10.1016/j.vaccine.2011.01.052.
8. Darden PM, Thompson DM, Roberts JR, Hale JJ, Pope C, Naifeh M, et al. Reasons for not vaccinating adolescents: National Immunization Survey of Teens, 2008-2010. *Pediatrics*. 2013 Apr;131(4):645-51. doi: 10.1542/peds.2012-2384.
9. Darden PM, Jacobson RM. Impact of a physician recommendation. *Hum Vaccin Immunother*. 2014;10(9):2632-5. doi: 10.4161/hv.29020.
10. Caldwell AC, Madden CA, Thompson DM, Garbe MC, Roberts JR, Jacobson RM, et al. The impact of provider recommendation on human papillomavirus vaccine and other adolescent vaccines. *Hum Vaccin Immunother*. 2021 Apr 3;17(4):1059-1067. doi: 10.1080/21645515.2020.1817713.
11. Rosenthal SL, Weiss TW, Zimet GD, Ma L, Good MB, Vichnin MD. Predictors of HPV vaccine uptake among women aged 19-26: importance of a physician's recommendation. *Vaccine*. 2011 Jan 29;29(5):890-5. doi: 10.1016/j.vaccine.2009.12.063.
12. Opel DJ, Heritage J, Taylor JA, Mangione-Smith R, Salas HS, Devere V, et al. The architecture of provider-parent vaccine discussions at health supervision visits. *Pediatrics*. 2013 Dec;132(6):1037-46. doi: 10.1542/peds.2013-2037.
13. Opel DJ, Mangione-Smith R, Robinson JD, Heritage J, Devere V, Salas HS, et al. The Influence of Provider Communication Behaviors on Parental Vaccine Acceptance and Visit Experience. *Am J Public Health*. 2015 Oct;105(10):1998-2004. doi: 10.2105/AJPH.2014.302425.
14. Sturm L, Donahue K, Kasting M, Kulkarni A, Brewer NT, Zimet GD. Pediatrician-Parent Conversations About Human Papillomavirus Vaccination: An Analysis of Audio Recordings. *J Adolesc Health*. 2017 Aug;61(2):246-251. doi: 10.1016/j.jadohealth.2017.02.006.

15. Hofstetter AM, Robinson JD, Lepere K, Cunningham M, Etsekson N, Opel DJ. Clinician-parent discussions about influenza vaccination of children and their association with vaccine acceptance. *Vaccine*. 2017 May 9;35(20):2709-2715. doi: 10.1016/j.vaccine.2017.03.077.
16. Opel DJ, Zhou C, Robinson JD, Henrikson N, Lepere K, Mangione-Smith R, et al. Impact of Childhood Vaccine Discussion Format Over Time on Immunization Status. *Acad Pediatr*. 2018 May-Jun;18(4):430-436. doi: 10.1016/j.acap.2017.12.009.
17. Brewer NT, Hall ME, Malo TL, Gilkey MB, Quinn B, Lathren C. Announcements Versus Conversations to Improve HPV Vaccination Coverage: A Randomized Trial. *Pediatrics*. 2017 Jan;139(1):e20161764. doi: 10.1542/peds.2016-1764.
18. Dempsey AF, Pyrznowski J, Lockhart S, Barnard J, Campagna EJ, Garrett K, et al. Effect of a Health Care Professional Communication Training Intervention on Adolescent Human Papillomavirus Vaccination: A Cluster Randomized Clinical Trial. *JAMA Pediatr*. 2018 May 7;172(5):e180016. doi: 10.1001/jamapediatrics.2018.0016.
19. Malo TL, Hall ME, Brewer NT, Lathren CR, Gilkey MB. Why is announcement training more effective than conversation training for introducing HPV vaccination? A theory-based investigation. *Implement Sci*. 2018 Apr 19;13(1):57. doi: 10.1186/s13012-018-0743-8.
20. Dempsey AF, Pyrznowski J, Campagna EJ, Lockhart S, O'Leary ST. Parent report of provider HPV vaccine communication strategies used during a randomized, controlled trial of a provider communication intervention. *Vaccine*. 2019 Feb 28;37(10):1307-1312. doi: 10.1016/j.vaccine.2019.01.051.
21. Hofstetter AM, Opel DJ, Stockwell MS, Hsu C, Zhou C, Mangione-Smith RM, et al. Associations Between Health Care Professional Communication Practices and Influenza Vaccination of Hospitalized Children. *Acad Pediatr*. 2021 Sep-Oct;21(7):1142-1150. doi: 10.1016/j.acap.2021.06.014.
22. Briss PA, Rodewald LE, Hinman AR, Shefer AM, Strikas RA, Bernier RR, et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults. The Task Force on Community Preventive Services. *Am J Prev Med*. 2000 Jan;18(1 Suppl):97-140. doi: 10.1016/s0749-3797(99)00118-x.
23. Hinman AR, Briss PA, Carande-Kulis VG, Bernier RR. Recommendations regarding interventions to improve vaccination coverage in children, adolescents, and adults. *Am J Prev Med*. Jan 2000;18(1):92-96.
24. Fu LY, Bonhomme LA, Cooper SC, Joseph JG, Zimet GD. Educational interventions to increase HPV vaccination acceptance: a systematic review. *Vaccine*. 2014 Apr 7;32(17):1901-20. doi: 10.1016/j.vaccine.2014.01.091.
25. Nyhan B, Reifler J, Richey S, Freed GL. Effective messages in vaccine promotion: a randomized trial. *Pediatrics*. 2014 Apr;133(4):e835-42. doi: 10.1542/peds.2013-2365.
26. Nyhan B, Reifler J. Does correcting myths about the flu vaccine work? An experimental evaluation of the effects of corrective information. *Vaccine*. 2015 Jan 9;33(3):459-64. doi: 10.1016/j.vaccine.2014.11.017.
27. Pluviano S, Watt C, Della Sala S. Misinformation lingers in memory: Failure of three pro-vaccination strategies. *PLoS One*. 2017 Jul 27;12(7):e0181640. doi: 10.1371/journal.pone.0181640.
28. Reddinger JL, Levine D, Charness G. Can targeted messages reduce COVID-19 vaccination hesitancy? A randomized trial. *Prev Med Rep*. 2022 Oct;29:101903. doi: 10.1016/j.pmedr.2022.101903.
29. Cole JW, M H Chen A, McGuire K, Berman S, Gardner J, Teegala Y. Motivational interviewing and vaccine acceptance in children: The MOTIVE study. *Vaccine*. 2022 Mar 15;40(12):1846-1854. doi: 10.1016/j.vaccine.2022.01.058. Erratum in: *Vaccine*. 2022 May 31;40(25):3482. doi: 10.1016/j.vaccine.2022.04.084.
30. Berenbrok LA, Gessler C, Kirisci L, Herrera-Restrepo O, Coley KC. Impact of pharmacist motivational interviewing on hepatitis B vaccination in adults with diabetes. *J Am Pharm Assoc* (2003). 2023 Jan-Feb;63(1):66-73.e1. doi: 10.1016/j.japh.2022.08.013.
31. Chan DNS, Choi KC, Lee PPK, So WKW. The Effects of Motivational Interviewing on Promoting Human Papillomavirus Vaccination Initiation and Completion Among South Asian Mother/Daughter Dyads: A Pilot Randomised Controlled Trial. *Int J Behav Med*. 2025 Aug;32(4):574-585. doi: 10.1007/s12529-025-10349-y.
32. Opel DJ, Robinson JD, Zhou C, Colborn K, Spielvogel H, Furniss A, et al. Tiered Clinician Vaccine Communication Strategy to Improve Childhood Vaccine Uptake: A Cluster Randomized Clinical Trial. *JAMA Netw Open*. 2025 Apr 1;8(4):e257814. doi: 10.1001/jamanetworkopen.2025.7814.
33. Voices for Vaccines. Becoming Trusted Messengers. Updated 2025. [Internet]. Pristupljeno: 15. 9. 2025. Dostupno: <https://www.voicesforvaccines.org/course/becoming-trusted-messengers/>

CURRICULUM VITAE



Christopher A Reis

Christopher A Reis, MD, FAAP, is a general pediatrician at Mayo Clinic Children's in Rochester, Minnesota. He graduated from the University of Minnesota, Twin Cities with a degree in biology prior to attending medical school at Oakland University William Beaumont School of Medicine. His postgraduate training was completed at Mayo Clinic, including a residency in pediatrics followed by a fellowship in pediatric infectious diseases. His academic interests include vaccine uptake and hesitancy in primary care pediatrics, as well as quality improvement to enhance vaccine administration through system level interventions and medical education.



Robert M Jacobson

Robert M Jacobson, MD, FAAP, is a primary care pediatrician in the Division of Community Pediatric and Adolescent Medicine at Mayo Clinic and holds joint appointments in the Divisions of Pediatric Infectious Diseases and Epidemiology. He serves as the Medical Directors for the adult and child immunization programs at Mayo Clinic in Southeast Minnesota. He also serves as a co-Chair of the AskMayoExpert Knowledge Content Board for Immunizations and Vaccinations. He also conducts research to improve vaccine uptake and has published 280 peer-reviewed publications. He is passionate about evidence-based medicine, population health science, and preventive care including and especially vaccines.

KOVID-19 U TRUDNOĆI: PUTEVI ZDRAVSTVENE ZAŠTITE I IZAZOVI ZDRAVSTVENOG SISTEMA U KAZAHSTANU – KVALITATIVNA STUDIJA

ORIGINALNI RAD PO POZIVU: KVALITATIVNO ISTRAŽIVANJE

INVITED ORIGINAL ARTICLE: QUALITATIVE RESEARCH

NAVIGATING COVID-19 IN PREGNANCY: CARE PATHWAYS AND SYSTEM CHALLENGES IN KAZAKHSTAN – A QUALITATIVE STUDY

Zhansaya Nurgaliyeva¹, Nataliya Glushkova¹

¹ Kazahstanski nacionalni univerzitet Al-Farabi, Fakultet medicinskih i zdravstvenih studija, Almaty, Kazakhstan

¹ Al-Farabi Kazakh National University, Faculty of Medicine and Health Care, Almaty, Kazakhstan

SAŽETAK

Uvod: Međunarodne studije sprovedene tokom KOVID-19 pandemije pokazale su da su trudnice često nailazile na značajne prepreke u ostvarivanju blagovremene i adekvatne zdravstvene zaštite. Međutim, veliki deo postojećih dokaza potiče iz kvantitativnog nadzora ili iz okruženja sa dobro uspostavljenom digitalnom infrastrukturom i standardizovanim kliničkim protokolima, što možda ne odražava realnost mnogih zdravstvenih sistema u zemljama sa srednjim dohotkom. Cilj ove studije je da se kvalitativno istraže iskustva trudnica i zdravstvenih radnika u vezi sa putevima zdravstvene zaštite kod KOVID-19 oboljenja, uključujući prepoznavanje simptoma, ambulantno lečenje i hospitalizaciju, u gradu Almatiju, u Kazahstanu.

Metode: U ovoj studiji je primenjen kvalitativni, deskriptivni, fenomenološki dizajn kako bi se istražila iskustva trudnica obolelih od KOVID-19 oboljenja i zdravstvenih radnika u domenu organizacije zdravstvene zaštite tokom pandemije. U studiju je uključeno 24 učesnika iz lokalnih domova zdravlja i bolničkih ustanova u gradu Almatiju, u Kazahstanu. Petnaest zdravstvenih radnika i devet trudnica, odnosno porodilja dobrovoljno i anonimno je dalo informisani pristanak za detaljne polustrukturisane intervjue, bilo uživo ili putem konferencijskog video poziva sa bezbednom vezom, u periodu od maja do avgusta 2023. godine.

Rezultati: Zdravstveni radnici su izvestili da je KOVID-19 pandemija značajno izmenila zdravstvenu zaštitu trudnica i porodilja zbog povećanog obima posla, straha od infekcije i prelaska na daljinsku zdravstvenu zaštitu. Neizvesnost u vezi sa kliničkim smernicama specifičnim za trudnoću i standardnim operativnim procedurama (SOP) doprinela je tome da se zdravstveni radnici oslanjaju na opšte protokole i neformalne prakse, dok je odložena hospitalizacija bila povezana sa poricanjem simptoma, strahom od prijema u bolnicu, samolečenjem i sistemskim ograničenjima. Trudnice i porodilje su često pogrešno tumačile KOVID-19 simptome kao simptome povezane sa trudnoćom ili kao znake blagog oblika bolesti, što je dovelo do samolečenja i odlaganja traženja pomoći. Lekarsko praćenje je u velikoj meri bilo nestrukturirano i zasnovano na komunikaciji putem telefona ili poruka. Iskustvo u ostvarenoj zdravstvenoj zaštiti je variralo, od blagovremene kliničke podrške do nedoslednog nadzora i davanja prednosti kućnom lečenju.

ABSTRACT

Introduction: International studies conducted during the COVID-19 pandemic have shown that pregnant women often experienced significant barriers to timely and appropriate care. However, much of the existing evidence is derived from quantitative surveillance or from settings with well-established digital infrastructure and standardized clinical pathways, which may not reflect the realities of many middle-income health systems. This study aims to qualitatively explore the experiences of pregnant women and healthcare professionals regarding COVID-19 care pathways, including symptom recognition, outpatient management, and hospitalization, in Almaty, Kazakhstan.

Methods: The present study applied a qualitative, descriptive, phenomenological design to explore how pregnant COVID-19 patients and healthcare professionals experienced the organization of care during the pandemic. The study included 24 participants from local primary health care and hospital settings in Almaty, Kazakhstan. Fifteen healthcare professionals and nine pregnant or postpartum women voluntarily and anonymously provided informed consent to in-depth semi-structured interviews, either face-to-face or via secure video conferencing, between May and August 2023.

Results: Healthcare professionals reported that COVID-19 substantially altered maternal health care due to increased workload, fear of infection, and a shift toward remote care. Uncertainty regarding pregnancy-specific clinical guidelines and standard operating procedures (SOPs) contributed to reliance on general protocols and informal practices, while delayed hospitalization was linked to symptom denial, fear of admission, self-treatment, and system constraints. Pregnant and postpartum women commonly misinterpreted COVID-19 symptoms as pregnancy-related or mild illness, leading to self-medication and delayed help-seeking. Follow-up was largely unstructured and based on communication via phone or messages. The experience of care varied, ranging from timely clinical support to inconsistent monitoring and preference for home-based management.

Conclusion: The study offers detailed insights into a fragile and fragmented COVID-19 care pathway for pregnant women in primary and hospital care set-

Autor za korespondenciju:

Zhansaya Nurgaliyeva
Fakultet medicinskih i zdravstvenih studija, Kazahstanski nacionalni univerzitet Al-Farabi
71 Al-Farabi Ave., Almaty, Republika Kazakhstan, 050040
Elektronska adresa: zhanlazim@gmail.com

Corresponding author:

Zhansaya Nurgaliyeva
Faculty of Medicine and Health Care, Al-Farabi Kazakh National University
71 Al-Farabi Ave., Almaty, Republic of Kazakhstan, 050040
E-mail: zhanlazim@gmail.com

Primljeno • Received: January 19, 2026; **Revidirano • Revised:** February 26, 2026; **Prihvaćeno • Accepted:** March 5, 2026; **Online first:** March 25, 2026

DOI: 10.5937/smcl7-64476

Zaključak: Studija pruža detaljan uvid u krhki i fragmentirani put zdravstvene zaštite trudnica obolelih od COVID-19 u sklopu primarne i bolničke zdravstvene zaštite u Almatiju. Nekoliko prioriteta za jačanje organizacije zdravstvene zaštite za trudnice obolele od COVID-19 i za buduće javnozdravstvene vanredne situacije uključuju poboljšanje kontinuiteta zdravstvene zaštite, smanjenje kašnjenja u eskaliranju zdravstvene zaštite i unapređenje bezbednosti zdravstvenih usluga za trudnice i porodilje tokom izbijanja zaraznih bolesti.

Ključne reči: trudnoća, COVID-19, kvalitativna studija, zdravstvena zaštita trudnica i porodilja, organizacija

tings in Almaty. Several priorities for strengthening care organization for pregnant women with COVID-19 and for future public health emergencies include improving continuity of care, reducing delays in escalation, and enhancing the safety of maternal health services during infectious disease outbreaks.

Keywords: pregnancy, COVID-19, qualitative study, maternal health care, organization

АННОТАЦИЯ

Кіріспе: COVID-19 пандемиясы кезеңінде жүргізілген халықаралық зерттеулер жүкті әйелдердің медициналық көмекке уақтылы және тиісті түрде қол жеткізуінде елеулі кедергілер болғанын көрсетті. Алайда қолда бар дәлелдердің басым бөлігі сандық мониторингтік деректерге немесе цифрлық инфрақұрылымы дамыған және клиникалық маршруттары стандартталған елдерге негізделген, бұл табысы орта деңгейдегі көптеген елдердің нақты жағдайын толық көрсете бермейді. Осы зерттеудің мақсаты – Алматы қаласында жүкті әйелдер мен медициналық қызметкерлердің COVID-19 кезіндегі медициналық көмекті ұйымдастыру, соның ішінде симптомдарды тану, амбулаториялық бақылау және госпитализациялау маршруттары жөніндегі тәжірибесін сапалық тұрғыдан зерттеу.

Әдістері: Зерттеу COVID-19 жұқтырған жүкті әйелдер мен медициналық қызметкерлердің пандемия кезеңіндегі медициналық көмекті ұйымдастыру тәжірибесін зерттеуге бағытталған сапалық сипаттамалық феноменологиялық дизайнға жүргізілді. Зерттеуге Алматы қаласындағы бастапқы медициналық-санитариялық көмек ұйымдары мен стационарлық деңгейден барлығы 24 қатысушы тартылды, оның ішінде 15 медициналық қызметкер және 9 жүкті немесе босанғаннан кейінгі кезеңдегі әйелдер болды. Барлық қатысушылар зерттеуге ерікті түрде және анонимді түрде қатысуға келісім беріп, 2023 жылғы мамыр–тамыз айлары аралығында бетпе-бет немесе қауіпсіз бейнеконференция арқылы жартылай құрылымданған тереңдетілген сұхбаттардан өтті.

Нәтижелері: Медициналық қызметкерлер COVID-19 пандемиясы ана мен бала денсаулығына көрсетілетін көмекті айтарлықтай өзгертті деп сипаттады, оның ішінде жұмыс жүктемесінің артуы, жұқтыру қаупі және қашықтан медициналық көмек көрсетуге көшу байқалды. Жүктілікке бейімделген клиникалық нұсқаулықтар мен стандартты операциялық рәсімдердің жеткіліксіздігі жалпы COVID-19 хаттамалары мен бейресми тәжірибелерге сүйенуге әкелді, ал госпитализацияның кешіктірілуі симптомдарды елемей, ауруханаға жатудан қорқу, өзін-өзі емдеу және жүйелік шектеулермен байланысты болды. Жүкті және босанғаннан кейінгі әйелдер COVID-19 симптомдарын жүктілікке тән өзгерістер немесе жеңіл респираторлық ауру ретінде қабылдап, медициналық көмекке кеш жүгіну және өзін-өзі емдеу жағдайлары жиі тіркелді. Бақылау көбіне құрылымданбаған түрде телефон арқылы немесе мессенджерлер көмегімен жүзеге асырылды. Медициналық көмекті қабылдау тәжірибесі әртүрлі болды: кейбір әйелдер уақтылы қолдауға ие болса, басқалары тұрақсыз бақылауды бастан кешіріп, үй жағдайында қалуды жөн көрді.

Қорытынды: Зерттеу Алматы қаласында жүкті әйелдерге COVID-19 кезінде көрсетілген медициналық көмектің бастапқы және стационарлық деңгейлерде фрагменттелген әрі осал маршруттарын жан-жақты сипаттайды. Алынған нәтижелер болашақ қоғамдық денсаулық сақтау төтенше жағдайларында жүкті әйелдерге көрсетілетін медициналық көмекті жетілдіру үшін күтімнің сабақтастығын арттыру, көмек көрсету деңгейіне уақтылы көшуге кедергілерді азайту және ана денсаулығы қызметтерінің қауіпсіздігін күшейту қажеттігін көрсетеді.

Түйінді сөздер: жүктілік, COVID-19, сапалық зерттеу, ана денсаулығы, медициналық көмекті ұйымдастыру

UVOD

Tokom pandemije KOVID-19 oboljenja, trudnice su identifikovane kao visokorizična grupa. U poređenju sa ženama reproduktivnog uzrasta koje nisu trudne, kod trudnica postoji veća verovatnoća razvoja teškog oblika bolesti, prijema u jedinicu intenzivne nege i nepovoljnih akušerskih ishoda, uključujući prevremeni porođaj [1–4]. Pored direktnih kliničkih rizika infekcije SARS-CoV-2 virusom, trudnoća stvara dodatnu osetljivost, jer su zdravlje majke i fetusa usko povezani, zbog čega kašnjenja ili prekidi u pružanju zdravstvene zaštite mogu biti potencijalno štetniji [5]. Sledstveno tome, tokom KOVID-19 pandemije na svetlo je izašla ne samo potreba za efikasnim kliničkim zbrinjavanjem infekcije kod trudnica, već se pokazalo i da je od ključnog značaja način na koji se zdravstvena zaštita za ovu populaciju organizuje, pruža i čini dostupnom [5,6].

Kada se pandemija brzo širi, klinički ishodi nisu određeni samo biološkom težinom infekcije već i načinom na koji zdravstveni sistemi odgovaraju na potrebe pacijenata. Kod trudnica obolelih od KOVID-19 infekcije, pravovremeno prepoznavanje simptoma, pristup testiranju, jasni putevi upućivanja na odgovarajuće lečenje i primerene odluke o ambulantnom odnosno bolničkom lečenju, ključni su za sprečavanje pogoršanja stanja i nepovoljnih ishoda [7]. Poremećaji u komunikaciji, neizvesnost u vezi sa kliničkom odgovornošću ili kašnjenja u hospitalizaciji mogu oboljenje koje bi se inače moglo staviti pod kontrolu pretvoriti u ozbiljnu pretnju i za majku i za fetus [8–10]. Stoga je razumevanje načina na koji putevi pružanja zdravstvene zaštite funkcionišu u praksi od suštinskog značaja za identifikovanje nedostataka koji mogu ugroziti bezbednost i efikasnost zdravstvene zaštite trudnica i porodilja tokom javnozdravstvenih vanrednih situacija.

Međunarodne studije sprovedene tokom pandemije KOVID-19 oboljenja pokazale su da su trudnice nailazile na značajne prepreke u ostvarivanju blagovremene i adekvatne zdravstvene zaštite. U to su spadali i strah od infekcije u zdravstvenim ustanovama, nesigurnost u vezi sa tim kada treba potražiti medicinsku pomoć, smanjen broj neposrednih kontakata sa kliničarima i oslanjanje na komunikaciju na daljinu [11–13]. Isto tako, zdravstveni radnici su izveštavali o velikom opterećenju poslom, kliničkim smernicama koje su se rapidno menjale i poteškoćama u koordinaciji zdravstvene zaštite među različitim službama [14–16]. Kvalitativna istraživanja iz zemalja sa visokim dohotkom opisala su kako su ovi izazovi uticali na komunikaciju, poverenje i donošenje odluka između trudnica i zdravstvenih radnika [17,18]. Sa druge strane, mora se imati u vidu da veliki deo postojećih dokaza potiče iz kvantitativnog nadzora ili iz okruženja sa dobro razvijenom digitalnom

INTRODUCTION

Pregnant women have been identified as a high-risk group during the COVID-19 pandemic. Compared with non-pregnant women of reproductive age, they face a higher likelihood of severe disease, intensive care unit admission, and adverse obstetric outcomes, including preterm birth [1–4]. Beyond the direct clinical risks of SARS-CoV-2 infection, pregnancy creates additional vulnerability because maternal and fetal health are closely intertwined, making delays or disruptions in care potentially more harmful [5]. As a result, the COVID-19 pandemic highlighted not only the need for effective clinical management of infection in pregnant women, but also the critical importance of how care is organized, delivered, and accessed for this population [5,6].

During a rapidly evolving pandemic, clinical outcomes are shaped not only by the biological severity of infection but also by how health systems respond to patient needs. For pregnant COVID-19 patients, timely recognition of symptoms, access to testing, clear referral pathways, and appropriate decisions about outpatient versus inpatient care are crucial for preventing deterioration and adverse outcomes [7]. Disruptions in communication, uncertainty about clinical responsibility, or delays in hospitalization can turn otherwise manageable illness into a serious threat for both mother and fetus [8–10]. Therefore, understanding how care pathways function in practice is essential for identifying gaps that may undermine the safety and effectiveness of maternal health care during public health emergencies.

International studies conducted during the COVID-19 pandemic have shown that pregnant women often experienced significant barriers to timely and appropriate care. These included fear of infection in healthcare facilities, uncertainty about when to seek help, reduced face-to-face contact with clinicians, and reliance on remote communication [11–13]. Likewise, healthcare professionals likewise reported heavy workloads, rapidly changing clinical guidance, and difficulties coordinating care across services [14–16]. Qualitative research from high-income countries has described how these challenges affected communication, trust, and decision-making between pregnant women and providers [17,18]. However, much of the existing evidence is derived from quantitative surveillance or from settings with well-established digital infrastructure and standardized clinical pathways, which may not reflect the realities of many middle-income health systems.

Despite a growing body of international research on pregnancy and COVID-19, important gaps remain [19]. Most qualitative studies have been conducted in

infrastrukturu i standardizovanim kliničkim putevima, što možda ne odražava realnost mnogih zdravstvenih sistema u zemljama sa srednjim dohotkom.

Uprkos sve većem broju međunarodnih istraživanja o trudnoći i KOVID-19 oboljenju, i dalje postoje značajne praznine u stečenom znanju i informacijama [19]. Većina kvalitativnih studija sprovedena je u zemljama sa visokim dohotkom, relativno stabilnim zdravstvenim sistemima i uspostavljenim kliničkim putevima. Nekoliko kliničkih studija iz Kazahstana dokumentovalo je uticaj KOVID-19 infekcije na zdravlje majki, uključujući veće stope nepovoljnih kliničkih ishoda i povećanu maternalnu smrtnost povezanu sa pandemijom. Nedavna multicentrična studija je pokazala da su trudnice sa KOVID-19 oboljenjem imale teže simptome i veću stopu prijema u jedinicu intenzivne nege u poređenju sa ženama koje nisu bile trudne, a nacionalni podaci ukazuju na nagli porast indirektnih uzroka maternalne smrtnosti tokom pandemijske godine [2,20,21]. Međutim, postojeća istraživanja iz Kazahstana prvenstveno su bila usmerena na kvantitativne kliničke ishode, uz malo kvalitativnih dokaza o tome kako su žene i zdravstveni radnici u stvarnosti doživljavali puteve pružanja zdravstvene zaštite. Ova studija ima za cilj da kvalitativno istraži iskustva trudnica i zdravstvenih radnika u vezi sa putevima zbrinjavanja trudnica obolelih od KOVID-19 infekcije, uključujući prepoznavanje simptoma, ambulantno lečenje i hospitalizaciju, u gradu Almatiju, u Kazahstanu.

MATERIJAL I METODE

Dizajn studije

U ovoj studiji primenjen je kvalitativni, deskriptivni, fenomenološki dizajn kako bi se istražilo na koji način su trudnice obolele od KOVID-19 oboljenja i zdravstveni radnici doživeli organizaciju zdravstvene zaštite tokom pandemije. Fenomenološki pristup izabran je kako bi se obuhvatila doživljena iskustva i percepcije učesnika o putevima zdravstvene zaštite, postojećim preprekama i načinima donošenja odluka u stvarnim kliničkim situacijama.

Okruženje i period istraživanja

Studija je sprovedena u gradu Almatiju, u Kazahstanu. Prikupljanje podataka je obavljeno između maja 2023. i avgusta 2023. godine. U tom periodu, zdravstvena zaštita trudnica obolelih od KOVID-19 oboljenja bila je regulisana nacionalnim kliničkim protokolima i regionalnim organizacionim procedurama, koje su tokom pandemije često revidirane.

Učesnici i uzorkovanje

Učesnici su regrutovani iz lokalnih ustanova primarne zdravstvene zaštite i bolničkih ustanova u gradu Alma-

high-income countries with relatively stable health systems and established clinical pathways. Several clinical studies from Kazakhstan have documented the impact of COVID-19 on maternal health, including higher rates of adverse clinical outcomes and increased maternal mortality associated with the pandemic. A recent multicentric study reported that pregnant women with COVID-19 experienced more severe symptoms and higher rates of intensive care unit admission compared with non-pregnant women, and national data indicate a sharp rise in indirect causes of maternal death during the pandemic year [2,20,21]. However, existing research from Kazakhstan has primarily focused on quantitative clinical outcomes, with little qualitative evidence on how care pathways were experienced by women and providers in the real world. The present study aims to qualitatively explore the experiences of pregnant women and healthcare professionals regarding COVID-19 care pathways, including symptom recognition, outpatient management, and hospitalization, in Almaty, Kazakhstan.

MATERIALS AND METHODS

Study design

The present study applied a qualitative, descriptive, phenomenological design to explore how pregnant COVID-19 patients and healthcare professionals experienced the organization of care during the pandemic. The phenomenological approach was chosen to capture the participants' lived experiences and perceptions of care pathways, barriers, and decision-making in real-world clinical settings.

Setting and study period

The study was conducted in Almaty, Kazakhstan. Data collection took place between May 2023 and August 2023. At the time, care for pregnant COVID-19 patients was regulated by national clinical protocols and regional organizational procedures, which were undergoing frequent revisions during the pandemic.

Participants and sampling

The participants were recruited for the study from local primary health care and hospital settings in Almaty, Kazakhstan. They were informed on the study protocol and invited to voluntarily and anonymously provide informed consent. Two groups of participants were recruited:

1. **Healthcare professionals** involved in the care of pregnant women with COVID-19 ($n = 15$), including obstetricians-gynecologists, midwives, infectious disease specialists, and hospital and primary care managers.

tiju, u Kazahstanu. Informisani su o protokolu studije i upućen im je poziv da dobrovoljno i anonimno daju informisani pristanak za učešće u studiji. Regrutovane su dve grupe učesnika:

1. **Zdravstveni radnici** uključeni u zbrinjavanje trudnica obolelih od KOVID-19 infekcije ($n = 15$), uključujući akušere-ginekologe, babice, specijaliste za infektivne bolesti, kao i rukovodioce bolnica i ustanova primarne zdravstvene zaštite.
2. **Trudnice i žene u postporođajnom periodu** sa potvrđenom KOVID-19 infekcijom tokom trudnoće ($n = 9$).

Učesnici su odabrani namenskim uzorkovanjem kako bi se obezbedilo da su direktno uključeni u pružanje zdravstvene zaštite u vezi sa KOVID-19 infekcijom, odnosno da su oboleli od ove infekcije. Prikupljanje učesnika je nastavljeno dok nije postignuta saturacija podataka. Saturacija podataka definisana je kao trenutak kada se iz intervjuova više nisu dobijali novi koncepti ili teme.

Kriterijumi za uključivanje u studiju i isključivanje iz studije

Zdravstveni radnici su mogli da učestvuju u studiji ako su bili aktivno uključeni u zbrinjavanje trudnica obolelih od KOVID-19 infekcije i ako su napismeno dali svoj informisani pristanak. Zdravstveni radnici koji nisu bili direktno uključeni u zbrinjavanje trudnica sa KOVID-19 oboljenjem ili nisu bili prisutni tokom perioda istraživanja bili su isključeni.

Trudnice i žene u postporođajnom periodu mogle su da učestvuju u studiji ako su bile starosti 18-49 godina, imale potvrđenu trudnoću u vreme oboljevanja od KOVID-19 infekcije i bile sposobne i voljne da učestvuju u intervjuu. Žene sa ozbiljnim komunikacionim barijerama ili one koje nisu dale informisani pristanak bile su isključene iz studije.

Prikupljanje podataka

Podaci su prikupljeni putem detaljnih, polustrukturisanih intervjuova sprovedenih licem u lice ili putem bezbedne video-konferencijske platforme (Zoom), u zavisnosti od toga šta su učesnici odabrali. Intervjui su trajali između 21 i 40 minuta.

Učesnici su intervjuisani 2023. godine, nakon najakutnijih faza KOVID-19 pandemije. Tokom intervjuova učesnici su podsticani da se osvrnu kako na svoja iskustva u vreme bolesti tako i na ranije talase pandemije, kada su se putevi zdravstvene zaštite, kliničke smernice i organizacija zdravstvenih usluga brzo menjali. Ovaj retrospektivna perspektiva omogućila je istraživanje načina na koji su se iskustva i percepcije zdravstvene zaštite menjali tokom vremena.

2. **Pregnant and postpartum women** with confirmed COVID-19 during pregnancy ($n = 9$).

Participants were selected through purposive sampling to ensure they were directly involved in or affected by COVID-19 care. Recruitment continued until data saturation was achieved. Data saturation was defined as the point when no new concepts or themes emerged from the interviews.

Inclusion and exclusion criteria

Healthcare professionals were eligible to participate in the study if they had been actively involved in the care of pregnant COVID-19 patients and if they provided written informed consent. The healthcare professionals not directly involved in maternal COVID-19 care or not present during the study period were excluded.

Pregnant and postpartum women were eligible to participate in the study if they were aged 18–49 years, had confirmed pregnancy at the time of COVID-19 infection, and were able and willing to participate in an interview. Women with severe communication barriers or those who did not provide informed consent were excluded from the study.

Data collection

Data were collected through in-depth, semi-structured interviews conducted either face-to-face or via secure video conferencing (Zoom), at the participants' preference. Interviews lasted between 21 and 40 minutes.

Participants were interviewed in 2023, after the most acute phases of the COVID-19 pandemic. During the interviews, participants were encouraged to reflect both on their experiences at the time of illness and on earlier pandemic waves, when care pathways, clinical guidelines, and the organization of health services were rapidly evolving. This retrospective viewpoint enabled the exploration of the ways that experiences and perceptions of care changed over time.

Interview guides were developed separately for healthcare professionals and pregnant women. For healthcare professionals, the questions focused on clinical protocols, care organization, hospitalization, and communication with patients. For the pregnant women, the questions addressed symptom recognition, help-seeking behavior, experiences with healthcare services, and follow-up during illness.

All interviews were audio-recorded and transcribed verbatim by the research team.

Interview guides

Separate semi-structured interview guides were developed for pregnant/postpartum women and for healthcare professionals.

Vodiči za intervju osmišljeni su odvojeno za zdravstvene radnike i trudnice. Za zdravstvene radnike pitanja su bila usmerena na kliničke protokole, organizaciju zdravstvene zaštite, hospitalizaciju i komunikaciju sa pacijentima. Za trudnice pitanja su se odnosila na prepoznavanje simptoma, ponašanje pri traženju pomoći, iskustva sa zdravstvenim službama i lekarsko praćenje tokom bolesti.

Načinjeni su zvučni zapisi svih intervjuova koji su potom doslovno transkribovani od strane istraživačkog tima.

Vodiči za intervju

Sastavljeni su odvojeni polustrukturisani vodiči za intervju sa trudnicama/ženama u postporođajnom periodu i za intervju sa zdravstvenim radnicima.

Sa trudnicama i ženama u postporođajnom periodu, intervjui su započinjali otvorenim pitanjima o njihovom iskustvu tokom trudnoće i postporođajnog perioda u vreme KOVID-19 infekcije. Diskusija se zatim fokusirala na to kako su žene prepoznale i tumačile simptome KOVID-19 oboljenja, kako su tražile zdravstvenu zaštitu i kako su doživljavale stavove i reakcije zdravstvenih radnika u primarnoj zdravstvenoj zaštiti i bolnicama. Intervjui su se završavali pitanjima o njihovom iskustvu lekarskog praćenja i kliničke komunikacije tokom bolesti.

Sa zdravstvenim radnicima, intervjui su započinjali opštim pitanjima o stručnom obrazovanju i radnom iskustvu. Naredna pitanja istraživala su njihovo poznavanje nacionalnih kliničkih protokola za KOVID-19 i regulative povezane sa trudnoćom, njihova iskustva u zbrinjavanju trudnica obolelih od KOVID-19 infekcije, ponašanje pacijentkinja prilikom traženja pomoći, puteve hospitalizacije i dostupnost resursa potrebnih za pružanje zdravstvene zaštite.

Polustrukturisani format omogućio je istraživačima da prate narativ učesnika, istovremeno obezbeđujući da ključne teme povezane sa putevima zdravstvene zaštite, donošenjem odluka i sistemskim preprekama budu dosledno obrađene u svim intervjuima.

Analiza podataka

Podaci su obrađeni primenom tematske analize. Transkripti su više puta čitani radi upoznavanja sa sadržajem, a zatim su induktivno kodirani uz pomoć softvera ATLAS.ti (verzija 24). Kodovi su grupisani u kategorije, a zatim u šire teme koje odražavaju obrasce u podacima.

Početno kodiranje sproveo je doktorand, nakon čega su kodovi i teme pregledani i dodatno usavršeni pod nadzorom mentora kako bi se obezbedila analitička preciznost i doslednost.

For pregnant and postpartum women, interviews began with open-ended questions about their pregnancy and postpartum experience during COVID-19. The discussion then focused on how women recognized and interpreted COVID-19 symptoms, how they sought care, and how they perceived the attitudes and responses of primary care and hospital-based providers. Interviews concluded with questions about their experience of follow-up and clinical communication during illness.

For healthcare professionals, interviews started with general questions about professional background and work experience. Subsequent questions explored their knowledge of national COVID-19 clinical protocols and regulatory documents related to pregnancy, their experiences in managing pregnant COVID-19 patients, patient help-seeking behavior, hospitalization pathways, and the availability of resources needed to provide care.

The semi-structured format allowed interviewers to follow participant narratives while ensuring that key topics related to care pathways, decision-making, and system-level barriers were consistently addressed across interviews.

Data analysis

Data were processed using thematic analysis. Transcripts were read repeatedly to achieve familiarization and then coded inductively using ATLAS.ti (Version 24). Codes were grouped into categories and then into broader themes reflecting patterns across the data.

Initial coding was conducted by a doctoral researcher, whereafter codes and themes were reviewed and refined under the supervision of the academic supervisors, to enhance analytic rigor.

Ethical considerations

All participants provided written informed consent prior to participation. To ensure confidentiality, personal identifiers were removed from interview transcripts, and participants were assigned unique codes (e.g., R1, R2). Interviews were conducted in secure settings, and all digital data were stored on password-protected devices. Ethical approval for the study was obtained from the Local Ethics Committee of Al-Farabi Kazakh National University (approval dated 9 June 2022; IRB-A470). The study was conducted in accordance with the principles of the Declaration of Helsinki at all stages.

RESULTS

Participant characteristics

The study included 24 participants: 15 healthcare professionals and 9 pregnant or postpartum women (Table 1).

Etički aspekti

Svi učesnici su pre uključivanja u studiju dali pisani informisani pristanak. Radi obezbeđivanja poverljivosti, lični identifikatori uklonjeni su iz transkripata intervjuva, a učesnicima su dodeljeni jedinstveni kodovi (npr. R1, R2). Intervjui su sprovedeni u bezbednim uslovima, a svi digitalni podaci čuvani su na uređajima zaštićenim lozinkom. Etičko odobrenje za studiju dobijeno je od Lokalnog etičkog komiteta Kazahstanskog nacionalnog univerziteta *Al-Farabi* (odobrenje od 9. juna 2022; IRB-A470). Studija je u svim fazama sprovedena u skladu sa principima Helsinške deklaracije.

Among the healthcare professionals, nine worked in primary health care and six in hospital settings. The sample included a broad range of professionals involved in maternal COVID-19 care, including one chief physician, one deputy chief physician, three obstetrician-gynecologists, three midwives, one infectious disease specialist, and six hospital-based clinicians. This ensured representation of both managerial and front-line clinical perspectives across different levels of care.

Among the pregnant and postpartum women, all participants were between 28 and 40 years of age, with slightly more than half of them aged 35–40 years. Most women had a higher level of education (77.8%) and

Tabela 1. Karakteristike zdravstvenih radnika i trudnica/žena u postporođajnom periodu

Table 1. Characteristics of healthcare professionals and pregnant/postpartum women

Zdravstveni radnici (n = 15) / Healthcare professionals (n = 15)	n
Nivo zdravstvene zaštite / Level of care	
Primarna zdravstvena zaštita - PZZ / Primary health care - PHC	9
Bolnice / Hospital	6
Stručna pozicija / Professional role	
Načelnik / Chief physician	1
Zamenik načelnika / Deputy chief physician	1
Ginekolog-akušer (PZZ) / Obstetrician-gynecologist (PHC)	3
Babica (PZZ) / Midwife (PHC)	3
Infektolog / Infectious disease specialist	1
Bolnički kliničar / Hospital-based clinicians	6
Trudnice i žene u postporođajnom periodu (n = 9) / Pregnant and postpartum women (n = 9)	
Godine starosti / Age (years)	
28-34	4 (45.5%)
35-40	5 (55.5%)
Obrazovanje / Education	
Srednje / Secondary	0 (0.0%)
Srednje stručno / Vocational	2 (22.2%)
Visoko / Higher education	7 (77.8%)
Broj porođaja / Parity	
Primipare / Primiparous	2 (22.2%)
Multipare (≥2 porođaja) / Multiparous (≥2 births)	7 (77.8%)
Nacionalna pripadnost / Ethnicity	
Kazahstanska / Kazakh	5 (55.6%)
Ruska / Russian	3 (33.3%)
Ostalo / Other	1 (11.1%)
Status trudnoće prilikom intervjuisanja / Pregnancy status at interview	
Trudnice / Pregnant	5 (55.6%)
– Prvi trimestar / – First trimester	1 (20.0%)
– Drugi trimestar / – Second trimester	4 (80.0%)
Postporođajni period (≤3 meseca) / Postpartum (≤3 months)	4 (44.4%)

REZULTATI

Karakteristike učesnika

Studija je obuhvatila 24 učesnika: 15 zdravstvenih radnika i 9 trudnica, odnosno žena u postporođajnom periodu (Tabela 1).

Među zdravstvenim radnicima, devetoro je radilo u primarnoj zdravstvenoj zaštiti, a šestoro u bolničkim ustanovama. Uzorak je uključivao širok spektar stručnjaka uključenih u zbrinjavanje trudnica obolelih od KOVID-19 infekcije, uključujući jednog načelnika, jednog zamenika načelnika, tri akušera-ginekologa, tri babice, jednog specijalistu za infektivne bolesti i šest bolničkih kliničara. Time je obezbeđena zastupljenost perspektiva i upravljačkih i kliničkih kadrova uključenih u prvu linije zdravstvene zaštite, na njenim različitim nivoima.

Među trudnicama i ženama u postporođajnom periodu, sve učesnice bile su starosti između 28 i 40 godina, pri čemu je nešto više od polovine bilo u starosnoj grupi od 35–40 godina. Većina žena je imala visoko obrazovanje (77,8%) i bile su multipare (77,8%). Većina se izjasnila da je kazahstanske nacionalnosti (55,6%), zatim ruske (33,3%), dok su ostale pripadale drugim etničkim grupama. U vreme intervjuja, pet žena (55,6%) su bile trudne, većinom u drugom trimestru, dok su četiri (44,4%) bile u periodu do tri meseca nakon porođaja.

Zdravstveni radnici

Najpre predstavljamo nalaze dobijene od zdravstvenih radnika, fokusirajući se na ono što je u njihovom iskustvu pružanja zdravstvene zaštite trudnicama obolelim

were multiparous (77.8%). The majority identified as Kazakh (55.6%), followed by those identifying as Russian (33.3%) and those of other ethnic backgrounds. At the time of the interview, five women (55.6%) were pregnant, most of them in their second trimester, and four (44.4%) were within three months postpartum.

Healthcare professionals

We first present findings obtained from healthcare professionals, focusing on what was most important in their experience of providing care to pregnant COVID-19 patients during the pandemic. Using their own words, we illustrate how clinicians navigated rapidly changing conditions, patient behaviors, and system-level constraints. Four main themes were identified: the impact of COVID-19 on healthcare work, the availability and use of clinical guidelines and SOPs, perceived patient responses to COVID-19, and delayed care and hospitalization. Each theme and its sub-themes are illustrated with verbatim quotations from the interviews (Table 2A).

Impact of COVID-19 on healthcare practices

COVID-19 substantially reshaped everyday clinical practice for healthcare professionals involved in the care of pregnant women. Participants consistently described a sharp increase in workload, administrative burden, and psychological stress, driven by the growing number of cases and the expansion of their clinical responsibilities. Fear of infection was a recurrent element of their experience and influenced how care was organized.

To reduce transmission risks, healthcare workers adopted new working practices, including strict use of

Tabela 2A. Pregled tema i podtema identifikovanih među zdravstvenim radnicima

Tema	Podteme (kodovi)
Uticaj KOVID-19 na zdravstvenu praksu	Povećano opterećenje na poslu Administrativno opterećenje Strah od infekcije Upotreba lične zaštitne opreme - LZO Prebacivanje na pružanje zdravstvenih usluga na daljinu
Kliničke smernice i standardne operativne procedure - SOP	Primena opštih KOVID-19 protokola Neizvesnost i dileme u vezi sa SOP Oslanjanje na neformalne procedure
Uočene reakcije pacijentkinja na KOVID-19	Poricanje simptoma Strah od testiranja i hospitalizacije Odlaganje prijavljivanja simptoma Samolečenje
Odlaganje zdravstvene zaštite i hospitalizacije	Odbijanje hospitalizacije Percipiranje KOVID-19 kao "običnog gripa" Porodične i društvene barijere Dostupnost slobodnih bolesničkih postelja (u ranoj fazi pandemije) Kućno lečenje

Table 2A. Outline of themes and sub-themes identified among healthcare professionals

Theme	Sub-themes (codes)
Impact of COVID-19 on healthcare work	Increased workload Administrative burden Fear of infection Use of personal protective equipment - PPE Shift to remote care
Clinical guidance and SOPs	Use of general COVID-19 protocols Uncertainty about SOPs Reliance on informal practices
Perceived patient responses to COVID-19	Symptom denial Fear of testing and hospitalization Delayed reporting Self-treatment
Delayed care and hospitalization	Refusal of hospitalization Perception of COVID-19 as "the common flu" Family and social barrier Bed availability (early pandemic) Home management

od KOVID-19 infekcije tokom pandemije bilo najvažnije. Koristeći njihove sopstvene reči, ilustrujemo kako su se kliničari suočavali sa uslovima koji su se brzo menjali, ponašanjem pacijentkinja i sistemskim ograničenjima. Identifikovane su četiri glavne teme: uticaj KOVID-19 na zdravstvenu praksu, dostupnost i primena kliničkih smernica i SOPs, uočene reakcije pacijentkinja na KOVID-19 i odlaganje zdravstvene zaštite i hospitalizacije. Svaka tema i njene podteme ilustrovane su doslovnim citatima iz intervjuja (Tabela 2A).

Uticaj KOVID-19 na zdravstvenu praksu

KOVID-19 je značajno preoblikovao svakodnevnu kliničku praksu zdravstvenih radnika uključenih u zbrinjavanje trudnica. Učesnici su dosledno opisivali nagli porast obima posla, administrativnog opterećenja i psihološkog stresa, koji je bio izazvan rastućim brojem slučajeva i proširenjem njihovih kliničkih odgovornosti. Strah od infekcije bio je element njihovog iskustva koji se ponavljao i uticao na način organizacije zdravstvene zaštite.

Da bi se smanjio rizik od prenosa infekcije, zdravstveni radnici su usvojili nove radne prakse, uključujući strogu upotrebu lične zaštitne opreme i komunikaciju sa pacijentkinjama na daljinu. Ove promene bile su posebno opterećujuće u svakodnevnoj praksi i doprinosile su umoru i emocionalnom opterećenju.

„Strah nam se uselio u misli, papirologija se povećala, a bili smo u veoma bliskom kontaktu sa trudnicama“ (R9, babica).

„Posao je postao komplikovaniji. Kada je žena imala KOVID, zvali smo je svaki dan, proveravali njeno stanje, popunjavali kontrolne liste. Sada stalno nosimo maske,

personal protective equipment and remote communication with patients. These changes were particularly burdensome in daily practice and contributed to fatigue and emotional strain.

“There was fear in our minds, paperwork increased, and we were in very close contact with pregnant women” (R9, midwife).

“The work became more complicated. When a woman had COVID, we called her every day, checked her condition, filled in checklists. Now we wear masks all the time, even in summer, which is especially uncomfortable” (R4, obstetrician-gynecologist).

Several participants described how digital tools became central to maintaining continuity of care, especially for women in isolation or with a positive PCR test. WhatsApp groups and remote consultations were widely used to provide information, monitor symptoms, and coordinate follow-up.

“We created a WhatsApp group for about a hundred pregnant women. We sent COVID-related information to all of them, answered questions, and conducted remote consultations. We also called them to remind them of appointments and sometimes even visited them at home for examinations and tests. It was very difficult” (R5, obstetrician-gynecologist).

These practices functioned as informal or ad hoc telemedicine strategies that emerged in response to reduced face-to-face contact and the absence of fully institutionalized digital care pathways.

Clinical guidelines and standard operating procedures (SOPs)

Healthcare professionals reported substantial uncertainty regarding the availability and use of clinical guidelines.

čak i leti, što je posebno neprijatno“ (R4, akušer-ginekolog).

Nekoliko učesnika je opisalo kako su digitalni alati postali ključni za održavanje kontinuiteta zdravstvene zaštite, posebno za žene u izolaciji ili sa pozitivnim PCR testom. *WhatsApp* grupe i konsultacije na daljinu široko su korišćene za pružanje informacija, praćenje simptoma i koordinaciju daljeg zdravstvenog nadzora.

„Napravili smo *WhatsApp* grupu za oko stotinu trudnica. Svima smo slali informacije u vezi sa KOVID-om, odgovarali na pitanja i sprovodili konsultacije na daljinu. Takođe smo ih zvali da ih podsetimo na preglede, a ponekad smo ih čak i posećivali kod kuće radi pregleda i testiranja. Bilo je veoma teško“ (R5, akušer-ginekolog).

Ove prakse funkcionisale su kao neformalne ili *ad hoc* telemedicinske strategije koje su nastale kao odgovor na smanjeni broj neposrednih kontakata i odsustvo potpuno institucionalizovanih digitalnih puteva zdravstvene zaštite.

Kliničke smernice i standardne operativne procedure (SOP)

Zdravstveni radnici su prijavili značajnu neizvesnost (dileme) u vezi sa dostupnošću i upotrebom kliničkih smernica za zbrinjavanje trudnica obolelih od KOVID-19. Iako je većina učesnika bila upoznata sa opštim nacionalnim protokolima za lečenje KOVID-19 infekcije, mnogi nisu bili sigurni da li postoje smernice specifične za trudnoću, a još manji broj je mogao da potvrdi postojanje SOP koje regulišu puteve pacijenata na nivou ustanove.

Učesnici su često navodili da se oslanjaju na opšte KOVID-19 protokole ili neformalne prakse, umesto na strukturirane smernice specifične za trudnoću. Ovaj nedostatak jasnoće doveo je do varijabilnosti u kliničkom donošenju odluka, naročito prilikom zbrinjavanja trudnica sa sumnjom na KOVID-19 ili potvrđenom infekcijom.

„Ne, ne postoji poseban protokol, pratimo opšti protokol“ (R9, babica).

„Postoji protokol za zbrinjavanje trudnica i žena na porođaju sa KOVID-19 infekcijom.“ (R6, akušer-ginekolog).

„Ne postoji protokol posebno za trudnice. Međutim, u susednim zemljama, kao što je Rusija, postoje jasni standardi i mi smo koristili njih.“ (R5, akušer-ginekolog).

Nekoliko učesnika nije bilo sigurno da li SOP postoje u njihovim institucijama i navelo je da takvi dokumenti, ukoliko postoje, nisu dosledno prosleđivani osoblju koje radi na prvoj liniji zdravstvene zaštite.

„Za trudnice... nisam baš sigurna. Pratili smo KOVID protokol, ali kada su trudnice dolazile, plašili smo se da ih zbrinjavamo kod kuće, pa smo radili testove i pokušavali da ih pošaljemo u bolnicu“ (R6, akušer-ginekolog).

delines for managing pregnant COVID-19 patients. Although most participants were aware of general national COVID-19 treatment protocols, many were unsure whether pregnancy-specific guidelines existed, and even fewer could confirm the presence of SOPs regulating patient pathways at the facility level.

Participants frequently described relying on general COVID-19 protocols or informal practices rather than structured, pregnancy-specific guidelines. This lack of clarity resulted in variability in clinical decision-making, particularly when managing pregnant women with suspected or confirmed infection.

“No, there isn’t a separate one, we follow the general protocol” (R9, midwife).

“There is a protocol for managing pregnant women and women in labor with COVID-19.” (R6, obstetrician-gynecologist).

“There is no protocol specifically for pregnant women. However, in neighboring countries, like Russia, there are clear standards, and we used those.” (R5, obstetrician-gynecologist).

Several participants were uncertain whether SOPs existed within their institutions and indicated that such documents, if available, were not consistently communicated to frontline staff.

“For pregnant women... I’m not really sure. We followed the COVID protocol, but when pregnant women came, we were afraid to manage them at home, so we took tests and tried to send them to hospital” (R6, obstetrician-gynecologist).

“I think there is one, maybe the senior midwife has it” (R8, midwife).

Overall, the findings indicate gaps in the dissemination and operationalization of clinical guidelines and SOPs, contributing to inconsistent care pathways for pregnant COVID-19 patients.

Perceived patient responses to COVID-19

Healthcare professionals described significant variations in how pregnant women responded to COVID-19 symptoms. While some women promptly contacted their doctors when symptoms appeared, others minimized or ignored early signs of infection, particularly when symptoms were mild. Fear of testing positive and being hospitalized emerged as a key reason for delayed reporting.

Several participants noted that women often questioned or dismissed positive PCR results when they experienced only minor symptoms, such as a sore throat, and in some cases repeated testing privately instead of informing their doctors.

“If the symptoms were mild, like just a sore throat, they didn’t take it seriously. Even with a positive PCR, they didn’t believe it and went to retest privately. They

„Mislim da postoji, možda ga ima glavna babica“ (R8, babica).

U celini, nalazi ukazuju na nedostatke u prosleđivanju i operativnoj primeni kliničkih smernica i SOP, što je doprinosilo neujednačenim putevima zbrinjavanja trudnica obolelih od KOVID-19 infekcije.

Uočene reakcije pacijentkinja na KOVID-19

Zdravstveni radnici su opisali značajne razlike u načinu na koji su trudnice reagovala na simptome KOVID-19 infekcije. Dok su neke žene odmah kontaktirale svoje lekare kada su se simptomi pojavili, druge su umanjivale ili ignorisale rane znake infekcije, naročito kada su simptomi bili blagi. Strah od pozitivnog testa i hospitalizacije pojavio se kao ključni razlog za odloženo prijavljivanje simptoma.

Nekoliko učesnika je navelo da su žene često dovodile u pitanje ili odbacivale pozitivan PCR rezultat kada su imale samo blage simptome, poput bola u grlu, a u nekim slučajevima su ponavljale testiranje privatno umesto da obaveste svog lekara.

„Ako su simptomi bili blagi, kao samo bol u grlu, nisu to shvatale ozbiljno. Nisu verovala čak ni pozitivnim PCR testu i išle su da se privatno ponovo testiraju. Plašile su se da ćemo ih poslati u bolnicu“ (R9, babica).

Samolečenje kod kuće pre kontaktiranja zdravstvenih radnika takođe je bilo uobičajeno. Prema rečima kliničara, neke žene su čekale jedan ili dva dana pokušavajući same da kontrolišu simptome, što je odlagalo lekarsku procenu.

„Neke odmah prijave simptome, ali druge pokušavaju da se leče kod kuće jedan ili dva dana. Mnoge nam ne kažu jer se plaše da ćemo tražiti da urade PCR test, a zatim ih hospitalizovati“ (R6, akušer-ginekolog).

Istovremeno, nekoliko zdravstvenih radnika je primetilo da su se svest i ozbiljnost pristupa povećavali kako je pandemija napredovala i kako su komplikacije postajale vidljivije.

„U početku su mnoge bile ravnodušne, ali nakon što su videle komplikacije izazvane KOVID-19 oboljenjem, počele su brže da traže pomoć“ (R8, babica).

U celini, kliničari su procenili da je većina žena na kraju ipak potražila zdravstvenu zaštitu, ali da je značajan deo odlagao prijavljivanje simptoma zbog straha od hospitalizacije i potcenjivanja težine bolesti.

„Načelno gledano, oko 70% trudnica nas je kontaktiralo na vreme“ (R6, akušer-ginekolog).

Odlaganje zdravstvene zaštite i hospitalizacije

Zdravstveni radnici su identifikovali odlaganje prijema u bolnicu kao jedan od najkritičnijih izazova u zbrinjavanju trudnica obolelih od KOVID-19 infekcije. Žene sa blagom ili asimptomatskom infekcijom često su

were afraid we would send them to hospital“ (R9, midwife).

Self-treatment at home before contacting health-care providers was also common. According to clinicians, some women waited one or two days trying to manage symptoms on their own, which delayed medical assessment.

“Some report their symptoms immediately, but others try to treat themselves at home for one or two days. Many don’t tell us because they are afraid we will ask them to take a PCR test and then hospitalize them” (R6, obstetrician-gynecologist).

At the same time, several healthcare workers observed that awareness and seriousness increased as the pandemic progressed, and complications became more visible.

“At first, many were indifferent, but after seeing complications from COVID-19, they started to seek help more promptly” (R8, midwife).

Overall, clinicians estimated that most women eventually sought care, but a substantial minority delayed reporting symptoms due to fear of hospitalization and underestimation of disease severity.

“In general, about 70% of pregnant women contacted us in time” (R6, obstetrician-gynecologist).

Delayed care and hospitalization

Healthcare professionals identified delayed hospital admission as one of the most critical challenges in managing pregnant COVID-19 patients. Women with mild or asymptomatic infection were commonly managed at home, but delays in escalation of care often occurred when symptoms worsened. Clinicians emphasized that late presentation increased the risk of complications and limited the effectiveness of timely intervention.

Pregnant women were typically treated as outpatients when symptoms were mild or absent, even with a positive PCR test.

“We manage them at home only if the infection is mild. If there is shortness of breath, fever above 38, cough, or intoxication, we hospitalize them” (R5, obstetrician-gynecologist).

“Asymptomatic women, those with a positive PCR test but no fever or symptoms, stay at home” (R9, midwife).

However, refusal of hospitalization contributed significantly to prolonged home management. Healthcare workers reported that many women declined admission even when it was medically indicated. The most common reasons included fear of COVID wards, belief that the illness was mild, family responsibilities, and mistrust of the diagnosis.

“Some didn’t believe they had COVID. They thought it was just the flu” (R5, obstetrician-gynecologist).

lečene kod kuće, ali su kašnjenja u eskaliranju zdravstvene zaštite često nastajala kada su se simptomi pogoršavali. Kliničari su naglasili da kasno javljanje lekaru povećava rizik od komplikacija i ograničava efikasnost pravovremenih intervencija.

Trudnice su obično lečene ambulantno kada su simptomi bili blagi ili odsutni, čak i uz pozitivan *PCR* test.

„Lečimo ih kod kuće samo ako je infekcija blaga. Ako postoji kratak dah, temperatura iznad 38, kašalj ili intoksikacija, hospitalizujemo ih“ (R5, akušer-ginekolog).

„Žene bez simptoma, one sa pozitivnim *PCR* testom ali bez temperature ili simptoma, ostaju kod kuće“ (R9, babica).

Međutim, odbijanje hospitalizacije značajno je doprinosilo produženom lečenju kod kuće. Zdravstveni radnici su prijavili da su mnoge žene odbijale prijem čak i kada je bio medicinski indikovano. Najčešći razlozi uključivali su strah od KOVID odeljenja, uverenje da je bolest blaga, porodične obaveze i nepoverenje u dijagnozu.

„Neke nisu verovala da imaju KOVID. Mislile su da je to samo grip“ (R5, akušer-ginekolog).

„Odbijale su jer nisu imale kome da ostave decu ili nekoga ko bi se brinuo o domaćinstvu“ (R6, akušer-ginekolog).

„Neke su se plašile da bi mogle da umru u bolnici“ (R4, akušer-ginekolog).

Iako je većina kliničara navela da su bolnice uglavnom primale trudnice kada je bilo slobodnih kreveta, na početku pandemije nedostatak kreveta je povremeno dovodio do toga da su žene sa blagim oblikom bolesti vraćane kući.

„Na početku su svi slati u bolnicu, ali pošto nije bilo dovoljno kreveta, žene sa blagim oblikom bolesti su ponekad vraćane i praćene od strane ambulantnih timova“ (R13, bolnički lekar).

Samo-medikacija je bilo još jedan važan faktor koji je doprinosio odlaganju eskaliranja zdravstvene zaštite. Zdravstveni radnici su prijavili da su neke žene pokušavale da kontrolišu simptome kućnim lekovima ili su izbegavale antivirusne lekove zbog zabrinutosti za bezbednost fetusa, često bez obaveštavanja lekara.

„Neke su se lečile kod kuće, samo su pile tečnost i izbegavale antivirusne lekove jer su se plašile da bi time mogle da naškode bebi“ (R5, akušer-ginekolog).

Uprkos svakodnevnom praćenju od strane timova primarne zdravstvene zaštite putem telefonskih poziva i *WhatsApp* poruka, odlaganje prijavljivanja simptoma i odbijanje hospitalizacije ostali su trajne prepreke pravovremenom lečenju.

„Svakog dana im šaljemo poruke u “četu”, govoreći im da ne misle da je to samo grip i da nas pozovu ako imaju temperaturu ili kašalj“ (R9, babica).

“They refused because they had no one to leave their children with, or no one to take care of the household” (R6, obstetrician-gynecologist).

“Some were afraid they might die in the hospital” (R4, obstetrician-gynecologist).

Although most clinicians reported that hospitals generally accepted pregnant women when beds were available, early in the pandemic bed shortages occasionally led to women with mild disease being sent back home.

“At the beginning, everyone was sent to hospital, but because there were not enough beds, women with mild disease were sometimes returned and monitored by outpatient teams” (R13, hospital physician).

Self-medication was another important factor contributing to delayed escalation of care. Healthcare workers reported that some women attempted to manage symptoms with home remedies or avoided antiviral medications due to concerns about fetal safety, often without informing their doctors.

“Some treated themselves at home, only drinking fluids and avoiding antivirals because they were afraid it could harm the baby” (R5, obstetrician-gynecologist).

Despite daily follow-up by primary care teams through phone calls and WhatsApp messages, delayed reporting and refusal of hospitalization remained persistent barriers to timely treatment.

“We message them every day in the chat, telling them not to think it’s just the flu and to call us if they have fever or a cough” (R9, midwife).

Pregnant and postpartum women

We next present findings obtained from pregnant and postpartum women, describing the way that they experienced COVID-19 illness, monitoring, and interactions with healthcare services. Three main themes were identified: symptom interpretation and self-treatment, self-monitoring and follow-up, and perceived quality of care. These themes reflect how women made sense of their symptoms, navigated follow-up during illness, and evaluated the support they received from healthcare providers. Verbatim quotations are used to illustrate each theme (Table 2B).

Symptom interpretation and self-treatment

Pregnant women described diverse ways of interpreting and responding to COVID-19 symptoms. In the early phase of the pandemic, many participants did not initially seek medical care because they attributed fatigue, weakness, and malaise to normal pregnancy-related changes or to a common respiratory infection. This led to delayed recognition of COVID-19 and, in several cases, to self-treatment at home.

Tabela 2B. Pregled tema i podtema identifikovanih među trudnicama i ženama u postporođajnom periodu

Tema	Podteme (kodovi)
Tumačenje simptoma i samolečenje	Tumačenje simptoma kao normalnih pojava u trudnoći Tretiranje KOVID-19 kao da je grip Samo-medikacija Odlaganje traženja medicinske pomoći
Samopraćenje i praćenje od strane zdravstvenih radnika	Nepostojanje svesti o potrebi za vođenjem dnevnika simptoma Nedostatak strukturiranog samopraćenja Oslanjanje na telefonske pozive i poruke
Percipirani kvalitet zdravstvene zaštite	Brza reakcija ginekologa Kućne posete i PCR testiranje Nedostatak kontinuiranog lekarskog praćenja Izbor da se ostane kod kuće

Trudnice i žene u postporođajnom periodu

Sledeće predstavljamo nalaze dobijene od trudnica i žena u postporođajnom periodu, opisujući način na koji su doživele obolevanje od KOVID-19 infekcije, lekarsko praćenje i interakcije sa zdravstvenim službama. Identifikovane su tri glavne teme: tumačenje simptoma i samolečenje, samopraćenje i praćenje od strane zdravstvenih radnika, i percipirani kvalitet zdravstvene zaštite. Ove teme odražavaju način na koji su žene tumačile svoje simptome, snalazile se u lekarskom praćenju tokom bolesti i procenjivale podršku koju su dobijale od zdravstvenih radnika. Za ilustraciju svake teme upotrebljeni su doslovni citati (Tabela 2B).

Tumačenje simptoma i samolečenje

Trudnice su opisale različite načine tumačenja i reagovanja na simptome KOVID-19 infekcije. U ranoj fazi pandemije, mnoge učesnice u početku nisu tražile medicinsku pomoć jer su umor, slabost i malaksalost pripisivale uobičajenim promenama povezanim sa trudnoćom ili običnoj respiratornoj infekciji. To je dovelo do odloženog prepoznavanja KOVID-19 oboljenja i, u nekoliko slučajeva, do samolečenja kod kuće.

“For almost two weeks I experienced weakness, headaches, and fatigue. I thought it was just how my fourth pregnancy was going. But then my whole body started aching, I had chills and a low-grade fever. I felt so bad I thought I was dying” (R4, pregnant woman).

Some women initially attempted to manage symptoms on their own before contacting healthcare providers, even when symptoms progressed.

“I had body aches and chills, like I was catching a cold. I started treating myself the way I usually do. When my temperature went up to 38.5, I called my gynecologist. She told me to call an ambulance, but I said I would try to bring the fever down first” (R2, pregnant woman).

Others reported more immediate help-seeking behavior, particularly during periods of high community transmission.

“I got sick at the peak of COVID, so I wrote to my gynecologist right away” (R9, postpartum woman).

Overall, the findings indicate that symptom misinterpretation and initial self-treatment were common, especially early in the pandemic, and contributed to delays in professional assessment and care.

Table 2B. Outline of themes and sub-themes identified among pregnant and postpartum women

Theme	Sub-themes (codes)
Symptom interpretation and self-treatment	Interpreting symptoms as normal pregnancy Treating COVID-19 as the flu Self-medication Delayed help-seeking
Self-monitoring and follow-up	Lack of awareness about symptom diary No structured self-monitoring Reliance on phone calls and messaging
Perceived quality of care	Rapid response from gynecologists Home visits and PCR testing Lack of continuous follow-up Preference to stay at home

„Skoro dve nedelje sam osećala slabost, glavobolje i umor. Mislila sam da je to jednostavno tok moje četvrte trudnoće. Ali onda je celo telo počelo da me boli, imala sam jezu i blago povišenu temperaturu. Osećala sam se toliko loše da sam mislila da umirem“ (R4, trudnica).

Neke žene su u početku pokušavale same da kontrolišu simptome pre nego što bi kontaktirale zdravstvene radnike, čak i kada su simptomi napredovali.

„Imala sam bolove u telu i jezu, kao da dobijam prehladu. Počela sam da se lečim onako kako to obično radim. Kada mi je temperatura porasla na 38,5, pozvala sam svojeg ginekologa. Rekla mi je da pozovem hitnu pomoć, ali sam rekla da ću prvo pokušati da spustim temperaturu“ (R2, trudnica).

Druge žene su prijavljivale da su se brže obratile za pomoć, naročito u periodima visoke transmisije u zajednici.

„Razbolela sam se na vrhuncu KOVID-a, pa sam odmah pisala svojem ginekologu“ (R9, žena u postporođajnom periodu).

U celini, nalazi ukazuju da su pogrešno tumačenje simptoma i početno samolečenje bili česti, naročito u ranoj fazi pandemije, a doprinosili su kašnjenju u dobijanju lekarskog mišljenja i ostvarivanju zdravstvene zaštite.

Samopraćenje i praćenje od strane zdravstvenih radnika

Većina trudnica i žena u postporođajnom periodu navela je da nisu bile informisane o potrebi vođenja dnevnika samopraćenja tokom oboljevanja od KOVID-19 infekcije. Iako su neke dobile opšti savet da se izoluju i prate svoje stanje, sistematsko praćenje simptoma, telesne temperature ili saturacije kiseonika retko je bilo sprovedeno od strane samih pacijentkinja.

„Moj ginekolog mi je rekla da se izolujem i pratim sebe, ali nije ništa rekla o dnevniku“ (R1, trudnica).

„Ne, nisam vodila nikakav dnevnik. Sami lekari su me zvali da proveru kako sam“ (R5, trudnica).

Nekoliko učesnica je navelo da se praćenje od strane medicinskog kadra uglavnom oslanjalo na telefonske pozive ili poruke zdravstvenih radnika, a ne na strukturisano samoprijavljivanje pacijentkinja.

„Ne sećam se da mi je doktor rekao nešto o dnevniku“ (R8, žena u postporođajnom periodu).

Kao rezultat toga, praćenje progresije bolesti u velikoj meri je zavisilo od inicijative kliničara, a ne od sistematskog dokumentovanja simptoma od strane pacijentkinja. To je ograničavalo mogućnost ranog otkrivanja pogoršanja i donošenja pravovremenih kliničkih odluka.

Ove prakse funkcionisale su kao neformalne ili *ad hoc* telemedicinske strategije koje su nastale kao

Self-monitoring and follow-up

Most pregnant and postpartum women reported that they were not informed about the need to keep a self-monitoring diary during COVID-19 illness. Although some received general advice to isolate and observe their condition, systematic tracking of symptoms, body temperature, or oxygen saturation was rarely implemented on the patient's part.

“My gynecologist told me to isolate and monitor myself, but she didn't say anything about a diary” (R1, pregnant woman).

“No, I didn't keep any diary. The doctors themselves called to check how I was doing” (R5, pregnant woman).

Several participants indicated that follow-up relied mainly on phone calls or messages from healthcare providers rather than on patient structured self-reporting.

“I don't remember my doctor telling me anything about a diary” (R8, postpartum woman).

As a result, disease progression monitoring depended largely on clinicians' outreach rather than on patients' systematic documentation of symptoms. This limited the ability to detect early deterioration and to guide timely clinical decisions.

These practices functioned as informal or *ad hoc* telemedicine strategies that emerged in response to reduced face-to-face contact and the absence of fully institutionalized digital care pathways.

Perceived quality of care

Pregnant and postpartum women reported mixed experiences in their interactions with healthcare providers during COVID-19 illness. Some participants described rapid responses from gynecologists and proactive follow-up, which gave them a sense of safety and support. Others, however, experienced limited or inconsistent contact after the initial consultation.

Several women highlighted prompt action by healthcare providers, including home visits, PCR testing, and continued communication after diagnosis.

“After I called my gynecologist, two doctors came to my home, took a PCR test, and the next day told me it was positive and to call an ambulance. After that, my gynecologist kept calling to check if everything was okay” (R3, pregnant woman).

In contrast, other participants reported minimal follow-up and lack of ongoing monitoring, even when symptoms persisted.

“Two weeks later I still felt weak, so I wrote to my doctor. She told me to rest more and stay home, but I wasn't given a PCR test and no one from the clinic checked on me again” (R6, postpartum woman).

odgovor na smanjeni broj neposrednih kontakata i odsustvo potpuno institucionalizovanih digitalnih puteva zdravstvene zaštite.

Percipirani kvalitet zdravstvene zaštite

Trudnice i žene u postporođajnom periodu prijavile su različita iskustva u interakciji sa zdravstvenim radnicima tokom oboljevanja od KOVID-19 infekcije. Neke učesnice su opisivale brze reakcije ginekologa i proaktivno praćenje, što im je davalo osećaj sigurnosti i podrške. Druge su, međutim, imale ograničen ili nedostupan kontakt nakon početne konsultacije.

Nekoliko žena je istaklo brzu reakciju zdravstvenih radnika, uključujući kućne posete, PCR testiranje i kontinuiranu komunikaciju nakon postavljanja dijagnoze.

„Nakon što sam pozvala svojeg ginekologa, dva lekara su došla kod mene kući, uzeli PCR test, a sledećeg dana su mi rekli da je pozitivan i da pozovem hitnu pomoć. Posle toga me je ginekolog stalno zvala da proveri da li je sve u redu“ (R3, trudnica).

Nasuprot tome, druge učesnice su prijavljivale minimalno dalje lekarsko praćenje i nedostatak kontinuiranog nadzora, čak i kada su se simptomi produžili.

„Dve nedelje kasnije i dalje sam se osećala slabo, pa sam pisala svom lekaru. Rekla mi je da se više odmaram i ostanem kod kuće, ali mi nije urađen PCR test i niko iz ambulate me više nije kontaktirao“ (R6, žena u postporođajnom periodu).

Neke žene su takođe dovodile u pitanje potrebu za hospitalizacijom, naročito kada su simptomi bili blagi, i radije su ostajale kod kuće.

„Nisam želela da budem hospitalizovana. Zašto bih? Delovalo je kao običan grip“ (R5, trudnica).

„Ostala sam kod kuće tokom cele trudnoće. Osećala sam slabost, ali nije bilo drugih komplikacija“ (R7, žena u postporođajnom periodu).

U celini, opaženi kvalitet zdravstvene zaštite u velikoj meri je zavisio od nivoa komunikacije i kontinuiteta koji su obezbeđivali zdravstveni radnici. Dok su neke žene osećale snažnu podršku, druge su doživljavale praznine u lekarskom praćenju i neizvesnost u vezi sa odgovarajućim zbrinjavanjem.

DISKUSIJA

Ova kvalitativna studija pruža uvid u to kako su zdravstvenu zaštitu trudnica obolelih od KOVID-19 infekcije doživljavali i zdravstveni radnici i same trudnice u Kazahstanu. Gledano iz obe perspektive, na organizaciju zdravstvene zaštite imali su uticaja odloženo prepoznavanje simptoma, limitirano strukturisano lekarsko praćenje i neizvesnost u vezi sa putevima hospitalizacije. Zdravstveni radnici su opisali veliko opterećenje poslom, smernice koje su se brzo menjale i odsustvo

Some women also questioned the need for hospitalization, particularly when symptoms were mild, and preferred to stay at home.

“I didn’t want to be hospitalized. Why should I? It seemed like just a regular flu” (R5, pregnant woman).

“I stayed at home throughout my pregnancy. I felt weak, but there were no other complications” (R7, postpartum woman).

Overall, the perceived quality of care depended largely on the level of communication and continuity provided by healthcare workers. While some women felt closely supported, others experienced gaps in follow-up and uncertainty about appropriate management.

DISCUSSION

This qualitative study provides insight into how care for pregnant COVID-19 patients was experienced by both healthcare professionals and the pregnant women themselves, in Kazakhstan. Across both perspectives, the organization of care was affected by delayed symptom recognition, limited structured follow-up, and uncertainty regarding hospitalization pathways. Healthcare professionals described heavy workloads, rapidly changing guidelines, and the absence of clear SOPs for managing pregnant COVID-19 patients, while pregnant women reported misinterpreting symptoms, relying on self-treatment, and experiencing variable levels of clinical follow-up. Together, these findings highlight the way that gaps in care pathways, communication, and operational guidelines influenced both help-seeking behavior and clinical decision-making during the pandemic.

Taken together, the findings obtained from healthcare professionals and pregnant women reveal a fragile and fragmented care pathway for COVID-19 in pregnancy. Women often delayed seeking care because they interpreted early symptoms as normal features of pregnancy or mild respiratory illness, while clinicians faced uncertainty about when and how to escalate care due to limited pregnancy-specific guidelines and unclear operational procedures. The absence of structured self-monitoring tools, such as symptom diaries, further reduced the clinicians’ ability to detect clinical deterioration at an early stage. As a result, both patient behavior and system-level constraints converged to produce delays in testing, referral, and hospitalization, increasing the risk of adverse maternal and fetal outcomes.

Our findings align with international qualitative evidence showing that maternal care during COVID-19 was frequently experienced as disrupted, uncertain, and emotionally demanding for both women and

jasnih SOP za zbrinjavanje trudnica obolelih od COVID-19 infekcije, dok su trudnice prijavile pogrešno tumačenje simptoma, oslanjanje na samolečenje i različite nivoe kliničkog praćenja. Zajedno, ovi nalazi ističu način na koji su praznine u putevima zdravstvene zaštite, komunikaciji i operativnim smernicama uticale i na ponašanje pri traženju pomoći i na kliničko donošenje odluka tokom pandemije.

Posmatrano zajedno, nalazi dobijeni od zdravstvenih radnika i trudnica otkrivaju krhost i fragmentisanost puta zbrinjavanja trudnica obolelih od COVID-19 infekcije. Žene su često odlagale da potraže lekarsku pomoć jer su rane simptome bolesti tumačile kao normalne karakteristike trudnoće ili blago respiratorno oboljenje, dok su se kliničari suočavali sa neizvesnošću o tome kada i kako eskalirati zdravstvenu zaštitu zbog ograničenih smernica specifičnih za trudnoću i nejasnih operativnih procedura. Odsustvo strukturisanih alata za samopraćenje, kao što su dnevnici simptoma, dodatno je smanjivalo mogućnost kliničara da u ranoj fazi uoče kliničko pogoršanje. Kao rezultat toga, i ponašanje pacijentkinja i sistemska ograničenja združeno su dovela do toga da se kasni sa testiranjem pacijentkinja, upućivanjem na dalje lečenje i hospitalizacijom, čime se povećavao rizik od nepovoljnih ishoda za majku i fetus.

Naši nalazi su u skladu sa međunarodnim kvalitativnim dokazima koji pokazuju da je zdravstvena zaštita trudnica i porodilja tokom oboljevanja od COVID-19 infekcije često percipirana kao narušena, neizvesna i emocionalno zahtevna i za žene i za zdravstvene radnike. Sinteze kvalitativnih dokaza i primarne studije dosledno su prijavljivale smanjen broj neposrednih kontakata, oslanjanje na komunikaciju na daljinu i povećanu anksioznost među trudnicama, uz značajnu reorganizaciju službi i opterećenje na službe za zdravstvenu zaštitu trudnica i porodilja [22–25]. Slično tome, zdravstveni radnici intervjuisani u našoj studiji opisivali su povećano radno opterećenje, administrativni teret i smernice koje su se rapidno menjale, što odražava izveštaje iz drugih okruženja gde su se zdravstveni radnici suočavali sa promenljivim politikama i operativnim izazovima dok su obezbeđivali zdravstvenu zaštitu trudnicama i porodiljama [18,26,27].

Povećana primena lekarskog praćenja zasnovanog na telefonskim razgovorima i porukama koja se uočava u našim nalazima u skladu je sa širim globalnim iskustvima brzog prelaska na telemedicinu u zdravstvenoj zaštiti trudnica i porodilja, a opisana je kao istovremeno neophodna ali i izazovna za održavanje kvaliteta i kontinuiteta zdravstvene zaštite [28–30]. Istovremeno, naša studija dodaje važnu perspektivu zemlje srednjeg dohotka iz Centralne Azije,

providers. Qualitative evidence syntheses and primary studies have consistently reported reduced face-to-face contact, reliance on remote communication, and heightened anxiety among pregnant women, alongside major service reconfiguration and strain on maternity services [22–25]. Similarly, healthcare professionals interviewed in our study described an increased workload, administrative burden, and rapidly changing guidelines, mirroring reports from other settings where providers faced shifting policies and operational challenges while maintaining maternal care [18,26,27].

The increased use of phone-based and messaging-based follow-up in our data is also consistent with broader global experiences of a rapid shift toward telemedicine in maternal care, described as both necessary and challenging for quality and continuity [28–30]. At the same time, our study adds an important middle-income, Central Asian perspective by highlighting how gaps in pregnancy-specific operational guidelines (standard operating procedures – SOPs) and inconsistent implementation of structured monitoring tools (e.g., symptom diaries) intersected with women's symptom misinterpretation and self-treatment, contributing to delays in escalation of care and hospitalization decisions – issues that are less prominent in much of the high-income qualitative literature [22].

The findings of this study need to be interpreted within the specific context of the Kazakhstani health system during the COVID-19 pandemic. Unlike many high-income countries with stable and well-institutionalized maternal healthcare pathways, which maintained consistent clinical guidance during the pandemic, Kazakhstan experienced frequent revisions of national COVID-19 protocols and regulatory documents, creating uncertainty regarding the responsibility for referral and hospitalization of pregnant COVID-19 patients.

This type of policy flux has also been described as a challenge for maintaining continuity of care in other settings [31]. In the absence of consistently implemented standard operating procedures, healthcare professionals in our study relied on informal practices, messaging platforms, and remote communication to manage women in their homes, reflecting broader trends of telemedicine expansion and communication challenges observed internationally during the pandemic [28,32].

At the same time, pregnant women navigated care in an environment characterized by changing rules, fear of hospitalization, and limited structured follow-up, which amplified tendencies toward self-treat-

naglašavajući kako su nedostaci u operativnim smernicama specifičnim za trudnoću i nedosledna primena strukturisanih alata za praćenje (npr. dnevnici simptoma) u interakciji sa pogrešnim tumačenjem simptoma i samolečenjem kod žena doprinosili kašnjenjima u eskaliranju zdravstvene zaštite i donošenju odluka o hospitalizaciji – pitanjima koja su manje izražena u velikom delu kvalitativne literature iz zemalja sa visokim dohotkom [22].

Nalaze ove studije treba tumačiti u specifičnom kontekstu zdravstvenog sistema Kazahstana tokom KOVID-19 pandemije. Za razliku od mnogih zemalja sa visokim dohotkom, te stabilnim i dobro institucionalizovanim putevima zdravstvene zaštite trudnica i porodilja, koje su tokom pandemije održavale dosledne kliničke smernice, Kazahstan je doživljavao česte revizije nacionalnih KOVID-19 protokola i regulative, što je stvaralo neizvesnost u vezi sa odgovornošću za upućivanje na dalje lečenje i hospitalizaciju trudnica obolelih od KOVID-19 infekcije.

Ovakav tip promenljivosti politika takođe je opisan kao izazov za održavanje kontinuiteta zdravstvene zaštite u drugim sredinama [31]. U odsustvu dosledno primenjivanih standardnih operativnih procedura, zdravstveni radnici u našoj studiji oslanjali su se na neformalne prakse, platforme za razmenu poruka i komunikaciju na daljinu kako bi zbrinjavali žene u njihovim domovima, što odražava šire trendove širenja telemedicines i izazove u komunikaciji zabeležene na međunarodnom nivou tokom pandemije [28,32].

Istovremeno, trudnice su se snalazile u sistemu zdravstvene zaštite u okruženju obeleženom promenljivim pravilima, strahom od hospitalizacije i ograničenim strukturisanim lekarskim praćenjem, što je pojačavalo sklonost ka samolečenju i odlaganju traženja pomoći. Ove sistemske karakteristike pomažu da se objasni zašto su praznine u putevima zdravstvene zaštite uočene u ovoj studiji bile posebno izražene u kazahstanskom kontekstu.

Nalazi ove studije ukazuju na nekoliko prioriteta za jačanje organizacije zdravstvene zaštite trudnica obolelih od KOVID-19 infekcije i za buduće javnozdravstvene vanredne situacije. Prvo, odsustvo dosledno primenjivanih standardnih operativnih procedura specifičnih za trudnoću naglašava potrebu za jasnim i operativnim kliničkim putevima koji definišu odgovornosti za praćenje simptoma, testiranje, upućivanje na dalje lečenje i hospitalizaciju. Drugo, strukturisani alati za samopraćenje, kao što su dnevnici simptoma i standardizovani protokoli lekarskog praćenja, trebalo bi da budu integrisani u rutinsko ambulantno zbrinjavanje kako bi se obezbedilo rano otkrivanje kliničkog pogoršanja. Treće, ko-

ment and delayed help-seeking. These system-level features help explain why gaps in care pathways observed in this study were particularly pronounced in the Kazakhstan setting.

The findings of this study highlight several priorities for strengthening the organization of care for pregnant COVID-19 patients and for future public health emergencies. Firstly, the absence of consistently implemented, pregnancy-specific SOPs underscores the need for clear and operational clinical pathways that define responsibilities for symptom monitoring, testing, referral, and hospitalization. Secondly, structured self-monitoring tools, such as symptom diaries and standardized follow-up protocols, should be integrated into routine outpatient management to support early detection of clinical deterioration. Thirdly, communication strategies between primary care, hospitals, and pregnant women need to be strengthened to reduce uncertainty and fear surrounding testing and hospitalization.

The widespread use of phone calls, messaging applications, and chat-based communication observed in this study can be understood as forms of informal or ad hoc telemedicine. These practices emerged as adaptive responses to reduced face-to-face contact, uncertainty in referral pathways, and the absence of fully institutionalized digital care models. While such communication helped maintain continuity of care, its informal nature also contributed to variability in monitoring, documentation, and escalation of care decisions. This finding aligns with international evidence highlighting rapid but uneven digital health adaptation during the COVID-19 pandemic.

Finally, while remote communication through phone calls and messaging platforms proved essential during the pandemic, these tools should be embedded within formal care pathways rather than relying on informal or ad hoc practices. Together, these measures could improve continuity of care, reduce delays in escalation of care, and enhance the safety of maternal health services during infectious disease outbreaks.

STUDY STRENGTHS AND LIMITATIONS

This study has several strengths. It draws on in-depth qualitative data from two key stakeholder groups – pregnant and postpartum women and healthcare professionals – allowing triangulation of perspectives on COVID-19 care pathways. The use of verbatim interviews and thematic analysis has enabled a detailed exploration of real-world experiences in both primary care and hospital settings. In addition, the study provides rare qualitative evidence from a middle-income, Central Asian context, where such data are scarce.

munikacijske strategije između primarne zdravstvene zaštite, bolnica i trudnica moraju biti ojačane kako bi se smanjila neizvesnost i strah u vezi sa testiranjem i hospitalizacijom.

Široka upotreba telefonskih poziva, aplikacija za razmenu poruka i komunikacije zasnovane na "četovima" uočena u ovoj studiji može se razumeti kao oblik neformalne ili *ad hoc* telemedicine. Ove prakse su se pojavile kao adaptivni odgovori na smanjen broj neposrednih kontakata, neizvesnost u putevima upućivanja na dalje lečenje i odsustvo potpuno institucionalizovanih digitalnih modela zdravstvene zaštite. Iako je takva komunikacija pomagala u održavanju kontinuiteta zdravstvene zaštite, njena neformalna priroda takođe je doprinosila varijabilnosti u lekarskom praćenju, dokumentovanju i donošenju odluka o eskaliranju zdravstvene zaštite. Ovaj nalaz je u skladu sa međunarodnim dokazima koji ukazuju na brzu, ali neujednačenu digitalnu adaptaciju u zdravstvu tokom KOVID-19 pandemije.

Na kraju, iako se komunikacija na daljinu putem telefonskih poziva i platformi za razmenu poruka pokazala kao ključna tokom pandemije, ovi alati trebalo bi da budu ugrađeni u formalne puteve zdravstvene zaštite, umesto da se oslanjaju na neformalne ili *ad hoc* prakse. Zajedno, ove mere mogle bi da unaprede kontinuitet zdravstvene zaštite, smanje kašnjenja u eskaliranju zdravstvene zaštite i povećaju bezbednost službi za zdravstvenu zaštitu trudnica i porodilja tokom epidemija zaraznih bolesti.

KVALITETI I OGRANIČENJA STUDIJE

Ova studija ima nekoliko kvaliteta. Zasniva se na detaljnim kvalitativnim podacima dobijenim od dve ključne grupe aktera – trudnica i žena u postporođajnom periodu i zdravstvenih radnika – što omogućava triangulaciju perspektiva o putevima zbrinjavanja kod oboljevanja od KOVID-19 infekcije. Primena doslovnih transkripcija intervju i tematske analize omogućila je detaljno istraživanje stvarnih iskustava u primarnoj zdravstvenoj zaštiti i bolničkim okruženjima. Pored toga, studija pruža retke kvalitativne dokaze iz konteksta zemlje srednjeg dohotka u Centralnoj Aziji, gde su takvi podaci oskudni.

Međutim, treba priznati i neka ograničenja. Svi učesnici su regrutovani iz jednog grada, što može ograničiti primenljivost nalaza na druge regione Kazahstana ili na ruralna područja. Iskustva se takođe mogu razlikovati u kasnijim fazama pandemije, kako su se kliničke smernice i organizacija zdravstvenih usluga razvijale. Ipak, doslednost tema među učesnicima sugeriše da nalazi obuhvataju ključne karakteristike puteva zbrinjavanja tokom obolevanja od KOVID-19 infekcije tokom perioda istraživanja.

However, some limitations should be acknowledged. All participants were recruited from a single city, which may limit the transferability of the findings to other regions of Kazakhstan or to rural settings. Experiences may also differ across later stages of the pandemic, as clinical guidelines and organization of health services evolved. Nevertheless, the consistency of themes across participants suggests that the findings capture key features of COVID-19 care pathways during the study period.

We found examples of dedicated and responsive care from healthcare professionals during the COVID-19 pandemic, and maternity staff should be acknowledged for their efforts to provide support under extremely challenging conditions. This qualitative study allowed both pregnant women and healthcare professionals to reflect on what was most important in the organization of COVID-19 care during pregnancy.

Future research should focus on how pregnancy-specific care pathways and digital follow-up tools can be integrated into routine maternal health services and sustained across different regions of Kazakhstan to improve continuity and timely escalation of care during public health emergencies.

ACKNOWLEDGEMENTS

This article showcases valuable findings from Zhansaya Nurgaliyeva's doctoral research project entitled "The State and Improvement of the Organization of Medical Care for Pregnant Women with Coronavirus Infection," conducted at Al-Farabi Kazakh National University.

Funding: This study received no external funding.

Ai application: Artificial intelligence tools were used for language editing and stylistic refinement only.

Conflict of interest: None declared.

Pronašli smo primere posvećene i odgovorne zdravstvene zaštite od strane zdravstvenih radnika tokom KOVID-19 pandemije, te osoblju u službama za zdravstvenu zaštitu trudnica i porodilja treba odati priznanje za njihove napore da pruže podršku u izuzetno teškim uslovima. Ova kvalitativna studija omogućila je i trudnicama i zdravstvenim radnicima da se osvrnu na ono što je bilo najvažnije u organizaciji zdravstvene zaštite u vezi sa obolevanjem od KOVID-19 infekcije tokom trudnoće.

Buduća istraživanja trebalo bi da se fokusiraju na to kako se putevi zdravstvene zaštite specifični za trudnoću i digitalni alati za praćenje mogu integrisati u rutinske službe zdravstvene zaštite trudnica i porodilja i održati u različitim regionima Kazahstana kako bi se poboljšao kontinuitet i pravovremeno eskaliranje zdravstvene zaštite tokom javnozdravstvenih vanrednih situacija.

IZJAVE ZAHVALNOSTI

Ovaj rad prikazuje vredne nalaze iz doktorskog istraživačkog projekta Žansaje Nurgaliyevе pod nazivom „Stanje i unapređenje organizacije medicinske zaštite trudnica sa koronavirusnom infekcijom“, sprovedenog na Kazahstanskom nacionalnom univerzitetu *Al-Farabi*.

Finansiranje: Ova studija nije dobila eksterno finansiranje.

Primena veštačke inteligencije: Alati veštačke inteligencije korišćeni su samo za jezičko uređivanje i stilsko unapređenje teksta.

Sukob interesa: Nije prijavljen.

LITERATURA / REFERENCES

- Bernstein K, Landau R. Management of maternal COVID-19: considerations for anesthesiologists. *Curr Opin Anaesthesiol*. 2021 Jun 1;34(3):246-253. doi: 10.1097/ACO.0000000000001001.
- Nurgaliyeva Z, Pivina L, Moynbayeva S, Alibayeva G, Suleimenova M, Kozhekenova N, et al. A Multicentric Study on Adverse COVID-19 Outcomes Among Pregnant and Nonpregnant Women in Multidisciplinary Hospitals of Kazakhstan. *Diagnostics (Basel)*. 2025 Apr 1;15(7):900. doi: 10.3390/diagnostics15070900.
- Zamparini J, Saggars R, Buga CE. A Review of Coronavirus Disease 2019 in Pregnancy. *Semin Respir Crit Care Med*. 2023 Feb;44(1):50-65. doi: 10.1055/s-0042-1758853.
- Mattar CN, Kalimuddin S, Sadarangani SP, Tagore S, Thain S, Thoon KC, et al. Pregnancy Outcomes in COVID-19: A Prospective Cohort Study in Singapore. *Ann Acad Med Singap*. 2020 Nov;49(11):857-869. doi: 10.47102/annals-acad-medsg.2020437.
- Afshar Y, Silverman NS, Han CS, Platt LD. Clinical guidance and perinatal care in the era of coronavirus disease 2019 (COVID-19). *J Perinat Med*. 2020 Nov 26;48(9):925-930. doi: 10.1515/jpm-2020-0400.
- COVID-19 Research Prioritization Group on MNCAH. Global research priorities on COVID-19 for maternal, newborn, child and adolescent health. *J Glob Health*. 2021 Nov 20;11:04071. doi: 10.7189/jogh.11.04071.
- Semaan A, Audet C, Huysmans E, Afolabi B, Assarag B, Banke-Thomas A, et al. Voices from the frontline: findings from a thematic analysis of a rapid online global survey of maternal and newborn health professionals facing the COVID-19 pandemic. *BMJ Glob Health [Internet]*. 2020 Jun 24 [Pristupljeno: 10. januar 2026.];5(6). Dostupno na: <https://gh.bmj.com/content/5/6/e002967>
- Murewanhema G, Nyakanda MI, Madziyire MG. Restoring and maintaining robust maternity services in the COVID-19 era: a public health dilemma in Zimbabwe. *Pan Afr Med J*. 2020 Nov 8;37(Suppl 1):32. doi: 10.11604/pamj.supp.2020.37.32.26798.
- Semaan A, Annerstedt KS, Beňová L, Dossou JP, Boyi Hounsou C, Agballa G, et al. Provision and utilization of maternal health services during the COVID-19 pandemic in 16 hospitals in sub-Saharan Africa. *Front Glob Womens Health*. 2023 Oct 31;4:1192473. doi: 10.3389/fghw.2023.1192473.
- The Lancet Digital Health. Pregnancy in a pandemic: inequalities in maternal health. *Lancet Digit Health*. 2022 Feb;4(2):e75. doi: 10.1016/S2589-7500(22)00005-X.
- Meaney S, Leita S, Olander EK, Pope J, Matvienko-Sikar K. The impact of COVID-19 on pregnant women's experiences and perceptions of antenatal maternity care, social support, and stress-reduction strategies. *Women Birth*. 2022 May;35(3):307-316. doi: 10.1016/j.wombi.2021.04.013.
- Women's experiences of maternity care in the first wave of the COVID-19 pandemic in Poland: a cross-sectional study [Internet]. [Pristupljeno: 11. januar 2026.]. Dostupno na: <https://medsciencepulse.com/article/01.3001.0054.7021/en>
- Green C, Board A, Squire C, Adams ET, Kim SY, Brown JA, et al. The Impact of the COVID-19 Pandemic on the Care of Pregnant Women with a Focus on Those who Use Substances: Lessons for the Future. *Disaster Med Public Health Prep*. 2025 Jun 17;19:e154. doi: 10.1017/dmp.2025.10089.
- Berggren K, Ekstedt M, Joelsson-Alm E, Swedberg L, Sackey P, Schandl A. Healthcare workers' experiences of patient safety in the intensive care unit during the COVID-19 pandemic: A multicentre qualitative study. *J Clin Nurs*. 2023 Oct;32(19-20):7372-7381. doi: 10.1111/jocn.16793.
- Rodríguez-Madrid MN, Pastor-Moreno G, Albert-Lopez E, Pastor-Valero M. «You knew you had to be there, it had to be done»: Experiences of health professionals who faced the COVID-19 pandemic in one public hospital in Spain. *Front Public Health*. 2023 Apr 20;11:1089565. doi: 10.3389/fpubh.2023.1089565.
- Bhattacharjee PK, Deka K. PSYCHOLOGICAL DISTRESS AND JOB SATISFACTION AMONG HEALTH CARE WORKERS ENGAGED IN COVID 19 PANDEMIC WORKING IN A TERTIARY HEALTH CARE SYSTEM IN ASSAM. *South East Eur J Public Health*. 2025 Mar 2;5699-705. doi:https://doi.org/10.70135/seejph.vi.5280.
- Forte DN, Stoltenberg M, Ribeiro SCDC, de Almeida IMMO, Jackson V, Daubman BR. The Hierarchy of Communication Needs: A Novel Communication Strategy for High Mistrust Settings Developed in a Brazilian COVID-19 ICU. *Palliat Med Rep*. 2024 Feb 9;5(1):86-93. doi: 10.1089/pmr.2023.0070.
- Dasgupta T, Bousfield E, Pathak Y, Horgan G, Peterson L, Mistry HD, et al. Healthcare providers' experiences of maternity care service delivery during the COVID-19 pandemic in the United Kingdom: a follow-up systematic review and qualitative evidence synthesis. *Front Glob Womens Health [Internet]*. 2024 Nov 28 [Pristupljeno: 11. januar 2026.];5. Dostupno na: <https://www.frontiersin.org/journals/global-womens-health/articles/10.3389/fghw.2024.1470674/full>

19. Kassa ZY, Scarf V, Turkmani S, Fox D. Impact of COVID-19 on antenatal care provision at public hospitals in the Sidama region, Ethiopia: A mixed methods study. *PLoS One*. 2024 Apr 18;19(4):e0301994. doi: 10.1371/journal.pone.0301994.
20. Ganikyzy Shaimerdenova G, Narkenovna Abuova G, Kulbayeva Nalibekkyzy S. Features of the course of severe and critical COVID-19 in pregnant women: A prospective cross-sectional study. *Int J Reprod Biomed*. 2024 May 15;22(3):229-234. doi: 10.18502/ijrm.v22i3.16167.
21. Nukeshtayeva K, Kayupova G, Yerdessov N, Bolatova Z, Zhamantayev O, Turmukhambetova A. Factors associated with maternal mortality in Kazakhstan: a pre- and during-pandemic comparison. *Front Public Health* [Internet]. 2024 Jun 3 [Pristupljeno: 11. januar 2026.];12. Dostupno na: <https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2024.1337564/full>
22. Flaherty SJ, Delaney H, Matvienko-Sikar K, Smith V. Maternity care during COVID-19: a qualitative evidence synthesis of women's and maternity care providers' views and experiences. *BMC Pregnancy Childbirth*. 2022 May 26;22(1):438. doi: 10.1186/s12884-022-04724-w.
23. Hendrix CL, Werchan D, Lenniger C, Ablow JC, Amstadter AB, Austin A, et al. COVID-19 Impacts on Perinatal Care and Maternal Mental Health: A Geotemporal Analysis of Healthcare Disruptions and Emotional Well-Being Across the United States [Internet]. Rochester, NY: Social Science Research Network; 2021 [Pristupljeno: 12. januar 2026.]. Dostupno na: <https://papers.ssrn.com/abstract=3857679>
24. Johnson MS, Skjerdingsstad N, Ebrahimi OV, Hoffart A, Johnson SU. Fear of giving birth alone: Experiences of psychological distress, symptoms of anxiety and depression, and coping- strategies of childbearing women during COVID-19. *Midwifery*. 2024 Apr;131:103951. doi: 10.1016/j.midw.2024.103951.
25. Groulx T, Bagshawe M, Giesbrecht G, Tomfohr-Madsen L, Hetherington E, Lebel CA. Prenatal Care Disruptions and Associations With Maternal Mental Health During the COVID-19 Pandemic. *Front Glob Womens Health*. 2021 Apr 23;2:648428. doi: 10.3389/fgwh.2021.648428.
26. Brown J, Moore K, Keer E, Kane Low L. A Qualitative Study Focused on Maternity Care Professionals' Perspectives on the Challenges of Providing Care During the COVID-19 Pandemic. *J Perinat Neonatal Nurs*. 2022 Jan-Mar 01;36(1):46-54. doi: 10.1097/JPN.0000000000000623.
27. Basnet B, Chapagain P, Subedi S, Dahal T, Neupane S, Khanal R, et al. Experiences of nurses providing maternity care in a public hospital during the COVID-19 pandemic in Nepal: A qualitative study. *PLOS Glob Public Health*. 2022 May 5;2(5):e0000322. doi: 10.1371/journal.pgph.0000322.
28. Galle A, Semaan A, Huysmans E, Audet C, Asefa A, Delvaux T, et al. A double-edged sword-telemedicine for maternal care during COVID-19: findings from a global mixed-methods study of healthcare providers. *BMJ Glob Health*. 2021 Feb;6(2):e004575. doi: 10.1136/bmjgh-2020-004575.
29. Markwei M, Goje O. Optimizing mother-baby wellness during the 2019 coronavirus disease pandemic: A case for telemedicine. *Womens Health (Lond)*. 2021 Jan-Dec;17:17455065211013262. doi: 10.1177/17455065211013262.
30. Pinnock H, Murphie P, Vogiatzis I, Poberezhets V. Telemedicine and virtual respiratory care in the era of COVID-19. *ERJ Open Res*. 2022 Jul 25;8(3):00111-2022. doi: 10.1183/23120541.00111-2022.
31. Riley V, Ellis N, Mackay L, Taylor J. The impact of COVID-19 restrictions on women's pregnancy and postpartum experience in England: A qualitative exploration. *Midwifery*. 2021 Oct;101:103061. doi: 10.1016/j.midw.2021.103061.
32. Chandrakar M. Telehealth and digital tools enhancing healthcare access in rural systems. *Discov Public Health*. 2024 Oct 21;21(1):144. <https://doi.org/10.1186/s12982-024-00271-1>.

CURRICULUM VITAE



Zhansaya Nurgaliyeva, PhD

Zhansaya Nurgaliyeva, PhD, is a public health researcher and senior lecturer at Al-Farabi Kazakh National University (Kazakhstan). Her research focuses on maternal and reproductive health, health systems organization, and qualitative research methods, with particular attention to care pathways during public health emergencies. She holds a PhD in Public Health and has been involved in academic teaching and research in epidemiology, biostatistics, and evidence-based medicine. Nurgaliyeva's work aims to strengthen maternal health services and inform policy and practice in middle-income health systems.



Natalia Glushkova, PhD, Professor

Natalia Glushkova, PhD, is a Professor of Public Health and Director of the Research Institute of Health Care at Al-Farabi Kazakh National University (Kazakhstan). She is a highly cited researcher with a strong publication record and a high h-index, reflecting the significant impact and visibility of her work. In 2024, Professor Glushkova was recognized as one of the 50 Best Researchers nationwide, selected through the "Best Researcher-2024" competition among scientists from research institutes and universities. Her research focuses on health systems organization, maternal and reproductive health, epidemiology, and strengthening evidence-based public health practice.

DEPRESIVNE SMETNJE MEĐU ČLANOVIMA PORODICE KOJI BRINU O PACIJENTIMA U KUĆNOM LEČENJU: PHQ-9 STUDIJA PRESEKA

ORIGINALNI RAD

ORIGINAL ARTICLE

DEPRESSIVE SYMPTOMS AMONG FAMILY MEMBERS PROVIDING INFORMAL CARE FOR PATIENTS RECEIVING HOME-BASED CARE: A PHQ-9 CROSS-SECTIONAL STUDY

Nikola Gavrilović¹

¹ Dom zdravlja Subotica, Služba kućnog lečenja i nege, Subotica, Srbija

¹ Health Center Subotica, Home Care Service, Subotica, Serbia

SAŽETAK

Uvod/Cilj: Porodični negovatelji pacijenata uključenih u kućno lečenje predstavljaju populaciju pod povećanim rizikom za razvoj depresivnih simptoma. Cilj ovog istraživanja bio je da se proceni prisustvo i intenzitet depresivnih simptoma primenom upitnika PHQ-9, kao i da se ispita povezanost između depresivnih smetnji i svakodnevnog funkcionisanja negovatelja.

Metode: Sprovedena je deskriptivno-analitička studija preseka među 77 porodičnih negovatelja pacijenata uključenih u Službu kućnog lečenja Doma zdravlja Subotica, u periodu mart–septembar 2025. godine. Za procenu depresivnih simptoma korišćen je upitnik Patient Health Questionnaire-9 (PHQ-9). U analizi su primenjeni t-test, Mann-Whitney U test, Kruskal–Wallis test i Spearmanov koeficijent korelacije.

Rezultati: Prosečan PHQ-9 skor iznosio je $8,48 \pm 6,14$. Skor ≥ 10 registrovan je kod 30 (38,9%) ispitanika. Minimalne ili blage simptome imalo je 47 (61,1%) negovatelja. Nije utvrđena statistički značajna razlika u PHQ-9 skoru prema polu ($p = 0,423$) niti prema primarnoj dijagnozi pacijenta ($p = 0,183$). U ukupnom uzorku utvrđena je statistički značajna blaga pozitivna korelacija između PHQ-9 skora i subjektivne procene uticaja simptoma na svakodnevno funkcionisanje ($r = 0,294$; $p = 0,009$).

Zaključak: Depresivni simptomi su prisutni kod značajnog dela porodičnih negovatelja pacijenata u kućnom lečenju. Intenzitet simptoma povezan je sa većom narušenošću svakodnevnog funkcionisanja, što ukazuje na potrebu sistematskog praćenja mentalnog zdravlja ove populacije.

Cljučne reči: porodični negovatelji, depresija, demencija, karcinom, moždani udar, skrining

ABSTRACT

Introduction/Objective: Family members providing informal care for patients receiving home-based care represent a population at increased risk of developing depressive symptoms. The aim of this study was to assess the presence and severity of depressive symptoms using the PHQ-9 questionnaire and to examine the association between depressive symptoms and caregivers' daily functioning.

Methods: A descriptive-analytical cross-sectional study was conducted among 77 family caregivers of patients enrolled in the Home Care Service of the Health Center Subotica between March and September 2025. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9). Statistical analysis included the t-test, Mann-Whitney U test, Kruskal–Wallis test, and Spearman's correlation coefficient.

Results: The mean PHQ-9 score was 8.48 ± 6.14 . A score ≥ 10 was recorded in 30 (38.9%) participants. Minimal or mild depressive symptoms were present in 47 (61.1%) caregivers. No statistically significant differences in PHQ-9 scores were observed according to caregiver sex ($p = 0.423$) or the patient's primary diagnosis ($p = 0.183$). In the overall sample, a statistically significant weak positive correlation was found between PHQ-9 score and the self-reported impact of symptoms on daily functioning ($r = 0.294$; $p = 0.009$).

Conclusion: Depressive symptoms are present in a substantial proportion of family caregivers providing home-based care. The intensity of depressive symptoms is associated with greater impairment in daily functioning, highlighting the importance of systematic monitoring of caregivers' mental health.

Keywords: family caregivers, depression, dementia, neoplasms, stroke, screening

Autor za korespondenciju:
Nikola Gavrilović
Služba kućnog lečenja i nege, Dom zdravlja Subotica
Kumičićeva 4, 24000 Subotica, Srbija
Elektronska adresa: gavrilovicnikola@yahoo.com

Corresponding author:
Nikola Gavrilović
Home Care Service, Health Center Subotica
4 Kumičićeva Street, 24000 Subotica, Serbia
E-mail: jgavrilovicnikola@yahoo.com

Primljeno • Received: November 25, 2025; Revidirano • Revised: February 26, 2026; Prihvaćeno • Accepted: March 3, 2026; Online first: March 25, 2026

DOI: 10.5937/smcl7-63023

UVOD

Prema demografskim i socijalnim promenama u savremenim društvima, broj osoba koje zahtevaju intenzivnu zdravstvenu negu kod kuće zbog onkoloških bolesti, neurodegenerativnih poremećaja poput demencije ili posledica ishemijskog cerebrovaskularnog incidenta (ICV), stalno raste [1]. U takvim okolnostima, članovi porodice – supružnici, deca ili drugi bliski srodnici – preuzimaju ključnu ulogu u nezi, bez formalne obuke ili institucionalne podrške, što povećava rizik od psihološkog opterećenja, uključujući simptome depresije [2].

Negovanje pacijenata u kućnim uslovima obuhvata širok spektar aktivnosti: asistenciju pri svakodnevnom potrebama, medicinsku i terapijsku podršku, nadzor, fizičku pomoć, ali i emocionalnu brigu, što sve može dovesti do zamora, stresa i narušavanja mentalnog zdravlja negovatelja [3]. Studije potvrđuju visoku prevalenciju depresivnih simptoma u ovoj populaciji. Na primer, među negovateljima osoba sa demencijom, čak 31% pokazuje simptome umerene depresije, dok 9% ispunjava kriterijume za tešku depresiju [4]. Meta-analiza negovatelja pacijenata sa onkološkim oboljenjima navodi da je prosečna prevalencija depresivnosti oko 42% [5].

Uloga negovatelja u kućnim uslovima ima dalekosežne implikacije i na funkcionisanje zdravstvenog sistema. Nedostatak sistemске podrške može dovesti do pogoršanja kvaliteta nege, povećanja rizika od sagorevanja i većih troškova zdravstvene zaštite [6]. Zbog toga je u savremenoj praksi važan pouzdan skrining depresivnosti među negovateljima.

Upitnik PHQ-9 široko se koristi kao standardni skrining alat u različitim populacijama. Njegova primena u populaciji porodičnih negovatelja potvrđena je u studijama o porodicama koje neguju decu oboljelu od raka, gde skoro polovina negovatelja ispunjava kriterijume za blagu depresiju [7], kao i u istraživanjima negovatelja starijih osoba u kućnoj nezi, gde je kod 41,8 % prisutna depresija i 64,5% anksioznost [8]. PHQ-9 se takođe pokazao validnim i kod negovatelja osoba sa intelektualnim teškoćama [9]. Prevalencija depresije određena PHQ-9 upitnikom kod negovatelja pacijenata sa moždanim udarom je iznosila 18,5% [10]. Negovatelji pacijenata sa teškim povredama mozga imaju potvrđene simptome depresije kod 61.2% ispitanika uz povezanost sa anksioznošću gde je veći skor PHQ-9 korelirao sa lošijim kvalitetom života negovatelja [11].

Porodični negovatelji suočavaju se sa posebnim problemima:

- Intenzitet i trajanje nege, naročito kod demencije i post-ICV stanja, direktno utiču na psihičko blagostanje [4].

INTRODUCTION

According to demographic and social changes in contemporary societies, the number of individuals requiring intensive home health care due to oncological diseases, neurodegenerative disorders such as dementia, or consequences of ischemic cerebrovascular incident (stroke) is constantly increasing [1]. In such circumstances, family members-spouses, children, or other close relatives-assume a key role in caregiving without formal training or institutional support, which increases the risk of psychological burden, including symptoms of depression [2].

Home caregiving encompasses a wide range of activities: assistance with daily needs, medical and therapeutic support, supervision, physical assistance, and emotional care, all of which may lead to fatigue, stress, and deterioration of caregivers' mental health [3]. Studies confirm a high prevalence of depressive symptoms in this population. For example, among caregivers of persons with dementia, as many as 31% show symptoms of moderate depression while 9% meet criteria for severe depression [4]. A meta-analysis of caregivers of oncology patients reports that the average prevalence of depression is approximately 42% [5].

The role of home caregivers also has far-reaching implications for the functioning of the healthcare system. Lack of systemic support may lead to deterioration in the quality of care, increased risk of burnout, and higher healthcare costs [6]. Therefore, reliable screening for depression among caregivers is important in contemporary practice.

The Patient Health Questionnaire-9 (PHQ-9) is widely used as a standard screening tool in various populations. Its application among family caregivers has been confirmed in studies of families caring for children with cancer, where nearly half of caregivers meet criteria for mild depression [7], as well as in studies of caregivers of older adults receiving home care, where depression was present in 41.8% and anxiety in 64.5% of participants [8]. The PHQ-9 has also proven valid among caregivers of persons with intellectual disabilities [9]. The prevalence of depression determined by the PHQ-9 questionnaire among caregivers of stroke patients was 18.5% [10]. Caregivers of patients with severe brain injuries have confirmed depressive symptoms in 61.2% of participants, with an association with anxiety, where a higher PHQ-9 score correlated with poorer quality of life among caregivers [11].

Family caregivers face several specific challenges:

- The intensity and duration of care, particularly in dementia and post-stroke conditions, directly affect psychological well-being [4].

- Neformalni status negovatelja, odsustvo naknade, podrške ili odmora dodatno pojačavaju emocionalni teret [3].
- Socijalna izolacija i zanemarivanje sopstvenog zdravlja povećavaju rizik za depresivne simptome [2].

U našoj zemlji i regionu nedostaju sistematski podaci o depresivnosti porodičnih negovatelja pacijenata u kućnom lečenju, posebno u odnosu na specifične dijagnostičke kategorije (onkološki pacijenti, demencija, post-ICV). Proučavanje ove populacije važno je kako bi se unapredilo razumevanje njihovog mentalnog zdravlja i omogućilo adekvatno planiranje daljih mera podrške.

Cilj ovog istraživanja bio je da se pomoću upitnika Patient Health Questionnaire-9 (PHQ-9) proceni prisustvo i intenzitet depresivnih simptoma među članovima porodice pacijenata uključenih u Službu kućnog lečenja, te da se ispita da li postoje razlike u nivou depresivnih smetnji u zavisnosti od osnovne dijagnoze pacijenta (onkološko oboljenje, demencija ili post-ishemijski cerebrovaskularni incident).

Sekundarni cilj bio je da se proceni u kojoj meri depresivne smetnje utiču na svakodnevno funkcionisanje negovatelja u obavljanju kućnih, radnih i socijalnih aktivnosti.

METODOLOGIJA

Sprovedena je deskriptivno-analitička studija preseka među članovima porodica pacijenata uključenih u Službu kućnog lečenja Doma zdravlja Subotica. Istraživanje je sprovedeno u periodu od marta do septembra 2025. godine.

Veličina uzorka je određena a priori. Korišćenjem G*Power softvera (verzija 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) i F tests – ANOVA: Fixed effects, omnibus, one-way (three groups) izračunata je veličina uzorka uz veličinu efekta 0.40, nivo značajnosti (α err prob = 0,05) i snagu ($1 - \beta$ err prob = 0,80). Prema postavljenim parametrima utvrđena je minimalna veličina uzorka od 66 jedinica posmatranja.

U analizu je uključeno ukupno 77 porodičnih negovatelja koji su kompletno popunili upitnik PHQ-9, dok su svi nepotpuni upitnici bili isključeni iz analize.

PHQ-9 je validirani instrument za skrining depresivnosti koji procenjuje učestalost devet simptoma tokom prethodne dve nedelje. To je upitnik od 9 stavki sa Likertovom skalom za samoprocenu. Ukupan skor kreće se u rasponu od 0–27 poena i klasifikuje težinu depresivnih simptoma u standardne kategorije. Što je viši ukupan rezultat, to su teži depresivni simptomi koje pojedinac doživljava.

Pored PHQ-9 skora, prikupljeni su podaci o polu i starosti porodičnih negovatelja kao i informacije o

- The informal status of caregivers, absence of financial compensation, support, or respite further increases the emotional burden [3].
- Social isolation and neglect of their own health increase the risk of depressive symptoms [2].

In our country and region, systematic data on depression among family caregivers of patients receiving home treatment are lacking, particularly in relation to specific diagnostic categories (oncological patients, dementia, post-stroke conditions). Studying this population is important in order to improve understanding of their mental health and enable adequate planning of support measures.

The aim of this study was to assess the presence and intensity of depressive symptoms among family members of patients enrolled in the Home Care Service using the PHQ-9, and to examine whether differences in the level of depressive symptoms exist depending on the patient's primary diagnosis (oncological disease, dementia, or post-ischemic cerebrovascular incident).

The secondary aim was to assess the extent to which depressive symptoms affect caregivers' daily functioning in performing household, work, and social activities.

METHODOLOGY

A descriptive-analytical cross-sectional study was conducted among family members of patients enrolled in the Home Care Service of the Primary Health Care Center Subotica. The study was carried out between March and September 2025.

The sample size was determined a priori. Using G*Power software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) and F tests – ANOVA: Fixed effects, omnibus, one-way (three groups), the required sample size was calculated assuming an effect size of 0.40, significance level (α err prob = 0.05), and statistical power ($1 - \beta$ err prob = 0.80). Based on these parameters, the minimum required sample size was 66 observational units.

A total of 77 family caregivers who fully completed the PHQ-9 were included in the analysis, while all incomplete questionnaires were excluded.

The PHQ-9 is a validated screening instrument for depression that assesses the frequency of nine symptoms over the previous two weeks. It is a 9-item self-report questionnaire using a Likert scale. The total score ranges from 0 to 27 points and classifies the severity of depressive symptoms into standard categories. Higher total scores indicate more severe depressive symptoms experienced by the individual.

In addition to the PHQ-9 score, data were collected on the sex and age of family caregivers, as well as in-

osnovnoj dijagnozi pacijenta zbog koje je uključen u kućno lečenje (onkološko oboljenje, demencija ili stanje nakon ishemijskog cerebrovaskularnog incidenta), kao i subjektivna procena uticaja simptoma na svakodnevno funkcionisanje negovatelja (ne, malo, dosta, izraženo).

Podaci su prikupljeni anonimno tokom rutinskih dolazaka članova porodica u ambulantu Službe kućnog lečenja, uz dobrovoljni pristanak ispitanika, u skladu sa etičkim principima Helsinške deklaracije. Istraživanje je odobreno od strane Etičkog odbora Doma zdravlja Subotica (del. br. 01-5/I/2025. od 20.02.2025).

Statistička analiza obavljena je korišćenjem deskriptivnih statističkih metoda i metoda za testiranje razlike između grupa ispitanika i povezanosti između PHQ-9 skora i ispitivanih parametara. Za testiranje razlike korišćeni su t-test, Mann-Whitney U test i Kruskal-Wallis test, a za ispitivanje povezanosti Spearmanov koeficijent korelacije. Analiza podataka je sprovedena u softverskom programu SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA), a kriterijum za statističku značajnost bio je $p < 0,05$.

REZULTATI

Studijom je obuhvaćeno 77 ispitanika, prosečne starosne dobi $49,68 \pm 15,05$ godina. Učestalost ženskih negovatelja iznosila je 46 (59,7%), prosečne starosti $48,30 \pm 13,77$ godina, dok je muških negovatelja bilo 31 (40,3%), prosečne starosti $51,71 \pm 16,79$ godina. Starosna dob ispitanika se nije značajno razlikovala prema polu ($p = 0,333$), što ukazuje da je ispitivana grupa homogena u odnosu na starosnu dob.

Za svakog negovatelja određen je ukupan PHQ-9 skor. Prosečna vrednost za ispitivani uzorak iznosila je $8,48 \pm 6,14$, sa rasponom vrednosti od 0 do 23 poena. Medijana PHQ-9 skora kod ženskih negovatelja iznosila je 7,5 (raspon 0–21), a kod muških 5,0 (raspon 0–23).

formation on the patient’s primary diagnosis that led to inclusion in home care (oncological disease, dementia, or condition following an ischemic cerebrovascular incident). A subjective assessment of the impact of symptoms on the caregiver’s daily functioning (none, mild, moderate, severe) was also recorded.

Data were collected anonymously during routine visits of family members to the outpatient clinic of the Home Care Service, with voluntary consent from participants, in accordance with the ethical principles of the Helsinki Declaration. The study was approved by the Ethics Committee of the Primary Health Care Center Subotica (decision no. 01-5/I/2025, dated February 20, 2025).

Statistical analysis was performed using descriptive statistical methods and methods for testing differences between groups and associations between PHQ-9 scores and the examined parameters. The t-test, Mann-Whitney U test, and Kruskal-Wallis test were used to test differences, while Spearman’s correlation coefficient was used to examine associations. Data analysis was conducted using SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA), and the criterion for statistical significance was set at $p < 0.05$.

RESULTS

The study included 77 participants with a mean age of 49.68 ± 15.05 years. Female caregivers accounted for 46 (59.7%) participants, with a mean age of 48.30 ± 13.77 years, while male caregivers accounted for 31 (40.3%) participants, with a mean age of 51.71 ± 16.79 years. There was no statistically significant difference in age between male and female participants ($p = 0.333$), indicating that the study group was homogeneous with respect to age.

For each caregiver, the total PHQ-9 score was calculated. The mean value for the study sample was 8.48 ± 6.14 , with a range from 0 to 23 points. The me-

Tabela 1. Deskriptivni pokazatelji PHQ-9 ukupnog skora

Deskriptivni parametri / Descriptive parameters	Pol / Sex		Ukupno / Total
	Žene / Female	Muškarci / Male	
Broj ispitanija / Number of respondents	46	31	77
Srednja vrednost / Mean value	8.85	7.94	8.48
Standardna devijacija / Standard deviation	5.86	6.59	6.14
Minimum / Minimum	0	0	0
25th percentile / 25th percentile	4.0	3.0	4.0
Medijana (50 percentila) / Median (50th percentile)	7.5	5.0	7.0
75 percentila / 75th percentile	13.25	13.0	13.0
Maksimum / Maximum	21.0	23.0	23.0

Table 1. Descriptive indicators of the PHQ-9 total score

Tabela 2. Distribucija kategorija depresivne smetnje prema PHQ-9

Kategorija / Category	Opseg skora / Score range	n	%
Nema tegoba do minimalna depresija / No complaints to minimal depression	0–4	24	31.2%
Blaga depresija / Mild depression	5–9	23	29.9%
Umerena depresija / Moderate depression	10–14	16	20.8%
Umereno teška depresija / Moderately severe depression	15–19	11	14.3%
Teška depresija / Severe depression	20–27	3	3.9%

Table 2. Distribution of categories of depressive disorder according to PHQ-9

Testirana je razlika ukupnog PHQ-9 skora između polova i nije utvrđena statistički značajna razlika ($p = 0,423$), **Tabela 1**.

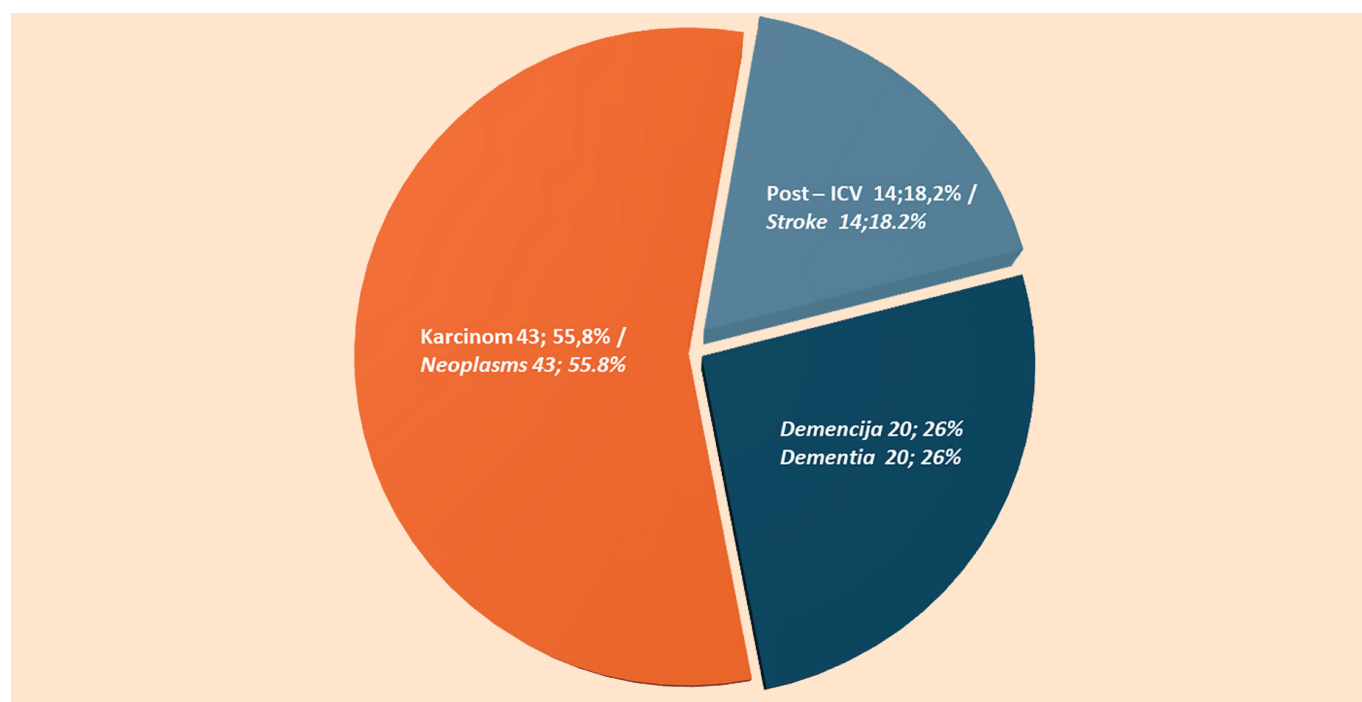
Na osnovu ukupnog PHQ-9 skora i kategorizacije težine depresivnih simptoma, minimalne ili blage simptome depresije imalo je 47 (61,1%) ispitanika. Minimalni simptomi (skor 0–4) bili su prisutni kod 24 (31,2%), dok je blage simptome (skor 5–9) imalo 23 (29,9%) negovatelja. Simptomi sa PHQ-9 skorom ≥ 10 registrovani su kod 30 (38,9%) ispitanika. Umereni simptomi (skor 10–14) bili su prisutni kod 16 (20,8%), umereno teški (skor 15–19) kod 11 (14,3%), a teški simptomi (skor 20–27) kod 3 (3,9%) negovatelja, **Tabela 2**.

Učestalost negovatelja prema osnovnoj dijagnozi pacijenta prikazana je na **Grafikonu 1**. Karcinom je bio zastupljen kod 43 (55,8%) pacijenata, demencija kod 20 (26,0%), dok je 14 (18,2%) pacijenata imalo dijagnozu post-ishemijskog cerebrovaskularnog incidenta.

dian PHQ-9 score among female caregivers was 7.5 (range 0–21), while among male caregivers it was 5.0 (range 0–23). The difference in total PHQ-9 scores between sexes was tested and no statistically significant difference was found ($p = 0.423$), **Table 1**.

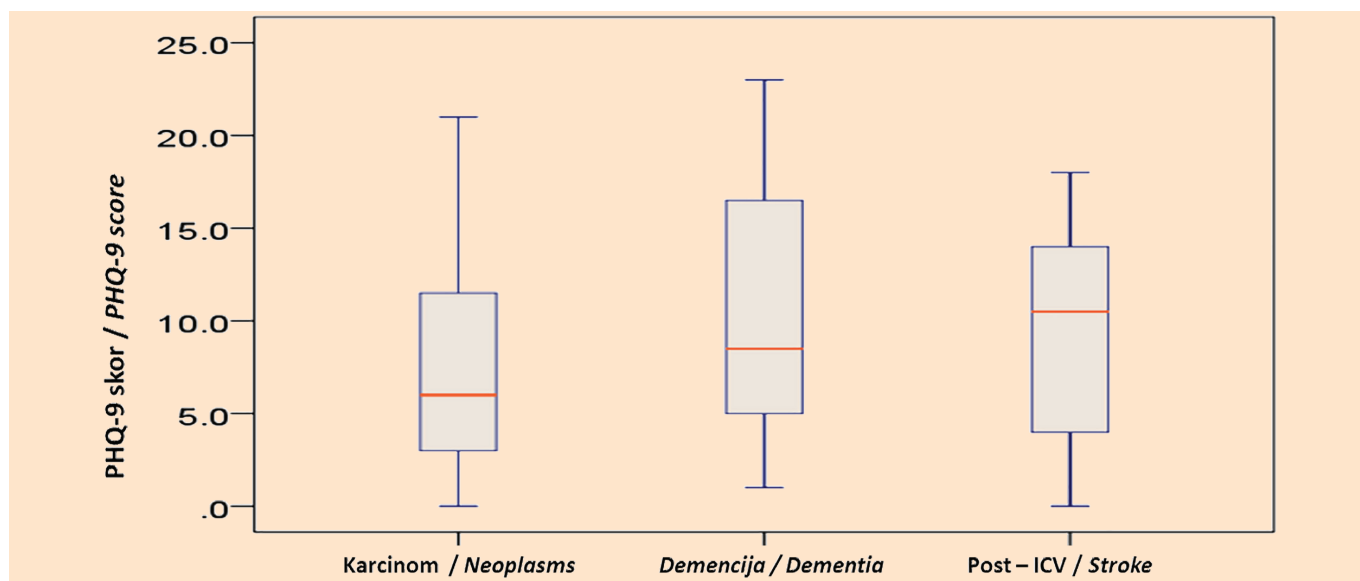
Based on the total PHQ-9 score and the categorization of depressive symptom severity, minimal or mild depressive symptoms were present in 47 (61.1%) participants. Minimal symptoms (score 0–4) were observed in 24 (31.2%) participants, while mild symptoms (score 5–9) were present in 23 (29.9%) caregivers. Symptoms with a PHQ-9 score ≥ 10 were recorded in 30 (38.9%) participants. Moderate symptoms (score 10–14) were present in 16 (20.8%), moderately severe symptoms (score 15–19) in 11 (14.3%), and severe symptoms (score 20–27) in 3 (3.9%) caregivers (**Table 2**).

The distribution of caregivers according to the patient's primary diagnosis is presented in **Graph 1**. Can-



Grafikon 1. Učestalost negovatelja prema osnovnoj dijagnozi pacijenta

Graph 1. Distribution of caregivers according to the patient's primary diagnosis


Grafikon 2. PHQ-9 skor prema osnovnoj dijagnozi pacijenta

Graph 2. PHQ-9 score according to patient's primary diagnosis

Medijana PHQ-9 skora kod negovatelja pacijenata sa karcinomom iznosila je 6,0 (0–21), kod negovatelja pacijenata sa demencijom 8,5 (1–23), dok je kod negovatelja pacijenata sa post-ICV medijana iznosila 10,5 (0–18). Razlika u vrednostima PHQ-9 skora između grupa prema primarnoj dijagnozi pacijenta nije bila statistički značajna ($p = 0,183$), **Grafikon 2**.

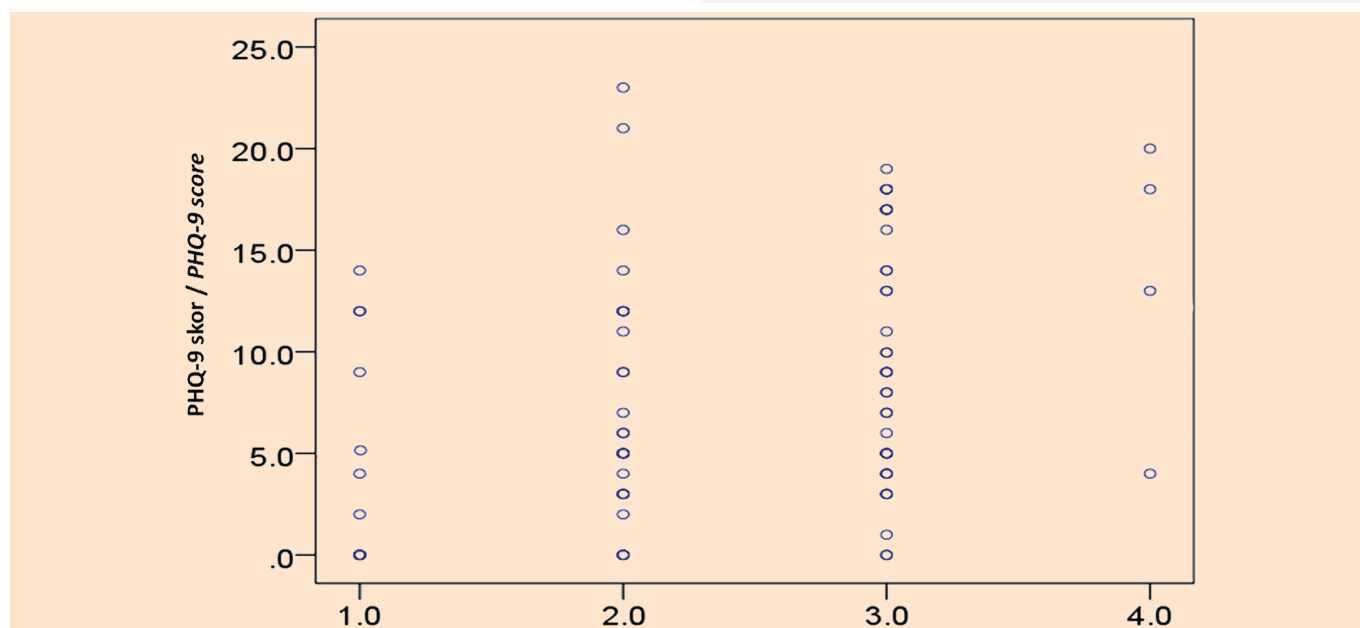
Ispitivanjem povezanosti između PHQ-9 skora i subjektivne procene uticaja simptoma na svakodnevno funkcionisanje kod ukupnog uzorka od 77 negovatelja utvrđena je statistički značajna blaga pozitivna korelacija ($r_s = 0,294$; $p = 0,009$), **Grafikon 3**.

Povezanost PHQ-9 skora sa svakodnevnim funkcionisanjem negovatelja prikazana je po grupama

cer was present in 43 (55.8%) patients, dementia in 20 (26.0%), while 14 (18.2%) patients had a diagnosis of post-ischemic cerebrovascular incident.

The median PHQ-9 score among caregivers of patients with cancer was 6.0 (0–21), among caregivers of patients with dementia 8.5 (1–23), while among caregivers of patients with post-ischemic cerebrovascular incident the median was 10.5 (0–18). The difference in PHQ-9 scores between groups according to the patient's primary diagnosis was not statistically significant ($p = 0.183$), **Graph 2**.

By examining the association between the PHQ-9 score and the subjective assessment of the impact of symptoms on daily functioning in the total sample of


Grafikon 3. Povezanost PHQ-9 skora i uticaja simptoma na svakodnevno funkcionisanje negovatelj

Graph 3. Correlation between PHQ-9 score and the impact of symptoms on caregivers' daily functioning

Tabela 3. Povezanost PHQ-9 skora i uticaja simptoma na svakodnevno funkcionisanje negovatelja u odnosu na primarnu dijagnozu pacijenta

Dijagnoza / <i>Diagnosis</i>	Broj / <i>Number</i>	r_s	p
Karcinom / <i>Neoplasms</i>	43	0.175	0.263
Demencija / <i>Dementia</i>	20	0.212	0.370
post – ICV / <i>post – ICV</i>	14	0.529	0.052

r_s – Spearmanov koeficijent korelacije / r_s – *Spearman's correlation coefficient*

ispitanika u zavisnosti od primarne dijagnoze pacijenta, **Tabela 3.** U grupi negovatelja pacijenata sa post-ICV umerena pozitivna korelacija ($r_s = 0,529$; $p = 0,052$), iako nije dostigla statističku značajnost. Kod negovatelja pacijenata sa karcinomom ($r_s = 0,175$; $p = 0,263$) i demencijom ($r_s = 0,212$; $p = 0,370$) nije utvrđena statistički značajna povezanost.

DISKUSIJA

U ovoj studiji prosečan PHQ-9 skor među članovima porodice koji neguju pacijente u kućnom lečenju iznosio je $8,48 \pm 6,14$, dok je 38,9% ispitanika imalo skor ≥ 10 . Ovi nalazi ukazuju da je značajan deo porodičnih negovatelja izložen umerenim i težim depresivnim simptomima. Tan i saradnici u svom istraživanju su potvrdili da je prosečan skor PHQ-9 kod negovatelja pacijenata sa demencijom iznosio 7,1 [12]. Prevalencija prijavljena u meta-analitičkoj studiji kod negovatelja osoba nakon moždanog udara ukazuju da je depresija prisutna kod 43,9% ispitanika [13], dok kod negovatelja pacijenata sa malignim bolestima depresivni simptomi dostižu približno 47% [5]. Nešto manja učestalost od 30,5% je bila kod negovatelja pacijenata sa demencijom [12]. Krovni pregled sistematskih pregleda i meta-analiza je objedinio dokaze o depresivnom morbiditetu kod negovatelja pacijenata obolelih od karcinoma i objedinjena globalna prevalenca depresije kod neformalnih negovatelja iznosila je 38% [14]. Ovakva podudarnost rezultata potvrđuje da su porodični negovatelji populacija sa povećanim rizikom za narušeno mentalno zdravlje.

U analizi prema polu nije utvrđena statistički značajna razlika u PHQ-9 skoru, što ukazuje da su depresivni simptomi podjednako zastupljeni među muškim i ženskim negovateljima. Ovaj nalaz je u skladu sa pojedinim savremenim studijama koje pokazuju da, iako žene češće preuzimaju ulogu negovatelja, intenzitet depresivnih simptoma ne mora nužno da se razlikuje prema polu [15]. Međutim pojedine studije potvrđuju na značajno veće angažovanje ženskog pola kada je u pitanju nega pacijenata sa demencijom, sa učestalošću od 68% [12]. Dodatno, novija istraživanja ukazuju da su kod ženskih negovatelja veće opterećenje i osećaj usamljenosti značajno povezani

Table 3. Correlation between PHQ-9 score and the impact of symptoms on caregivers' daily functioning according to the patient's primary diagnosis

77 caregivers, a statistically significant weak positive correlation was found ($r_s = 0.294$; $p = 0.009$), **Graph 3.**

The association between the PHQ-9 score and caregivers' daily functioning is presented by groups of participants according to the patient's primary diagnosis (**Table 3**). In the group of caregivers of patients with post-ischemic cerebrovascular incident, a moderate positive correlation was observed ($r_s = 0.529$; $p = 0.052$), although it did not reach statistical significance. No statistically significant association was found among caregivers of patients with cancer ($r_s = 0.175$; $p = 0.263$) and dementia ($r_s = 0.212$; $p = 0.370$).

DISCUSSION

In this study, the average PHQ-9 score among family members caring for patients receiving home treatment was 8.48 ± 6.14 , while 38.9% of participants had a score ≥ 10 . These findings indicate that a substantial proportion of family caregivers are exposed to moderate and more severe depressive symptoms. Tan and colleagues reported in their study that the average PHQ-9 score among caregivers of patients with dementia was 7.1 [12]. The prevalence reported in a meta-analytic study among caregivers of stroke survivors indicates that depression was present in 43.9% of participants [13], while depressive symptoms among caregivers of patients with malignant diseases reach approximately 47% [5]. A somewhat lower prevalence of 30.5% was reported among caregivers of patients with dementia [12]. An umbrella review of systematic reviews and meta-analyses synthesized evidence on depressive morbidity among caregivers of cancer patients and reported a pooled global prevalence of depression among informal caregivers of 38% [14]. Such consistency of findings confirms that family caregivers represent a population at increased risk for impaired mental health.

The analysis by sex showed no statistically significant difference in PHQ-9 scores, indicating that depressive symptoms were equally represented among male and female caregivers. This finding is consistent with some contemporary studies showing that although women more often assume the caregiving role, the intensity of depressive symptoms does not necessarily differ by sex [15]. However, some studies confirm significantly greater involvement of women in caregiving

sa intenzitetom depresivnih simptoma, pri čemu smisao životne svrhe može imati medijatorsku ulogu u tom odnosu [16].

Ispitivanje razlika prema primarnoj dijagnozi pacijenta nije pokazalo statistički značajne razlike u nivou depresivnih simptoma između grupa. Iako su medijane bile numerički više kod negovatelja pacijenata sa post-ICV i demencijom, dobijene razlike nisu dostigle nivo statističke značajnosti. Ovaj nalaz može biti posledica relativno malog uzorka i varijabilnosti unutar grupa. Međutim, numerički trend viših vrednosti kod negovatelja pacijenata sa neurološkim oboljenjima u skladu je sa ranijim istraživanjima koja ukazuju da neurokognitivni poremećaji i nagla funkcionalna zavisnost pacijenta predstavljaju značajan psihološki teret za negovatelje [4,15].

Sekundarni cilj istraživanja odnosio se na povezanost depresivnih simptoma i svakodnevnog funkcionisanja negovatelja. U ukupnom uzorku utvrđena je statistički značajna blaga pozitivna korelacija između PHQ-9 skora i subjektivne procene uticaja simptoma na svakodnevno funkcionisanje. Ovaj nalaz ukazuje da sa porastom intenziteta depresivnih simptoma raste i stepen narušenosti radnih, porodičnih i socijalnih aktivnosti negovatelja. Sličnu povezanost između psihološkog opterećenja i smanjenog kvaliteta života potvrđuju i ranije meta-analize [17].

U podgrupnoj analizi prema dijagnozi pacijenta uočena je umerena pozitivna korelacija kod negovatelja pacijenata sa post-ICV, sa nivoom bliskim statističkoj značajnosti. Ovakav trend može ukazivati na specifičnu ranjivost ove grupe. Nagla pojava cerebrovaskularnog incidenta i iznenadna promena funkcionalnog statusa pacijenta mogu dovesti do intenzivnog psihološkog opterećenja članova porodice koji preuzimaju ulogu negovatelja bez prethodne pripreme. Nasuprot tome, kod hroničnih stanja poput demencije ili malignih bolesti, duži tok bolesti može omogućiti postepenu adaptaciju i razvoj mehanizama suočavanja. Slično tome, u zajedničkim analizama neformalnih negovatelja osoba sa teškim mentalnim poremećajima pokazano je da su veće funkcionalno oštećenje korisnika nege i ženski pol značajno povezani sa depresivnim simptomima, dok je duže trajanje bolesti bilo povezano sa manjim rizikom za depresiju, što se tumači procesom adaptacije negovatelja [18].

Klinički značaj ovih nalaza ogleda se u potrebi sistematskog prepoznavanja i praćenja mentalnog zdravlja porodičnih negovatelja u okviru Službe kućnog lečenja. PHQ-9 se u ovom istraživanju pokazao kao praktičan i primenljiv instrument za rutinski skrining depresivnih simptoma, što je u skladu sa preporukama savremenih istraživanja o integraciji

for patients with dementia, with a prevalence of 68% [12]. Additionally, recent research indicates that greater burden and feelings of loneliness among female caregivers are significantly associated with the intensity of depressive symptoms, while a sense of life purpose may play a mediating role in this relationship [16].

The analysis of differences according to the patient's primary diagnosis did not reveal statistically significant differences in the level of depressive symptoms between groups. Although the medians were numerically higher among caregivers of patients with post-ICV and dementia, the observed differences did not reach statistical significance. This finding may be a consequence of the relatively small sample size and variability within groups. However, the numerical trend toward higher values among caregivers of patients with neurological diseases is consistent with previous studies indicating that neurocognitive disorders and sudden functional dependence of the patient represent a significant psychological burden for caregivers [4,15].

The secondary aim of the study referred to the association between depressive symptoms and caregivers' daily functioning. In the overall sample, a statistically significant weak positive correlation was found between PHQ-9 scores and the subjective assessment of the impact of symptoms on daily functioning. This finding indicates that as the intensity of depressive symptoms increases, the degree of impairment in caregivers' work, family, and social activities also increases. A similar association between psychological burden and reduced quality of life has been confirmed in previous meta-analyses [17].

In the subgroup analysis according to the patient's diagnosis, a moderate positive correlation was observed among caregivers of patients with post-ICV, with a level close to statistical significance. This trend may indicate a specific vulnerability of this group. The sudden onset of a cerebrovascular incident and the abrupt change in the patient's functional status may lead to intense psychological burden for family members who assume the caregiving role without prior preparation. In contrast, in chronic conditions such as dementia or malignant diseases, the longer disease course may allow gradual adaptation and the development of coping mechanisms. Similarly, pooled analyses of informal caregivers of individuals with severe mental disorders have shown that greater functional impairment of the care recipient and female sex are significantly associated with depressive symptoms, while longer disease duration is associated with a lower risk of depression, which is interpreted as a process of caregiver adaptation [18].

The clinical significance of these findings lies in the need for systematic recognition and monitoring of the mental health of family caregivers within home care

procene mentalnog zdravlja negovatelja u primarnu zdravstvenu zaštitu [6,19].

Ograničenje studije predstavlja relativno mali uzorak, posebno u podgrupama prema dijagnozi pacijenta, što može umanjiti statističku snagu analize i otežati detekciju značajnih razlika. Buduća istraživanja sa većim uzorkom i uključivanjem dodatnih sociodemografskih i psihosocijalnih varijabli mogla bi pružiti detaljniji uvid u faktore rizika za depresivne smetnje među porodičnim negovateljima. Istraživanja među negovateljima osoba sa demencijom pokazala su da su pojedini sociodemografski faktori, uključujući starost, obrazovanje i odnos sa pacijentom, značajno povezani sa psihološkim blagostanjem negovatelja, što dodatno opravdava potrebu za njihovim sistematskim ispitivanjem u budućim studijama [20].

ZAKLJUČAK

Rezultati ove studije pokazuju da su depresivni simptomi značajno prisutni među članovima porodica koji brinu o pacijentima uključenim u Službu kućnog lečenja, pri čemu je nešto više od trećine ispitanika imalo PHQ-9 skor ≥ 10 . Nivo depresivnih simptoma se nije razlikovao prema polu i primarnoj dijagnozi pacijenta, ali uočene razlike vrednosti ukupnog PHQ-9 skora ukazuju na moguće varijacije u opterećenju među podgrupama.

Pozitivna povezanost između intenziteta depresivnih simptoma i subjektivne procene narušenosti svakodnevnog funkcionisanja negovatelja ukazuje da porast depresivnih simptoma prati izraženiji uticaj na radne, porodične i socijalne aktivnosti negovatelja.

Dobijeni rezultati naglašavaju značaj sistematskog prepoznavanja i praćenja mentalnog zdravlja porodičnih negovatelja u okviru kućnog lečenja. PHQ-9 se pokazao kao praktičan i primenljiv instrument za skrining depresivnih simptoma u ovoj populaciji.

Imajući u vidu ograničenja studije, uključujući relativno manji broj ispitanika u pojedinim podgrupama, opravdana su buduća istraživanja sa većim uzorcima kako bi se potvrdili nalazi ove studije. Uključivanje šireg spektra sociodemografskih i psihosocijalnih varijabli mogla bi omogućiti preciznije sagledavanje faktora rizika i razvoj ciljanih intervencija podrške.

Sukob interesa: Nije prijavljen.

In this study, the PHQ-9 proved to be a practical and applicable instrument for routine screening of depressive symptoms, which is consistent with recommendations from contemporary research advocating the integration of caregiver mental health assessment into primary health care [6,19].

A limitation of this study is the relatively small sample size, particularly in the subgroups according to the patient's diagnosis, which may reduce the statistical power of the analysis and make detection of significant differences more difficult. Future studies with larger samples and the inclusion of additional sociodemographic and psychosocial variables could provide a more detailed insight into the risk factors for depressive symptoms among family caregivers. Studies among caregivers of persons with dementia have shown that certain sociodemographic factors, including age, education, and relationship with the patient, are significantly associated with caregivers' psychological well-being, which further justifies the need for their systematic investigation in future studies [20].

CONCLUSION

The results of this study show that depressive symptoms are significantly present among family members caring for patients enrolled in the Home Care Service, with slightly more than one-third of participants having a PHQ-9 score ≥ 10 . The level of depressive symptoms did not differ according to sex or the patient's primary diagnosis; however, observed differences in total PHQ-9 scores suggest possible variations in burden among subgroups.

The positive association between the intensity of depressive symptoms and the subjective assessment of impairment in caregivers' daily functioning indicates that an increase in depressive symptoms is accompanied by a more pronounced impact on caregivers' work, family, and social activities.

The obtained results emphasize the importance of systematic recognition and monitoring of the mental health of family caregivers within home care services. The PHQ-9 proved to be a practical and applicable instrument for screening depressive symptoms in this population.

Considering the limitations of the study, including the relatively small number of participants in certain subgroups, future research with larger samples is justified in order to confirm the findings of this study. The inclusion of a broader range of sociodemographic and psychosocial variables could enable a more precise identification of risk factors and the development of targeted support interventions.

Conflict of interest: None declared.

LITERATURA / REFERENCES

1. United Nations Department of Economic and Social Affairs. World population ageing 2020: highlights [Internet]. New York: United Nations; 2020 [cited 2025 Nov 24]. 40 p. Available from: https://digitallibrary.un.org/record/3898412/files/undesa_pd-2020_world_population_ageing_highlights.pdf
2. Kilmer G, Omura JD, Bouldin ED, Walker J, Spears K, Gore J, et al. Changes in health indicators among caregivers-United States, 2015–2016 to 2021–2022. *MMWR Morb Mortal Wkly Rep*. 2024 Aug 29;73(34):740–6. doi: 10.15585/mmwr.mm7334a2.
3. Lane NE, Hoben M, Amuah JE, Hogan DB, Baumbusch J, Gruneir A, et al. Prevalence and correlates of anxiety and depression in caregivers to assisted living residents during COVID-19: a cross-sectional study. *BMC Geriatr*. 2022 Aug 12;22(1):662. doi: 10.1186/s12877-022-03294-y.
4. Abdelhalim DS, Ahmed MM, Hussein HA, Khalaf OO, Sarhan MD. Burden of Care, Depression, and Anxiety Among Family Caregivers of People With Dementia. *J Prim Care Community Health*. 2024 Jan-Dec;15:21501319241288029. doi: 10.1177/21501319241288029.
5. Pan YC, Lin YS. Systematic Review and Meta-Analysis of Prevalence of Depression Among Caregivers of Cancer Patients. *Front Psychiatry*. 2022 May 12;13:817936. doi: 10.3389/fpsy.2022.817936.
6. World Health Organization. WHO calls for urgent transformation of care and support systems for older people [Internet]. Geneva: WHO; 2024 Oct 1 [cited 2025 Nov 24]. Available from: <https://www.who.int/news/item/01-10-2024-who-calls-for-urgent-transformation-of-care-and-support-systems-for-older-people>
7. Alaqeel M, Alkhathaami F, Alshangiti A, Alanazi A, Alothri MA, Alqarni AT, et al. Depression and Quality of Life Among Caregivers of Pediatric Cancer Patients. *Cureus*. 2022 Apr 18;14(4):e24256. doi: 10.7759/cureus.24256.
8. Polikandrioti M, Tsami A, Tsoulou V, Maggita A. Quality of Life, Anxiety, and Depression in Caregivers of Community-Dwelling Heart Failure Patients. *Healthcare (Basel)*. 2025 Aug 13;13(16):1986. doi: 10.3390/healthcare13161986.
9. Lin JD, Lin LP, Kuo MT, Hsu SW, Lee TN, Lai CI, et al. Assessment of the 9-item Patient Health Questionnaire (PHQ-9) as a screening tool for symptoms of depression in community caregivers for adults with intellectual disabilities. *Res Dev Disabil*. 2014 Jan;35(1):178–84. doi: 10.1016/j.ridd.2013.10.008.
10. Wan Ab Rahman WMA, Mazlan M. The Prevalence of Depression and Its Correlates Among Informal Caregivers of Stroke Patients in an Urban Community. *Cureus*. 2024 Jan 1;16(1):e51486. doi: 10.7759/cureus.51486.
11. Yan Y, Li M, Cai T, Wang X, Dong Y, Hu X, et al. Mood assessments of family caregivers of patients with severe brain injury in China. *Qual Life Res*. 2024 Feb;33(2):481–90. doi: 10.1007/s11136-023-03539-2.
12. Tan KP, Ang JK, Koh EBY, Pang NTP, Mat Saher Z. Relationship of Psychological Flexibility and Mindfulness to Caregiver Burden, and Depressive and Anxiety Symptoms in Caregivers of People with Dementia. *Int J Environ Res Public Health*. 2023 Feb 27;20(5):4232. doi: 10.3390/ijerph20054232.
13. Alemayehu TT, Geremew GW, Tegegne AA, Chanie GS, Walegn G, Nakie G, et al. The global prevalence of depression and its associated factors among caregivers of stroke survivors. Updated systematic review and meta-analysis. *J Public Health (Berl)*. 2025 Jun 28. doi: 10.1007/s10389-025-02501-5.
14. Habtie TE, Adisu MA, Feleke SF, Kitaw TA. Burden Beyond the Bedside: A Global Synthesis of Depression in Informal Cancer Caregivers: An Umbrella Review. *J Pain Symptom Manage*. 2026 Feb;71(2):e123–32. doi: 10.1016/j.jpainsymman.2025.10.033.
15. Soh XC, Hartanto A, Ling N, Reyes M, Sim L, Majeed NM. Prevalence of depression, anxiety, burden, burnout, and stress in informal caregivers: An umbrella review of meta-analyses. *Arch Gerontol Geriatr Plus*. 2025;2(3):100197. doi: 10.1016/j.aggp.2025.100197.
16. Aragonés Barberá I, Sanchis-Sanchis A, Morales-Murillo CP, Grau Sevilla MD; Familia y factores de riesgo y protección en discapacidad y psicopatología. Campus Capacitas. The effect of burden and loneliness on depression in female caregivers through purpose in life. *BMC Public Health*. 2025 Dec 8;26(1):168. doi: 10.1186/s12889-025-25882-4.
17. Gutiérrez-Sánchez B, Orgeta V, López-Martínez C, Del-Pino-Casado R. Association between Social Support and Depressive Symptoms in Informal Caregivers of Adult and Older Dependents: A Systematic Review and Meta-Analysis. *J Clin Med*. 2023 Oct 11;12(20):6468. doi: 10.3390/jcm12206468.
18. Liang Q, Xu M, Qiu L, Liu Y, Tian Y, Zuo X, et al. Prevalence and associated factors of burden, depression, and anxiety among informal caregivers of individuals with severe mental disorders within the “686 program”: a community-based cross-sectional study. *Soc Psychiatry Psychiatr Epidemiol*. 2026 Jan 29. doi: 10.1007/s00127-025-03040-w.
19. Alreshidi SM. Psychometric properties of the Patient Health Questionnaire-9 for Saudi Caregivers: A Cross-Sectional Study in Saudi Arabia. *Inquiry*. 2024 Jan-Dec;61:469580231221287. doi: 10.1177/00469580231221287.
20. Tatomirescu LF, Glavce CS, Prada GI, Borosanu A, Turcu S. Socio-demographic factors linked to psychological well-being in dementia caregivers. *Healthcare (Basel)*. 2025 Sep 7;13(17):2235. doi: 10.3390/healthcare13172235.

UTICAJ GEOMETRIJE LEVE KOMORE, ISKAZANE DEBLJINOM INTERVENTRIKULARNOG SEPTUMA I ZADNJEG ZIDA KOMORE, NA ISHOD AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA

ORIGINALNI RAD

ORIGINAL ARTICLE

IMPACT OF LEFT VENTRICULAR GEOMETRY, EXPRESSED AS INTERVENTRICULAR SEPTAL AND POSTERIOR WALL THICKNESS, ON THE OUTCOME OF ACUTE ISCHEMIC STROKE

Dejan Munjiza¹, Biljana Georgievski-Brkić^{1,2}, Filip Vitošević¹, Ljubica Dimitrijević¹, Marjana Vukićević^{1,2}

¹ Specijalna bolnica „Sveti Sava“, Beograd, Srbija

¹ Special Hospital Sveti Sava, Belgrade, Serbia

² Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Kragujevac, Srbija

² University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia

SAŽETAK

Uvod/Cilj: Značajni udeo zdravstvenog opterećenja stanovništva obuhvata akutni moždani udar. Varijable dobijene transtorakalnom ehokardiografijom predstavljaju jasne prediktore ishoda kardioloških oboljenja, ali je i sve više dokaza o njihovom značaju u predviđanju ishoda neuroangioloških oboljenja.

Cilj rada jeste da se dokaže hipoteza da je promena geometrije leve komore iskazana porastom dimenzije zidova leve komore primenljiv marker lošeg ishoda akutnog moždanog udara.

Materijali i metode: Metodologija je bazirana na analizi ultrazvučnih varijabli 167 pacijenata koji su pretrpeli akutni moždani udar ishemijske geneze, uz analizu varijabli modifikovanog Rankin skora definisanog pri otpustu sa lečenja, a kao pokazatelj ishoda bolesti u funkcionalnom smislu.

Rezultati: Rad ukazuje na korelaciju između debljine kako interventrikularnog septuma tako i zadnjeg zida leve komore sa jedne i funkcionalnog stanja bolesnika, sa druge strane. Hipoteza se pokazala tačnom, odnosno porastom dijametra interventrikularnog septuma i/ili zadnjeg zida leve komore, raste i mogućnost lošijeg ishoda bolesti.

Zaključak: Oba praćena parametra pokazuju pozitivnu prediktivnu vrednost u odnosu na stepen funkcionalnosti pacijenata pri otpustu.

Ključne reči: moždani udar, promena geometrije leve komore, ehokardiografija

ABSTRACT

Introduction/Objective: Acute stroke represents a significant component of the overall health burden of the population. Parameters obtained by transthoracic echocardiography are well-established predictors of outcomes in cardiovascular diseases, while increasing evidence indicates their importance in predicting outcomes in neurovascular disorders.

This study aims to test the hypothesis that changes in left ventricular geometry, expressed as an increase in left ventricular wall thickness, represent a useful marker of poor outcome in patients with acute ischemic stroke.

Materials and methods: The methodology was based on the analysis of echocardiographic variables in 167 patients with acute ischemic stroke, together with variables of the modified Rankin Scale assessed at hospital discharge, used as an indicator of functional outcome.

Results: The study indicates a correlation between the thickness of both the interventricular septum and the posterior wall of the left ventricle, on the one hand, and the functional status of patients, on the other. The results confirmed the study hypothesis, demonstrating that an increase in interventricular septal thickness and/or posterior left ventricular wall thickness is associated with a higher probability of unfavorable outcome.

Conclusion: Both evaluated echocardiographic parameters showed positive predictive value in relation to functional outcomes.

Keywords: stroke, changes in left ventricular geometry, echocardiography

Autor za korespondenciju:
Dejan Munjiza
Specijalna bolnica „Sveti Sava“
Nemanjina 2, 11000 Beograd, Srbija
Elektronska adresa: munjizad@gmail.com

Corresponding author:
Dejan Munjiza
Special Hospital Sveti Sava
2 Nemanjina Street, 11000 Belgrade, Serbia
E-mail: munjizad@gmail.com

Primljeno • Received: February 2, 2026; Revidirano • Revised: March 5, 2026; Prihvaćeno • Accepted: March 10, 2026; Online first: March 25, 2026

DOI: 10.5937/smcl7-64559

UVOD

Moždani udar i dalje zauzima drugo mesto na skali uzroka smrtnosti, a na globalnom nivou predstavlja treći po učestalosti zajednički uzrok smrti i invaliditeta [1]. Nadalje, postojeće prognoze upućuju na dalji rast stope incidencije ovog oboljenja u tekućoj deceniji, odnosno do 2030. godine, prvenstveno u zemljama sa niskim dohotkom, i to bez razlike u odnosu na pol ili godine [2]. Broj novoobolelih sa moždanim udarom raste od 1990. godine, uporedo sa povećanjem smrtnosti, a u istom razdoblju su se smanjile stope incidencije standardizovane prema starosti [3]. Pregled meta-analiza pokazuje da je u Evropi incidencija moždanog udara oko 191,9 na 100.000 osoba-godina uz prevalenciju koja je procenjena na oko 9,1% kod muškaraca i oko 9,2% kod žena, uz trend porasta [4]. Ova bolest predstavlja četvrti uzrok smrtnosti u Sjedinjenim Američkim Državama [5].

Klasični faktori rizika ateroskleroze predstavljaju ujedno i faktore rizika ishemijskog moždanog udara, pa ne čudi činjenica da moždani udar u ogromnoj većini slučajeva prati više kardioloških komorbiditeta. Otuda ideja da osnovne varijable geometrije miokarda leve komore dobijene transtorakalnom ehokardiografijom, odnosno debljinu interventrikularnog septuma (IVS) i zadnjeg zida (ZZ) leve komore, procenimo kao potencijalne prediktore ishoda kod akutnog moždanog udara.

Cilja rada je da se proceni povezanost debljine interventrikularnog septuma (IVS) i zadnjeg zida (ZZ) leve komore, kao „sirovih“ i svima dostupnih *bed-side* ehokardiografskih parametara, a koji ne zahtevaju sofisticiranije kompjuterske programe, sa ishodom lečenih pacijenata sa moždanim udarom ishemijskog tipa. Ovo je učinjeno testiranjem hipoteze da je povećana debljina interventrikularnog septuma (IVS) i zadnjeg zida (ZZ) leve komore potencijalni pokazatelj ishoda ovog oboljenja.

MATERIJALI I METODE

Svi podaci su prikupljeni retrospektivno, nakon okončanja hospitalizacije, iz bolničke medicinske dokumentacije, za ukupno 167 bolesnika lečenih od akutnog ishemijskog moždanog udara u Jedinici intenzivne nege nivoa III Specijalne bolnice „Sveti Sava“, i to u periodu od 1. septembra 2024. godine do 1. septembra 2025. godine. Pored opštih demografskih odrednica uzorka (pol i starost ispitanika), uzeti su i podaci o klasičnim faktorima rizika uz ispitivane parametre transtorakalnih ehokardiografskih studija, odnosno debljine interventrikularnog septuma (IVS) i zadnjeg zida (ZZ) leve komore, merenih na parasternalnom uzdužnom preseku (engl. *parasternal long axis* – PLAX).

Ostvareni rezultati lečenja ispitanika, procenjeni primenom modifikovane Rankin skale pri otpustu

INTRODUCTION

Stroke remains the second leading cause of mortality and, globally, represents the third most common combined cause of death and disability [1]. Furthermore, current projections indicate a continued increase in the incidence of this disease during the present decade, up to 2030, primarily in low-income countries and without significant differences with respect to sex or age [2]. Since 1990, the number of newly diagnosed stroke cases has been increasing in parallel with mortality, although age-standardized incidence rates have decreased over the same period [3]. A review of meta-analyses indicates that, in Europe, the incidence of stroke is approximately 191.9 per 100,000 person-years, with prevalence estimated at about 9.1% in men and 9.2% in women, and with a continuing upward trend [4]. Stroke represents the fourth leading cause of death in the United States [5].

Classical risk factors for atherosclerosis are also major risk factors for ischemic stroke; therefore, it is not surprising that in the vast majority of cases multiple cardiological comorbidities accompany stroke. This fact prompted the idea of evaluating basic parameters of left ventricular myocardial geometry obtained by transthoracic echocardiography – namely, the thickness of the interventricular septum (IVS) and of the left ventricular posterior wall (PW), as potential predictors of outcome in acute stroke.

The present study aims to assess the association between the thickness of the interventricular septum (IVS) and the posterior wall (PW) of the left ventricle, as “raw” and universally available bedside echocardiographic parameters that do not require more sophisticated computer programs, and the outcome of patients treated for ischemic stroke. This was done by testing the hypothesis that increased IVS thickness and left ventricular PW thickness are potential indicators of the outcome of this disease.

MATERIALS AND METHODS

Data were collected retrospectively from hospital medical records, after patient discharge, for a total of 167 patients treated for acute ischemic stroke in the Level III Intensive Care Unit of the Special Hospital *Sveti Sava*, between September 1, 2024 and September 1, 2025. In addition to the general demographic sample characteristics (sex and age of the participants), data were also collected regarding classical risk factors along with the examined parameters of transthoracic echocardiographic studies, namely the interventricular septum (IVS) thickness and the thickness of the left ventricular posterior wall (PW), measured in the parasternal long-axis view (PLAX).

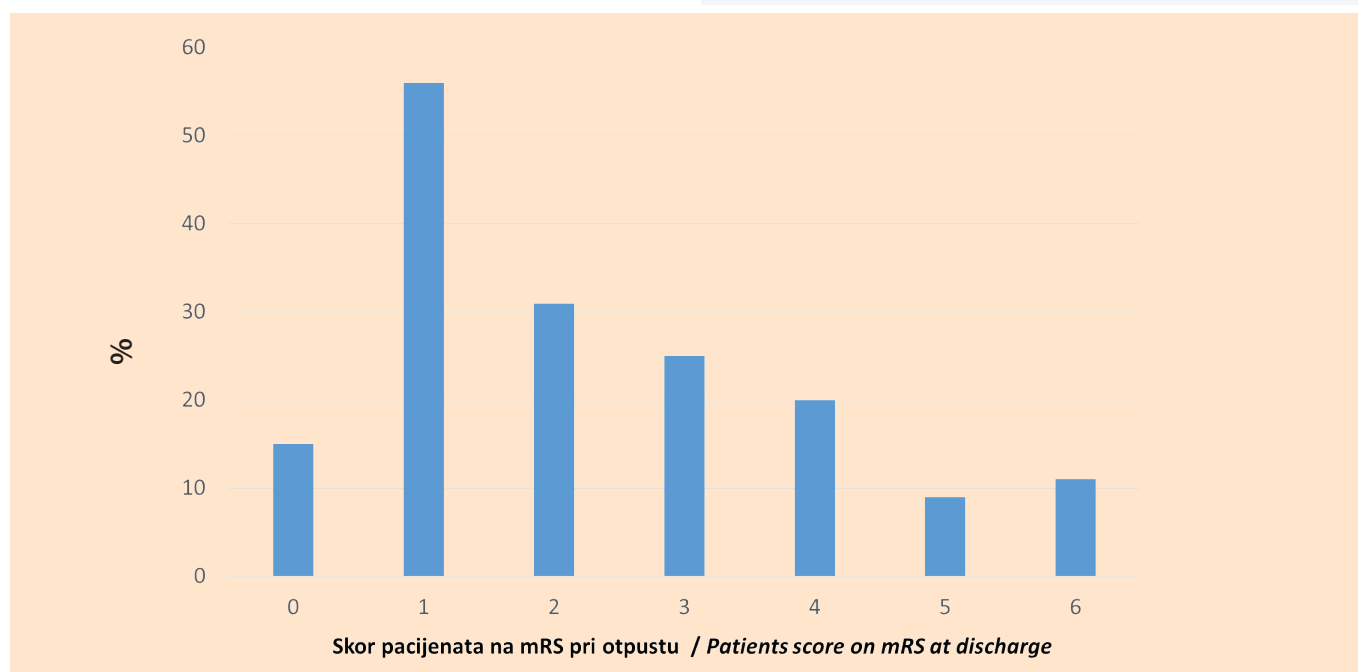
Tabela 1. Raspodela odgovora na modifikovanoj Rankin skali (mRS)

mRS	Opis / Description - Levels	n (%)
0	Potpuni oporavak / No symptoms at all	15 (9.0%)
1	Bez značajne onesposobljenosti – pacijent sposoban za obavljanje svih aktivnosti / No significant disability: despite symptoms, able to carry out all usual duties and activities	56 (33.4%)
2	Laka onesposobljenost – pacijent sposoban za samozbrinjavanje ali ne i za sve premorbidne aktivnosti / Slight disability: unable to perform all previous activities but able to look after own affairs without assistance	31 (18.6%)
3	Umerena onesposobljenost – pacijentu je neophodna pomoć ali je sposoban za samostalni hod / Moderate disability: requiring some help but able to walk without assistance	25 (15.0%)
4	Umereno teška onesposobljenost – pacijent nije sposoban za samostalni hod / Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance	20 (12.0%)
5	Teška onesposobljenost – pacijent je nepokretan i kompletno zavisao od tuđe nege i pomoći / Severe disability: bedridden, incontinent and requiring constant nursing care and attention	9 (5.4%)
6	Smrtni ishod – pacijent je preminuo / Death	11 (6.6%)
UKUPNO / TOTAL		167 (100%)

iz bolnice, predstavljali su obeležje ishoda oboljenja, s obzirom da je navedena skala najučestaliji klinički alat za procenu stepena invaliditeta nakon moždanog udara. Sve ultrazvučne preglede obavio je iskusni kardiolog – ehokardiografista u prvih 72 sata od prijema na Odeljenje intenzivne nege, aparatom GE LOGIQ S8. **Tabela 1** razvrstava ispitanike prema njihovom skor na modifikovanoj Rankin skali (mRS), dok **Grafikon 1** predstavlja grafički prikaz distribucije bolesnika prema ovoj karakteristici.

Table 1. Distribution of responses on the Modified Rankin scale (mRS)

The achieved patient treatment outcomes were assessed using the modified Rankin Scale at hospital discharge and were taken to represent the indicator of disease outcome, as this scale is the most commonly used clinical tool for assessing the degree of disability after stroke. All ultrasound examinations were performed by an experienced cardiologist–echocardiographer within the first 72 hours after admission to the Intensive Care Unit, using a GE LOGIQ S8 device. **Table 1** classifies the participants according to their score on the modified Rankin



Grafikon 1. Prikaz raspodele subjekata (relativna učestalost) po grupama modifikovane Rankin skale

Figure 1. Relative frequency distribution of modified Rankin Scale categories

Opis podataka je predstavljen u formi apsolutne i relativne učestalosti (n,%) uz primenu aritmetičke sredine sa standardnom devijacijom (as ± sd) ili medijane (opseg, min – max), što su diktirali statistički oblik i raspodela promjenljivih. Povezanost stepena ishoda oboljenja sa ispitivanim ehokardiografskim statističkim karakteristikama je ocenjena upotrebom Spearmanovog koeficijenta korelacije. Za proveru statističke značajnosti radnih hipoteza uzet je alfa nivo od 0,05. Za statističku analizu podataka korišćen je programski alat IBM SPSS Statistics 24 (SPSS Inc, Chicago, IL, USA).

REZULTATI

Analizom je obuhvaćeno ukupno 167 pacijenata lečenih od akutnog ishemijskog moždanog udara. Prosek starosti uzorka je bio oko 67 godina (67,1 godina sa standardnom devijacijom 12,2 godina), od čega je 108 ispitanika bilo muškog a 59 ženskog pola. Najstariji bolesnik je imao 91 godinu, a najmlađi 35 godina. Demografski opis uzorka i raspodela faktora rizika predstavljeni su u Tabeli 2. Svi analizirani subjekti su imali urađenu transtorakalnu ehokardiografsku studiju kojom je meren dijametar interventrikularnog septuma (IVS) i zadnjeg zida (ZZ) leve komore po standardima Američkog društva ehokardiografista (engl. *American Society of Echocardiography – ASE*) i Evropskog udruženja za kardiovaskularni imidžing (engl. *European Association of Cardiovascular Imaging – EACVI*). Prosečne vrednosti za obe varijable sa standardnim devijacijama su prikazane u Tabeli 3.

Dijametar IVS, definisan prema ASE/EACVI preporukama kao univerzalni i široko rasprostranjeni marker geometrije leve komore, korišćen je kao determinanta ishoda oboljenja posmatranog uzorka. Testiranje rezultata lečenja prema dijametru IVS/ZZ je sprovede-

Scale (mRS), while Figure 1 is a graphical representation of the distribution of patients according to this characteristic.

The description of the data is presented in the form of absolute and relative frequencies (n, %) with the use of the arithmetic mean with standard deviation (mean ± SD) or the median (range, min-max), as dictated by the statistical form and distribution of the variables. The association between the degree of disease outcome and the examined echocardiographic statistical characteristics was evaluated using Spearman's correlation coefficient. For testing the statistical significance of the working hypotheses, an alpha level of 0.05 was used. The IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA) software was used for statistical data analysis.

RESULTS

The analysis included a total of 167 patients treated for acute ischemic stroke. The average age of the sample was approximately 67 years (67.1 years with a standard deviation of 12.2 years), of whom 108 were male, and 59 were female. The oldest patient was 91 years old, while the youngest was 35 years old. The demographic characteristics of the sample and the distribution of risk factors are presented in Table 2. All analyzed subjects underwent a transthoracic echocardiographic study wherein the diameter of the interventricular septum (IVS) and of the left ventricular posterior wall (PW) were measured according to the standards of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI). The mean values for both variables with standard deviations are presented in Table 3.

The IVS diameter, defined in keeping with ASE/EACVI recommendations as a universal and widely used marker of left ventricular geometry, was used as a

Tabela 2. Demografske varijable, faktori rizika i medijana ishoda bolesti

Variable / Variables	
Pol, n (%) / Sex, n (%)	
muški / male	108 (64.7%)
ženski / female	59 (35.3%)
Starost, as ± sd / Age, mean ± sd	67.1 ± 12.2
Hipertenzija, n (%) / Hypertension, n (%)	152 (91%)
Atrijalna fibrilacija, n (%) / Atrial fibrillation, n (%)	60 (35.9%)
Diabetes mellitus, n (%) / Diabetes mellitus, n (%)	45 (26.9%)
Hiperlipidemija, n (%) / Hyperlipidemia, n (%)	43 (25.7%)
Pušenje, n (%) / Smoking, n (%)	57 (34.1%)
Zloupotreba alkohola, n (%) / Alcohol abuse, n (%)	9 (5.4%)
Gojaznost, n (%) / Obesity, n (%)	16 (9.6%)
Skor na Rankin skali, medijana (opseg) / Score on the Rankin scale, median (range)	2 (0–6)

Table 2. Demographic variables, risk factors and median score of disease outcome

Tabela 3. Ehokardiografski parametri

Varijable / Variables	as $\pm$ sd / Mean $\pm$ sd	Minimum	Maximum
IVS, as $\pm$ sd / IVS, mean $\pm$ sd	10.18 $\pm$ 2.57	7	17
ZZLK, as $\pm$ sd / LVPW, mean $\pm$ sd	9.85 $\pm$ 2.77	7	19

IVS – interventrikularni septum; ZZLK – zadnji zid leve komore

Table 3. Echocardiographic parameters

Varijable / Variables	as $\pm$ sd / Mean $\pm$ sd	Minimum	Maximum
IVS, as $\pm$ sd / IVS, mean $\pm$ sd	10.18 $\pm$ 2.57	7	17
ZZLK, as $\pm$ sd / LVPW, mean $\pm$ sd	9.85 $\pm$ 2.77	7	19

IVS – interventricular septum; LVPW – left ventricular posterior wall

Tabela 4. Spirmanov koeficijent i verovatnoća

Varijable / Variables	Povezanost / Mean $\pm$ sd	Skor na modifikovanoj Rankin skali / Modified Rankin scale score
IVS / IVS	r_s	0,91
	p	0,01
ZZLK / LVPW	r_s	0,88
	p	0,01

IVS – interventrikularni septum; ZZLK – zadnji zid leve komore

Table 4. Spearman's correlation coefficients and p-values

Varijable / Variables	Povezanost / Mean $\pm$ sd	Skor na modifikovanoj Rankin skali / Modified Rankin scale score
IVS / IVS	r_s	0,91
	p	0,01
ZZLK / LVPW	r_s	0,88
	p	0,01

IVS – interventricular septum; LVPW – left ventricular posterior wall

no upotrebom neparametarske korelacije navedenih varijabli i krajnjeg dobijenog skora na modifikovanoj Rankin skali.

Analizom, putem Spirmanove korelacije, pokazan je značajan stepen korelacije između ishoda bolesti i dijametra IVS sa pozitivnim predznakom ($r_s = 0,91$; $p = 0,01$; **Tabela 4**), odnosno, da lošija geometrija leve komore, izražena porastom dijametra IVS, povećava stepen funkcionalne onesposobljenosti bolesnika nakon akutnog ishemijskog moždanog udara.

Dijametar posteriornog zida leve komore, definisan po istim preporukama, takođe je testiran kao potencijalna varijabla prognoze kliničkog ishoda. I ovde, veća vrednost varijable značajno korelira sa višim stepenom Rankin skora ($r_s = 0,88$; $p = 0,01$; **Tabela 4**), odnosno veći dijametar zadnjeg zida leve komore sugerise nepovoljniji klinički tok kod pacijenata sa akutnim ishemijskim moždanim udarom.

DISKUSIJA

Ispitivanje je obuhvatilo 167 bolesnika oba pola, sa akutnim ishemijskim moždanim udarom, uz dominaciju muškaraca (64,7%). Ukupna prosečna starost pacijenata je bila oko 67 godina.

Među prikupljenim, poređenim i analiziranim ultrazvučnim obeležjima ovog uzorka, kao pokazatelji lošeg kliničkog ishoda sa statistički relevantnim stepenom pozitivne povezanosti su se pokazali i dijametar interventrikularnog septuma kao i dijametar zadnjeg zida leve komore, definisani standardima Američkog društva ehokardiografista (ASE) i Evropskog udruženja za kardiovaskularni imidžing (EACVI) [6,7]. Dakle, po-

determinant of disease outcome in the observed sample. Testing of treatment outcomes in relation to the IVS/PW diameter was carried out using non-parametric correlation between these variables and the final obtained score on the modified Rankin Scale.

Spearman's correlation analysis showed a significant degree of correlation between disease outcome and the IVS diameter, with a positive correlation coefficient ($r_s = 0,91$; $p = 0,01$; **Table 4**), indicating that poorer left ventricular geometry, expressed by an increase in IVS diameter, increases the degree of functional disability of patients after acute ischemic stroke.

The diameter of the posterior left ventricular wall, defined in keeping with the same recommendations, was also tested as a potential variable for the prognosis of clinical outcome. Here also, a higher value of the variable significantly correlated with a higher score on the modified Rankin Scale ($r_s = 0,88$; $p = 0,01$; **Table 4**), i.e., a larger diameter of the left ventricular posterior wall suggested a less favorable clinical course in patients with acute ischemic stroke.

DISCUSSION

The study included 167 patients of both sexes with acute ischemic stroke, with a predominance of men (64.7%). The overall mean age of the patients was approximately 67 years.

Among the collected, compared, and analyzed ultrasound characteristics of this sample, the diameter of the interventricular septum as well as the diameter of the posterior wall of the left ventricle, defined by the standards of the American Society of Echocardiography

rast debljine kako interventrikularnog septuma tako i zadnjeg zida leve komore povećava stepen funkcionalne onesposobljenosti bolesnika nakon akutnog ishemijskog moždanog udara.

U savremenim uslovima, u većini radova se kao osnovni markeri geometrije leve komore koriste jasno definisani parametri kao što su masa leve komore ili relativna debljina zida leve komore (engl. *left ventricular relative wall thickness - LV RWT*), što je svakako ispravnije jer bolje prognostički korelira sa ishodima kardiovaskularnih bolesti [8–12], ali zahteva sofisticiranije ehokardiografske softvere i nije primenjivo za *bed-side* preglede kakvi su kod akutnog moždanog udara najizvodljiviji zbog stanja bolesnika. Drugi motiv za rad sa bazičnim podacima je činjenica da su upravo sirovi podaci o debljini IVS analizirani i od strane drugih autora kod bolesnika sa hipertenzijom [13], koja se tradicionalno smatra najdefinisanijim faktorom rizika od moždanog udara. Pokazano je da povećana debljina interventrikularnog septuma predstavlja nezavisan i značajan prediktor budućeg razvoja koronarne bolesti i infarkta miokarda. Takođe, u populaciji pacijenata sa atrijalnom fibrilacijom uključenih u *Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)* studiju, hipertrofija leve komore (engl. *left ventricular hypertrophy - LVH*) definisana kao umereno ili znatno uvećana debljina interventrikularnog septuma pokazala se kao prediktor ukupnog mortaliteta i moždanog udara, nezavisno od klasičnih kliničkih faktora rizika, dok je definicija hipertrofije leve komore bazirana na debljini IVS imala jaču i konzistentniju prognostičku vrednost u poređenju sa samom masom leve komore [14].

U opštoj populaciji, povećana masa leve komore procenjena ehokardiografski, predstavlja nezavisan i snažan prediktor nepovoljnih kardiovaskularnih ishoda, uključujući incidentne kardiovaskularne događaje i ukupni mortalitet, čak i nakon korekcije za tradicionalne faktore rizika [15].

Manji je broj studija koje se bave direktnim uticajem debljine interventrikularnog septuma i/ili zadnjeg zida leve komore na ishod pacijenata obolelih od akutnog ishemijskog moždanog udara, ali one postoje i uglavnom se baziraju na naprednijim podacima geometrije ili na ocenu globalne sistolne funkcije leve komore. Studija koju su sprovedli Adeoje i saradnici pokazuje da se debljina interventrikularnog septuma razlikovala kod pacijenata sa ishemijskim moždanim udarom, ali nije identifikovana kao nezavisni prediktor ishoda nakon akutnog moždanog udara [16]. Napominjemo da je u ovoj studiji, analiziran ishod u kraćem, jednomesečnom periodu nakon ishemijskog moždanog udara kod populacije koja je mlađa od populacije naše studije, te da je istraživanje sprovedeno u

(ASE) and the European Association of Cardiovascular Imaging (EACVI) [6,7], proved to be indicators of poor clinical outcome with a statistically relevant degree of positive association. Thus, an increase in the thickness of both the interventricular septum and the left ventricular posterior wall increases the degree of functional disability of patients after acute ischemic stroke.

In most modern studies, clearly defined parameters such as left ventricular mass or left ventricular relative wall thickness (LV RWT) are used as the basic markers of left ventricular geometry, which is certainly more appropriate because it better correlates prognostically with the outcomes of cardiovascular diseases [8–12]. However, such diagnostics requires more sophisticated echocardiographic software and is not applicable for bedside examinations such as those that are most feasible in acute stroke due to the condition of the patient. Another motive for working with basic data is the fact that raw data on IVS thickness have also been analyzed by other authors in patients with hypertension [13], which is traditionally considered the most clearly defined risk factor for stroke. It has been shown that increased interventricular septum thickness represents an independent and significant predictor of the future development of coronary disease and myocardial infarction. Furthermore, in the population of patients with atrial fibrillation included in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, left ventricular hypertrophy (LVH), defined as moderately or markedly increased interventricular septum thickness, proved to be a predictor of overall mortality and stroke, independent of classical clinical risk factors, while the definition of left ventricular hypertrophy based on IVS thickness had stronger and more consistent prognostic value compared with left ventricular mass alone [14].

In the general population, increased left ventricular mass assessed echocardiographically represents an independent and powerful predictor of adverse cardiovascular outcomes, including incident cardiovascular events and overall mortality, even after adjustment for traditional risk factors [15].

There are fewer studies dealing with the direct impact of interventricular septum thickness and/or left ventricular posterior wall thickness on the outcome of patients with acute ischemic stroke, but they do exist and are generally based on more advanced geometric data or on the assessment of left ventricular global systolic function. A study conducted by Adeoje et al. showed that interventricular septum thickness differed in patients with ischemic stroke, but it was not identified as an independent predictor of outcome after acute stroke [16]. We note that in this study the outcome was

Africi. Drugi autori, dolaze do podataka koji su u skladu sa našim istraživanjem, odnosno da je povećana relativna debljina zida leve komore (LV RWT) bila povezana sa višom smrtnošću nakon ishemijskog moždanog udara, što sugerise da promene u strukturi leve komore, uključujući zadebljanje zidova, imaju prognostičku važnost [17]. Povezanost sa našim rezultatima se ogleda u činjenici da se LV RWT, između ostalog, računa u dimenziji zadnjeg zida leve komore.

Slična istraživanja su rađena i kod bolesnika sa hemoragijskim moždanim udarom, koji nisu bili uključeni u naše istraživanje, ali ih navodimo s obzirom da u ovoj varijanti moždanog udara, po dostupnoj literaturi, debljina interventrikularnog septuma i debljina zadnjeg zida leve komore nisu pokazale značajnu povezanost sa ishodom bolesti [18].

ZAKLJUČAK

Oba ciljana ultrazvučna parametara pokazuju značajnu pozitivnu prediktivnu vrednost za ishod bolesti. Naime, među analiziranim kategorijama bolesnika, postoji statistički značajna povezanost između dijametara, kako interventrikularnog septuma tako i posteriornog zida leve komore, sa postignutim ishodom lečenja akutnog ishemijskog moždanog udara, ocenjenog putem modifikovan Rankin skale, i to tako što porast debljine zidova leve komore favorizuje lošiji funkcionalni ishod moždanog udara.

Moždani udar, kao deo spektra kardiovaskularnih bolesti, retko se javlja izolovano od kardioloških komorbiditeta, koji sami po sebi utiču na način lečenja osnovne bolesti. Danas je terapija vođena savremenim algoritmima ali je i dalje akcenat na individualizaciji, koju diktiraju patofiziologija svih paralelnih komorbiditeta i druge specifičnosti svakog bolesnika. Moždani udar je, dakle, uobičajeno multimorbidno stanje gde postoji međusobna interakcija patoloških stanja, usled čega postoji potreba za multidisciplinarnim pristupom dijagnostici, lečenju i proceni prognoze bolesnika.

SPIŠAK SKRAĆENICA

IVS – interventrikularni septum

ZZ – zadnji zid (leve komore)

PLAX – parasternalni uzdužni presek (engl. *parasternal long axis*)

ASE – Američko društvo ehokardiografista (engl. *American Society of Echocardiography*)

EACVI – Evropsko udruženje za kardiovaskularni imidžing (engl. *European Association of Cardiovascular Imaging*)

LV RWT – relativna debljina zida leve komore (engl. *left ventricular relative wall thickness*)

Sukob interesa: Nije prijavljen.

analyzed in a shorter, one-month period after ischemic stroke in a population that was younger than the population of our study, and that the research was conducted in Africa. Other authors have obtained data consistent with our research, namely that increased left ventricular relative wall thickness (LV RWT) was associated with higher mortality after ischemic stroke, suggesting that changes in the structure of the left ventricle, including wall thickening, have prognostic significance [17]. The association with our results is reflected in the fact that LV RWT, among other things, is calculated using the dimension of the posterior wall of the left ventricle.

Similar studies have also been conducted in patients with hemorrhagic stroke, who were not included in our research, but we mention them given that in this variant of stroke, according to the available literature, the thickness of the interventricular septum and the thickness of the left ventricular posterior wall did not show a significant association with disease outcome [18].

CONCLUSION

Both targeted ultrasound parameters show significant positive predictive value for the disease outcome. Namely, among the analyzed categories of patients, there is a statistically significant association between the diameters of both the interventricular septum and the left ventricular posterior wall and the achieved outcome of treatment of acute ischemic stroke, as assessed using the modified Rankin scale. The association is such that an increase in the thickness of the walls of the left ventricle favors a poorer functional outcome of stroke.

Stroke, as part of the spectrum of cardiovascular diseases, rarely occurs isolated from cardiological comorbidities, which themselves influence the manner of treatment of the underlying disease. Today, therapy is guided by modern algorithms, but the emphasis is still on individualization, which is dictated by the pathophysiology of all parallel comorbidities and other specific characteristics of each patient. Stroke is therefore commonly a multimorbid condition wherein there is interaction between pathological states, which creates the need for a multidisciplinary approach to the diagnosis, treatment, and assessment of patient prognosis.

LIST OF ABBREVIATIONS/ACRONYMS

IVS – interventricular septum

PW – posterior wall (of the left ventricle)

PLAX – parasternal long axis

ASE – American Society of Echocardiography

EACVI – European Association of Cardiovascular Imaging

LV RWT – left ventricular relative wall thickness

Conflict of interest: None declared

LITERATURA / REFERENCES

- Feigin VL, Brainin M, Norrving B, Martins SO, Pandian J, Lindsay P, et al. World Stroke Organization: Global Stroke Fact Sheet 2025. *Int J Stroke*. 2025 Feb;20(2):132-44. doi: 10.1177/17474930241308142.
- Pu L, Wang L, Zhang R, Zhao T, Jiang Y, Han L. Projected Global Trends in Ischemic Stroke Incidence, Deaths and Disability-Adjusted Life Years From 2020 to 2030. *Stroke*. 2023 May;54(5):1330-9. doi: 10.1161/STROKEA-HA.122.040073. Erratum in: *Stroke*. 2024 Jan;55(1):e23. doi: 10.1161/STR.0000000000000452.
- GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021 Oct;20(10):795-20. doi: 10.1016/S1474-4422(21)00252-0.
- Soto A, Guillén-Grima F, Morales G, Muñoz S, Aguinaga-Ontoso I, Fuentes-Aspe R. [Prevalence and incidence of ictus in Europe: systematic review and meta-analysis]. *An Sist Sanit Navar*. 2022 Apr 28;45(1):e0979. Spanish. doi: 10.23938/ASSN.0979.
- Imoisili OE, Chung A, Tong X, Hayes DK, Loustalot F. Prevalence of Stroke - Behavioral Risk Factor Surveillance System, United States, 2011-2022. *MMWR Morb Mortal Wkly Rep*. 2024 May 23;73(20):449-55. doi: 10.15585/mmwr.mm7320a1.
- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015 Jan;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016 Apr;29(4):277-314. doi: 10.1016/j.echo.2016.01.011.
- Ghali JK, Liao Y, Cooper RS. Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. *J Am Coll Cardiol*. 1998 Jun;31(7):1635-40. doi: 10.1016/s0735-1097(98)00131-4.
- Yamaguchi S, Shimabukuro M, Abe M, Arakaki T, Arasaki O, Ueda S. Comparison of the prognostic values of three calculation methods for echocardiographic relative wall thickness in acute decompensated heart failure. *Cardiovasc Ultrasound*. 2019 Dec 3;17(1):30. doi: 10.1186/s12947-019-0179-6.
- Zhang Y, Qiao S, Hao H, Li Q, Bao X, Wang K, et al. The predictive value of relative wall thickness on the prognosis of the patients with ST-segment elevation myocardial infarction. *BMC Cardiovasc Disord*. 2023 Jul 31;23(1):383. doi: 10.1186/s12872-023-03379-5.
- Sun D, Schaff HV, Nishimura RA, Geske JB, Dearani JA, Ducharme MT, et al. Posterior Wall Thickness Associates With Survival Following Septal Myectomy for Obstructive Hypertrophic Cardiomyopathy. *JACC Heart Fail*. 2022 Nov;10(11):831-7. doi: 10.1016/j.jchf.2022.06.009.
- Gardin JM. The Value of Left Ventricular Relative Wall Thickness in Predicting Ventricular Arrhythmia and Related Death. *J Am Coll Cardiol*. 2016 Jan 26;67(3):313-5. doi: 10.1016/j.jacc.2015.10.078.
- Yang Y, Li Z, Guo X, Zhou Y, Chang Y, Yang H, et al. Interventricular Septum Thickness for the Prediction of Coronary Heart Disease and Myocardial Infarction in Hypertension Population: A Prospective Study. *J Clin Med*. 2022 Dec 1;11(23):7152. doi: 10.3390/jcm11237152.
- Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Left ventricular geometry and outcomes in patients with atrial fibrillation: the AFFIRM Trial. *Int J Cardiol*. 2014 Jan 1;170(3):303-8. doi: 10.1016/j.ijcard.2013.11.002.
- Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990 May 31;322(22):1561-6. doi: 10.1056/NEJM199005313222203.
- Adeoye AM, Ovbiagele B, Akinyemi JO, Ogah OS, Akinyemi R, Gebregziabher M, et al. Echocardiographic Abnormalities and Determinants of 1-Month Outcome of Stroke Among West Africans in the SIREN Study. *J Am Heart Assoc*. 2019 Jun 4;8(11):e010814. doi: 10.1161/JAHA.118.010814.
- Park CS, Park JB, Kim Y, Yoon YE, Lee SP, Kim HK, et al. Left Ventricular Geometry Determines Prognosis and Reverse J-Shaped Relation Between Blood Pressure and Mortality in Ischemic Stroke Patients. *JACC Cardiovasc Imaging*. 2018 Mar;11(3):373-82. doi: 10.1016/j.jcmg.2017.02.015.
- Tatar S, Kesriklioğlu S, Şalvarcı A, Yaşaroğlu MY, Tokgözü OS. The effect of aortic arch calcification on in-hospital mortality in patients with hemorrhagic stroke. *Neurology Asia*. 2025 Mar;30(1):19-25. doi: 10.54029/2025uyc.

UČESTALOST METABOLIČKIH POREMEĆAJA I HIPERTENZIJE KOD ŽENA PRE MENOPAUZE I U MENOPAUZI

ORIGINALNI RAD

ORIGINAL ARTICLE

THE PREVALENCE OF METABOLIC DISORDERS AND HYPERTENSION IN WOMEN DURING PERIMENOPAUSE AND MENOPAUSE

Sonja Smiljić¹, Srna Šapić², Vojkan Nestorović¹, Zvezdan Milanović¹,
Mirjana Dejanović¹, Andrijana Karanović¹

¹ Univerzitet u Prištini – Kosovska Mitrovica, Medicinski fakultet, Kosovska Mitrovica, Srbija

¹ University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia

² Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

² University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SAŽETAK

Uvod/Cilj: Kardiometaboličke bolesti, uključujući diabetes mellitus tip 2 i hipertenziju, među vodećim su uzrocima morbiditeta i mortaliteta u Srbiji. U mlađem životnom dobu prevalenca kardiometaboličkih bolesti veća je kod muškaraca nego kod žena, ali ova prednost postepeno nestaje sa starenjem, posebno u menopauzi, i tada su žene pod većim kardiovaskularnim rizikom.

Cilj našeg istraživanja bio je da ukažemo na učestalost nepromenljivih i promenljivih faktora rizika i njihovu povezanost sa metaboličkim poremećajima i hipertenzijom kod žena pre menopauze i u menopauzi.

Metod: U ispitivanje je bilo uključeno 200 sredovečnih žena: 131 (65,5%) u perimenopauzi, koje su imale tipične znake perimenopauze duže od 6 meseci, i 69 (34,5%) žena u menopauzi, sa odsustvom ciklusa dužim od 12 meseci, starosti između 50 i 59 godina. Pacijentkinje su se javile lekaru na redovan preventivni pregled tokom decembra 2024. godine.

Rezultati: Hipertenzija je statistički značajno učestalija kod žena u menopauzi (84,1%), u odnosu na žene pre menopauze ($p < 0,001$). Žene u menopauzi su značajno češće imale metaboličke poremećaje, povećanu telesnu masu i gojaznost, i to kod 66,7% ispitanica, kao i veći obim struka kod 63,8% ispitanica ($p = 0,003$). Nivoi ukupnog holesterola, LDL-holesterola i triglicerida su bili statistički značajno viši kod žena u menopauzi u odnosu na žene pre menopauze ($p = 0,002$). Diabetes mellitus je statistički značajno učestaliji kod žena u menopauzi, gde je zastupljen kod 27% žena ($p = 0,002$). Učestalost hipotireoze je statistički značajno veća kod žena pre menopauze (14,7%) u odnosu na žene u menopauzi (4,3%) ($p = 0,027$). Ove dve grupe ispitanica nisu se značajno razlikovale u odnosu na zanimanje, porodični status i faktore rizika, kao što su sedentarne navike, navika pušenja cigareta i porodično opterećenje za oboljevanje od HTA.

Zaključak: Žene u menopauzi su značajno češće imale hipertenziju, gojaznost, dislipidemiju i diabetes mellitus 2. Zato su neophodni preventivni pregledi žena u perimenopauzi i menopauzi kako bi se pravovremeni prepoznali i lečili kardiometabolički poremećaji i time sprečile teže kardiovaskularne bolesti.

Gljučne reči: menopauza, hipertenzija, kardiometabolički poremećaj

ABSTRACT

Introduction/Objective: Cardiometabolic diseases, including type 2 diabetes (T2D) and cardiovascular disease, and their associated factors, such as hypertension, dyslipidemia, insulin resistance, and obesity, are among the leading causes of morbidity and mortality. At a young age, the prevalence of cardiometabolic diseases is higher in men than in women, but this female advantage gradually disappears with aging, particularly after menopause, when cardiometabolic risk factors accumulate. Our research aimed to highlight the prevalence of metabolic disorders and their association with hypertension in women during perimenopause and menopause.

Method: The study included 200 middle-aged women: 131 (65.5%) perimenopausal women who had experienced typical perimenopausal signs for more than 6 months, and 69 (34.5%) menopausal women with absent menstrual cycles for more than 12 months, aged 50-59 years. The patients visited their physician for a routine preventive examination in December 2024.

Results: Hypertension was statistically significantly more common in women in menopause (84.1%) compared to premenopausal women ($p < 0.001$). Women in menopause had significantly higher rates of metabolic disorders, increased body mass and obesity, with 66.7% of the participants affected, as well as a larger waist circumference in 63.8% of the participants ($p = 0.003$). Menopausal women had statistically significantly higher levels of triglycerides, LDL cholesterol, and total cholesterol than premenopausal women ($p = 0.002$). Among women going through menopause, diabetes mellitus was statistically substantially more prevalent, affecting 27% of them ($p = 0.002$). Premenopausal women had a statistically significantly greater prevalence of hypothyroidism (14.7%) than did menopausal women (4.3%) ($p = 0.027$). These two groups of participants did not differ significantly in terms of sedentary habits, smoking, or family history of hypertension.

Conclusion: Type 2 diabetes, obesity, dyslipidaemia, and hypertension were all substantially more common in menopausal women. Preventive screenings are therefore crucial for women going through menopause and perimenopause to promptly detect and treat cardiometabolic disorders and prevent more serious cardiovascular diseases.

Keywords: menopause, hypertension, cardiometabolic disorder

Autor za korespondenciju:

Sonja Smiljić

Medicinski fakultet, Univerzitet u Prištini – Kosovska Mitrovica

Anri Dinana b.b, 38220 Kosovska Mitrovica, Srbija

Elektronska adresa: sonja.smiljic@med.pr.ac.rs

Corresponding author:

Sonja Smiljić

Faculty of Medicine, University of Priština – Kosovska Mitrovica

bb Anri Dinana Street, 38220 Kosovska Mitrovica, Serbia

E-mail: sonja.smiljic@med.pr.ac.rs

Primljeno • Received: January 17, 2026; **Revidirano • Revised:** February 6, 2026; **Prihvaćeno • Accepted:** March 16, 2026; **Online first:** March 25, 2026

DOI: 10.5937/smlck7-64151

UVOD

Kardiometaboličke bolesti, uključujući diabetes mellitus tip 2 i hipertenziju, su među vodećim uzrocima morbiditeta i mortaliteta u Srbiji. U mlađem životnom dobu, prevalenca kardiometaboličkih bolesti je veća kod muškaraca nego kod žena, ali ova prednost postepeno nestaje sa starenjem, posebno u menopauzi, i tada su žene pod većim kardiovaskularnim rizikom. Iako je reproduktivno starenje karakteristično za oba pola, faze reproduktivnog starenja su bolje opisane kod žena. Estrogeni su prototip ženskih hormona i u godinama pre menopauze ispoljavaju punu aktivnost. Menopauza je faza života u kojoj se dešava ne samo pad estrogena i relativni višak androgena već i brojne psihofiziološke promene koje su posledica hormonskog disbalansa [1].

Očekivano je da će u 2025. godini širom sveta biti preko 1 milijarda žena u menopauzi [2]. Žene se češće suočavaju sa neadekvatnom dijagnostikom i terapijom kardiovaskularnih bolesti u poređenju sa muškarcima. Čak i kada su kod žena prisutni tradicionalni kardiovaskularni faktori rizika, lekar im ne pridaje adekvatnu važnost što dovodi do lošijeg ishoda bolesti. Hipertenzija je češća među ženama i nosi dvostruko veći rizik od mortaliteta u poređenju sa muškarcima [3]. Žene sa dijabetesom imaju veći rizik od ishemijske bolesti srca, i to za 3 do 7 puta u odnosu na muškarce kod kojih je samo 2 do 3 puta veći rizik ako boluju od diabetes mellitus tip 2 [4]. Diabetes mellitus tip 2 je potvrđen kod jedne od devet žena. Iako se čini da nema korelacije između početka menopauze i višeg nivoa glukoze, povećan rizik od metaboličkog sindroma se pojavljuje nakon prelaza u menopauzu [5]. U menopauzi dodatni faktori značajno povećavaju kardiovaskularni rizik. Tako je nedavna meta-analiza pokazala da pušenje cigareta za 25% povećava relativni rizik od velikih kardiovaskularnih događaja kod žena u poređenju sa muškarcima [6].

Faktori rizika specifični za ženski pol i njihova povezanost sa rizikom od KVB postaju sve više istraživani i poznati i naglašavaju važnost temeljne reproduktivne i akušerske anamneze za stratifikaciju kardiovaskularnog rizika. Faktori rizika specifični za pol uključujući hipertenzivni poremećaj u trudnoći, gestacijski dijabetes, prevremeni porođaj i abrupciju placente, preuranjenu menarhu, ranu menopauzu i vazomotorne simptome u menopauzi, i sindrom policističnih jajnika, sterilitet i lečenje steriliteta, autoimune bolesti i depresiju, povezani su sa povećanim kardiovaskularnim rizikom [7,8].

Hipertenzija je veoma rasprostranjen i moćan kardiovaskularni faktor rizika kod žena koji je povezan sa infarktom srca, srčanom slabošću, moždanim udarom, atrijskom fibrilacijom, perifernom arterijskom boles-

INTRODUCTION

Cardiometabolic diseases, including type 2 diabetes mellitus and hypertension, are among the leading causes of morbidity and mortality in Serbia. At a younger age, the prevalence of cardiometabolic diseases is higher in men than in women; however, this advantage gradually diminishes with aging, particularly during menopause, when women are at increased cardiovascular risk. Although reproductive aging is characteristic of both sexes, the stages of reproductive aging are better described in women. Estrogens are the prototype female hormones and exhibit full activity in the years preceding menopause. Menopause is a stage of life characterized not only by a decline in estrogen levels and a relative excess of androgens, but also by numerous psychophysiological changes resulting from hormonal imbalance [1].

It is expected that by 2025, there will be more than 1 billion women in menopause worldwide [2]. Women more often face inadequate diagnosis and treatment of cardiovascular diseases compared to men. Even when traditional cardiovascular risk factors are present in women, physicians do not attribute adequate importance to them, which leads to poorer disease outcomes. Hypertension is more common among women and carries a twofold higher risk of mortality compared to men [3]. Women with diabetes have a higher risk of ischemic heart disease, by 3 to 7 times, compared to men, in whom the risk is only 2 to 3 times higher in the presence of type 2 diabetes mellitus [4]. Type 2 diabetes mellitus has been confirmed in one out of nine women. Although there appears to be no correlation between the onset of menopause and higher glucose levels, an increased risk of metabolic syndrome emerges after the transition to menopause [5]. During menopause, additional factors significantly increase cardiovascular risk. A recent meta-analysis showed that smoking increases the relative risk of major cardiovascular events by 25% in women compared to men [6].

Sex-specific risk factors and their association with cardiovascular disease (CVD) risk are increasingly being studied and recognized, emphasizing the importance of a detailed reproductive and obstetric history for cardiovascular risk stratification. Sex-specific risk factors, including hypertensive disorders in pregnancy, gestational diabetes, preterm delivery and placental abruption, early menarche, early menopause and vasomotor symptoms in menopause, polycystic ovary syndrome, infertility and infertility treatment, autoimmune diseases, and depression, are associated with increased cardiovascular risk [7,8].

Hypertension is a highly prevalent and powerful cardiovascular risk factor in women, associated with myocardial infarction, heart failure, stroke, atrial fibrillation, peripheral arterial disease, and chronic kidney

ti i hroničnom bolesti bubrega. Sistolni krvni pritisak počinje da raste oko vremena prelaska u menopauzu i postaje sve češće povišen nakon 65 godina kod žena u poređenju sa muškarcima. Mlade žene sa hipertenzijom su u većem riziku od oštećenja ciljnih organa u poređenju sa muškarcima istih godina. Pad nivoa estrogena dovodi do autonomne disfunkcije, generalizovane endotelne disfunkcije i povećane aktivnosti renin-angiotenzin-aldosteron sistema i tako doprinosi povećanju krvnog pritiska [9,10].

Dislipidemija je dobro poznati faktor rizika za KVB, sa direktnom relacijom između LDL holesterola i aterosklerotske kardiovaskularne bolesti. Kod žene je hiperlipidemija češća u periodu menopauze. Tako žene u menopauzi češće imaju veći nivo ukupnog holesterola, triglicerida i LDL holesterola i smanjeni nivo HDL holesterola, što ih stavlja u veći rizi za KVB [11,12]. Visoki nivoi non-HDL holesterola i triglicerida su važniji faktori rizika za KVB kod žena nego kod muškaraca, posebno kod žena sa dijabetesom. Povećani indeks telesne mase (BMI) je povezan sa povećanim kardiovaskularnim rizikom kod oba pola, ali postoje polne razlike u distribuciji masti, visceralne i potkožne. U menopauzi kod žena se poveća količina visceralnih masti u poređenju sa ženama pre menopauze sličnih godina, što doprinosi insulinskoj rezistenciji i inflamaciji [1,11–13].

Cilj našeg istraživanja bio je da ukažemo na učestalost nepromenljivih i promenljivih faktora rizika i njihovu povezanost sa metaboličkim poremećajima i hipertenzijom kod žena pre menopauze i u menopauzi.

METODOLOGIJA

Prospektivnom studijom obuhvatili smo 200 sredovečnih žena koje su se javile lekaru na redovan preventivni pregled tokom decembra 2024. godine.

Istraživanje je dizajnirano kao studija preseka i obuhvatilo je 200 sredovečnih žena koje su se javile na redovan preventivni pregled tokom decembra 2024. godine. Sve ispitanice su dale pisani informisani pristanak za učešće u istraživanju, a studija je sprovedena u skladu sa etičkim standardim. Pacijentkinje smo podelili u dve grupe. Bila je 131 (65,5%) žena u perimenopauzi koje su imale tipične znake perimenopauze duže od 6 meseci i 69 (34,5%) žena u menopauzi sa odsustvom ciklusa duže od 12 meseci, a starosti između 50 i 59 godina. Na osnovu uzete ginekološke anamneze pacijentkinje su bile podeljene u ove dve grupe. Dijagnoza arterijske hipertenzije kod ispitanika je postavljena na osnovu preporuka Evropskog udruženja za hipertenziju.

Od svih pacijentkinja dobijeni su socio-demografski podaci: godine života, mesto stanovanja, porodični status, obrazovanje i zanimanje. Takođe, uzeti su anamnestički podaci (ranije bolesti, porodične bolesti, pušenje,

disease. Systolic blood pressure begins to rise around the time of the menopausal transition and becomes more frequently elevated after the age of 65 in women compared to men. Young women with hypertension are at greater risk of target organ damage compared to men of the same age. The decline in estrogen levels leads to autonomic dysfunction, generalized endothelial dysfunction, and increased activity of the renin-angiotensin-aldosterone system, thereby contributing to elevated blood pressure [9,10].

Dyslipidemia is a well-known risk factor for CVD, with a direct relationship between LDL cholesterol and atherosclerotic cardiovascular disease. In women, hyperlipidemia is more common during menopause. Thus, women in menopause more frequently have higher levels of total cholesterol, triglycerides, and LDL cholesterol, as well as lower levels of HDL cholesterol, placing them at higher risk for CVD [11,12]. High levels of non-HDL cholesterol and triglycerides are more important risk factors for CVD in women than in men, particularly in women with diabetes. Increased body mass index (BMI) is associated with increased cardiovascular risk in both sexes; however, there are sex differences in fat distribution, including visceral and subcutaneous fat. During menopause, women experience an increase in visceral fat compared to premenopausal women of similar age, which contributes to insulin resistance and inflammation [1,11–13].

Our study aimed to assess the prevalence of non-modifiable and modifiable risk factors and their association with metabolic disorders and hypertension in premenopausal and menopausal women.

METHODOLOGY

A prospective study included 200 middle-aged women who attended a routine preventive medical examination during December 2024.

The study was a cross-sectional design and included 200 middle-aged women who presented for a routine preventive examination in December 2024. All participants provided written informed consent to participate in the study, and the study was conducted in accordance with ethical standards.

The patients were divided into two groups. There were 131 (65.5%) women in perimenopause who had typical signs of perimenopause for more than 6 months, and 69 (34.5%) women in menopause with absence of menstruation for more than 12 months, aged between 50 and 59 years. Based on the gynecological history, the patients were classified into these two groups. The diagnosis of arterial hypertension was established according to the European Society of Hypertension recommendations.

konzumacije alkohola, obim fizičke aktivnosti). Od laboratorijskih analiza određivane su krvna slika i bihemija, urađen je klinički pregled sa dodatnim dijagnostičkim procedurama, EKG, ehokardiografija i EHO abdomena.

Istraživanje je sprovedeno u skladu sa važećim etičkim standardima i principima dobre kliničke prakse, uz poštovanje smernica Helsinške deklaracije.

Statistička analiza

Statističke analize podataka su sprovedene korišćenjem softverskog programa SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Kontinuirane varijable nisu imale normalnu raspodelu pa su prikazane kao medijana (*min_max*) a razlika između grupa je testirana Mann-Whitney testom. Kategorijalne varijable su prikazane kao broj (procenat) i razika učestalosti je testirana hi-kvadrat testom.

Kriterijum za statističku značajnost je bio $p < 0,05$.

REZULTATI

Istraživanjem je obuhvaćeno 200 ispitanica ženskog pola. Ispitanice su bile podeljene u dve grupe. Prvu grupu su činile žene pre menopauze, mlađe od 49 godina i žene u menopauzi starosti od 50 do 59 godina (Tabela 1).

Sociodemografske karakteristike bile su ujednačene. Zanimanje i obim fizičke aktivnosti bio je sličan kod obe grupe ispitanika kao i navika pušenja cigareta. Postojala je statistički značajna razlika u ste-

Sociodemographic data were obtained from all patients, including age, place of residence, marital status, education, and occupation. Anamnestic data were also collected (previous diseases, family history, smoking, alcohol consumption, and level of physical activity). Laboratory analyses included complete blood count and biochemical parameters. A clinical examination was performed, along with additional diagnostic procedures, including ECG, echocardiography, and abdominal ultrasound.

The study was conducted in accordance with current ethical standards and the principles of Good Clinical Practice, as outlined in the Declaration of Helsinki.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables did not have a normal distribution and were therefore presented as median (Min–Max), and differences between groups were tested using the Mann–Whitney test. Categorical variables were presented as numbers (percentages), and differences in frequency were tested using the chi-square test.

The criterion for statistical significance was $p < 0.05$.

RESULTS

The study included 200 female participants. The participants were divided into two groups. The first group consisted of premenopausal women younger than 49 years

Tabela 1. Kardiovaskularni faktori rizika kod žena pre menopauze i kod žena u menopauzi

Table 1. Cardiovascular risk factors in premenopausal and menopausal women

	Ispitivane grupe / Study groups		P
	Pre menopauze / Premenopause	Menopauza / Menopause	
Ukupan broj, n (%) / Total number, n (%)	131 (65.5%)	69 (34.5%)	
Zanimanje / Occupation			
Sedentarno / Sedentary	71 (54.2%)	41 (59.4%)	0.497
Fizički aktivne / Physically active	60 (45.8%)	28 (40.6%)	
Porodična anamneza / Family history			
Pozitivna / Positive	77 (58.8%)	40 (58.0%)	0.912
Negativna / Negative	54 (41.2%)	29 (42.0%)	
Pušenje / Smoking			
Ne / No	85 (64.9%)	41 (59.4%)	0.477
Da / Yes	46 (35.1%)	28 (40.6%)	
Gojaznost (BMI) / Obesity (BMI)			
Do 25 / Up to 25	66 (50.4%)	23 (33.3%)	0.021
Više od 25 / More than 25	65 (49.6%)	65 (55.7%)	
Obim struka / Waist circumference			
Do 84 cm / Up to 84 cm	76 (58.0%)	25 (36.2%)	0.003
Iznad 84 cm / More than 84 cm	55 (42%)	44 (63.8%)	

Podaci su prikazani kao broj (%), boldirana p vrednost – statistički značajna razlika

Data are presented as numbers (%); bold p-values indicate a statistically significant difference.

penu uhranjenosti i veličini obima struka. Kod žena u menopauzi značajno su češće bili prisutni parametri gojaznosti, BMI viši od 25 ($p = 0,021$) i obim struka veći od 84 cm ($p = 0,003$) (Tabela 1).

Žene u menopauzi su češće imale hipertenziju ($p < 0,001$) i diabetes mellitus tip 2 ($p = 0,002$). Poremećaj ritma je bio podjednako čest kod obe grupe ispitanika kao deficit vitamina D. Hipotireoza je bila značajno češća ($p = 0,027$) kod mlađe grupe žena u perimenopauzi, i sve one su bile na supstitucionoj terapiji (Tabela 2).

Dislipidemiju smo procenili kroz vrednost ukupnog holesterola, LDL holesterola, HDL holesterola i triglicerida. Žene u menopauzi imale su povišenu vrednost ukupnog holesterola i LDL holesterola dok se vrednost HDL holesterola nije statistički značajno razlikovala. Ukupni holesterol kod žena pre menopauze je iznosio 5,4 mmol/l (opseg 2,9–11,4), a kod žena u menopauzi 6,0 mmol/l (opseg 3,4–8,3), ($p < 0,001$). Vrednost LDL holesterola kod žena pre meneopaze bila je 3,0 mmol/l (opseg 1,4–6,0), kod žena u menopauzi 3,6 mmol/l (opseg 1,4–5,6), ($p = 0,001$). Vrednosti triglicerida su bile statistički značajno veće kod žena u menopauzi i iznosile su 1,7 mmol/l (opseg 0,6–5,2) u poređenju sa nivoom kod žena pre meneopaze 1,4 mmol/l (opseg 0,1–14,0), ($p = 0,002$) (Tabela 3).

Visoke vrednosti homocisteina (iznad 16 $\mu\text{mol/l}$) su značajno bile učestalije kod žena pre meneopaze 9

and menopausal women aged 50 to 59 years (Table 1).

Sociodemographic characteristics were comparable between the groups. Occupation and level of physical activity were similar in both groups, as was cigarette smoking. There was a statistically significant difference in nutritional status and waist circumference. In menopausal women, obesity-related parameters were significantly more frequent, including BMI > 25 ($p = 0.021$) and waist circumference > 84 cm ($p = 0.003$) (Table 1).

Women in menopause more frequently had hypertension ($p < 0.001$) and type 2 diabetes mellitus ($p = 0.002$). Arrhythmia was equally common in both groups, as was vitamin D deficiency. Hypothyroidism was significantly more frequent ($p = 0.027$) in the younger group of women in perimenopause, and all of them were receiving substitution therapy (Table 2).

Dyslipidemia was assessed by measuring total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Women in menopause had elevated total and LDL cholesterol levels, while HDL cholesterol levels did not differ significantly. Total cholesterol in premenopausal women was 5.4 mmol/L (range 2.9–11.4), and in menopausal women, 6.0 mmol/L (range 3.4–8.3) ($p < 0.001$). LDL cholesterol levels in premenopausal women were 3.0 mmol/L (range 1.4–6.0), and in menopausal women, 3.6 mmol/L (range 1.4–5.6) ($p = 0.001$). Triglyceride levels were significantly higher in meno-

Tabela 2. Zastupljenost pridruženih bolesti kod pacijentkinja pre menopauze i u menopauzi

Table 2. Prevalence of comorbidities in patients before menopause and in menopause

Ukupan broj. n (%) / Total number. n (%)	Ispitivane grupe / Study groups		P
	Pre menopauze / Premenopause	Menopauza / Menopause	
	131 (65.5%)	69 (34.5%)	
Diabetes mellitus / Diabetes mellitus			
Ne n (%) / No n (%)	66 (94.3%)	27 (73.0%)	0.002
Da n (%) / Yes n (%)	4 (5.7%)	10 (27.0%)	
Hipertenzija / Hypertension			
Ne n (%) / No n (%)	64 (41.2%)	11(15.9%)	< 0.001
Da n (%) / Yes n (%)	77 (58.8%)	68 (84.1%)	
Aritmije / Arrhythmias			
Ne n (%) / No n (%)	59 (88.1%)	31 (97.0%)	0.143
Da n (%) / Yes n (%)	8 (11.9%)	1 (3.0%)	
Hipotireoza / Hypothyroidism			
Ne n (%) / No n (%)	110 (85.3%)	66 (95.7%)	0.027
Da n (%) / Yes n (%)	19 (14.7%)	3 (4.3%)	
Nivo vitamina D / Vitamin D level			
Normalna vrednost n (%) / Normal value. n (%)	23 (33.8%)	10 (19.6%)	0.152
Insuficijencija n (%) / Insufficiency. n (%)	35 (51.5%)	35 (68.6%)	
Deficit n (/%) / Deficiency. n (/%)	10 (14.7%)	6 (11.8%)	

Podaci su prikazani kao broj (%). boldirana p vrednost – statistički značajna razlika

Data are presented as numbers (%); bold p-values indicate a statistically significant difference.

Tabela 3. Biohemijske varijable kod žena pre menopauze i u menopauzi

Varijable / Variables	Ispitivane grupe / Study groups		P
	Pre menopauze / Premenopause	Menopauza / Menopause	
Ukupan broj, n (%) / Total number, n (%)	131 (65.5%)	69 (34.5%)	
Ukupan holesterol (mmol/l) / Total cholesterol (mmol/l)	5.4 (2.9–11.4)	6.0 (3.4–8.3)	< 0.001
HDL holesterol (mmol/l) / HDL cholesterol (mmol/l)	1.5 (0.7–3.8)	1.4 (0.8–2.9)	0.257
LDL holesterol (mmol/l) / LDL cholesterol (mmol/l)	3.0 (1.4–6.0)	3.6 (1.4–5.6)	0.001
Trigliceridi (mmol/l) / Triglycerides (mmol/l)	1.4 (0.1–14.0)	1.7 (0.6–5.2)	0.002
Homocistein / Homocysteine			
Ispod 16 (μmol/l) / Less than 16 (μmol/l)	27 (75.0%)	39 (95.1%)	0.012
Iznad 16 (μmol/l) / More than 16 (μmol/l)	9 (25.0%)	2 (4.9%)	
Mokraćna kiselina / Uric acid			
Ispod 400 / Less than 400	63 (70.8%)	41 (78.8%)	0.294
Iznad 400 / More than 400	26 (29.2%)	11 (21.2%)	

Numeričke varijable su prikazane kao medijana i opseg (min–max) a kategorijalne kao broj (%), boldirana p vrednost – statistički značajna razlika

(25,0%) u odnosu na učestalosti kod žena u menopauzi 2 (4,9%), ($p = 0,012$).

DISKUSIJA

Učestalost veće telesne mase i gojaznosti nastavlja trend rasta, pri čemu su žene zastupljenije u odnosu na muškarce u populaciji gojaznih. Na to ukazuju skorije studije o prevalenci gojaznosti među starijim od 60 godina kod muškaraca od 37,5% i 39,4% kod žena [1]. Promena u reproduktivnim hormonima tokom menopauze i tranzicija u menopauzu doprinose ubrzanom rastu težine i ova pojava je posebno izražena tokom

Table 3. Biochemical variables in premenopausal and menopausal women

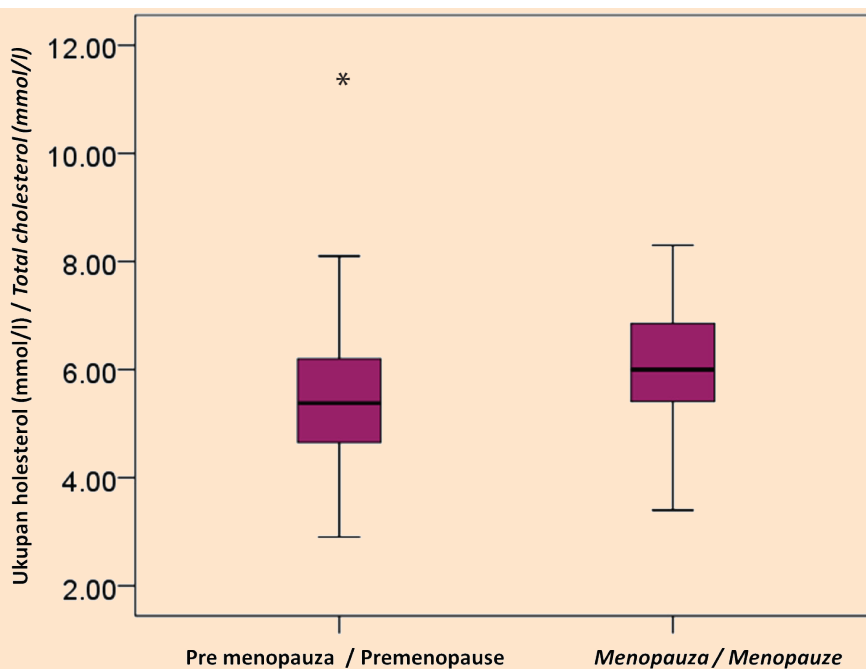
Numerical variables are presented as median and range (min–max), and categorical variables as numbers (%); bold p-values indicate statistically significant differences

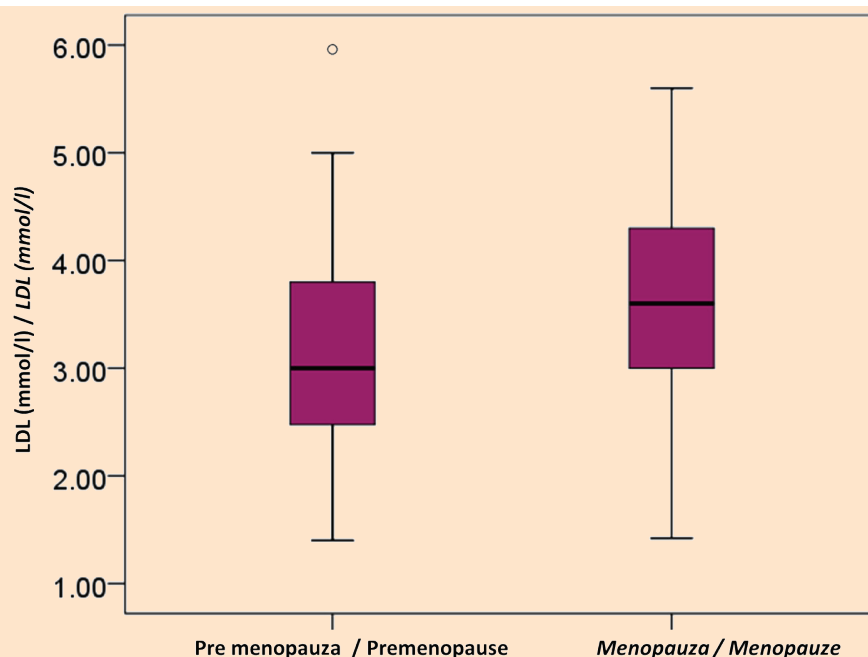
pausal women, amounting to 1.7 mmol/L (range 0.6–5.2), compared to 1.4 mmol/L (range 0.1–14.0) in premenopausal women ($p = 0.002$) (Table 3).

Elevated homocysteine levels (above 16 μmol/L) were significantly more frequent in premenopausal women 9 (25.0%) compared to menopausal women 2 (4.9%) ($p = 0.012$).

DISCUSSION

The prevalence of increased body weight and obesity continues to rise, with women being more represented than men in the obese population. This is supported

**Grafikon 1.** Vrednosti ukupnog holesterola kod žena pre menopauze i u menopauzi**Graph 1.** Total cholesterol levels in premenopausal and menopausal women

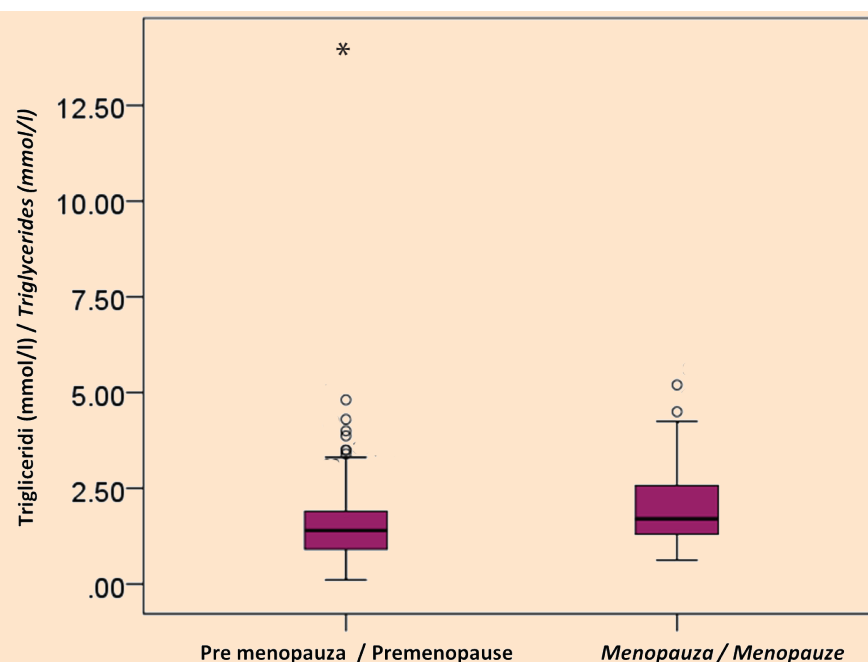

Grafikon 2. Vrednosti LDL-holesterola kod žena pre menopauze i u menopauzi

Graph 2. LDL cholesterol levels in premenopausal and menopausal women

tranzicije menopauze i u prvih nekoliko godina nakon poslednje menstruacije. Tako veća učestalost diabetes mellitusa tip 2 kod žena može biti posledica gojaznosti. Inflamacija u aterogenezi povezana sa gojaznošću i dijabetesom dovodi do povećanog kardiovaskularnog rizika. Kod žena je verovatnije da će se predijabetes razviti u diabetes mellitus tip 2 [9,14].

U originalnoj kohorti Framinghamske studije, postojala je povezanost između nivoa glikoziliranog hemoglobina (HgA1c) i kardiovaskularnih bolesti kod žena, ali ne i kod muškaraca. Za svako povećanje HgA1c za

by recent studies on the prevalence of obesity among individuals older than 60 years, showing rates of 37.5% in men and 39.4% in women [1]. Changes in reproductive hormones during menopause and the menopausal transition contribute to accelerated weight gain, a phenomenon that is particularly pronounced during the menopausal transition and in the first few years after the last menstruation. Thus, the higher prevalence of type 2 diabetes mellitus in women may be a consequence of obesity. Inflammation in atherogenesis, associated with obesity and diabetes, increases cardio-


Grafikon 3. Vrednosti triglicerida kod žena pre menopauze i u menopauzi

Graph 3. Triglyceride levels in premenopausal and menopausal women

1%, relativne šanse za kardiovaskularne bolesti su porasle za 1,39 puta kod žena. U meta-analizi, stopa fatalne koronarne bolesti bila je veća među pacijentima sa dijabetesom u poređenju sa onima bez dijabetesa (5,4% naspram 1,6%) [14]. Rana dijagnoza dijabetesa je neophodna posebno radi sprečavanja mikrovaskularnih komplikacija.

Hipertenzija može biti posledica disfunkcije vaskularnog endotela i disbalansa endotelinih medijatora (endotelina, azot oksida, prostaciklina) koji kontrolišu vaskularnu funkciju. Estrogeni indukuju sintezu azot oksida (NO), povećavaju formiranje inozitol 1,4,5-trisfosfata (IP3), koji stimuliše oslobađanje Ca^{2+} iz endoplazmatskog retikuluma. Ca^{2+} formira kompleks sa kalmodulinom, koji se zatim vezuje i izaziva početnu aktivaciju eNOS-a. Aktivirana eNOS podstiče transformaciju L-arginina u L-citrulin i proizvodnju NO, koji izaziva relaksaciju glatkih mišica vaskulature (VMS). Jasan je potencijalni efekti estrogena na vaskularni endotel. Povećan vaskularni tonus uzrokuje hipertenziju, što dovodi do oštećenja krvnih sudova [10]. Estrogeni podstiču vazodilataciju i mogu ublažiti hipertenziju. Takođe mogu smanjiti vaskularnu propustljivost, reaktivne vrste kiseonika (ROS) i infiltraciju inflamatornim ćelijama. Estrogeni takođe mogu usporiti napredovanje ateroskleroze poboljšanjem lipidnog profila i smanjiti tromboemboliju smanjenjem agregacije trombocita. Verovatno je da oksidativni stres i povećano stvaranje reaktivnih vrsta kiseonika predstavljaju zajedničku molekularnu osnovu koja povezuje imunoinflamaciju sa hipertenzijom što je kod žena u menopauzi sa padom estrogena češće.

Dislipidemija je dobro poznati faktor rizika sa direktnom relacijom između LDL-holesterola i aterosklerotske kardiovaskularne bolesti. Studije koje su uključivale žene su pokazale da je smanjenje LDL-holesterola povezano sa smanjenim rizikom od KVB i u primarnoj i u sekundarnoj prevenciji. INTERHEART je bila velika studija kontrole slučaja koja je nastojala da kvantifikuje rizik od različitih faktora rizika koji se mogu primeniti za kardiovaskularne bolesti. Pušenje i abnormalni lipidni profil (definisano kao povišen odnos ApoB/ApoA1) bili su dva najjača faktora rizika za infarkt miokarda [7,15]. Terapija statinima ima prednosti u smanjenju rizika od KVB, iako starije žene za 20% manje od muškaraca koriste statine, što može biti zbog ređeg propisivanja leka ili veće prevalencije mialgija povezanih sa statinima [16]. Nivo holesterola može da varira tokom životnog veka, od mlade odrasle osobe do trudnoće i do prelaska u menopauzu, a lečenje treba da bude određeno prema tome. Žene su pod povećanim rizikom od dislipidemije u periodu menopauze što se karakteriše višim ukupnim holesterolom, trigliceridima

vascular risk. Women are more likely to progress from prediabetes to type 2 diabetes mellitus [9,14].

In the original Framingham cohort, an association between glycated hemoglobin (HbA1c) levels and cardiovascular disease was observed in women but not in men. For each 1% increase in HbA1c, the relative odds of cardiovascular disease increased by 1.39 times in women. In a meta-analysis, the rate of fatal coronary disease was higher among patients with diabetes compared to those without diabetes (5.4% vs. 1.6%) [14]. Early diagnosis of diabetes is essential, particularly for preventing microvascular complications.

Hypertension may result from vascular endothelial dysfunction and an imbalance of endothelial mediators (endothelin, nitric oxide, prostacyclin) that regulate vascular function. Estrogens induce nitric oxide (NO) synthesis and increase the formation of inositol 1,4,5-trisphosphate (IP3), which stimulates the release of Ca^{2+} from the endoplasmic reticulum. Ca^{2+} forms a complex with calmodulin, which then binds and initiates activation of endothelial nitric oxide synthase (eNOS). Activated eNOS promotes the conversion of L-arginine to L-citrulline and the production of NO, which induces relaxation of vascular smooth muscle. The potential effects of estrogen on the vascular endothelium are evident. Increased vascular tone leads to hypertension, which in turn causes vascular damage [10]. Estrogens promote vasodilation and may attenuate hypertension. They may also reduce vascular permeability, reactive oxygen species (ROS), and inflammatory cell infiltration. Estrogens may also slow the progression of atherosclerosis by improving lipid profile and reducing thromboembolism by decreasing platelet aggregation. Oxidative stress and increased production of reactive oxygen species likely represent a common molecular basis linking immunoinflammation with hypertension, which is more frequent in menopausal women due to decreased estrogen levels.

Dyslipidemia is a well-known risk factor with a direct relationship between LDL cholesterol and atherosclerotic cardiovascular disease. Studies including women have shown that reduction of LDL cholesterol is associated with reduced cardiovascular risk in both primary and secondary prevention. INTERHEART was a large case-control study that aimed to quantify the risks associated with various cardiovascular disease risk factors. Smoking and abnormal lipid profile (defined as an elevated ApoB/ApoA1 ratio) were the two strongest risk factors for myocardial infarction [7,15]. Statin therapy has benefits in reducing cardiovascular risk; however, older women use statins 20% less frequently than men, which may be due to less frequent prescribing or a higher prevalence of statin-associated myalgia [16].

i LDL-holesterolom a nižim HDL-holesterolom. Visoki nivo non-HDL-holesterol a triglicerida su važniji faktori rizika za KVB kod žena nego kod muškaraca, posebno žene sa dijabetesom [17]. Povišen nivo lipoproteina(a) se smatra faktorom rizika koji ispoljava protrombotički, proinflamatorni i proaterogeni efekat kod oba pola.

Hipertenzija, dijabetes, fizička neaktivnost i upotreba alkohola bili su snažnije povezani sa infarktom miokarda kod žena nego kod muškaraca što je pokazala Interheart studija [7]. Prospektivna multicentrična studija imidžinga za procenu bola u grudima (PROMISE) pokazala je da su žene sa stabilnim simptomima koronarne bolesti imale veće opterećenje faktorima rizika od muškaraca [8].

Povećani indeks telesne mase (BMI) je povezan sa povećanim rizikom od KVB kod oba pola ali postoje polne razlike u distribuciji masti, visceralne i potkožne [18]. Žene pretežno akumuliraju potkožno masno tkivo, dok muškarci akumuliraju više visceralnih masti. U menopauzi kod žena se povećava količina visceralnih masti i infiltracije mišića mastima u poređenju sa ženama pre menopauze sličnih godina, što doprinosi insulinskoj rezistenciji i inflamaciji [1,19]. Pojedini faktori rizika za KVB su povezani sa većom količinom masti i gojaznošću. Tako je hipertenzija povezana sa prekomernom težinom i gojaznošću kod žena, a dijabetes je povezan sa abdominalnom gojaznošću kod žena [18]. Smanjenje težine je povezano sa padom nivoa holesterola, nižim krvnim pritiskom i smanjenjem rizika za razvoja diabetes mellitus tipa 2.

Rezultati našeg istraživanja su u skladu sa nalazima evropskih studija koje pokazuju da se učestalost metaboličkih poremećaja i hipertenzije značajno povećava nakon menopauze. Takođe, rezultati biohemijskih analiza lipidnog profila ukazuju na značajno više vrednosti ukupnog i LDL holesterola kod žena u postmenopauzi u poređenju sa ženama pre menopauze, što dodatno potvrđuje nepovoljne metaboličke promene u ovom periodu života [20].

Kod grupe žena u perimenopauzi značajno češće se potvrđuje hipotireoza gde je najčešći uzrok Hashimoto tireoiditis. Razlog za veći broj potvrđenih slučajeva hipotireoze osim boljih dijagnostičkih mogućnosti je hronični stres i poremećaj imunog sistema zbog modernog načina života. Hormonski disruptori iz okoline (u plastici, kozmetici, pesticidima) i nedostaci mikronutrijenata mogu biti razlog sve češćeg oboljevanja od hipotireoze [21]. Žene su posebno osetljive zbog uticaja estrogena na imuni odgovor i hormonske oscilacije mogu izazvati autoimunu bolest kod genetski predisponiranih žena [22].

Prisustvo estrogenskih receptora (ERa i ERb) u velikom broju u visceralnom masnom tkivu [18] podrža-

Cholesterol levels may vary throughout the life course, from young adulthood to pregnancy and the menopausal transition, and treatment should be determined accordingly. Women are at increased risk of dyslipidemia during menopause, characterized by higher total cholesterol, triglycerides, and LDL cholesterol, and lower HDL cholesterol. High levels of non-HDL cholesterol and triglycerides are more important risk factors for cardiovascular disease in women than in men, especially in women with diabetes [17]. Elevated lipoprotein(a) levels are considered a risk factor with prothrombotic, proinflammatory, and proatherogenic effects in both sexes.

Hypertension, diabetes, physical inactivity, and alcohol use were more strongly associated with myocardial infarction in women than in men, as demonstrated by the INTERHEART study [7]. The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) showed that women with stable symptoms of coronary disease had a higher burden of risk factors compared to men [8].

Increased body mass index (BMI) is associated with increased cardiovascular risk in both sexes; however, there are sex differences in fat distribution, including visceral and subcutaneous fat [18]. Women predominantly accumulate subcutaneous fat, whereas men accumulate more visceral fat. During menopause, women experience increased visceral and intramuscular fat infiltration compared with premenopausal women of similar age, contributing to insulin resistance and inflammation [1,19]. Certain cardiovascular risk factors are associated with increased fat mass and obesity. Hypertension is associated with overweight and obesity in women, while diabetes is associated with abdominal obesity in women [18]. Weight reduction is associated with lower cholesterol levels, lower blood pressure, and a reduced risk of developing type 2 diabetes mellitus.

The results of our study are consistent with findings from European studies showing that the prevalence of metabolic disorders and hypertension significantly increases after menopause. In addition, lipid profile analyses indicate significantly higher levels of total and LDL cholesterol in postmenopausal women than in premenopausal women, further confirming unfavorable metabolic changes during this period of life [20].

In the group of perimenopausal women, hypothyroidism was significantly more frequently observed, with Hashimoto's thyroiditis being the most common cause. In addition to improved diagnostic capabilities, the higher number of confirmed cases of hypothyroidism may be related to chronic stress and immune system disturbances associated with modern lifestyles. Environmental endocrine disruptors (found in plastics, cosmetics, and pesticides) and micronutrient deficien-

va direktnu ulogu estrogena u modulaciji funkcije visceralnog masnog tkiva. Estrogen inhibira taloženje lipida u adipocitima, koristeći dva načina, direktnim smanjenjem lipogeneze kroz slabljenje aktivnosti enzima lipoprotein lipaza (LPL), a indirektno utičući na lipolizu kroz poboljšanje funkcija lipolitičkog enzima hormon-senzitivne lipaze (HSL) [23]. Estrogen takođe indirektno reguliše lučenje leptina od strane masnog tkiva i utiče na unos hrane, potrošnju energije i samim tim na povećanje telesne mase [1,18].

Ograničenja ovog istraživanja jeste relativno mala veličina uzorka, koja može uticati na statističku snagu studije i generalizaciju dobijenih rezultata. Iz tog razloga u ovom istraživanju nisu sprovedene multivarijantne analize. Buduća istraživanja na većem uzorku ispitanika mogla bi omogućiti primenu kompleksnijih statističkih metoda i dodatnu potvrdu dobijenih nalaza.

ZAKLJUČAK

Žene kao i muškarci imaju tradicionalne promenljive kardiovaskularne faktore rizika, ali osim njih žene imaju i polno specifične koji značajno povećavaju kardiovaskularni rizik. Postoji polni dimorfizam u distribuciji telesne masti i potkrepljujući dokazi o regulatornoj ulozi estrogena, posebno 17 β -estradiola u metabolizmu i regionalnoj distribuciji masnog tkiva. Sklonost ka androidnoj distribuciji masti je prepoznata kod starijih žena i verovatno je odgovorna za kaskadu hroničnih zdravstvenih poremećaja, uključujući hipertenziju, diabetes mellitus tipa 2 i velike kardiovaskularne događaje. Ovi podaci su značajni zdravstvenom sistemu jer kontrola telesne mase kod svih uzrasta, a posebno kod žena u menopauzi treba da predstavlja prioritetni cilj. Eksperimentalni podaci i kliničke studije ukazuju na složene razlike u regulaciji vazomotorne funkcije mikrovaskularnih krvnih sudova kod žena i muškaraca što doprinose razumevanju polnih razlika i specifičnosti rizika za ishemijsku bolest kod žena. Bolje razumevanje patofizioloških mehanizma može pomoći u planiranju novih strategija za prevenciju, otkrivanje i lečenje kardiometaboličkih bolesti koje su u potpunosti prilagođeni ženama.

Sukob interesa: Nije prijavljen.

Notifikacija: Rad je prethodno prezentovan na 34. Evropskom sastanku o hipertenziji i kardiovaskularnoj zaštiti, održanom od 23. do 26. maja 2025. godine u Milanu, Italija. Sažetak je objavljen u *Journal of Hypertension* (2025), Vol. 43, Br. suppl. 1.

cies may contribute to the rising incidence of hypothyroidism [21]. Women are particularly susceptible due to the influence of estrogen on immune response, and hormonal fluctuations may trigger autoimmune disease in genetically predisposed individuals [22].

The presence of estrogen receptors (ER α and ER β) in large numbers in visceral adipose tissue [18] supports the direct role of estrogen in modulating visceral fat function. Estrogen inhibits lipid accumulation in adipocytes through two mechanisms: directly, by reducing lipogenesis via decreased activity of lipoprotein lipase (LPL), and indirectly, by influencing lipolysis through enhancement of hormone-sensitive lipase (HSL) activity [23]. Estrogen also indirectly regulates leptin secretion from adipose tissue and affects food intake and energy expenditure, thereby influencing body weight [1,18].

A limitation of this study is its relatively small sample size, which may affect statistical power and the generalizability of the results. For this reason, multivariate analyses were not performed. Future studies with larger sample sizes may allow the application of more complex statistical methods and further validation of these findings.

CONCLUSION

Women, like men, have traditional modifiable cardiovascular risk factors; however, in addition, they have sex-specific factors that significantly increase cardiovascular risk. There is sexual dimorphism in body fat distribution, supported by evidence of the regulatory role of estrogen, particularly 17 β -estradiol, in metabolism and regional fat distribution. A tendency toward android fat distribution is observed in older women and is likely responsible for a cascade of chronic health disorders, including hypertension, type 2 diabetes mellitus, and major cardiovascular events. These findings are important for the healthcare system, as body weight control at all ages, particularly in menopausal women, should be a priority. Experimental data and clinical studies indicate complex differences in the regulation of vasomotor function of microvascular blood vessels between women and men, contributing to the understanding of sex differences and the specific risk of ischemic heart disease in women. A better understanding of pathophysiological mechanisms may help plan new strategies tailored to women for the prevention, detection, and treatment of cardiometabolic diseases.

Conflict of interest: None declared

Notification: This paper was previously presented at the 34th European Meeting on Hypertension and Cardiovascular Protection, May 23–26, 2025, Milan, Italy. The abstract was published in the *Journal of Hypertension* (2025), Vol. 43, Suppl. 1.

LITERATURA / REFERENCES

1. Rehman A, Lathief S, Charoenngam N, Pal L. Aging and Adiposity-Focus on Biological Females at Midlife and Beyond. *Int J Mol Sci*. 2024 Mar 4;25(5):2972. doi: 10.3390/ijms25052972.
2. Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014 Oct;21(10):1038-62. doi: 10.1097/GME.0000000000000319.
3. Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. *Am J Prev Cardiol*. 2020 Jun 6;2:100028. doi: 10.1016/j.ajpc.2020.100028.
4. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia*. 2014 Aug;57(8):1542-51. doi: 10.1007/s00125-014-3260-6.
5. Nguyen AH, Hurwitz M, Sullivan SA, Saad A, Kennedy JLW, Sharma G. Update on sex specific risk factors in cardiovascular disease. *Front Cardiovasc Med*. 2024 Feb 6;11:1352675. doi: 10.3389/fcvm.2024.1352675.
6. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011 Oct 8;378(9799):1297-305. doi: 10.1016/S0140-6736(11)60781-2.
7. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al.; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008 Apr;29(7):932-40. doi: 10.1093/eurheartj/ehn018.
8. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pellikka PA, et al. Sex Differences in Demographics, Risk Factors, Presentation, and Noninvasive Testing in Stable Outpatients With Suspected Coronary Artery Disease: Insights From the PROMISE Trial. *JACC Cardiovasc Imaging*. 2016 Apr;9(4):337-46. doi: 10.1016/j.jcmg.2016.02.001.
9. Kalyani RR, Lazo M, Ouyang P, Turkbey E, Chevalier K, Brancati F, et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. *Diabetes Care*. 2014;37(3):830-8. doi: 10.2337/dc13-1755.
10. Smiljić S, Ilić A. The impact of dyslipidemia and hyperhomocysteinemia on the development of arterial hypertension. *Galenika Medical Journal*. 2024;3(9):7-13. doi: 10.5937/Galmed24090075.
11. Joyner JM, Hutley LJ, Cameron DP. Estrogen receptors in human preadipocytes. *Endocrine*. 2001 Jul;15(2):225-30. doi: 10.1385/ENDO:15:2:225.
12. Mou H, Zhang J, Guo Y, Xu L, Luo X. Effects of key physiological parameters on cardiovascular disease and osteoporosis risk in perimenopausal and postmenopausal women. *Sci Rep*. 2025 Jan 22;15(1):2814. doi: 10.1038/s41598-025-86613-8. Erratum in: *Sci Rep*. 2025 Mar 25;15(1):10251. doi: 10.1038/s41598-025-95430-y.
13. Nie G, Yang X, Wang Y, Liang W, Li X, Luo Q, et al. The Effects of Menopause Hormone Therapy on Lipid Profile in Postmenopausal Women: A Systematic Review and Meta-Analysis. *Front Pharmacol*. 2022 Apr 12;13:850815. doi: 10.3389/fphar.2022.850815.
14. Mahabadi AA, Massaro JM, Rosito GA, Levy D, Murabito JM, Wolf PA, et al. Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham Heart Study. *Eur Heart J*. 2009 Apr;30(7):850-6. doi: 10.1093/eurheartj/ehn573.
15. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al.; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004 Sep 11-17;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9.
16. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol*. 2012 Feb 7;59(6):572-82. doi: 10.1016/j.jacc.2011.09.067. Erratum in: *J Am Coll Cardiol*. 2012 Apr 17;59(16):1491.
17. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care*. 2003 Jan;26(1):16-23. doi: 10.2337/diacare.26.1.16.
18. Welsh A, Hammad M, Piña IL, Kulinski J. Obesity and cardiovascular health. *Eur J Prev Cardiol*. 2024 Jun 3;31(8):1026-35. doi: 10.1093/eurjpc/zwae025.
19. Nilsson S, Quick A, Henriksson M, Lawesson SS, Holm AS, Leander K. Menopausal Vasomotor Symptoms and Subclinical Atherosclerotic Cardiovascular Disease: A Population-Based Study. *J Am Heart Assoc*. 2024 Sep 3;13(17):e033648. doi: 10.1161/JAHA.123.033648.
20. Marchi R, Dell'Agnolo CM, Lopes TCR, Gravena AAF, Demitto MO, Brischiliari SCR, et al. Prevalence of metabolic syndrome in pre- and postmenopausal women. *Arch Endocrinol Metab*. 2017 Mar-Apr;61(2):160-6. doi: 10.1590/2359-39970000000253.
21. Wyne KL, Nair L, Schneiderman CP, Pinsky B, Antunez Flores O, Guo D, et al. Hypothyroidism Prevalence in the United States: A Retrospective Study Combining National Health and Nutrition Examination Survey and Claims Data, 2009-2019. *J Endocr Soc*. 2022 Nov 10;7(1):bvac172. doi: 10.1210/jendso/bvac172.
22. Vargas-Uricoechea H, Castellanos-Pinedo A, Urrego-Noguera K, Pinzón-Fernández MV, Meza-Cabrera IA, Vargas-Sierra H. A Scoping Review on the Prevalence of Hashimoto's Thyroiditis and the Possible Associated Factors. *Med Sci (Basel)*. 2025 Apr 10;13(2):43. doi: 10.3390/medsci13020043.
23. Pant A, Chew DP, Mamas MA, Zaman S. Cardiovascular Disease and the Mediterranean Diet: Insights into Sex-Specific Responses. *Nutrients*. 2024 Feb 19;16(4):570. doi: 10.3390/nu16040570.

POVEZANOST LABORATORIJSKIH PARAMETARA SA TOKOM BOLESTI KOD PACIJENATA SA FOLIKULARNIM LIMFOMOM – PETOGODIŠNJE ISKUSTVO JEDNOG CENTRA

ORIGINALNI RAD

ORIGINAL ARTICLE

LABORATORY PARAMETERS AND THEIR RELATIONS WITH DISEASE OUTCOME IN PATIENTS WITH NON-HODGKIN FOLLICULAR LYMPHOMA – SINGLE CENTRE FIVE-YEAR FOLLOW-UP

Danijela Jovanović^{1,2}, Snežana Sretenović^{1,2}, Sanja Aleksić¹, Ana Dragović¹, Ivana Andrejević¹

¹ Univerzitetski klinički centar Kragujevac, Klinika za hematologiju, Kragujevac, Srbija

¹ University Clinical Center Kragujevac, Clinic for Hematology, Kragujevac, Serbia

² Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za internu medicinu, Kragujevac, Srbija

² University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia

SAŽETAK

Uvod/Cilj: Ne-Hoćkinov folikularni limfom predstavlja drugi po učestalosti među ne-Hoćkinovim limfomima, odnosno najčešći indolentni limfom. Iako retko, ova bolest može pokazati agresivnost, sklonost ka komplikacijama, ali i rezistentnost na primenjenu terapiju i česte relapse.

Cilj rada je analiza laboratorijskih parametara pacijenata u trenutku postavljanja dijagnoze i njihove povezanosti sa ishodom bolesti, komplikacijama, terapijskim odgovorom i preživljavanjem.

Materijal i metode: U našem centru analizirano je 47 pacijenata kod kojih u periodu od 2018. do januara 2024. godine postavljena dijagnoza folikularnog limfoma. Analizirani su inicijalni laboratorijski parametri krvne slike, parametri hemostaze (PT, aPTT, fibrinogen, D-dimer) kao i biohemijski parametri, dok su u toku bolesti posmatrani terapijski odgovor na prvu terapijsku liniju, preživljavanje bez znakova bolesti, kao i sveukupno preživljavanje.

Rezultati: Parametri krvne slike, kao i većina biohemijskih parametara, nisu pokazali korelaciju sa tokom bolesti. Kompletnu remisiju postizali su pacijenti sa nižim vrednostima LDH ($p = 0,029$), dok je sveukupno preživljavanje bilo duže kod pacijenata sa nižim vrednostima fibrinogena ($p = 0,019$), višim procentom monocita ($p = 0,007$), kao i nižim koncentracijama D-dimera ($p < 0,000$). Na preživljavanje bez znakova bolesti uticali su niži nivo fibrinogena ($p = 0,019$), niži nivo D-dimera ($p = 0,031$), niži nivo LDH ($p = 0,019$), kao i viši procenat monocita u perifernoj krvi ($p = 0,005$). Pacijenti sa inicijalno povišenim vrednostima D-dimera imali su PFS $24,50 \pm 4,81$ meseci, dok su oni sa D-dimerom u granicama referentnih vrednosti imali PFS $36,48 \pm 5,99$ meseci ($p = 0,015$).

Zaključak: U iskustvu našeg centra parametri hemostaze, fibrinogen i D-dimer pokazali su značajnu korelaciju sa tokom bolesti.

Ključne reči: folikularni limfom, fibrinogen, D-dimer, tok bolesti

ABSTRACT

Introduction/Objective: Follicular lymphoma, a subtype of non-Hodgkin lymphoma, is the second most common non-Hodgkin lymphoma and the most frequent indolent lymphoma. Although rare, this disease may exhibit aggressive behavior, a tendency toward complications, as well as resistance to administered therapy and frequent relapses.

This study aimed to analyze laboratory parameters at the time of diagnosis and their association with disease outcome, complications, treatment response, and survival.

Material and methods: A total of 47 patients diagnosed with follicular lymphoma between 2018 and January 2024 were analyzed at our center. Baseline laboratory parameters included complete blood count, hemostasis parameters (PT, aPTT, fibrinogen, D-dimer), and biochemical parameters. During the course of the disease, treatment response to first-line therapy, progression-free survival, and overall survival were evaluated.

Results: Complete blood count parameters, as well as most biochemical parameters, showed no correlation with disease course. Complete remission was achieved in patients with lower LDH levels ($p = 0,029$), while overall survival was longer in patients with lower fibrinogen levels ($p = 0,019$), a higher percentage of monocytes ($p = 0,007$), and lower D-dimer levels ($p < 0,000$). Progression-free survival was associated with lower fibrinogen levels ($p = 0,019$), lower D-dimer levels ($p = 0,031$), lower LDH levels ($p = 0,019$), and a higher percentage of peripheral blood monocytes ($p = 0,005$). Patients with initially elevated D-dimer levels had a PFS of 24.50 ± 4.81 months, whereas those with D-dimer levels within the reference range had a PFS of 36.48 ± 5.99 months ($p = 0,015$).

Conclusion: In our center's experience, hemostasis parameters, particularly fibrinogen and D-dimer, showed a significant correlation with disease course.

Keywords: follicular lymphoma, fibrinogen, D-dimer, disease course

Autor za korespondenciju:

Danijela Jovanović

Klinika za hematologiju, Univerzitetski klinički centar Kragujevac

Zmaj Jovina 30, 34000 Kragujevac, Srbija

Elektronska adresa: daziv81@yahoo.com

Corresponding author:

Danijela Jovanović

Clinic for Hematology, University Clinical Center Kragujevac

30 Zmaj Jovina Street, 34000 Kragujevac, Serbia

E-mail: daziv81@yahoo.com

Primljeno • Received: December 26, 2025; **Revidirano • Revised:** February 13, 2026; **Prihvaćeno • Accepted:** March 16, 2026; **Online first:** March 25, 2026

DOI: 10.5937/smcl7-63730

UVOD

Limfomi predstavljaju maligne bolesti limfocita i njihovih progenitora i u zavisnosti od porekla mogu biti porekla B limfocita, T limfocita ili NK limfocita, po histološkoj slici dele se na dve velike grupe: Hočkinovi i ne-Hočkinovi limfomi, a po toku na agresivne i indolentne limfome [1].

Indolentni limfomi su posebna grupu limfoproliferativnih bolesti koji i pored toga što po klasifikaciji pripadaju malignim bolestima uglavnom su hroničnog toka. Folikularni ne-Hočkinov limfom (NHL) predstavlja drugi po učestalosti svih B limfocitnih NHL sa učestalošću od 25%, ali i najučestaliji indolentni limfom kome pripada čak 60% pacijenata [2]. Procenjena incidenca ove bolesti iznosi 2,5 pacijenta na 100.000 stanovnika godišnje. Od ovog podtipa limfoma češće oboljevaju stariji, te se najveći broj novodijagnostikovanih slučajeva detektuje u starosnoj dobi od 55–75 godina [3]. Zahvaljujući novim terapijskim modalitetima prosečno preživljavanje pacijenata sa folikularnim limfomom iznosi 15–20 godina [4]. Iako retko, ova bolest može pokazati agresivnost, sklonost ka komplikacijama, ali i rezistentnost na primenjivanu terapiju i česte relapse. Sa ciljem prepoznavanja pacijenata koji će imati nepovoljan tok bolesti razvijeni su brojni prognostički i prediktivni skorovi (FLIPI skor, PRIMA-PI skor, POD24) [5].

Cilj rada je analizirati laboratorijske parametre pacijenata pri dijagnozi i njihovu povezanost sa ishodom bolesti, terapijskim odgovorom i preživljavanjem.

MATERIJAL I METODE

Istraživanje je sprovedeno kao retrospektivna studija u Klinici za hematologiju UKC Kragujevac, u periodu od 2018. do januara 2024. godine gde je analizirano 47 pacijenata koji su lečeni u navedenom periodu Klinici pod dijagnozom folikularnog limfoma. Od laboratorijskih parametara analizirani su krvna slika (broj leukocita, leukocitarna formula, hemoglobin, broj trombocita), hemostaza (protrpmbinsko vreme (PT), aktivirano parcijalno tromboplastinsko vreme (aPTT) , fibronogen, D-dimer) kao i biohemijski parametri (urea, kreatinin, jonogram, hepatogram, laktat dehidrogenaza (LDH), *ac. uricum*) koji su uzorkovani prilikom inicijalnog ispitivanja pacijenta pri postavljanju dijagnoze, a pre primene prve terapijske linije. Pacijenti su nakon toga praćeni i lečeni prema indikacijama, praćeni na redovnim ambulantnim kontrolama. Tokom petogodišnjeg praćenja posmatrani su: odgovor na prvu terapijsku liniju, preživljavanje bez znakova bolesti, kao i sveukupno preživljavanje pacijenata. Statistička analiza sprovedena je korišćenjem IBM SPSS 22.0 programa za statističku obradu podataka. Normalnost raspodele za kontinuirana

INTRODUCTION

Lymphomas are malignant diseases of lymphocytes and their progenitors and, depending on their origin, may arise from B lymphocytes, T lymphocytes, or NK lymphocytes. Histologically, they are divided into two major groups: Hodgkin and non-Hodgkin lymphomas, and, according to their clinical course, into aggressive and indolent lymphomas [1].

Indolent lymphomas represent a distinct group of lymphoproliferative diseases that, although classified as malignant, generally have a chronic course. Follicular non-Hodgkin lymphoma (NHL) is the second most common B-cell NHL, accounting for 25% of cases, and is also the most common indolent lymphoma, comprising up to 60% of patients [2].

The estimated incidence of this disease is 2.5 patients per 100,000 population annually. This subtype more frequently affects older individuals, with the majority of newly diagnosed cases occurring between 55 and 75 years of age [3]. Thanks to new therapeutic modalities, the average survival of patients with follicular lymphoma is 15–20 years [4]. Although rare, this disease may demonstrate aggressive behavior, a tendency toward complications, resistance to applied therapy, and frequent relapses. To identify patients at risk of an unfavorable disease course, numerous prognostic and predictive scores have been developed (FLIPI, PRIMA-PI, POD24) [5].

This study aimed to analyze laboratory parameters at diagnosis and their association with disease outcome, therapeutic response, and survival.

MATERIAL AND METHODS

The study was a retrospective analysis of 47 patients treated at the Clinic of Hematology, University Clinical Center Kragujevac, from 2018 to January 2024, with a diagnosis of follicular lymphoma. Laboratory parameters included complete blood count (white blood cell count, leukocyte differential, hemoglobin, platelet count), hemostatic parameters (prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer), as well as biochemical parameters (urea, creatinine, electrolytes, liver function tests, lactate dehydrogenase (LDH), uric acid), all of which were sampled during the initial patient evaluation at the time of diagnosis and before the initiation of first-line therapy. Patients were subsequently followed and treated according to treatment indications and monitored through regular outpatient visits. During the five-year follow-up period, the following were observed: response to first-line therapy, progression-free survival, and overall survival. Statistical analysis was performed using IBM SPSS 22.0 software. Normality of distribution for continuous variables was tested using the Shapiro–

ne varijable testirana je korišćenjem Shapiro-Wilk-ovog testa jer je studija analizirana na uzorku manjem od 50 ispitanika. Za podatke koji su imali normalnu raspodelu korišćeni su parametarski testovi (Independent Sample T test), u slučaju odstupanja od normalne raspodele primenjivali smo neparametarske testove (Mann Whitney U test). Za određivanje korelacije između kvantitativnih varijabli koristili smo Pearsonov koeficijent korelacije u slučaju varijabli koje prate normalnu raspodelu, a Spearmanov koeficijent kada je postojalo odstupanje od normalne raspodele. Za statistički značajne p vrednosti smatrane su p vrednosti manje od 0,05. Studija je u celini sprovedena poštujući sve odredbe Helsinške deklaracije. Odobrena je i od strane Etičkog Odbora UKC Kragujevac (broj Odluke 1/25-835).

REZULTATI

Analizom rezultata utvrđeno je da je našu populaciju pacijenta dominantno činila populacija ženskog pola, 34 žene i 13 muškaraca, medijane starosti 60 godina (32–89). Većina pacijenata je na dijagnozi imala proširenu i uznapredovalu bolest, klinički stadijum CS III ili CS IV. Deskriptivna statistika naše ispitivane populacije prikazana je u **Tabeli 1**. Prema aktuelnim vodičima za

Wilk test due to the sample size being fewer than 50 subjects. For normally distributed data, parametric tests (Independent Samples t-test) were used; for data that deviated from normality, nonparametric tests (Mann–Whitney U test) were applied. To determine correlations between quantitative variables, Pearson's correlation coefficient was used for normally distributed variables, and Spearman's coefficient when deviation from normal distribution was present. A p -value of less than 0.05 was considered statistically significant. The study was conducted in full accordance with the principles of the Helsinki Declaration and was approved by the Ethics Committee of the University Clinical Center Kragujevac (Decision No. 1/25-835).

RESULTS

Analysis of the results showed that our patient population was predominantly female (34 women and 13 men) and had a median age of 60 years (32–89). The majority of patients had disseminated and advanced disease at diagnosis, clinical stage III or IV. Descriptive statistics of the studied population are presented in **Table 1**. According to current guidelines for the treatment of follicular lymphoma, during the observed period,

Tabela 1. Deskriptivne demografske karakteristike, kao i podaci o bolesti ispitivane populacije

Table 1. Descriptive demographic characteristics and disease-related data of the study population

Parametar / Parameter	Kategorija / Category	n (%)
Starost / Age	60 godina / years	
Pol / Sex	Muški / Male	13 (27.6%)
	Ženski / Female	34 (72.4%)
ECOG / ECOG	0	20 (42.5%)
	1	23 (48.9%)
	≥ 2	4 (8.6%)
FLIPI / FLIPI	≤ 1	9 (19%)
	2	11 (23.4%)
	≥ 3	27 (57.6%)
Prisustvo ektranodalne bolesti / Presence of extranodal disease	da / yes	18 (38.3%)
	ne / no	29 (61.7%)
Bulky bolest / Bulky disease	da / yes	8 (17%)
	ne / no	39 (83%)
Postizanje CR / Achievement of CR	da / yes	28 (59.6%)
	ne / no	19 (40.4%)
Primena terapije održavanja / Maintenance therapy	da / yes	37 (78.7%)
	ne / no	10 (21.3%)
Klinički stadijum bolesti / Clinical stage	I	0 (0%)
	II	2 (4.3%)
	III	15 (31.9%)
	IV	30 (63.8%)

lečenje folikularnog limfoma, u navedenom periodu posmatranja pacijenti su tretirani imunohemioterapijom po protkolu R-CHOP (rituximab + ciklofosamid + doksorubicin + vinkristin + prednizolon) u 34,8%, dok je imunohemioterapiju po protokolu G-CHOP (obinutuzumab + ciklofosamid + doksorubicin + vinkristin + prednizolon) primilo 65,2% pacijenata. Prosečan broj primenjenih ciklusa terapije za obe terapijske opcije bio je 7 (3–8). Što se tiče odgovora na prvu primenjenu terapijsku liniju 25 (53%) pacijenata postiglo je kompletnu remisiju bolesti, 17 (36%) pacijenata parcijalnu remisiju bolesti i 5 (11%) pacijenata stabilnu bolest. U korelaciji parametara krvne slike i biohemijskih parametara većina ispitivanih parametara nije pokazala statistički značajnu korelaciju sa tokom bolesti. Sa druge strane parametri hemostaze, fibrinogen, D-dimer, kao i pojedinačni parametri koncentracije laktat dehidrogenaze u serumu i % monocita u perifernoj krvi (PK) pokazali su značajnu korelaciju, prikazano u **Tabeli 2**. Koncentracija LDH u serumu naše grupe pacijenata ukazuje kroz koeficijent korelacije da što je niža vrednost LDH, duže je preživljavanje bez bolesti, kao i verovatnoća postizanja kompletne remisije, dok nije uočena korelacija sa sveukupnim preživljavanjem. Procenat monocita pozitivno korelira sa vremenom do progresije kao i sveukupnim preživljavanjem, dok ne utiče na postizanje kompletne remisije. Vrednosti fibrinogena i D-dimera pokazuju negativnu korelaciju sa preživljavanjem, dok ne utiču na postizanje CR.

Posebno je analizirana vrednost D-dimera i fibrinogena kod pacijenata sa folikularnim limfomom.

patients were treated with immunochemotherapy according to the R-CHOP protocol (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone) in 34.8%, while immunochemotherapy according to the G-CHOP protocol (obinutuzumab + cyclophosphamide + doxorubicin + vincristine + prednisolone) was administered in 65.2% of patients. The average number of administered therapy cycles for both therapeutic options was 7 (3–8). Regarding response to the first applied line of therapy, 25 (53%) patients achieved complete remission, 17 (36%) achieved partial remission, and 5 (11%) had stable disease. In the correlation analysis of hematological and biochemical parameters, most examined parameters did not show a statistically significant correlation with disease course, while, on the other hand, hemostatic parameters, fibrinogen, and D-dimer, as well as individual parameters such as serum lactate dehydrogenase concentration and the percentage of monocytes in peripheral blood, showed significant correlation, as presented in **Table 2**. Serum LDH concentration in our patient group shows, as indicated by the correlation coefficient, that lower LDH values are associated with longer progression-free survival and a higher probability of achieving complete remission, whereas no correlation with overall survival was observed. The percentage of monocytes positively correlates with time to progression and overall survival, but does not influence the achievement of complete remission. Fibrinogen and D-dimer values show a negative correlation with survival, while they do not influence the achievement of complete remission.

Tabela 2. Korelacija parametara krvne slike, hemostaze i diferencijalne leukocitarne formule sa parametrima toka bolesti (ukupno preživljavanje (OS), preživljavanje bez bolesti (PFS), postizanje kompletnog odgovora na prvu terapijsku liniju (CR))

Table 2. Correlation of hematological parameters, hemostatic parameters, and differential leukocyte count with disease outcome parameters (overall survival (OS), progression-free survival (PFS), achievement of complete response to first-line therapy (CR))

		OS	PFS	CR
LDH / LDH	Correlation coefficient	-0.153	-0.361	-0.375
	<i>p</i>	0.321	0.019	0.029
	N	44	42	47
% monocita u PK / % of monocytes in PK	Correlation coefficient	0.438	0.409	0.250
	<i>p</i>	0.007	0.005	0.154
	N	36	45	34
Fibrinogen / Fibrinogen	Correlation coefficient	-0.353	-0.361	-0.263
	<i>p</i>	0.019	0.019	0.133
	N	44	42	47
Koncentracija D-dimera ng/ml / D-dimer concentration ng/ml	Correlation coefficient	-0.555	-0.334	0.250
	<i>p</i>	< 0.001	0.031	0.154
	N	44	42	47

Pacijenti koji su pri dijagnozi imali povišene vrednosti D-dimera imali su kraće preživljavanje bez bolesti, i to pacijenti sa inicijalno povišenim vrednostima D-dimera imali su PFS $24,50 \pm 4,81$ meseci, dok su oni sa D-dimerom u granicama referentnih vrednosti imali PFS $36,48 \pm 5,99$ ($p = 0,015$). Slične rezultate dobili smo i sa vrednostima fibrinogena, pri čemu su pacijenti sa vrednostima fibrinogena u referentnom opsegu imala PFS $28,42 \pm 3,89$ meseci, odnosno oni sa inicijalno povišenim vrednostima fibrinogena PFS $15,91 \pm 5,09$ ($p = 0,044$).

Takođe, analizirane su i vrednosti D-dimera i njihova povezanost sa postizanjem kompletne remisije. Pacijenti koji su na prvu terapijsku liniju postignu kompletu remisiju imali su niže vrednosti D-dimera ($521,12 \pm 150,8$ ng/ml), dok pacijenti koji nisu postigli kompletu remisiju imali su više vrednosti D-dimera ($613,18 \pm 156,4$ ng/ml), $p = 0,054$.

DISKUSIJA

Razvojem brojnih terapijskih opcija koje su doprinele boljem preživljavanju pacijenata sa limfomom kao i primena personalizovane medicine, predstavile su potrebu za što jasnijim definisanjem prognoze toka bolesti i predikcije reagovanja na određene terapijske modalitete. U tom svetlu poslednjih godina brojna istraživanja usmerena su ka pronalaženju jednostavnog, a preciznog prognostičkog modela, testirajući brojne lako dostupne parametre i njihovu korelaciju sa tokom bolesti.

Najveći broj istraživanja u ovoj oblasti posvećen je agresivnim limfomima, dok je mali broj studija obuhvatio i niskogradusne limfome. Literaturni podaci nam ukazuju da se od laboratorijskih parametara u ne-Hoćkinovom limfomu tipa difuzni B krupnoćelijski limfom (NHL DBCL) najviše možemo osloniti na vrednosti D-dimera, vrednosti LDH, kao i kliničkim karakteristikama kako pacijenata (starost, performans status), tako i bolesti (klinički stadijum, genetski i molekularni potpis bolesti).

Naša studija ukazala je da od laboratorijskih parametara na tok bolesti kod folikularnog limfoma najviše uticaja ima preterapijska vrednost LDH, udeo monocita i bazofila u leukocitarnoj formuli kao i hemostazni parametri, fibrinogen i D-dimer. Studija Rachmani i saradnika posmatrala je parametar D-dimera kod pacijenata sa NHL DBCL i takođe potvrđuje da D-dimer pozitivno korelira sa tokom bolesti, što je on viši preterapijski, prognoza pacijenata je lošija [6]. Do sličnih rezultata došli su i Huang i saradnici, s tim što su D-dimer osim sa tokom bolesti korelirali i sa drugim lošim prognostnim parametrima (stadijumom bolesti, ECOG statusom, prisustvom B simp-

The D-dimer and fibrinogen levels in patients with follicular lymphoma were analyzed separately. Patients who had elevated D-dimer values at diagnosis had shorter progression-free survival, with patients with initially elevated D-dimer values having PFS of 24.50 ± 4.81 months, while those with D-dimer within reference values had PFS of 36.48 ± 5.99 months ($p = 0.015$). Similar results were observed for fibrinogen levels: patients with fibrinogen within the reference range had PFS of 28.42 ± 3.89 months, whereas those with initially elevated fibrinogen had PFS of 15.91 ± 5.09 months ($p = 0.044$). D-dimer values and their association with achieving complete remission were also analyzed, and patients who achieved complete remission after first-line therapy had lower D-dimer values (521.12 ± 150.8 ng/ml), while those who did not achieve complete remission had higher values (613.18 ± 156.4 ng/ml), $p = 0.054$.

DISCUSSION

The development of numerous therapeutic options that have improved the survival of lymphoma patients, as well as the application of personalized medicine, has created a need for a clearer definition of disease prognosis and for the prediction of response to specific therapeutic modalities. In this context, numerous studies in recent years have focused on identifying simple yet precise prognostic models by testing readily available parameters and their correlation with disease course.

The majority of studies in this field have focused on aggressive lymphomas, while only a small number have included low-grade lymphomas. Available literature indicates that, among laboratory parameters in diffuse large B-cell lymphoma (DLBCL), the most reliable are D-dimer levels, LDH levels, and clinical characteristics of both the patient (age, performance status) and the disease (clinical stage, genetic and molecular profile).

Our study showed that among laboratory parameters influencing disease course in follicular lymphoma, the most significant are pre-treatment LDH values, the proportions of monocytes and basophils in the leukocyte differential, and hemostatic parameters, fibrinogen, and D-dimer. The study by Rachmani et al. evaluated D-dimer levels in patients with DLBCL and confirmed that D-dimer levels positively correlate with disease course, with higher pre-treatment values indicating a worse prognosis [6]. Similar results were reported by Huang et al., who correlated D-dimer not only with disease course but also with other adverse prognostic parameters (disease stage, ECOG status, presence of B symptoms, IPI score), as were those of Liu et al. [7,8]. In the study by Geng

toma, IPI skorom), kao i Liu i saradnici [7,8]. U studiji Genga i saradnika laboratorijski parametri korelirani sa tokom bolesti kod pacijenata sa NHL DBCL pokazali su da starost, stadijum bolesti i vrednost LDH kao i vrednosti D-dimera predstavljaju negativan prognostični parametar u univarijantnoj analizi, dok se u multivarijantnoj samo LDH pojavljuje kao negativan prognostični parametar. Ipak autori zaključuju da vrednost D-dimera korelira sa veličinom tumorske mase i da veće prognozne vrednosti ima kod pacijenata u nižim kliničkim stadijumima [9]. U radu Bi i saradnika, D-dimer je prepoznat kao prognostični parametar kod pacijenata obolelih od NK-T ćelijskog NHL, približavajući prognozu ranih stadijuma sa visokim D-dimerom onom koju imaju uznapredovali stadijumi bez obzira na vrednosti D-dimera [10]. O analizi laboratorijskih parametara kod pacijenata sa indolentnim limfomima veoma je malo literaturnih podataka. Podaci uglavnom obuhvataju sve ne-Hoćkinove limfome, ili retko daju osvrt na pojedinačne podgrupe. U studiji Mazura i saradnika kod svih NHL upoređivani su parametri hemostaze (fibrinogen i D-dimer) sa parametrima neoangiogeneze (vaskularnog endotelnog faktora rasta (VEGF) i faktora rasta fibroblasta (FGF)), gde su potvrdili da D-dimer korelira sa stadijumom bolesti, dok su odnos fibrinogena i D-dimera u korelaciji sa odnosom VEGF/bFGF i doprinose neoangiogenezi u NHL [11]. Što se tiče radova koji su posmatrali nivo fibrinogena, jedan interesantan rad na malom broju ispitanika sugerše da je fibrinogen dobar prognostični parametar, kako na osnovu visokih preterapijskih vrednosti kao lošeg prognostičnog parametra, tako i na promenu fibrinogena nakon prvog ciklusa terapije. Pacijenti koji su normalizovali fibrinogen nakon prvog ciklusa terapije imali su bolje preživljavanje u odnosu na one kod kojih je fibrinogen ostao visok [12]. Dodatno razjašnjenje značaja nivoa fibroinogena kao i profila monocita periferne krvi kod pacijenata obolelih od NHL pruža nam studija Živković i saradnika. U ovoj studiji visoke vrednosti fibrinogena imaju negativan prognostični potencijal, kao i u našoj studiji. U njihovoj detaljnoj analizi posmatrane su i vrednosti tkivnog faktora, gde su u podgrupama limfoma (NHL DBCL, folikularni limfom, kao i Hoćkinov limfom) potvrđene i razlike među ovim podtipovima. Kod svih grupa prisutne su više vrednosti tkivnog faktora uz povećanje broja klasičnih monocita, dok kod folikularnog limfoma, kao niskogradusnog nema povećanja intermedijernih monocita, a samim tim je manja i sklonost ka hiperkoagulabilnosti. U navedenoj studiji nije kao poseban parametar analiziran procenat monocita u perifernoj krvi, već samo pojedinačne podgrupe, analizirane putem protočne citometrije

et al., laboratory parameters correlated with disease course in DLBCL patients showed that age, disease stage, LDH values, and D-dimer values represent negative prognostic factors in univariate analysis, while in multivariate analysis only LDH remained a negative prognostic factor, although the authors concluded that D-dimer correlates with tumor burden and has greater prognostic value in patients with lower clinical stages [9]. In the study by Bi et al., D-dimer was identified as a prognostic marker in patients with NK/T-cell lymphoma, bringing the prognosis of early-stage patients with high D-dimer levels closer to that of advanced-stage patients, regardless of D-dimer levels [10]. Data on laboratory parameters in patients with indolent lymphomas are scarce, as studies often include all non-Hodgkin lymphomas or provide only rare insights into specific subgroups. In the study by Mazur et al., hemostatic parameters (fibrinogen and D-dimer) were compared with neoangiogenesis parameters (vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)), confirming that D-dimer correlates with disease stage, while the fibrinogen/D-dimer ratio correlates with the VEGF/bFGF ratio and contributes to neoangiogenesis in NHL [11]. Regarding studies analyzing fibrinogen levels, one interesting study on a small number of subjects suggests that fibrinogen is a good prognostic parameter, both based on high pre-treatment values as a negative prognostic factor and on changes after the first cycle of therapy, where patients who normalized fibrinogen after the first cycle had better survival compared to those in whom fibrinogen remained elevated [12]. Additional clarification of the significance of fibrinogen levels and the profile of peripheral blood monocytes in NHL patients is provided by the study by Živković et al., which showed that high fibrinogen levels were associated with a negative prognosis, consistent with our findings. In their detailed analysis, tissue factor values were also examined, and differences among lymphoma subtypes (DLBCL, follicular lymphoma, and Hodgkin lymphoma) were confirmed. In all groups, higher tissue factor values were observed with increased classical monocytes, whereas in follicular lymphoma, as a low-grade lymphoma, there was no increase in intermediate monocytes and, consequently, a lower tendency toward hypercoagulability. In the aforementioned study, the percentage of monocytes in peripheral blood was not analyzed as a separate parameter; instead, individual subgroups were examined by flow cytometry and classified as classical or intermediate monocytes based on pan-monocytic marker expression [13].

i klasifikovane kao klasični i intermedijarni monociti prema ekspresiji panmonocitnih markera [13].

ZAKLJUČAK

U iskustvu našeg centra parametri hemostaze, fibrinogen i D-dimer pokazali su značajnu korelaciju sa tokom bolesti. Ograničenja naše sprovedene studije obuhvataju mali broj ispitanika, ali i činjenicu da u analizu nisu uključeni pacijenti koji su dijagnostikovani, ali u navedenom periodu nisu lečeni.

Sukob interesa: Nije prijavljen.

CONCLUSION

In our center's experience, hemostatic parameters, fibrinogen, and D-dimer showed significant correlations with disease course. Limitations of our study include a small sample size and the exclusion of patients diagnosed but not treated during the observed period.

Conflict of interest: None declared.

LITERATURA / REFERENCES

- Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022 Jul;36(7):1720-48. doi: 10.1038/s41375-022-01620-2. Erratum in: *Leukemia*. 2023 Sep;37(9):1944-51. doi: 10.1038/s41375-023-01962-5.
- Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022 Sep 15;140(11):1229-53. doi: 10.1182/blood.2022015851. Erratum in: *Blood*. 2023 Jan 26;141(4):437. doi: 10.1182/blood.2022019016.
- Cerhan JR. Epidemiology of Follicular Lymphoma. *Hematol Oncol Clin North Am*. 2020 Aug;34(4):631-46. doi: 10.1016/j.hoc.2020.02.001.
- Hübel K, Ghielmini M, Ladetto M, Gopal AK. Controversies in the Treatment of Follicular Lymphoma. *Hemasphere*. 2020 Jan 10;4(1):e317. doi: 10.1097/HS9.0000000000000317.
- Cartron G, Trotman J. Time for an individualized approach to first-line management of follicular lymphoma. *Haematologica*. 2022 Jan 1;107(1):7-18. doi: 10.3324/haematol.2021.278766.
- Rahchamani M, Sedghi M, Hakimi A, Nejatianfar M, Javaheri T, Tavakoli R, et al. Prognostic value of red blood cell distribution width and D-Dimer in diffuse large B-cell lymphoma: Systematic review and meta-analysis. *Cancer Rep (Hoboken)*. 2024 Jan;7(1):e1936. doi: 10.1002/cnr.21936.
- Huang H, Fan L, Fu D, Lin Q, Shen J. High pretreatment plasma D-dimer levels predict poor survival in patients with diffuse large B-cell lymphoma in the real world. *Transl Cancer Res*. 2021 Apr;10(4):1723-31. doi: 10.21037/tcr-20-2908.
- Liu B, Li B, Zhou P, Yue W, Wang T, Wang J, et al. Prognostic value of pretreatment plasma D-dimer levels in patients with diffuse large B cell lymphoma (DLBCL). *Clin Chim Acta*. 2018 Jul;482:191-8. doi: 10.1016/j.cca.2018.04.013.
- Geng YD, Chen YR, Jin J, Wang XD, Zhang S, Li DJ. Prognostic Value of D-Dimer in Patients with Diffuse Large B-cell Lymphoma: A Retrospective Study. *Curr Med Sci*. 2019 Apr;39(2):222-7. doi: 10.1007/s11596-019-2023-5.
- Bi XW, Wang L, Zhang WW, Sun P, Yan SM, Liu PP, et al. High Pretreatment D-Dimer Levels Correlate with Adverse Clinical Features and Predict Poor Survival in Patients with Natural Killer/T-Cell Lymphoma. *PLoS One*. 2016 Mar 31;11(3):e0152842. doi: 10.1371/journal.pone.0152842.
- Mazur G, Poreba M, Wrobel T, Poreba R, Pyszel A, Beck B, et al. Correlation between Angiogenic and Coagulation-Fibrinolysis Factors and Stage of Disease in Non Hodgkin's Lymphoma Patients. *Blood*. 2005 Nov 16;106(11):4678. doi: 10.1182/blood.V106.11.4678.4678.
- Tarek N, Younes S, Suliman MA, Ibrahim GA. Predictive utility of plasma fibrinogen level in B-cell lymphoma: a single-center cohort study. *Egypt. J. Haematol*. 2023 Apr-Jun;48(2):155-60. doi: 10.4103/ejh.ejh_67_22.
- Živković E, Mitrović-Ajtić O, Subotički T, Ivanović J, Otašević V, Đikić D, et al. Thromboinflammatory Biomarkers in Lymphomas: Linking Inflammation to Thrombosis Risk. *Int J Mol Sci*. 2025 Feb 26;26(5):2058. doi: 10.3390/ijms26052058.

AGING AS A MODULATOR OF MULTIPLE SCLEROSIS PATHOPHYSIOLOGY

Jasmina Đuretić¹

¹ Univerzitet u Beogradu, Farmaceutski fakultet, Katedra za patobiologiju, Beograd, Srbija

¹ University of Belgrade, Faculty of Pharmacy, Department of Pathobiology, Belgrade, Serbia

SAŽETAK

Populacija starijih pacijenata sa multiplom sklerozom se značajno povećava, uključujući osobe sa kasnim (nakon 50. godine) i veoma kasnim (nakon 60. godine) početkom bolesti. Starenje moduliše imunski i nervni sistem, doprinoseći transformaciji kliničkog toka u progresivni obrazac i povećanju rizika za razvoj progresije bolesti nezavisno od relapsa (PIRA). Takođe, multipla skleroza sa početkom u kasnijem životnom dobu karakteriše se češćim progresivnim fenotipom, manjom pojavom inflamatornih relapsa i kraćim vremenom do ostvarivanja invaliditeta. Starenje imunskog sistema (imunosenescencija) dovodi do sužavanja raznovrsnosti T-ćelijskog receptorskog repertoara, promena u broju i funkciji CD4+ i CD8+ T-limfocita, kao i do disbalansa u odnosu efektorskih i regulatornih T-limfocita. Na nivou centralnog nervnog sistema starenje doprinosi neurodegeneraciji kroz povećanu degeneraciju oligodendrocita, disfunkciju mikroglije, akumulaciju gvožđa, oksidativni stres, disfunkciju mitohondrija i smanjenje neuroprotektivnih mehanizama. Smanjena proliferacija i diferencijacija neuralnih stem ćelija, kao i strukturne i funkcionalne promene glutamatnih receptora, prevashodno N-metil-D-aspartat receptora, dodatno kompromituju neuroprotektivne i reparativne mehanizme. Razumevanje interakcija starenja i patofizioloških mehanizama multiple skleroze ključno je za razvoj ciljanih terapijskih strategija za sve brojniju populaciju starijih pacijenata sa multiplom sklerozom. Cilj ovog rada je da, kroz integrativni pregled dostupne literature, sagleda ulogu procesa starenja u modulaciji ključnih patofizioloških mehanizama multiple skleroze.

Ključne reči: starenje, multipla skleroza, imunosenescencija, neurodegeneracija

ABSTRACT

The number of older patients with multiple sclerosis is rising significantly, including individuals with late-onset disease (after age 50) and very late-onset disease (after age 60). Aging affects the immune and nervous systems, contributing to a shift in the clinical course towards a progressive pattern and increasing the risk of disease progression independent of relapse activity (PIRA). Additionally, late-onset multiple sclerosis is characterised by a more frequent progressive phenotype, fewer inflammatory relapses, and a shorter time to disability accumulation. Immune system aging (immunosenescence) leads to a reduced diversity of the T-cell receptor repertoire, changes in the number and function of CD4+ and CD8+ T lymphocytes, and an imbalance between effector and regulatory T cells. At the central nervous system level, aging contributes to neurodegeneration through increased oligodendrocyte degeneration, microglial dysfunction, iron accumulation, oxidative stress, mitochondrial dysfunction, and diminished neuroprotective mechanisms. Reduced proliferation and differentiation of neural stem cells, as well as structural and functional changes in glutamate receptors, primarily N-methyl-D-aspartate receptors, further compromise neuroprotective and reparative processes. Understanding the interactions between aging and the pathophysiological mechanisms of multiple sclerosis is crucial for developing targeted therapeutic strategies for the increasing population of older patients with multiple sclerosis. This paper aims to examine, through an integrative review of the available literature, the role of the aging process in modulating key pathophysiological mechanisms of multiple sclerosis.

Keywords: aging, multiple sclerosis, immunosenescence, neurodegeneration

Autor za korespondenciju:

Jasmina Đuretić

Katedra za patobiologiju, Farmaceutski fakultet, Univerzitet u Beogradu

Vojvode Stepe 450, 11221 Beograd, Srbija

Elektronska adresa: jasmina@pharmacy.bg.ac.rs

Corresponding author:

Jasmina Đuretić

Department of Pathobiology, Faculty of Pharmacy, University of Belgrade

450 Vojvode Stepe Street, 11221 Belgrade, Serbia

E-mail: jasmina@pharmacy.bg.ac.rs

Primljeno • Received: January 29, 2026;

Revidirano • Revised: March 2, 2026;

Prihvaćeno • Accepted: March 10, 2026;

Online first: March 25, 2026

DOI: 10.5937/smcl7-64495

UVOD

Prema podacima Internacionalne federacije za multiplu sklerozu od 2,8 miliona ljudi koji boluju od multiple skleroze, 1 od 10 osoba ima 65 godina i više. Multipla skleroza je bolest koja može trajati decenijama i većina ovih starijih bolesnika ima multiplu sklerozu duže od 20 godina [1]. Početak multiple skleroze je najčešće između 20. i 40. godine života, a relapsno-remitentni oblik bolesti pogađa oko 85% bolesnika [2]. Primarno-progresivna i sekundarno progresivna multipla skleroza počinju u sličnim godinama života tj. oko 45. godine i karakterišu se razvojem koji dovodi do akumulacije invaliditeta u sličnom vremenskom periodu [3,4]. Pokazano je da početni oblik bolesti, bilo da je reč o relapsno-remitentnom ili primarno-progresivnom obliku, zapravo ne utiče značajno na uzrast u kome dolazi do ostvarivanja ključnih faza invaliditeta [4]. Poslednjih decenija incidencija kasnog početka multiple skleroze tj. početka bolesti nakon 50. godine života se značajno povećala [5]. Takođe, uočeno je i značajno povećanje incidencije veoma kasnog početka multiple skleroze tj. nakon 60. godine života [6,7]. Kod pacijenata sa kasnim početkom multiple skleroze češće se javljao progresivni tok bolesti od samog početka [5].

Hronološko starenje predstavlja fiziološki proces, koji ima svoje reperkusije kako na centralni nervni sistem (CNS), tako i na imunski sistem. S druge strane, hronični inflamatorni proces i neurodegeneracija, koji su povezani sa multiplom sklerozom doprinose ubrzanom procesu biološkog starenja CNS [8]. Starenje imunskog sistema (imunosenescencija) pogađa kako urođeni tako i adaptivni imunski sistem. Posledice su brojne počevši od smanjenog imunološkog nadzora nad ćelijama koje su oštećene ili stare, preko promena u zastupljenosti i funkciji ćelija urođene imunosti, pa do izrazitih promena u T-ćelijskom kompartmanu [9,10].

Poslednjih godina uveden je koncept „progresije nezavisno od relapsne aktivnosti“ (engl. *progression independent of relapse activity*, PIRA), koji se odnosi na akumulaciju invaliditeta, bez prethodnog akutnog pogoršanja bolesti i koji ukazuje na neurodegeneraciju koja postoji nezavisno od zapaljenskog procesa u multiploj sklerozu [11]. U studiji Tur et al. (2022.) pokazano je da je stariji uzrast prilikom prvog napada bio u korelaciji sa većim rizikom od razvoja PIRA. Preciznije, rizik od razvoja PIRA se povećavao za 43% za svaku deceniju starosti više prilikom prvog napada [11]. Proces starenja povećava vulnerabilnost neurona, doprinosi akumulaciji oštećenja nervnog tkiva i istovremeno smanjuje njegovu funkcionalnu rezilijentnost i reparativni potencijal [12].

Cilj ovog rada je da, kroz integrativni pregled dostupne literature, sagleda ulogu procesa starenja u

INTRODUCTION

According to the Multiple Sclerosis International Federation, of the 2.8 million of people living with multiple sclerosis worldwide, one in ten people are aged 65 years or older. Because multiple sclerosis is a chronic condition that can persist for decades, most of these older patients have lived with the disease for more than 20 years [1]. The onset of multiple sclerosis most commonly occurs between the ages of 20 and 40, and the relapsing-remitting form of the disease affects approximately 85% of patients [2]. Primary-progressive and secondary-progressive multiple sclerosis typically begin at similar ages, around 45 years, and are characterized by disease progression that leads to the accumulation of disability over a comparable period of time [3,4]. Studies have shown that the initial form of multiple sclerosis, whether relapsing-remitting or primary-progressive, does not significantly influence the age at which key stages of disability are reached [4]. In recent decades, the incidence of late-onset multiple sclerosis, defined as disease onset after the age of 50, has increased significantly [5]. A notable rise has also been observed in the incidence of very late-onset multiple sclerosis, with disease onset occurring after the age of 60 [6,7]. In patients with late-onset multiple sclerosis, the disease more frequently follows a progressive course from the very onset [5].

Chronological aging is a physiological process that affects both the central nervous system (CNS) and the immune system. Conversely, chronic inflammatory processes and neurodegeneration associated with multiple sclerosis contribute to an accelerated process of biological aging of the CNS [8]. Aging of the immune system (immunosenescence) affects both the innate and adaptive immune systems. Its consequences are numerous, ranging from reduced immune surveillance of damaged or senescent cells, through changes in the distribution and function of innate immune cells, to pronounced alterations in the T-cell compartment [9,10].

In the recent years, the concept of "progression independent of relapse activity" (PIRA) has been introduced. It refers to the accumulation of disability in the absence of a preceding acute relapse and indicates neurodegeneration occurring independently of the inflammatory process in multiple sclerosis [11]. The study by Tur et al. (2022) showed that older age at the time of the first attack was associated with a higher risk of developing PIRA. More specifically, the risk of PIRA increased by 43% for each additional decade of age at the first attack in patients with multiple sclerosis [11]. The aging process increases neuronal vulnerability, promotes the accumulation of neural tissue damage,

modulaciji ključnih patofizioloških mehanizama multiple skleroze.

UTICAJ STARENJA NA REMODELOVANJE IMUNSKOG SISTEMA

Imunosencijencija predstavlja starenjem uslovljene strukturne i funkcionalne promene imunskog sistema, koje dovode do poremećaja njegove efikasnosti [13]. Starenje dovodi do promena u broju i funkciji imunskih ćelija, oslabljenog adaptivnog imunskog odgovora, održavanja niskostepene inflamacije i metaboličkih promena u imunskom sistemu [9,13].

Starenjem uslovljena involucija timusa, dovodi do progresivnog sužavanja perifernog repertoara naivnih T-limfocita. Ovaj deficit se delimično kompenzuje pojačanom homeostatskom proliferacijom i klonalnom ekspanzijom postojećih T-ćelijskih populacija, što rezultuje relativnom ekspanzijom memorijskog T-ćelijskog pula. Takvo remodelovanje adaptivnog imunskog sistema ima za posledicu smanjenu imunološku plastičnost i narušenu sposobnost generisanja efikasnih odgovora na nove ili tumorske antigene [14]. Homeostatska proliferacija i antigen-zavisna klonalna ekspanzija postojećih T-ćelijskih populacija predstavljaju mehanizme koji mogu omogućiti preživljavanje i ekspanziju autoreaktivnih T-ćelijskih klonova. Starenjem uslovljeno sužavanje raznovrsnosti T-ćelijskog receptorskog repertoara dovodi do narušene efikasnosti imunskog sistema i oslabljenih reparativnih mehanizama, čime se stvara okruženje pogodno za egzacerbaciju patološkog procesa i progresiju bolesti [15]. Pokazano je da starenje dovodi do značajnih promena u broju i funkciji CD4⁺ i CD8⁺ T-limfocita, pri čemu su ove promene izraženije u populaciji CD8⁺ T-ćelija, kako kod ljudi tako i u animalnim modelima [16,17]. Takođe, starenjem dolazi do povećanja broja regulatornih T-ćelija kod ljudi [18], a sličan trend zabeležen je i u animalnim modelima multiple skleroze [19,20]. Funkcionalna aktivnost regulatornih T-ćelija ostaje nepromenjena ili je čak povećana starenjem kod ljudi [18]. Međutim, rezultati studija na životinjama sugerišu da je moguće da akumulacija perifernih regulatornih T-ćelija (CD4⁺FoxP3⁺) odlaže početak bolesti kod starih jedinki, dok nakon njenog nastanka smanjena migracija ovih ćelija u CNS onemogućuje adekvatnu kontrolu progresivnog toka bolesti [20]. Kod starih miševa sa indukovanim animalnim modelom multiple skleroze uočena je izraženija plastičnost regulatornih T-limfocita (CD4⁺FoxP3⁺), koja se ogleda u ko-ekspresiji interferona (IFN)- γ i /ili interleukina (IL)-17 sa FoxP3, u poređenju sa mladim jedinkama [20]. Ovakva plastičnost regulatornih T-limfocita kod starih jedinki može dovesti do smanjenja njihove supresivne funkcije i posledičnog pojačavanja patoloških procesa u CNS-u.

and simultaneously reduces both functional resilience and the capacity for repair [12].

The aim of this paper is to examine, through an integrative review of the available literature, the role of the aging process in modulating the key pathophysiological mechanisms of multiple sclerosis.

INFLUENCE OF AGING ON IMMUNE SYSTEM REMODELING

Immunosenescence refers to the age-related structural and functional changes in the immune system that result in impaired immune efficiency [13]. Aging results in alterations in both the number and function of immune cells, a weakened adaptive immune response, persistent low-grade inflammation, and metabolic changes within the immune system [9,13].

Age-related involution of the thymus causes a gradual reduction in the peripheral repertoire of naïve T lymphocytes. This deficit is partially compensated by increased homeostatic proliferation and clonal expansion of existing T-cell populations, leading to a relative enlargement of the memory T-cell pool. This remodeling of the adaptive immune system leads to diminished immune plasticity and a reduced capacity to mount effective responses against new or tumor antigens [14]. Homeostatic proliferation and antigen-driven clonal expansion of existing T-cell populations are mechanisms that can support the survival and expansion of autoreactive T-cell clones. Aging-induced reduction in the diversity of the T-cell receptor repertoire impairs immune system efficiency and weakens reparative mechanisms, thereby creating conditions that favor exacerbation of the pathological process and disease progression [15]. Studies have shown that aging causes significant changes in the number and function of CD4⁺ and CD8⁺ T lymphocytes, with these changes being more pronounced in the CD8⁺ T-cell population, both in humans and in animal models [16,17]. Aging also results in an increased number of regulatory T-cells in humans [18], with a similar trend observed in animal models of multiple sclerosis [19,20]. The functional activity of regulatory T-cells remains unchanged, or may even increase, with aging in humans [18]. However, findings from animal studies suggest that the accumulation of peripheral regulatory T-cells (CD4⁺FoxP3⁺) may delay disease onset in older individuals, while after onset, their reduced migration into the CNS limits effective control of the progressive course of the disease [20]. In aged mice with an induced animal model of multiple sclerosis, regulatory T lymphocytes (CD4⁺FoxP3⁺) exhibited greater plasticity, reflected by the co-expression of interferon (IFN)- γ and/or interleukin (IL)-17 with FoxP3, compared to younger mice [20]. This plasticity

Pored toga, izražen disbalans između efektorskih i regulatornih T-ćelija može imati značajan uticaj na klinički tok multiple skleroze kod starijih bolesnika [18,20]. Ključni aspekti fiziološkog starenja T-limfocita prisutni su i kod pacijenata sa multiplom sklerozom [21,22]. Međutim, u studiji sprovedenoj na pacijentima sa multiplom sklerozom koji nisu prethodno dobijali imunomodulatornu terapiju, uočeno je značajno povećanje zastupljenosti aktiviranih i citotoksičnih CD4⁺ T-limfocita, posebno kod pacijenata starijih od 60 godina [21]. Akumulacija citotoksičnih CD4⁺ T-limfocita u starijoj populaciji bolesnika sa multiplom sklerozom može predstavljati važan patofiziološki mehanizam, imajući u vidu njihovu sposobnost da direktno oštećuju ćelije CNS-a i doprinose neurodegenerativnim procesima.

Sekretorni fenotip povezan sa senescencijom (engl. *senescence-associated secretory phenotype*, SASP) obuhvata skup funkcionalnih promena senescentnih ćelija, koje se manifestuju razvojem proinflamatornog fenotipa i povećanim oslobađanjem citokina, hemokina i drugih medijatora inflamacije [23]. U demijelinizovanim lezijama utvrđeno je povećanje ćelijske senescencije u mikroglijalnim ćelijama, koje je koreliralo sa smanjenim kapacitetom remijelinizacije kod starih miševa. Analiza SASP pokazala je povišenu koncentraciju hemokina C-C motiv ligand 11 (CCL11), poznatog i kao eotaksin-1 u lezijama starih jedinki, što je dovedeno u vezu sa narušenom maturacijom oligodendrocita [24]. Ovi nalazi sugerišu da bi ciljanje SASP faktora, poput eotaksina-1, naročito kod starijih bolesnika, moglo predstavljati potencijalni terapijski pristup za poboljšanje remijelinizacije u multiploj sklerozi.

ULOGA STARENJA U NEURODEGENERATIVNIM PROCESIMA MULTIPLE SKLEROZE

Starenje je glavni faktor rizika za većinu neurodegenerativnih bolesti i predstavlja jedan od ključnih bioloških procesa koji modulišu neurodegenerativne mehanizme u multiploj sklerozi. Mehanizmi kojima starenje potencijalno doprinosi neurodegeneraciji uključuju genomsku nestabilnost, skraćanje telomera, epigenetske promene, poremećenu homeostazu proteina, disfunkciju mitohondrija, ćelijsku senescenciju, poremećenu regulaciju nutrijentne signalizacije, iscrpljenost matičnih ćelija i izmenjenu intercelularnu komunikaciju [25,26]. Hronični inflamatorni proces u multiploj sklerozi, u kombinaciji sa kompromitovanom remijelinizacijom, doprinosi aksonalnoj degeneraciji, progresivnoj atrofiji CNS-a i egzacerbaciji kliničke manifestacije bolesti [27].

Multipla skleroza sa kasnim početkom karakteriše se češćim progresivnim fenotipom, manjom pojavom inflamatornih relapsa i kraćim vremenom do ostvarivanja

of regulatory T lymphocytes in older individuals can reduce their suppressive function, leading to an increase in pathological processes within the CNS. Moreover, a marked imbalance between effector and regulatory T-cells may significantly influence the clinical course of multiple sclerosis in elderly patients [18,20]. Key features of physiological T-lymphocyte aging are also observed in patients with multiple sclerosis [21,22]. However, in a study of multiple sclerosis patients who were naïve to immunomodulatory therapy, a significant increase in activated and cytotoxic CD4⁺ T lymphocytes was observed, particularly in patients over 60 years of age [21]. The accumulation of cytotoxic CD4⁺ T lymphocytes in the elderly population of multiple sclerosis patients may represent a key pathophysiological mechanism, given their capacity to directly damage CNS cells and contribute to neurodegenerative processes.

The senescence-associated secretory phenotype (SASP) encompasses a set of functional changes in senescent cells, characterized by the development of a pro-inflammatory profile and increased secretion of cytokines, chemokines, and other inflammatory mediators [23]. In demyelinated lesions, increased cellular senescence was observed in microglial cells, correlating with reduced remyelination capacity in aged mice. Analysis of SASP revealed elevated levels of the chemokine C-C motif ligand 11 (CCL11), also known as eotaxin-1, in the lesions of older individuals, which was associated with impaired oligodendrocyte maturation [24]. These findings suggest that targeting SASP factors, such as eotaxin-1, particularly in elderly patients, may represent a potential therapeutic strategy to enhance remyelination in Multiple Sclerosis.

THE ROLE OF AGING IN THE NEURODEGENERATIVE PROCESSES OF MULTIPLE SCLEROSIS

Aging is a major risk factor for most neurodegenerative diseases and one of the key biological processes that modulate neurodegenerative mechanisms in multiple sclerosis. Mechanisms through which aging may contribute to neurodegeneration include genomic instability, telomere shortening, epigenetic alterations, impaired protein homeostasis, mitochondrial dysfunction, cellular senescence, dysregulated nutrient signaling, stem cell exhaustion, and altered intercellular communication [25,26]. The chronic inflammatory process in multiple sclerosis, combined with impaired remyelination, contributes to axonal degeneration, progressive CNS atrophy, and worsening of the disease's clinical manifestations [27].

Late-onset multiple sclerosis is characterized by a more frequent progressive phenotype, fewer inflam-

invaliditeta [8,28]. Kod pacijenata kod kojih bolest započinje u mlađem životnom dobu, pokazano je da sa starenjem dolazi do smanjenja inflamatorne aktivnosti u CNS-u, nezavisno od dužine trajanja bolesti, što se klinički manifestuje redukcijom učestalosti relapsa [29]. Nasuprot tome, demijelinizacija i neurodegenerativni procesi postaju izraženiji sa starenjem bolesnika [8,30].

Veća životna dob u trenutku prvog kliničkog ispoljavanja multiple skleroze povezuje se sa povećanom verovatnoćom razvoja PIRA, što ukazuje na značajnu ulogu starenja u oblikovanju toka bolesti [31]. Savremena istraživanja pokazuju da se progresija bolesti može detektovati već u najranijim fazama multiple skleroze, pri čemu inflamatorni i neurodegenerativni mehanizmi funkcionišu kao deo jedinstvenog patofiziološkog kontinuuma u okviru kojeg se i pogoršanje vezano za relaps (engl. *relapse-associated worsening*, RAW) i PIRA javljaju od samog početka bolesti, dok starenje predstavlja jedan od ključnih modulatora kliničkog fenotipa bolesti [11,31].

Istraživanja na starim pacovima pokazuju da tokom starenja CNS-a dolazi do povećane degeneracije oligodendrocita i njihovih prekursora, što rezultuje gubitkom mijelina i sekundarno doprinosi razvoju aksonalne degeneracije [32]. Jedna od najizraženijih promena u oligodendrocitima povezanim sa starenjem jeste akumulacija oštećenja DNK, kojoj u značajnoj meri doprinose njihovi visoki metabolički zahtevi [33]. Ovi procesi dovode do smanjene sposobnosti remijelinizacije, čime se u multiploj sklerozi, naročito kod starijih bolesnika, dodatno pospešuje progresija neurodegenerativnih promena i akumulacija invaliditeta.

UTICAJ STARENJA NA AKTIVACIONI STATUS I FUNKCIONALNU DINAMIKU MIKROGLIJE U MULTIPLOJ SKLEROZI

Starenje moduliše aktivaciju i zastupljenost mikroglije, posebno u području oko plaka kod pacijenata sa multiplom sklerozom [34]. Proces starenja utiče kako na strukturne, tako i na funkcionalne karakteristike mikroglije. Studije na životinjskim modelima ukazuju da mikroglijalne ćelije sa starenjem zadobijaju hronično aktivirani fenotip, praćen smanjenjem njihove fagocitne sposobnosti [35,36]. Pored toga, starenje kompromituje i njihovu ulogu u imunološkom nadzoru mikrookruženja, dovodeći do smanjene dinamičnosti i gubitka razgranatog morfološkog fenotipa [37]. Ove starenjem uslovljene morfološke i funkcionalne promene mikroglije, koje obuhvataju perzistentnu niskostpenu aktivaciju uz istovremenu fagocitnu disfunkciju, mogu predstavljati jedan od ključnih mehanizama koji su u osnovi PIRA, doprinoseći degeneraciji aksona u odsustvu izraženog akutnog inflamatornog procesa.

matory relapses, and a shorter time to disability [8,28]. In patients whose disease begins at a younger age, aging has been shown to be associated with a decrease in inflammatory activity in the CNS, regardless of disease duration, which is clinically manifested by a reduced frequency of relapses [29]. In contrast, demyelination and neurodegenerative processes become more pronounced with advancing age [8,30].

Older age at the time of the first clinical manifestation of multiple sclerosis is associated with an increased likelihood of developing PIRA, indicating a significant role of aging in shaping the course of the disease [31]. Recent research shows that disease progression can be detected even in the earliest stages of multiple sclerosis, with inflammatory and neurodegenerative mechanisms operating as part of a single pathophysiological continuum in which both relapse-associated worsening (RAW) and PIRA occur from the very beginning of the disease, while aging represents one of the key modulators of the clinical phenotype [11,31].

Research in aged rats shows that during CNS aging there is increased degeneration of oligodendrocytes and their precursors, resulting in myelin loss and secondarily contributing to the development of axonal degeneration [32]. One of the most pronounced age-related changes in oligodendrocytes is the accumulation of DNA damage, which is largely driven by their high metabolic demands [33]. These processes reduce the capacity for remyelination, which in multiple sclerosis, particularly in older patients, further accelerates neurodegenerative progression and disability accumulation.

THE INFLUENCE OF AGING ON MICROGLIAL ACTIVATION AND FUNCTIONAL DYNAMICS IN MULTIPLE SCLEROSIS

Aging modulates microglial activation and abundance, particularly in the peri-plaque regions of patients with multiple sclerosis [34]. It affects both the structural and functional characteristics of microglia. Studies in animal models indicate that with aging, microglia acquire a chronically activated phenotype, accompanied by reduced phagocytic capacity [35,36]. In addition, aging impairs their role in immune surveillance of the microenvironment, resulting in reduced dynamism and a loss of their branched morphological phenotype [37]. These age-related morphological and functional changes in microglia, including persistent low-level activation with concomitant phagocytic dysfunction, may represent a key mechanism underlying PIRA, contributing to axonal degeneration even in the absence of pronounced acute inflammation.

Fiziološko starenje dovodi do akumulacije gvožđa u mikroglijalnim ćelijama. Takođe, kod pacijenata sa multiplom sklerozom, demijelinizacija oslobađa gvožđe iz oštećenih oligodendrocita i mijelina, koje potom preuzimaju mikroglijalne ćelije i makrofage. Posledično, dolazi do akumuliranja gvožđa u mikroglijalnim ćelijama, posebno na ivicama hronično aktivnih lezija. Ovo taloženje gvožđa povezuje se sa proinflamatornim fenotipom mikroglije, kao i povećanom sintezom slobodnih radikala kiseonika, što doprinosi hroničnoj neuroinflamaciji i progresivnoj neurodegeneraciji kod starijih bolesnika sa multiplom sklerozom [38].

STARENJEM USLOVLJENE PROMENE REPARATIVNIH MEHANIZAMA U MULTIPLOJ SKLEROZI

Patofiziološki mehanizmi koji su u osnovi PIRA povezuju se sa kompartmentalizacijom inflamatornog procesa unutar CNS-a, uz smanjeno učešće perifernih limfocita, kao i sa poremećajem reparativnih mehanizama [39]. Početak progresivnog toka bolesti korelira sa starenjem uslovljenim smanjenjem remijelinizacionog kapaciteta [40]. Kumulativno delovanje prethodno već opisanih mehanizama poput povećane degeneracije oligodendrocita, oksidativnog stresa, akumulacije gvožđa i mikroglijalne disfunkcije značajno ograničava remijelinizacioni kapacitet CNS-a u uslovima starenja. Pokazano je da se sa starenjem kod miševa smanjuje sposobnost neuralnih stem i progenitorskih ćelija da proliferišu i diferentuju, pri čemu epigenetske promene na nivou promotorskih regiona dovode do nishodne regulacije gena odgovornih za ove procese [41].

Starenje dovodi do strukturnih i funkcionalnih alteracija jonskih glutamatnih receptora, što je posebno izraženo kod *N*-metil-D-aspartat receptora (NMDAR), koji su ekspimirani kako na neuronima, tako i na ćelijama imunskog sistema [42,43]. S druge strane, kod pacijenata sa multiplom sklerozom pokazano je značajno povećanje nivoa glutamata [44]. U uslovima povišene koncentracije glutamata i starenjem izmenjene NMDAR signalizacije, može doći do slabljenja neuroprotektivnih mehanizama i povećanja rizika od glutatomom posredovane ekscitotoksičnosti. Primenom NMDAR antagonista u animalnom modelu multiple skleroze ostvaren je izraženiji terapijski efekat kod starih u odnosu na mlade jedinke, kako u pogledu kliničke slike, tako i u pogledu parametara oksidativnog stresa i antioksidativne zaštite moždanog tkiva [45].

Od neprocenljivog značaja je fokusiranje budućih istraživanja na razvoj terapijskih strategija usmerenih na delimičnu restauraciju remijelinizacionog kapaciteta kod starijih bolesnika sa multiplom sklerozom. Potencijalni pristupi obuhvataju farmakološku modulaci-

Physiological aging leads to iron accumulation in microglial cells. In patients with multiple sclerosis, demyelination releases iron from damaged oligodendrocytes and myelin, which is subsequently taken up by microglia and macrophages. As a result, iron accumulates in microglial cells, particularly at the edges of chronically active lesions. This iron deposition is associated with a proinflammatory microglial phenotype and increased synthesis of reactive oxygen species, contributing to chronic neuroinflammation and progressive neurodegeneration in elderly patients with multiple sclerosis [38].

AGING-ASSOCIATED CHANGES IN REPARATIVE MECHANISMS IN MULTIPLE SCLEROSIS

The pathophysiological mechanisms underlying PIRA are associated with compartmentalization of the inflammatory process within the CNS, reduced participation of peripheral lymphocytes, and disruption of reparative mechanisms [39]. The onset of a progressive disease course is associated with aging, resulting from reduced remyelination capacity [40]. The cumulative effect of the mechanisms described above, such as increased oligodendrocyte degeneration, oxidative stress, iron accumulation, and microglial dysfunction, significantly limits CNS remyelination capacity under aging conditions. Studies in mice have shown that aging reduces the proliferative and differentiative capacity of neural stem and progenitor cells, with epigenetic changes at promoter regions consequently regulating the genes responsible for these processes [41].

Aging induces structural and functional alterations of ionic glutamate receptors, particularly pronounced in *N*-methyl-D-aspartate receptors (NMDARs), which are expressed on both neurons and immune cells [42,43]. Conversely, patients with multiple sclerosis exhibit a significant increase in glutamate levels [44]. Under conditions of elevated glutamate concentration and aging-altered NMDAR signaling, neuroprotective mechanisms may be weakened, increasing the risk of glutamate-mediated excitotoxicity. Using NMDAR antagonists in an animal model of multiple sclerosis, a more pronounced therapeutic effect was achieved in old compared to young individuals, both in terms of the clinical picture and in terms of parameters of oxidative stress and antioxidant protection of brain tissue [45].

It is of utmost importance to focus future research on developing therapeutic strategies aimed at partially restoring remyelination capacity in elderly patients with multiple sclerosis. Potential approaches include pharmacological modulation of the SASP profile and microglial activity to create a pro-regener-

ju SASP profila i aktivnosti mikroglije u cilju stvaranja pro-regenerativnog mikrookruženja [24], primenu lekova koji utiču na funkciju mitohondrija i smanjuju oksidativni stres u oligodendrocitima i njihovim prekursorima [46], korišćenje molekula koji podstiču proliferaciju i diferencijaciju neuralnih stem i progenitorskih ćelija [47], kao i ciljanje glutamatne signalizacije, uključujući upotrebu NMDAR antagonista [45], u selektovanim podgrupama starijih bolesnika. Ovakvi pristupi mogli bi da doprinesu očuvanju rezidualnog reparativnog potencijala CNS-a i uspore akumulaciju invaliditeta, a njihovu efikasnost i bezbednost trebalo bi sistematski ispitati u kliničkim studijama koje eksplicitno uključuju stariju populaciju bolesnika.

ZAKLJUČAK

Poslednje dve decenije beleži se porast broja starijih pacijenata sa multiplom sklerozom, uključujući one kod kojih je bolest započela u mlađem životnom dobu (20-40 godina), kao i one sa kasnim početkom bolesti nakon 50. godine života. Proces starenja dovodi do značajnih promena imunskog i nervnog sistema, koje interaguju sa autoimunskim mehanizmom oštećenja CNS-a tokom multiple skleroze i doprinose transformaciji kliničkog toka u progresivni obrazac. Tokom vremena patofiziologija bolesti evoluira od aktivnih inflamatornih lezija ka hronično aktivnim, sporo ekspanzivnim lezijama koje karakteriše proinflamatorna mikroglija. Razumevanje uticaja starenja na molekularne i ćelijske mehanizme koji pokreću i održavaju bolest ključno je za primenu ciljanih terapija kod starijih bolesnika. Ova populacija bi trebalo da bude uključena u kliničke studije novih lekova, posebno onih koji modulišu aktivaciju mikroglije, poboljšavaju funkciju mitohondrija, pospešuju neuroprotekciju i remijelinizaciju ili antagonizuju NMDAR.

Zahvalnica: Ovaj rad finansiralo je Ministarstvo nauke, tehnološkog razvoja i inovacija Republike Srbije kroz dva ugovora sa Univerzitetom u Beogradu – Farmaceutskim fakultetom, broj 451-03-33/2026-03/200161 i broj 451-03-34/2026-03/200161.

Sukob interesa: Nije prijavljen.

active microenvironment [24], administration of drugs that enhance mitochondrial function and reduce oxidative stress in oligodendrocytes and their precursors [46], use of molecules that promote proliferation and differentiation of neural stem and progenitor cells [47], as well as targeting glutamate signaling, including the use of NMDAR antagonists [45], in selected subgroups of elderly patients. Such approaches could help preserve the residual reparative potential of the CNS and slow the accumulation of disability, and their effectiveness and safety should be systematically evaluated in clinical studies that explicitly include elderly patients.

CONCLUSION

Over the past two decades, the number of elderly patients with multiple sclerosis has increased, including individuals whose disease began at a younger age (20–40 years) as well as those with late-onset disease after 50 years of age. Aging induces significant changes in the immune and nervous systems, which interact with the autoimmune mechanisms of CNS damage in multiple sclerosis and contribute to the transformation of the clinical course into a progressive pattern. Over time, the pathophysiology of multiple sclerosis evolves from active inflammatory lesions to chronically active, slowly expanding lesions characterized by proinflammatory microglia. Understanding the effects of aging on the molecular and cellular mechanisms that initiate and sustain the disease is crucial for applying targeted therapies in elderly patients. This population should be included in clinical trials of new drugs, particularly those that modulate microglial activation, enhance mitochondrial function, promote neuroprotection and remyelination, or antagonize NMDARs.

Acknowledgement: This work has been financed by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia through two contracts with the University of Belgrade Faculty of Pharmacy, number 451-03-33/2026-03/200161 and number 451-03-34/2026-03/200161.

Conflict of interest: None declared.

LITERATURA / REFERENCES

- Multiple Sclerosis International Federation. Living well with MS as you grow older [Internet]. London: Multiple Sclerosis International Federation; 2022 [cited 2025 Oct 1]. Available from: <https://www.msif.org/wp-content/uploads/2023/01/Ageing-Booklet-WEB-Final.pdf>
- Cunill V, Massot M, Clemente A, Calles C, Andreu V, Núñez V, et al. Relapsing-Remitting Multiple Sclerosis Is Characterized by a T Follicular Cell Pro-Inflammatory Shift, Reverted by Dimethyl Fumarate Treatment. *Front Immunol*. 2018 May 29;9:1097. doi: 10.3389/fimmu.2018.01097.
- Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in multiple sclerosis. *Neurology*. 2011 Sep 27;77(13):1246-52. doi: 10.1212/WNL.0b013e318230a17d.
- Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain*. 2006 Mar;129(Pt 3):595-605. doi: 10.1093/brain/awh714.
- Prosperini L, Lucchini M, Ruggieri S, Tortorella C, Haggiag S, Mirabella M, et al. Shift of multiple sclerosis onset towards older age. *J Neurol Neurosurg Psychiatry*. 2022 Apr 27;jnnp-2022-329049. doi: 10.1136/jnnp-2022-329049.
- Solaro C, Ponzio M, Moran E, Tanganelli P, Pizio R, Ribizzi G, et al. The changing face of multiple sclerosis: Prevalence and incidence in an aging population. *Mult Scler*. 2015 Sep;21(10):1244-50. doi: 10.1177/1352458514561904.
- Capasso N, Virgilio E, Covelli A, Giovannini B, Foschi M, Montini F, et al. Aging in multiple sclerosis: from childhood to old age, etiopathogenesis, and unmet needs: a narrative review. *Front Neurol*. 2023 Jun 2;14:1207617. doi: 10.3389/fneur.2023.1207617.
- Filippi M, Preziosa P, Barkhof F, Ciccarelli O, Cossarizza A, De Stefano N, et al. The ageing central nervous system in multiple sclerosis: the imaging perspective. *Brain*. 2024 Nov 4;147(11):3665-80. doi: 10.1093/brain/awae251.
- Gao H, Nepovimova E, Adam V, Heger Z, Valko M, Wu Q, et al. Age-associated changes in innate and adaptive immunity: role of the gut microbiota. *Front Immunol*. 2024 Sep 16;15:1421062. doi: 10.3389/fimmu.2024.1421062.
- Lewis ED, Wu D, Meydani SN. Age-associated alterations in immune function and inflammation. *Prog Neuropsychopharmacol Biol Psychiatry*. 2022 Aug 30;118:110576. doi: 10.1016/j.pnpbp.2022.110576.
- Tur C, Carbonell-Mirabent P, Cobo-Calvo Á, Otero-Romero S, Arrambide G, Midaglia L, et al. Association of Early Progression Independent of Relapse Activity With Long-term Disability After a First Demyelinating Event in Multiple Sclerosis. *JAMA Neurol*. 2023 Feb 1;80(2):151-60. doi: 10.1001/jamaneurol.2022.4655.
- Iaffaldano P, Portaccio E, Lucisano G, Simone M, Manni A, Guerra T, et al.; Italian Multiple Sclerosis Register. Multiple Sclerosis Progression and Relapse Activity in Children. *JAMA Neurol*. 2024 Jan 1;81(1):50-8. doi: 10.1001/jamaneurol.2023.4455. Erratum in: *JAMA Neurol*. 2024 Jan 1;81(1):88. doi: 10.1001/jamaneurol.2023.5461.
- Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. Immunosenescence: molecular mechanisms and diseases. *Signal Transduct Target Ther*. 2023 May 13;8(1):200. doi: 10.1038/s41392-023-01451-2.
- Thomas R, Wang W, Su DM. Contributions of Age-Related Thymic Involution to Immunosenescence and Inflammaging. *Immun Ageing*. 2020 Jan 20;17:2. doi: 10.1186/s12979-020-0173-8.
- Amoriello R, Mariottini A, Ballerini C. Immunosenescence and Autoimmunity: Exploiting the T-Cell Receptor Repertoire to Investigate the Impact of Aging on Multiple Sclerosis. *Front Immunol*. 2021 Dec 1;12:799380. doi: 10.3389/fimmu.2021.799380.
- Nikolich-Zugich J, Li G, Uhrhlab JL, Renkema KR, Smithey MJ. Age-related changes in CD8 T cell homeostasis and immunity to infection. *Semin Immunol*. 2012 Oct;24(5):356-64. doi: 10.1016/j.smim.2012.04.009.
- Stojić-Vukanić Z, Pilipović I, Djikić J, Vujnović I, Nacka-Aleksić M, Bufan B, et al. Strain specificities in age-related changes in mechanisms promoting and controlling rat spinal cord damage in experimental autoimmune encephalomyelitis. *Exp Gerontol*. 2018 Jan;101:37-53. doi: 10.1016/j.exger.2017.11.002.
- Churov AV, Mamashov KY, Novitskaia AV. Homeostasis and the functional roles of CD4+ Treg cells in aging. *Immunol Lett*. 2020 Oct;226:83-9. doi: 10.1016/j.imlet.2020.07.004.
- Djikić J, Nacka-Aleksić M, Pilipović I, Kosec D, Arsenović-Ranin N, Stojić-Vukanić Z, et al. Age-related changes in spleen of Dark Agouti rats immunized for experimental autoimmune encephalomyelitis. *J Neuroimmunol*. 2015 Jan 15;278:123-35. doi: 10.1016/j.jneuroim.2014.12.014.
- Wang W, Thomas R, Oh J, Su DM. Accumulation of pTreg cells is detrimental in late-onset (aged) mouse model of multiple sclerosis. *Aging Cell*. 2022 Jun;21(6):e13630. doi: 10.1111/acer.13630.
- Zuroff L, Rezk A, Shinoda K, Espinoza DA, Elyahu Y, Zhang B, et al. Immune aging in multiple sclerosis is characterized by abnormal CD4 T cell activation and increased frequencies of cytotoxic CD4 T cells with advancing age. *EBio-Medicine*. 2022 Aug;82:104179. doi: 10.1016/j.ebiom.2022.104179.
- Eschborn M, Pawlitzki M, Wirth T, Nelke C, Pfeuffer S, Schulte-Mecklenbeck A, et al. Evaluation of Age-Dependent Immune Signatures in Patients With Multiple Sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2021 Oct 19;8(6):e1094. doi: 10.1212/NXI.0000000000001094.
- Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther*. 2023 Jun 8;8(1):239. doi: 10.1038/s41392-023-01502-8.
- Gross PS, Durán-Laforet V, Ho LT, Melchor GS, Zia S, Manavi Z, et al. Senescent-like microglia limit remyelination through the senescence associated secretory phenotype. *Nat Commun*. 2025 Mar 7;16(1):2283. doi: 10.1038/s41467-025-57632-w.
- Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol*. 2019 Oct;15(10):565-81. doi: 10.1038/s41582-019-0244-7.
- Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature*. 2016 Nov 10;539(7628):180-6. doi: 10.1038/nature20411.
- Mey GM, Mahajan KR, DeSilva TM. Neurodegeneration in multiple sclerosis. *WIREs Mech Dis*. 2023 Jan;15(1):e1583. doi: 10.1002/wsbm.1583.
- Alroughani R, Akhtar S, Ahmed S, Behbehani R, Al-Hashel J. Is Time to Reach EDSS 6.0 Faster in Patients with Late-Onset versus Young-Onset Multiple Sclerosis? *PLoS One*. 2016 Nov 1;11(11):e0165846. doi: 10.1371/journal.pone.0165846.
- Coerver EM, Kaçar S, Ciccarelli O, Sormani MP, Barkhof F, Arnold DL, et al. Ageing is associated with reduced inflammatory disease activity independent of disease duration in relapsing multiple sclerosis trial populations. *Mult Scler*. 2024 Sep;30(10):1296-308. doi: 10.1177/13524585241272938.
- Zuo M, Ramaglia V, Gommerman JL. Age-related changes in multiple sclerosis and experimental autoimmune encephalomyelitis. *Semin Immunol*. 2022 Jan;59:101631. doi: 10.1016/j.smim.2022.101631.
- Portaccio E, Bellinva A, Fonderico M, Pastò L, Razzolini L, Totaro R, et al. Progression is independent of relapse activity in early multiple sclerosis: a real-life cohort study. *Brain*. 2022 Aug 27;145(8):2796-805. doi: 10.1093/brain/awac111.
- Sugiyama I, Tanaka K, Akita M, Yoshida K, Kawase T, Asou H. Ultrastructural analysis of the paranodal junction of myelinated fibers in 31-month-old-rats. *J Neurosci Res*. 2002 Nov 1;70(3):309-17. doi: 10.1002/jnr.10386.

33. Tse KH, Herrup K. DNA damage in the oligodendrocyte lineage and its role in brain aging. *Mech Ageing Dev.* 2017 Jan;161(Pt A):37-50. doi: 10.1016/j.mad.2016.05.006.
34. Kessler W, Thomas C, Kuhlmann T. Microglia activation in periplaque white matter in multiple sclerosis depends on age and lesion type, but does not correlate with oligodendroglial loss. *Acta Neuropathol.* 2023 Dec;146(6):817-28. doi: 10.1007/s00401-023-02645-2.
35. Thomas AL, Lehn MA, Janssen EM, Hildeman DA, Chougnnet CA. Naturally-aged microglia exhibit phagocytic dysfunction accompanied by gene expression changes reflective of underlying neurologic disease. *Sci Rep.* 2022 Nov 14;12(1):19471. doi: 10.1038/s41598-022-21920-y.
36. Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol.* 2013 Feb;39(1):19-34. doi: 10.1111/j.1365-2990.2012.01306.x.
37. Damani MR, Zhao L, Fontainhas AM, Amaral J, Fariss RN, Wong WT. Age-related alterations in the dynamic behavior of microglia. *Aging Cell.* 2011 Apr;10(2):263-76. doi: 10.1111/j.1474-9726.2010.00660.x.
38. Gillen KM, Mubarak M, Nguyen TD, Pitt D. Significance and In Vivo Detection of Iron-Laden Microglia in White Matter Multiple Sclerosis Lesions. *Front Immunol.* 2018 Feb 19;9:255. doi: 10.3389/fimmu.2018.00255.
39. Calabrese M, Preziosa P, Scalfari A, Colato E, Marastoni D, Absinta M, et al. Determinants and Biomarkers of Progression Independent of Relapses in Multiple Sclerosis. *Ann Neurol.* 2024 Jul;96(1):1-20. doi: 10.1002/ana.26913.
40. Kuhlmann T, Moccia M, Coetzee T, Cohen JA, Correale J, Graves J, et al; International Advisory Committee on Clinical Trials in Multiple Sclerosis. Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol.* 2023 Jan;22(1):78-88. doi: 10.1016/S1474-4422(22)00289-7.
41. Li M, Guo H, Carey M, Huang C. Transcriptional and epigenetic dysregulation impairs generation of proliferative neural stem and progenitor cells during brain aging. *Nat Aging.* 2024 Jan;4(1):62-79. doi: 10.1038/s43587-023-00549-0.
42. Magnusson KR. Aging of the NMDA receptor: from a mouse's point of view. *Future Neurol.* 2012 Sep;7(5):627-37. doi: 10.2217/fnl.12.54.
43. Boldyrev AA, Bryushkova EA, Vladychenskaya EA. NMDA receptors in immune competent cells. *Biochemistry (Mosc).* 2012 Feb;77(2):128-34. doi: 10.1134/S0006297912020022.
44. Al Gawwam G, Sharquie IK. Serum Glutamate Is a Predictor for the Diagnosis of Multiple Sclerosis. *ScientificWorldJournal.* 2017;2017:9320802. doi: 10.1155/2017/9320802.
45. Bufan B, Ćuruvija I, Blagojević V, Grujić-Milanović J, Prijić I, Radosavljević T, et al. NMDA Receptor Antagonist Memantine Ameliorates Experimental Autoimmune Encephalomyelitis in Aged Rats. *Biomedicines.* 2024 Mar 23;12(4):717. doi: 10.3390/biomedicines12040717.
46. Campbell G, Licht-Mayer S, Mahad D. Targeting mitochondria to protect axons in progressive MS. *Neurosci Lett.* 2019 Sep 25;710:134258. doi: 10.1016/j.neulet.2019.05.012.
47. Harlow DE, Honce JM, Miravalle AA. Remyelination Therapy in Multiple Sclerosis. *Front Neurol.* 2015 Dec 10;6:257. doi: 10.3389/fneur.2015.00257.

HIRURŠKI TRETMAN RADIJACIJOM INDUKOVANOG OSTEOSARKOMA PREDNJEG ZIDA GRUDNOG KOŠA NAKON KARCINOMA DOJKE: PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

SURGICAL TREATMENT OF RADIATION-INDUCED ANTERIOR CHEST WALL OSTEOSARCOMA AFTER BREAST CARCINOMA: A CASE REPORT

Stevan Čičić¹, Aleksandar Ristanović^{1,2}, Mladen Prčević³, Nebojša Marić^{1,2}, Mlađana Savić¹

¹ Vojnomedicinska akademija, Klinika za grudnu i kardiohirurgiju, Beograd, Srbija

² Univerzitet odbrane, Vojnomedicinske akademija, Medicinski fakultet, Beograd, Srbija

³ Vojnomedicinska akademija, Klinika za plastičnu hirurgiju i opekotine, Beograd, Srbija

¹ Military Medical Academy, Clinic for Chest and Cardiosurgery, Belgrade, Serbia

² University of Defense, Military Medical Academy, Medical Faculty, Belgrade, Serbia

³ Military Medical Academy, Clinic for Plastic Surgery and Burns, Belgrade, Serbia

SAŽETAK

Uvod/Cilj: Radioterapija kod karcinoma dojke može retko da dovede do pojave radijacijom indukovano osteosarkoma (RIOS), jako agresivnog maligniteta. Cilj ovog rada je da prikaže specifičan hirurški tretman i agresivnost ovog retkog malignog tumora.

Prikaz slučaja: Pacijentkinja stara 63 godine, primljena je na Odeljenje grudne hirurgije Vojnomedicinske akademije zbog velike egzulcerišuće sternalne mase sa secernacijom purulentnog sadržaja, koja je inicijalno pogrešno shvaćena kao recidiv 15 godina nakon tretmana karcinoma dojke, i anemije. Biopsijom je dokazan visoko gradusni osteosarkom na terenu prethodnog tretmana radioterapijom. Isključenjem metastatske bolesti, nakon neoadjuvantne hemioterapije, učinjena je resekcija sarkoma, sternuma i anteriornih delova, od III–VII rebara, uz pripadajuća meka tkiva zida grudnog koša. Rekonstrukcija zida grudnog koša je učinjena titanijumskim pločicama i klipsevima, kao i miokutanom režnjem najšireg leđnog mišića (lat. *musculus latissimus dorsi*). Usled pojave recidiva, učinjena je dodatna resekcija manubriuma i anteriornih okrajaka II rebara, uz pripadajuća meka tkiva. Godinu dana nakon prve operacije, verifikovana je promena potkožja leve pektoralne regije, suspekt na recidiv, koja je odstranjena radi histopatološke verifikacije.

Zaključak: RIOS zida grudnog koša pokazuje agresivniji tok i lošiju prognozu od sporadičnih sarkoma, sa većom stopom recidiva uprkos širokoj resekciji, kao što je pokazano u ovom slučaju. Rekonstrukcija titanijumskim pločicama i klipsevima, nakon opsežne resekcije prednjeg grudnog zida, pruža izvodljivu rigidnu alternativu za uspostavljanje stabilnosti. Ovaj slučaj naglašava važnost prepoznavanja RIOS-a kao retke, ali ozbiljne kasne komplikacije radioterapije karcinoma dojke, te ističe složenost i specifičnost hirurškog lečenja i rekonstrukcije neophodnih za optimalne ishode.

Ključne reči: sternalna masa, resekcija, rigidna rekonstrukcija, titanijumske pločice, titanijumski klipsevi, miokutani režanj, rekonstrukcija mekih tkiva

ABSTRACT

Introduction/Objective: Radiotherapy for breast cancer can rarely lead to radiation-induced osteosarcoma (RIOS), a highly aggressive malignancy. This article aims to present the specificity of the surgical treatment applied and the level of aggressiveness of this rare malignant tumor.

Case report: A 63-year-old female patient was admitted to the Chest Surgery Department of the Military Medical Academy due to a large exulcerated sternal mass releasing a purulent secretion, initially misdiagnosed as recurrent breast carcinoma 15 years post-treatment, and anemia. Biopsy confirmed high-grade osteosarcoma following prior radiotherapy. After metastasis was ruled out, the patient received neoadjuvant chemotherapy and underwent radical resection of the sarcoma, sternum, anterior III–VII ribs, and adjacent soft tissues. Chest wall reconstruction was achieved using titanium bars, clips, and a latissimus dorsi myocutaneous flap. Upon local recurrence, further resection of the manubrium and anterior II ribs, with soft tissues, was performed. A year after the initial operation, a suspicious subcutaneous mass in the left pectoral region was excised for histopathological analysis.

Conclusion: RIOS of the chest wall exhibits a more aggressive course and worse prognosis than sporadic chest wall sarcomas, with higher rates of recurrence despite wide resection, as demonstrated in this case. Reconstruction with titanium bars and clips, after extensive anterior chest wall resection, provides a rigid and feasible alternative for restoring stability. This case underscores the importance of recognizing RIOS as a rare but serious late complication of breast cancer radiotherapy and highlights the complexity and specificity of surgical management and reconstruction for optimal outcomes.

Keywords: sternal mass, resection, rigid reconstruction, titanium bars, titanium clips, myocutaneous flap, soft tissue reconstruction

Autor za korespondenciju:

Stevan Čičić

Klinika za grudnu i kardiohirurgiju, Vojnomedicinska akademija
Crnotravska 17, 11000 Beograd, Srbija

Elektronska adresa: stevanmed@yahoo.com

Corresponding author:

Stevan Čičić

Clinic for Chest and Cardiosurgery, Military Medical Academy
17 Crnotravska Street, 11000 Belgrade, Serbia

E-mail: stevanmed@yahoo.com

Primljeno • Received: December 12, 2025; **Revidirano • Revised:** January 13, 2026; **Prihvaćeno • Accepted:** January 19, 2026; **Online first:** March 25, 2026

DOI: 10.5937/smcl7-63424

UVOD

Osteosarkomi čine 10%–15% svih primarnih malignih tumora zida grudnog koša koji su zastupljeni u svega 1%–2% svih primarnih tumora [1]. Povezanost radioterapije (RT) u sklopu onkološkog lečenja karcinoma dojke i pojave radijacijom indukovano osteosarkoma (RIOS) u zračnoj regiji, iako je izuzetno retko, već je opisano i poznato. Ovi osteosarkomi su po pravilu znatno većeg malignog potencijala i ređi nego sporadični osteosarkomi. Hirurgija je i dalje prvi izbor u multimodalnom lečenju ovih sarkoma.

PRIKAZ SLUČAJA

Pacijentkinja, starosti 63 godine, primljena je na Kliniku za grudnu hirurgiju Vojnomedicinske akademije zbog velike egzulcerišuće sternalne mase sa secernacijom purulentnog sadržaja i anemijom. Onkološko lečenje karcinoma dojke, 15 godina unazad, započeto je obostranom mastektomijom, nakon čega je u adjuvantnom režimu nastavljeno primenom hemioterapije (HT) (četiri ciklusa adriamicin-ciklofosamid + četiri ciklusa taxotera) i radioterapije. Potom je od strane nadležnog konzilijuma indicovana primena hormonalne terapije (tamoksifen) u trajanju od pet godina.

U sklopu redovnih kontrola onkologa, snimanjem grudnog koša multislajsnim skenerom (engl. *multi-slice computed tomography* – MSCT), otkrivena je osteolitična tumorska promena veličine pet centimetara u predelu sternuma, koja je išla u prilog metastaskom karcinomu dojke uz opisane nespecifične mikronodularne promene u plućima. Scintigrafija skeleta pokazala je da opisana promena zauzima distalne partije tela grudne kosti i ksifoidnog nastavka i da pokazuje pojačanu akumulaciju radiofarmaka.

Na onkološkom konzilijumu promena je inicijalno shvaćena kao relaps primarnog karcinoma, te je lečenje prema konzilijarnoj odluci nastavljeno primenom hormonske terapije.

Na MSCT-u grudnog koša, učinjenom nakon pet meseci od inicijalnog na kojem je viđena promena, postojala je progresija sa tumorom ukupne veličine 5 cm x 5 cm x 8,5 cm, te je pacijentkinja upućena na biopsiju ovog tumora (patohistološki (PH) nalaz: nekonk-luzivan). Rebiopsija je zatim učinjena mesec dana kasnije i patohistološki je potvrđeno da se radi o osteosarkomu, te je konzilijarno indicovana i sprovedena HT po protokolu adriamicin-ifosfamid (ukupno četiri ciklusa).

Na kontrolnom MSCT-u grudnog koša i abdomena, četiri meseca nakon PH verifikacije i neposredno nakon poslednjeg ciklusa HT, opisuje se velika ekspanzivna tumorska masa tela sternuma sa većim kalcifikatima i cističnom komponentom koja vrši destrukciju kosti, egzulceriše kožu i propagira retrosternalno sa kom-

INTRODUCTION

Osteosarcomas account for 10%–15% of all primary malignant tumors of the chest wall, which, in turn, account for only 1%–2% of all primary tumors [1]. The association between radiotherapy (RT) applied as a part of breast cancer oncological treatment and the occurrence of radiation-induced osteosarcoma (RIOS) in the radiation region, although extremely rare, has been previously described. These osteosarcomas have a significantly higher malignant potential and are rarer than sporadic osteosarcomas. Surgery is still the treatment of first choice in the multimodal treatment of these sarcomas.

CASE REPORT

A 63-year-old female patient was admitted to the Clinic for Thoracic Surgery of the Military Medical Academy due to a large exulcerated sternal mass with purulent discharge and anemia. The patient had received oncological treatment for breast cancer 15 years earlier. She first underwent bilateral mastectomy, followed by adjuvant chemotherapy (CHT) (four cycles of Adriamycin–Cyclophosphamide and four cycles of Taxotere) and radiotherapy. Finally, the tumor board recommended hormonal therapy (tamoxifen) for a period of five years.

During routine follow-up, a multi-slice computed tomography (MSCT) chest scan revealed an osteolytic tumor lesion measuring five centimeters in the region of the sternum, suggestive of metastatic breast carcinoma, along with described multiple nonspecific micronodular changes in the lungs. Bone scintigraphy showed that the described lesion involved the distal portions of the sternal body and the xiphoid process and demonstrated increased radiotracer uptake.

The oncological tumor board initially interpreted the lesion as a relapse of the primary carcinoma, and made a decision that treatment should be continued with hormonal therapy.

The chest MSCT performed five months after the initial scan that had initially detected the lesion, showed a progression, with the tumor measuring 5 cm x 5 cm x 8.5 cm in total. The patient was therefore referred for biopsy of the tumor (pathohistological (PH) finding: inconclusive). A rebiopsy was performed one month later, and pathohistological analysis confirmed osteosarcoma. Based on the decision made by the tumor board, chemotherapy according to the adriamycin–ifosfamide protocol was indicated and administered (a total of four cycles).

The follow-up MSCT of the chest and abdomen performed four months after pathohistological (PH) verification and immediately after the last cycle of che-



Slika 1. Egzulcerišući purulentno secernirajući tumor prednjeg zida grudnog koša pre prve operacije

Figure 1. Exulcerated purulent-secreting tumor of the anterior chest wall before the first operation



Slika 2. Rigidna rekonstrukcija titanijumskim klipsevima i pločicama – prva operacija

Figure 2. Rigid reconstruction with titanium clips and bars – first operation

presijom desne pretkomore i potiskivanjem medijastinuma ulevo (**Slika 1**). U plućnom parenhimu nalaz bez fokalnih lezija, u medijastinumu bez limfadenopatije; nalaz u abdomenu uredan.

Multidisciplinarnim pristupom, nakon konzilijarnog prikaza, doneta je odluka o sprovođenju hirurškog lečenja – široke resekcije osteosarkoma anteriornog zida grudnog koša sa rigidnom i mekotktivnom rekonstrukcijom defekta.

U sklopu preoperativne pripreme učinjeno je snimanje torakodorsalnih arterija kolor Doplerom, pri čemu je nalaz bio uredan – obe arterije su imale fiziološki protok, a propratne vene su bile bez znakova tromboze. Izvršena je *en bloc* resekcija osteosarkoma sa većim delom tela sternuma i ksifoidnog nastavka sternuma, uz resekciju anteriornih delova III–VII rebara obostrano do četiri cm od margina tumorske mase, sa pratećim mekotktivnim strukturama prednjeg zida grudnog koša i resekcijom perikarda. Za rigidnu rekonstrukciju korišćeni su titanijumski klipsevi i titanijumske pločice. Ideja rekonstrukcije nije bila simulacija zamene strukturama nalik sternumu nego horizontalno spajanje pločicama – premošćavanje paralelnih rebara. Učinjena je fiksacija klipseva na paralelnim rebrima III, IV i V rebru desno i levo i premošćavanje pločicama koje spajaju klipseve na pomenutim rebrima (**Slika 2**). Uz pomoć specijalno dizajniranih instrumenata ali i klip-

motherapy, revealed a large expansive tumor mass of the body of the sternum, with larger calcifications and a cystic component causing bone destruction, exulcerating the skin, and propagating retrosternally with compression of the right atrium and displacement of the mediastinum to the left (**Image 1**). In the pulmonary parenchyma there were no focal lesions; the mediastinum showed no lymphadenopathy; the abdominal findings were unremarkable.

Through a multidisciplinary approach, after presentation to the tumor board, a decision was made to proceed with surgical treatment – a wide resection of the osteosarcoma of the anterior chest wall with rigid and soft-tissue reconstruction of the defect.

As part of preoperative preparation, imaging of the thoracodorsal arteries was performed using color Doppler ultrasonography. The findings were normal – both arteries showed physiological flow, and the accompanying veins had no signs of thrombosis.

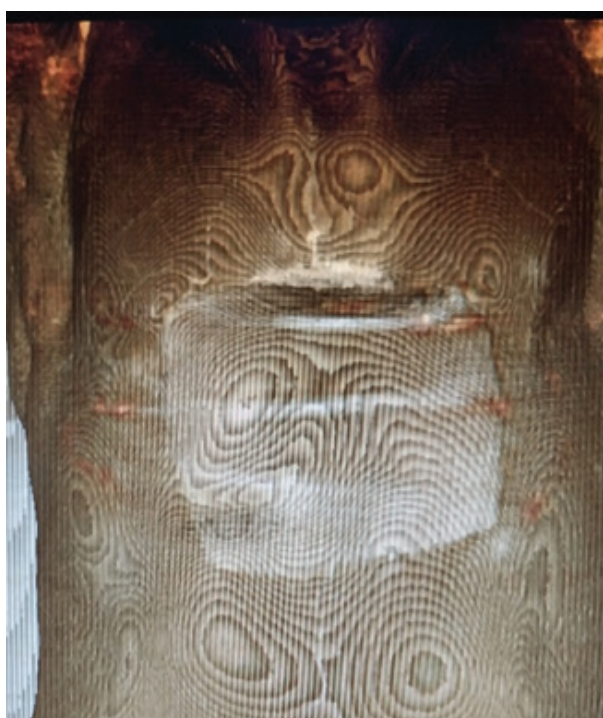
An *en bloc* resection of the osteosarcoma was performed together with the greater part of the body of the sternum and the xiphoid process, with resection of the anterior portions of the third through seventh ribs bilaterally up to four centimeters from the margins of the tumor mass, along with the adjacent soft-tissue structures of the anterior chest wall and resection of the pericardium. Titanium clips and bars were used



Slika 3. Odignut miokutani flap latisimusa – prva operacija

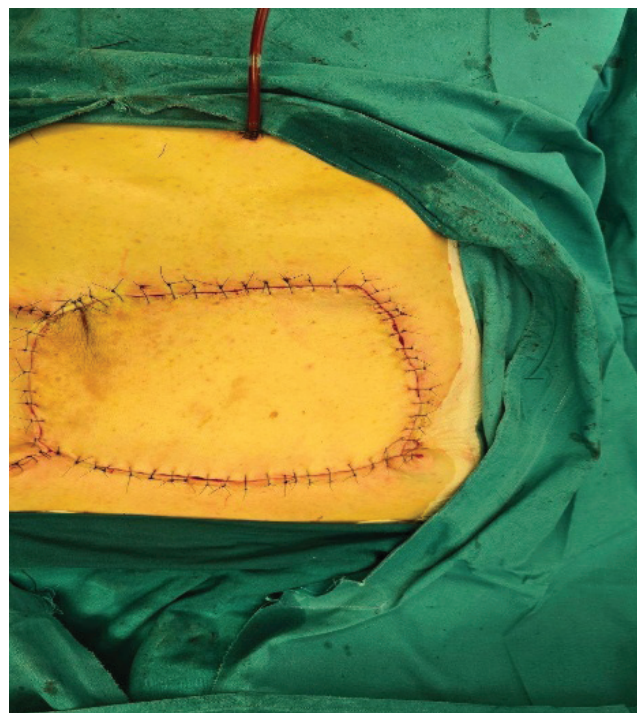
Figure 3. Raised latissimus dorsi myocutaneous flap – first operation

seva, moguće je upravljati velikim opsegom različitih uglova u sve tri ose i napraviti najstabilniji i najbolji 3D izgled.



Slika 5. Multiplanarna rekonstrukcija mekotkivnih komponenti nakon druge operacije

Figure 5. Multiplanar reconstruction of soft-tissue components after the second operation



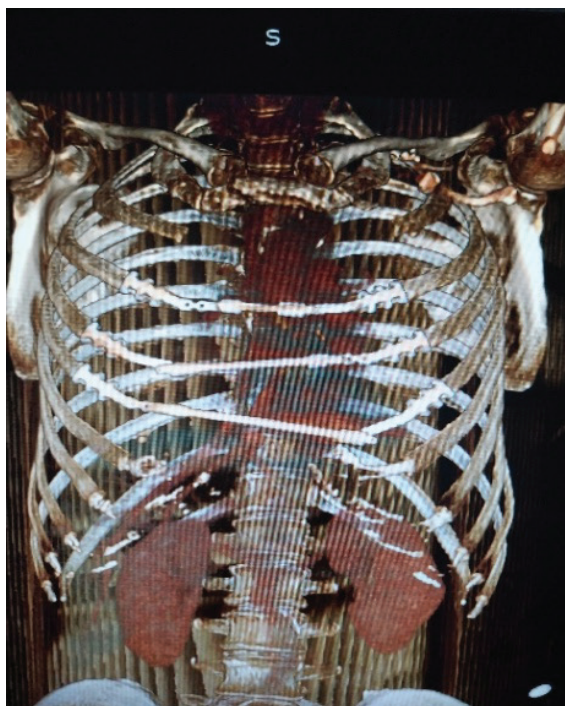
Slika 4. Zatvoren defekt anteriornog zida grudnog koša – prva operacija

Figure 4. Closed defect of the anterior chest wall – first operation

for rigid reconstruction. The concept of reconstruction was not to simulate replacement with structures resembling the sternum but rather to connect the ribs horizontally, with bars bridging the parallel ribs. Clips were fixed to the parallel ribs III, IV, and V on the right and left sides, and bridging bars were placed connecting the clips on the aforementioned ribs (Figure 2). With the help of specially designed instruments, as well as the clips themselves, it is possible to manipulate a wide range of different angles in all three axes and achieve the most stable and optimal three-dimensional configuration.

After osteosynthesis, reconstruction of the defect was performed using a myocutaneous flap of the latissimus dorsi muscle, while the secondary defect on the back was partially closed directly, sewn in layers, and partially reconstructed using a previously harvested Thiersch skin graft from the region of the right thigh.

The patient was extubated early and generally tolerated the intervention well. After drainage was reduced, the bilateral pleural drains, as well as the aspiration drain for control of bleeding from the myocutaneous flap, were removed. The wounds healed *per primam*, with adequate acceptance of the graft and myocutaneous flap and daily dressing. The patient was discharged for further home treatment on the twentieth postoperative day without significant complications.



Slika 6. Multiplanarna rekonstrukcija rigidnih komponenti nakon druge operacije

Figure 6. Multiplanar reconstruction of rigid components after the second operation

Nakon rigidne rekonstrukcije, učinjena je rekonstrukcija defekta miokutanim režnjem najšireg leđnog mišića, a sekundarni defekt na leđima je delimično direktno ušiven po slojevima, a delimično rekonstruisan prethodno uzetim graftom kože po Tiršu sa regije desne natkolenice.

Pacijentkinja je rano ekstubirana i generalno je dobro podnela navedenu intervenciju. Po smanjenju drenaže, odstranjeni su obostrani pleuralni drenovi kao i aspiracioni dren za kontrolu krvarenja režnja. Rane su zarasle *per primam*, uz adekvatno prihvatanje grafta i miokutanog flapa i svakodnevno previjanje. Pacijentkinja je otpuštena na dalje kućno lečenje dvadesetog postoperativnog dana bez značajnih komplikacija.

Dobijen je sledeći PH nalaz: solitarni tumor 220 mm x 130 mm, visoko gradusni osteosarkom (engl. *osteosarcoma high grade*) (G3) u pT2 stadijumu (*WHO Classification of Bone Tumors, 5th Edition*). Na resekcionom rubu grudne kosti prisutno tumorsko tkivo RR1; na ostalim strukturama bez tumorskog tkiva. Imunofenotip tumorskih ćelija: Vimentin +, SATB +/-, SMA +/-, CD 31 -, CD 34 -, EMA -, S100 -/+.

Konzilijarnom odlukom, tri meseca nakon operacije, lečenje je nastavljeno primenom tri ciklusa hemioterapije po protokolu adriamicin-ifosfamid. Kontrolno MSCT snimanje grudnog koša, šest meseci nakon operacije i

The following PH finding was obtained: solitary tumor measuring 220 mm x 130 mm, high-grade osteosarcoma (G3) in pT2 stage (*WHO Classification of Bone Tumors, 5th Edition*). Tumor tissue was present at the sternal resection margin (R1); no tumor tissue was present in the other structures. Immunophenotype of the tumor cells: Vimentin +, SATB +/-, SMA +/-, CD31 -, CD34 -, EMA -, S100 -/+.

In keeping with the tumor board decision, three months after the operation, treatment was continued with three cycles of chemotherapy according to the adriamycin – ifosfamide protocol. Follow-up MSCT imaging of the chest, six months after surgery and one and a half months after the last administered cycle of chemotherapy, showed the following finding: presence of the residual/recurrent previously described tumor lesion of the proximal part of the sternum measuring 45 mm x 62 mm.

The tumor board again indicated surgical treatment, and seven months after the first operation a partial resection of the distal part of the manubrium of the sternum was performed with en bloc resection of the anterior portions of the second ribs bilaterally and wedge resection of the portion of the left lung adherent to the tumor, i.e., subtotal resection of the sternum with preservation of the sternoclavicular and sternocostal connections with wedge resection of the left lung. In the second operation there was no need for additional reconstruction.

The following PH finding was obtained: *Osteosarcoma "high-grade" in textu ossealis costae infiltrativum*. No tumor tissue was present at the sternal resection margin (R0). Tumor cells were present in the lateral soft-tissue structures of the chest wall and in the lungs – R1 resection.

MSCT of the chest, three months after the second operation, detected three oval-shaped, soft-tissue lesions, partially calcified, with central hypodense zones suggestive of necrosis. The first lesion was positioned mediastinally, para-aortically, at position 6. The second was on the right side, anteriorly, supradiaphragmally, adjacent to the diaphragmatic pleura and posterior contour of the anterior chest wall. The third lesion was positioned paramediastinally, adjacent to the superior vena cava. All three lesions measured approximately two centimeters in diameter, primarily corresponding to residual/recurrent disease or metastases of the treated neoplastic lesion.

The tumor board indicated cyclophosphamide monotherapy for the duration of one month.

Less than a year after the first operation, clinical examination verified a tumor lesion in the subcutaneous tissue of the left pectoral region, which was oval-

jedan i po mesec nakon poslednjeg ordiniranog ciklusa hemioterapije pokazalo je sledeći nalaz – prisutan rest/recidiv ranije opisivane tumorske promene proksimalnog dela sternuma, prečnika 45 mm x 62 mm.

Ponovo je konzilijum indikovao operativno lečenje, te je sedam meseci nakon prve operacije učinjena parcijalna resekcija distalnog dela manubrijuma grudne kosti sa *en bloc* resekcijom prednjih delova drugog rebra obostrano i klinastom resekcijom uz tumor adherentnog dela levog pluća, odnosno subtotalna resekcija sternuma sa poštedom sternoklavikularnih i sternokostalnih veza sa klinastom resekcijom levog pluća. U drugoj operaciji nije bilo potrebe za dodatnom rekonstrukcijom.

Dobijen je sledeći PH nalaz: *Osteosarcoma „high-grade“ in textu ossealis costae infiltrativum*. Na resekcijom rubu grudne kosti nema tumorskog tkiva R0. Na mekotkivnim strukturama zida grudnog koša bočno i u plućima prisutne tumorske ćelije – R1 resekcija.

Na MSCT-u grudnog koša, tri meseca od druge operacije, detektuju su tri ovalne mekotkivne promene, delimično kalcifikovane, sa centralnim hipodenznim zonama u prilog nekrozi – prva promena medijastinalno paraaortalno na poziciji 6, druga, sa desne strane anteriorno supradijafragmalno uz dijafragmalnu pleuru i posteriornu konturu anteriornog zida grudnog koša, i treća paramedijastinalno uz gornju šuplju venu; sve tri promera oko dva centimetra najpre odgovaraju restu/recidivu ili metastazama tretirane neoplazme.

Konzilijum je indikovao ciklofosamid u monoterapiji u trajanju od mesec dana.

Nepunih godinu dana nakon prve operacije, kliničkim pregledom je verifikovana tumorska promena potkožja leve pektoralne regije, ovalnog oblika, promera oko četiri centimetra, bezbolna, mobilna u odnosu na podlogu, suspektna na recidiv, te je odstranjena radi PH verifikacije. Odlučeno je da se ostale promene ne reseciraju u tom trenutku.

Godinu dana nakon inicijalne hirurgije, pacijentkinja je dobrog opšteg stanja, motivisana za dalje multidisciplinarno sagledavanje i odabir najefektivnijeg, ali i najracionalnijeg pristupa lečenju.

DISKUSIJA

Osteosarkomi zida grudnog koša imaju značajno lošiju prognozu od sarkoma drugih regija, sa petogodišnjim preživljavanjem od 15%–20% [1]. Radijacijom indukovani osteosarkomi (RIOS) imaju još goru prognozu od sporadičnih osteosarkoma, odlikuje ih visok gradus, značajna mitotska aktivnost, agresivniji tok i lošija prognoza [2,3]. Kad god je to moguće, za tumore zida grudnog koša potrebno je preoperativno učiniti biopsiju. Iglena ili kor biopsija je uglavnom dovoljna. Incizi-

shaped, approximately four centimeters in diameter, painless, mobile relative to the underlying tissue, suspect of recurrence. The lesion was therefore removed for PH verification. It was decided that the other lesions would not be resected at that time.

A year after the initial surgery, the patient is in good general condition, motivated for further multidisciplinary evaluation and selection of the most effective, but also the most rational therapeutic approach.

DISCUSSION

Osteosarcomas of the chest wall have a significantly poorer prognosis than sarcomas of other regions, with a five-year survival rate of 15%–20% [1]. Radiation-induced osteosarcomas (RIOS) have an even worse prognosis than sporadic osteosarcomas; they are characterized by high grade, significant mitotic activity, a more aggressive course, and poorer prognosis [2,3]. Whenever possible, tumors of the chest wall should undergo preoperative biopsy. Needle or core biopsy is generally sufficient. Incisional biopsy may be performed to obtain a larger sample in rare tumors.

In our patient, the lesion was identified and monitored on consecutive contrast-enhanced CT scans of the chest and abdomen. The introduction of PET-CT imaging into standard preoperative preparation, along with magnetic resonance imaging of the head, might better select patients, potentially better demarcate the tumor, and ultimately provide better surgical outcomes.

After pathohistological confirmation, multidisciplinary assessment, and induction chemotherapy, surgery is the treatment of choice when feasible [4]. The greatest challenge in the surgical treatment of this disease is planning and performing reconstruction of the defect created by radical resection of such a tumor. Historically, reconstruction of the resected sternum has always been more difficult than reconstruction of other bony structures. However, with the introduction of the technique that uses titanium clips and bars, it has become feasible [5]. Titanium has exceptional strength, it is not prone to frequent infections, and when the described technique is applied it can mimic the normal movements of the chest wall [6,7].

In the literature, the expert consensus is that for high-grade tumors of the chest wall a distance of four centimeters from the macroscopically visible tumor is necessary. However, in radiation-induced osteosarcomas, additional caution is required because of the high rate of local recurrence (39%) and spreading of malignancy (27%) [8]. Rigid reconstruction, particularly in subtotal sternotomy, is feasible and may be considered as the initial treatment for osteosarcomas of the

ona biopsija se može učiniti radi obezbeđivanja većeg uzorka kod retkih tumora.

Kod naše pacijentkinje promena je identifikovana i praćena na konsektivnim skener snimcima grudnog koša i abdomena sa kontrastom. Uvođenje PET CT snimanja u standardnoj preoperativnoj pripremi, uz magnetnu rezonancu glave, možda bi bolje selektovalo pacijente, potencijalno bolje demarkiralo tumor, i u krajnjem ishodu hirurški dalo bolje rezultate.

Nakon patohistološke potvrde, multidisciplinarne procene i indukcione hemioterapije, hirurgija je metod izbora, ukoliko je izvodljiva [4]. Najveći izazov za hirurški tretman ove bolesti jeste planiranje i sprovođenje rekonstrukcije defekta nastalog radikalnom resekcijom ovakvih tumora. Resecirani sternum je kroz istoriju uvek bio teži za rekonstrukciju od ostalih koštanih struktura, ipak uvođenjem tehnike titanijumskih klipseva i pločica postao je izvodljiv [5]. Titanijum ima izuzetnu čvrstinu, nije podložan čestim infekcijama, a primenom opisane tehnike može da imitira uobičajene pokrete grudnog koša [6,7].

U literaturi, konsenzus stručnjaka jeste da je za visokogradusne tumore zida grudnog koša neophodna udaljenost četiri centimetra od makroskopski vidljivog tumora, ipak kod radijacijom indukovanih osteosarkoma treba biti dodatno oprezan zbog visoke stope lokalnog recidiva (39%) i širenja maligniteta (27%) [8]. Rigidna rekonstrukcija, pogotovo kod subtotalne sternotomije je izvodljiva i možda bi trebalo da bude inicijalni tretman kod osteosarkoma distalnog sternuma, u slučaju da bolest nije proširena, ali svakom pacijentu treba pristupiti individualno.

Transpozicija miokutanog režnja najšireg leđnog mišića je često dovoljna za mekotkivni defekt, ipak u slučaju da nije dovoljna može se planirati i transpozicija transversalnog režnja *ravnog trbušnog mišića* (lat. *musculus rectus abdominis*). Sekundarni defekt na leđima nastao nakon transpozicije miokutanog režnja najšireg leđnog mišića se aproksimira i smanjuje okolnim tkivom, pogotovo kod osoba koje imaju, uslovno rečeno „višak tkiva“, a ostatak se pokriva autotransplantatom kože po Tiršu iz regije natkolenice, u našem slučaju sa desne strane.

Postoperativni tok je protekao uredno, sa manjim bolovima, mada kod resekcija koštanih struktura bol može biti neizdrživ i teško kupiran kombinacijom opioidnih i neopiodnih analgetika sa tendencijom da pređe u bol hroničnog karaktera. Manjem bolu sigurno doprinosi disekcija neurovaskularne peteljke prilikom pripreme rebara radi aplikacije titanijumskih klipseva. Ukoliko bi se titanijumski klipsevi pritegli neurovaskularnom peteljkom za rebra to bi dovelo do značajnog bola. R0 resekcija je obavezna za bolje preživljavanje.

distal sternum when the disease is not disseminated, although each patient should be approached individually.

Transposition of the myocutaneous latissimus flap is often sufficient for the soft-tissue defect. However, if it is insufficient, transposition of a transverse rectus abdominis muscle flap can also be applied. The secondary defect on the back created after transposition of the myocutaneous latissimus flap is approximated and reduced by surrounding tissues, especially in individuals who have “excess tissue,” while the remainder is covered with a Thiersch skin autograft from the thigh region, in our case from the right side.

Postoperative recovery was uneventful, with mild pain, although in resections of bony structures the pain can be unbearable and difficult to manage with a combination of opioid and non-opioid analgesics, and may have the tendency of becoming chronic. The precise dissection of the neurovascular pedicle during the preparation of the ribs for the application of titanium clips certainly contributes to less pain. If the titanium clips were to clamp the neurovascular bundle to the ribs, this would lead to significant pain. R0 resection is mandatory for improved survival.

In our patient, in the first procedure, due to a positive sternal margin and microscopic presence of tumor cells, the operation did not achieve R0 resection, while the lateral soft-tissue margins and resected ribs achieved R0 resection. During the second operation, after recurrence, the lateral soft-tissue component did not achieve R0 resection, whereas the sternum did.

In such patients, a multidisciplinary approach is essential. In addition to surgery, induction and adjuvant chemotherapy may be effective. In our patient, chemotherapy was ineffective. In R1 resections, adjuvant radiotherapy may be attempted. However, since the osteosarcoma developed in previously irradiated tissue, the final effect and the potential benefit-to-harm ratio are issues of concern. In certain circumstances, stereotactic body radiation therapy (SBRT) may yield acceptable results [9]. In some cases, the use of SBRT as adjuvant therapy after breast cancer, or, in fact, the use of more precise radiation therapy compared with conventional methods, may potentially reduce the incidence of RIOS [10].

Conflict of interest: None declared.

Kod naše pacijentkinje, u prvom aktu, zbog pozitivne margine sternuma i mikroskopskog prisustva tumorskih ćelija, operacija nije zadovoljila R0 resekciju, dok su bočne mekotkivne margine i resecirana rebra zadovoljile R0 resekciju. Pri drugoj operaciji, nakon recidiva, bočna mekotkivna komponenta nije zadovoljila R0 resekciju dok sternum jeste.

Kod ovakvih pacijenata, važan je multidisciplinarni pristup. Osim hirurgije, indukciona i adjuvantna hemoterapija mogu imati efekta. Kod naše pacijentkinje, hemoterapija nije bila učinkovita. Za R1 resekcije može da se pokuša sa adjuvantnom radioterapijom, ali s obzirom da je osteosarkom nastao na terenu radijacije, postavlja se pitanje krajnjeg efekta i odnosa – potencijalna dobit naspram potencijalne štete. U određenim okolnostima stereotaktička telesna radioterapija (engl. *stereotactic body radiation therapy* (SBRT)) može dati prihvatljive rezultate [9]. U pojedinim slučajevima, primena SBRT u adjuvantnom režimu, nakon karcinoma dojke, odnosno, primena preciznije zračne terapije u odnosu na konvencionalnu, potencijalno smanjuje učestalost radijacijom indukovano osteosarkoma [10].

Sukob interesa: Nije prijavljen.

LITERATURA / REFERENCES

1. Shah AA, D'Amico TA. Primary chest wall tumors. J Am Coll Surg. 2010 Mar;210(3):360-6. doi: 10.1016/j.jamcollsurg.2009.11.012.
2. Virtanen A, Pukkala E, Auvinen A. Incidence of bone and soft tissue sarcoma after radiotherapy: a cohort study of 295,712 Finnish cancer patients. Int J Cancer. 2006 Feb 15;118(4):1017-21. doi: 10.1002/ijc.21456.
3. Bjerkehagen B, Småstuen MC, Hall KS, Skjeldal S, Smeland S, Fosså SD. Why do patients with radiation-induced sarcomas have a poor sarcoma-related survival? Br J Cancer. 2012 Jan 17;106(2):297-306. doi: 10.1038/bjc.2011.559.
4. Schwarz RE, Burt M. Radiation-associated malignant tumors of the chest wall. Ann Surg Oncol. 1996 Jul;3(4):387-92. doi: 10.1007/BF02305669.
5. Scarci M. Veritas® and STRATOSTM: An Innovative Paradigm for Chest Wall Reconstruction with a Biological Patch and Titanium Bars. CTSNet [Internet]. Chicago (IL): CTSNet; 2011 Jan 2 [Accessed: Dec 7, 2025]. Available from: <https://www.ctsnet.org/article/veritas%C2%AE-and-stratos%E2%84%A2-innovative-paradigm-chest-wall-reconstruction-biological-patch-and>
6. Palade E, Titu IM, Fodor L, Ciorba IM, Jentimir I, Teterea F, et al. Sternal Resections: An Attempt to Find the Ideal Reconstruction Method. Medicina (Kaunas). 2025 Apr 21;61(4):763. doi: 10.3390/medicina61040763.
7. Coonar AS, Wihlm JM, Wells FC, Qureshi N. Intermediate outcome and dynamic computerised tomography after chest wall reconstruction with the STRATOS titanium rib bridge system: video demonstration of preserved bucket-handle rib motion. Interact Cardiovasc Thorac Surg. 2011 Jan;12(1):80-1. doi: 10.1510/icvts.2010.249615.
8. Inchaustegui ML, Kon-Liao K, Ruiz-Arellanos K, Silva GAE, Gonzalez MR, Pretell-Mazzini J. Treatment and Outcomes of Radiation-Induced Soft Tissue Sarcomas of the Extremities and Trunk-A Systematic Review of the Literature. Cancers (Basel). 2023 Nov 25;15(23):5584. doi: 10.3390/cancers15235584.
9. Brown LC, Lester RA, Grams MP, Haddock MG, Olivier KR, Arndt CA, et al. Stereotactic body radiotherapy for metastatic and recurrent ewing sarcoma and osteosarcoma. Sarcoma. 2014;2014:418270. doi: 10.1155/2014/418270.
10. Pollock BE, Link MJ, Stafford SL, Parney IF, Garces YI, Foote RL. The Risk of Radiation-Induced Tumors or Malignant Transformation After Single-Fraction Intracranial Radiosurgery: Results Based on a 25-Year Experience. Int J Radiat Oncol Biol Phys. 2017 Apr 1;97(5):919-23. doi: 10.1016/j.ijrobp.2017.01.004.

PENILE FRACTURE ASSOCIATED WITH URETHRAL INJURY – CASE REPORT

Nebojša Prijović¹, Branko Stanković^{1,2}, Milan Radovanović^{1,2}, Veljko Šantrić^{1,2}, Uroš Babić^{1,2}

¹ Univerzitetski klinički centar Srbije, Klinika za urologiju, Beograd, Srbija

¹ University Clinical Center of Serbia, Clinic of Urology, Belgrade, Serbia

² Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

² University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SAŽETAK

Uvod: Fraktura penisa predstavlja retko urgentno urološko stanje koje nastaje tokom povrede penisa u erekciji, najčešće tokom seksualnog odnosa. U 10%-21% slučajeva, fraktura penisa je udružena sa povredom uretre. Dijagnoza se najčešće postavlja kliničkim pregledom, ali su dopunske dijagnostičke metode korisne u proceni mesta rupture kavernoznih tela i otkrivanju povrede uretre. Ovo urgentno stanje zahteva hitno hirurško zbrinjavanje jer je odlaganje povezano sa lošijim ishodima.

Prikaz slučaja: Muškarac star 43 godine javio se u Urgentni centar Univerzitetskog kliničkog centra Srbije, zbog povrede penisa u erekciji tokom seksualnog odnosa, sa anamnestičkim podacima da je osetio bol i čuo zvuk „pucanja“, nakon čega je došlo do nagle detumescencije penisa i pojave hematoma penisa, kao i pojave krvi tokom mokrenja. Kliničkim pregledom uspostavljena je sumnja na frakturu penisa. Ultrazvučnim pregledom je utvrđena ruptura tunike albuginee (lat. *tunica albuginea*) desnog kavernoznog tela, a retrogradnom uretrocistografijom utvrđena je ruptura penilne uretre. Pacijent je iste večeri operisan. Kao hirurški pristup, primenjena je središnja penoskrotalna incizija, zatim je učinjena sutura desnog kavernoznog tela i penilne uretre preko nežno plasiranog urinarnog katetera. Postoperativni tok je bio uredan. Pacijent je na kontrolnim pregledima naveo uredne erekcije, uredno mokrenje i zadovoljstvo izgledom penisa.

Zaključak: Fraktura penisa je retko urgentno urološko stanje, relativno retko udruženo sa lezijom uretre. Prikaz našeg slučaja ukazuje na značaj inicijalne ultrazvučne i radiografske dijagnostike. U slučaju kada je mesto povrede preoperativno prisutno, ventralna penoskrotalna incizija može biti pogodan hirurški pristup. Pravovremeno prepoznavanje i hirurško lečenje frakture penisa udružene sa lezijom uretre daje odlične funkcionalne rezultate.

Ključne reči: fraktura penisa, povreda uretre, urgentno urološko stanje, hitno hirurško zbrinjavanje

ABSTRACT

Introduction: Penile fracture is a rare urologic emergency that may occur when the erect penis is injured, most often during sexual intercourse. In 10%-21% of cases, it is associated with urethral injury. The diagnosis is most often made by clinical examination, but additional diagnostic methods are useful in evaluating the site of rupture of the corpora cavernosa and detecting urethral injury. This medical emergency requires urgent surgical management as delays are associated with worse outcomes.

Case report: A 43-year-old man reported to the Emergency Center of the University Clinical Center of Serbia due to an injury to the erect penis during sexual intercourse. The anamnestic data were that he had felt pain and heard a “popping” sound, upon which sudden detumescence of the penis occurred and penile hematoma appeared, as well as blood during urination. Suspicion of a penile fracture was established on clinical examination. An ultrasound examination showed a rupture of the tunica albuginea of the right cavernous body, and retrograde urethrocytography revealed a rupture of the penile urethra. The patient underwent surgery that same evening. The surgical approach was a median penoscrotal incision, followed by suturing of the right cavernous body and penile urethra through a gently placed urinary catheter. Postoperative recovery was uneventful. During follow-up examinations, the patient reported normal erections, regular urination and satisfaction with the appearance of his penis.

Conclusion: Penile fracture is a rare urologic emergency, which is relatively rarely associated with urethral injury. The presentation of our case indicates the importance of initial ultrasound and radiographic diagnostics. In the case where the site of injury is present preoperatively, a ventral penoscrotal incision may be a suitable surgical approach. Timely recognition and surgical treatment of penile fracture associated with urethral injury gives excellent functional results.

Keywords: penile fracture, urethral injury, urologic emergency, urgent surgical management

Autor za korespondenciju:

Nebojša Prijović

Klinika za urologiju, Univerzitetski klinički centar Srbije

Resavska 51, 11000 Beograd, Srbija

Elektronska adresa: nebojsa.prijovic@yahoo.com

Corresponding author:

Nebojša Prijović

Clinic of Urology, University Clinical Center of Serbia

51 Resavska Street, 11000 Belgrade, Serbia

E-mail: nebojsa.prijovic@yahoo.com

Primljeno • Received: February 11, 2026; Revidirano • Revised: March 10, 2026; Prihvaćeno • Accepted: March 13, 2026; Online first: March 25, 2026

DOI: 10.5937/smcl7-64882

UVOD

Fraktura penisa je urgentno urološko stanje u kojem tokom povrede penisa u erekciji dolazi do prekida kontinuiteta tunike albuginee i rupture kavernoznih tela [1]. Fraktura penisa je retko stanje u urgentnoj urologiji [2]. Najčešće do frakture penisa dolazi tokom energičnog seksualnog odnosa, ali se može desiti i tokom penilne manipulacije, masturbacije i traume penisa u erekciji [3]. U 10%–21% pacijenata ruptura kavernoznih tela udružena je sa povredom uretre [4,5]. Klinički se fraktura penisa manifestuje penilnim hematomom, deformitetom penisa, bolom i momentalnom detumescencijom penisa [1]. Pacijent može prilikom nastanka frakture čuti zvuk „pucanja” [1]. U slučaju udružene povrede uretre, može biti prisutna uretroragija [1]. Sumnja na frakturu penisa postavlja se na osnovu anamneze i kliničkog nalaza, a potvrđuje se ultrazvučnim pregledom ili magnetnom rezonancom penisa [6]. Kada postoji sumnja na povredu uretre, neophodna je retrogradna uretrocistografija [3]. Fraktura penisa se leči hirurški, i po mogućstvu što ranije, jer odlaganje intervencije utiče na ishode lečenja [3].

Cilj ovog rada je prikaz slučaja pacijenta sa frakturom penisa udruženom sa rupturom penilne uretre koji je urgentno hirurški lečen sa dobrim postoperativnim funkcionalnim ishodima. Od pacijenta je dobijen pisani informisani pristanak za objavljivanje ovog prikaza slučaja.

PRIKAZ SLUČAJA

Muškarac star 43 godine javio se u večernjim časovima u urološku ambulantu Urgentnog centra Univerzitetskog kliničkog centra Srbije zbog povrede penisa tokom seksualnog odnosa. Pacijent navodi da je imao seksualni odnos sa svojom izvanbračnom partnerkom, u njenom stanu, uz penetraciju otpozadi (lat. *coitus more ferarum*; engl. *rear-entry intercourse*, i.e., *doggy style*), kada je osetio bol i čuo zvuk „pucanja”, nakon čega je došlo do momentalnog prestanka erekcije. Primetio je hematom u predelu penisa kao i krv prilikom mokrenja.

Pacijent je naveo da nema hroničnih bolesti, te da ne koristi hroničnu terapiju. Objektivno, na prijemu su bili prisutni otok, hematom i deformacija penisa. Takođe, na meatusu uretre je bila vidljiva uretroragija (Slika 1). Učinjen je ultrazvučni pregled penisa linearnom sondom, gde je konstatovano prisustvo penilnog hematoma sa znacima prekida kontinuiteta tunike albuginee desnog kavernoznog tela sa vidljivim aktivnim krvarenjem (Slika 2). Učinjena je potom retrogradna uretrocistografija gde je uočena ekstraluminacija kontrasta iz penilne uretre (Slika 3). Indikovano je hitan prijem i hitno hirurško lečenje po prijemu, te je

INTRODUCTION

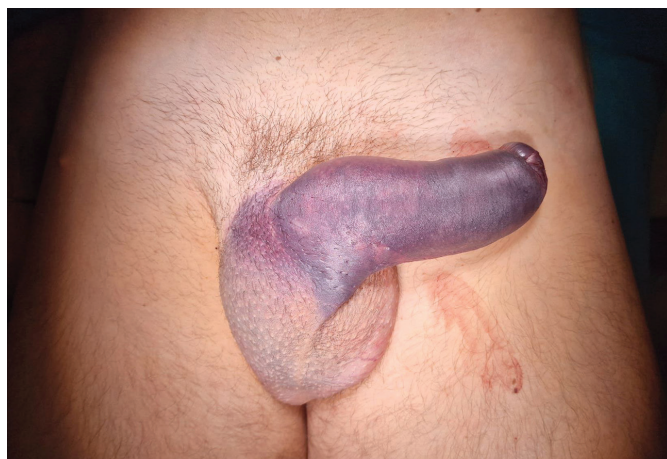
Penile fracture is a urologic emergency characterized by disruption to the continuity of the tunica albuginea and rupture of the corpora cavernosa following trauma to the erect penis [1]. Penile fracture is a rare condition in emergency urology [2]. It most commonly occurs during vigorous sexual intercourse but may also result from penile manipulation, masturbation, or trauma to the erect penis [3]. In 10%-21% of patients, rupture of the corpora cavernosa is associated with urethral injury [4,5]. Clinically, a penile fracture presents with penile hematoma, deformity, pain, and immediate detumescence [1]. Patients may report hearing a characteristic “popping” sound at the moment of injury [1]. In cases of associated urethral injury, urethrorrhagia may be present [1]. Suspicion of penile fracture is based on anamnesis and clinical findings and is confirmed by ultrasonography or magnetic resonance imaging of the penis [6]. When urethral injury is suspected, retrograde urethrocytography is necessary [3]. Penile fracture is treated surgically, preferably as early as possible, since delays in intervention adversely affect treatment outcomes [3].

The aim of this paper is to present a case of penile fracture associated with rupture of the penile urethra that was treated with emergency surgery, resulting in favorable postoperative functional outcomes. Written informed consent for publication of this case report was obtained from the patient.

CASE REPORT

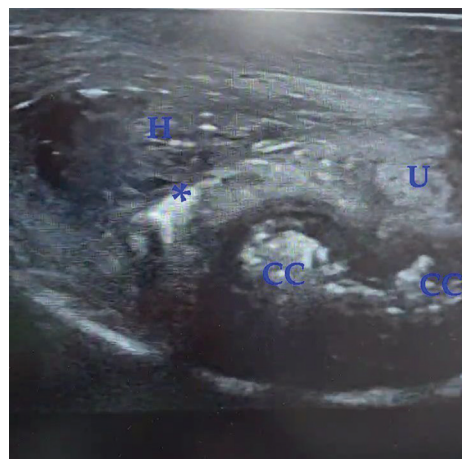
A 43-year-old man presented in the evening hours at the urology outpatient clinic of the University Clinical Center of Serbia Emergency Center, due to penile trauma sustained during sexual intercourse. The patient reported that he was having rear-entry intercourse (i.e., “doggy style”; Latin: *coitus more ferarum*) with his extramarital partner, in her apartment, when he experienced pain and heard a “popping” sound, followed by immediate detumescence. He noticed penile hematoma as well as blood during urination.

The patient reported no chronic illnesses and was not on any regular therapy. On physical examination at admission, penile swelling, hematoma, and deformity were present. Urethrorrhagia was also observed at the urethral meatus (Figure 1). Ultrasonographic examination of the penis using a linear probe revealed a penile hematoma with disruption of the tunica albuginea of the right corpus cavernosum and evidence of active bleeding (Figure 2). Retrograde urethrocytography subsequently demonstrated contrast extravasation from the penile urethra (Figure 3). Emergency admission and immediate surgical treatment were indicated,



Slika 1. Klinička prezentacija frakture penisa kod našeg pacijenta – otečeni penis sa hematomom uz vidljive tragove krvi zbog uretroragije

Figure 1. Clinical presentation of penile fracture in our patient – swollen penis with hematoma and visible blood due to urethrorrhagia



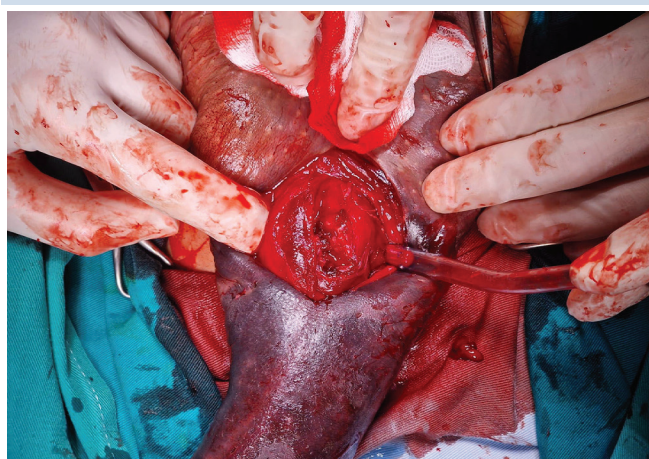
Slika 2. Ultrazvučni pregled penisa pokazuje penilni hematom i krvarenje iz desnog kavernoznog tela (H – hematoma, U – urethra, CC – kavernoza tela, * krvarenje)

Figure 2. Ultrasound examination of the penis showing penile hematoma and bleeding from the right corpus cavernosum (H – hematoma, U – urethra, CC – corpora cavernosa, * bleeding)



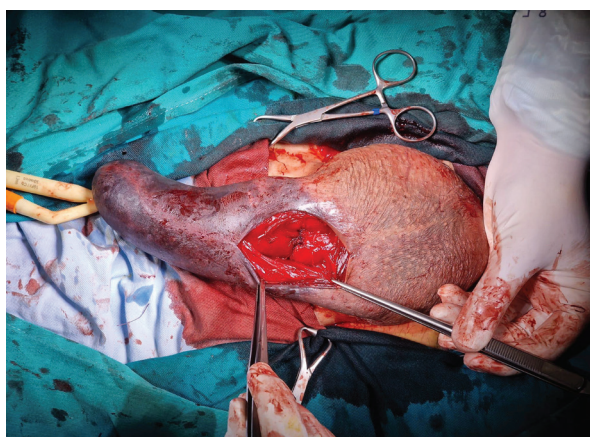
Slika 3. Retrogradna uretrocistografija pokazuje ekstraluminaciju kontrasta iz penilne uretre

Figure 3. Retrograde urethrocytography showing contrast extravasation from the penile urethra



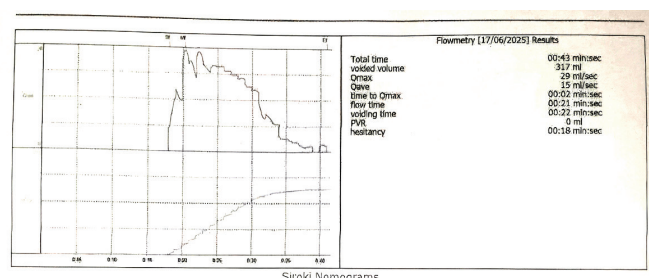
Slika 4. Intraoperativni nalaz ukazuje na rupturu desnog kavernoznog tela i penilne uretre

Figure 4. Intraoperative finding demonstrating rupture of the right corpus cavernosum and penile urethra



Slika 5. Prikaz nakon izvršene suture desnog kavernoznog tela i penilne uretre pojedinačnim šavovima

Figure 5. Appearance after repair of the right corpus cavernosum and penile urethra using interrupted sutures



Slika 6. Normalna, zvonasta kriva na uroflowmetriji, na kontrolnom pregledu

Figure 6. Normal bell-shaped uroflowmetry curve at follow-up examination

pacijent nakon četiri sata od inicijalnog pregleda uveden u operacionu salu.

U uslovima opšte anestezije učinjena je središnja penoskrotalna incizija po *raphe* penisa i skrotuma. Izvršena je incizija ovojnice inbibiranih hematomom. Ispreparisana su oba kavernoza tela. Evakuisan je hematoma pored desnog kavernoznog tela, a u nivou korena penisa smo uočili ventralnu rupturu desnog kavernoznog tela u dužini od oko 2 cm. U istom nivou smo uočili i rupturu penilne uretre u dužini od oko 1 cm (Slika 4). Plasirali smo Folijev urinarni kateter (Foley CH 16) pod vizuelnom i manuelnom kontrolom u mokraćnu bešiku, i dobili bistar urin. Učinjena je suturu desnog kavernoznog tela pojedinačnim šavovima korišćenjem 3-0 resorptivnog polifilamentnog šava. Učinili smo suturu penilne uretre pojedinačnim šavovima korišćenjem 5-0 resorptivnog monofilamentnog šava (Slika 5). Zatim je učinjena sutura ivica incizije i previjanje.

Pacijentu je ordinirana antibiotska profilaksa i tromboprofilaksa. Postoperativni tok je bio uredan. Pacijent je otpušten kući dobrog opšteg stanja četvrtog postoperativnog dana sa urinarnim kateterom. Na kontrolnim pregledima su skinuti konci sa rane. Potom je petnaestog postoperativnog dana učinjena retrogradna uretrocistografija pored katetera na kojoj nije uočena ekstraluminacija kontrastnog sredstva. Na sledećoj kontroli, devetnaestog postoperativnog dana, izvađen je urinarni kateter. Pacijentu je savetovano uzdržavanje od seksualnih aktivnosti narednih mesec dana. Tokom daljih kontrola pacijent je naveo da su erekcije uredne, da je zadovoljan izgledom penisa, kao i da uredno mokri. Nakon osam meseci, urađena je uroflowmetrija koja je pokazala normalnu, zvonastu krivu sa maksimalnim protokom (Q_{max}) 29 ml/s (Slika 6).

DISKUSIJA

Fraktura penisa predstavlja retko urgentno urološko stanje. U Sjedinjenim Američkim Državama, fraktura penisa ima procenjenu incidenciju od 1,0–1,8 na 100.000 hospitalizacija [2]. Ovo stanje predstavlja rupturu tunike albuginee kavernoznih tela prilikom povrede penisa u erekciji [1]. Studije pokazuju da se fraktura penisa javlja kod mlađih i sredovečnih muškaraca, prosečne starosti nešto ispod 40 godina [2,4]. U našem slučaju, u pitanju je sredovečni muškarac starosti 43 godine. S obzirom na anatomiju tunike albuginee, najčešće mesto njene rupture je lokalizovano gde je ona najtanja – ventralno ili lateralno, i najčešće distalno od suspenzornog ligamenta [1,7,8]. U našem slučaju, postojala je unilateralna ventralna ruptura desnog kavernoznog tela. Ruptura kavernoznih tela je najčešće jednostrana i bez udružene povrede uretre, u oko 80% slučajeva [3], dok se ruptura uretre događa u oko 10%

and the patient was transferred to the operating room four hours after the initial examination.

Under general anesthesia, a midline penoscrotal incision was performed along the penile and scrotal raphe. The hematoma-infiltrated tissue layers were incised. Both corpora cavernosa were dissected. A hematoma adjacent to the right corpus cavernosum was evacuated, and at the level of the penile root, a ventral rupture of the right corpus cavernosum measuring approximately two cm was identified. At the same level, a rupture of the penile urethra measuring approximately one cm was also identified (Figure 4). A Foley urinary catheter (Foley CH 16) was inserted into the bladder under visual and manual control, yielding clear urine. The right corpus cavernosum was repaired using interrupted sutures with 3-0 absorbable multifilament material. The penile urethra was repaired using interrupted sutures with 5-0 absorbable monofilament material (Figure 5). The incision was then closed, and a dressing was applied.

The patient received antibiotic prophylaxis and thromboprophylaxis. The postoperative course was uneventful. The patient was discharged from hospital in good general condition on the fourth postoperative day with a urinary catheter in place. At follow-up visits, skin sutures were removed. On postoperative day 15, retrograde urethrocystography performed with the catheter in situ showed no contrast extravasation. At the next follow-up, on postoperative day 19, the urinary catheter was removed. The patient was advised to abstain from sexual activity for one month. During subsequent follow-up, the patient reported normal erections, satisfaction with penile appearance, and normal urination. Eight months later, uroflowmetry demonstrated a normal bell-shaped curve with a maximum flow rate (Q_{max}) of 29 ml/s (Figure 6).

DISCUSSION

Penile fracture is a rare urologic emergency. In the United States, its estimated incidence ranges from 1.0 to 1.8 cases per 100,000 hospitalizations [2]. This condition is, in fact, the rupture of the tunica albuginea of the corpora cavernosa following trauma to the erect penis [1]. Studies indicate that penile fracture typically occurs in younger and middle-aged men, with a mean age slightly below 40 years [2,4]. In our case, the patient was a middle-aged, 43-year-old man. Based on the anatomical characteristics of the tunica albuginea, rupture most commonly occurs at its thinnest point – ventrally or laterally, most often distally to the suspensory ligament [1,7,8]. In our case, a unilateral ventral rupture of the right corpus cavernosum was identified. Rupture of the corpora cavernosa is usually unilateral

21% slučajeva [4,5] i često je udružena sa bilateralnom rupturom kavernoznih tela [3].

Do frakture penisa u zapadnim zemljama najčešće dolazi tokom energičnog seksualnog odnosa (preko 80% slučajeva), mnogo ređe tokom masturbacije ili traume penisa u erekciji [3]. U zemljama Srednjeg istoka dominantan uzrok nastanka frakture penisa je „taghaandan“, odnosno nasilno postizanje detumescencije penisa u erekciji [9]. Najčešće seksualne poze u kojima dolazi do frakture penisa su tzv. „doggy style“ i „misionarska poza“ [10,11], kada rigidni penis sklizne iz vagine i udari u perineum ili pubičnu kost [1]. I kod muškaraca koji upražnjavaju seks sa drugim muškarcima, najčešća seksualna poza pri kojoj nastaje fraktura penisa je tzv. „doggy style“ poza [12]. Najčešće do frakture penisa dolazi prilikom seksualnog odnosa u „stresnim situacijama“, poput vanbračnog seksualnog odnosa, na radnom mestu ili na neuobičajenim mestima [13]. U našem slučaju, pacijent je imao seksualni odnos sa vanbračnom partnerkom, u njenom stanu. Studija iz Sjedinjenih Američkih Država iz 2021. godine pokazala je češću upotrebu psihoaktivnih supstanci kod pacijenata hospitalizovanih zbog frakture penisa [2].

Anamnestički, pacijent može navesti da je čuo zvuk „pucanja“ i da je osetio bol, nakon čega je došlo do nagle detumescencije penisa. Fraktura penisa se klinički manifestuje penilnim hematomom, otokom i deformacijom penisa, pri čemu hematoma izaziva devijaciju penisa na suprotnu stranu. Opisani izgled penisa naziva se „patlidžan deformacija“. U slučaju rupture Bakove fascije, hematoma može da se proširi na skrotum, perineum i suprapubičnu regiju [1,3,8]. Ukoliko postoji lezija uretre, može biti prisutna uretroragija iz meatusa uretre [1]. Pacijent u našem slučaju je prijavio sve navedene anamnestičke podatke, a objektivnim pregledom su konstatovani svi gorenavedeni klinički znaci frakture penisa.

Dijagnoza frakture penisa se postavlja uglavnom na osnovu anamnestičkih podataka i kliničkog nalaza, dok je u nejasnim situacijama potrebno uraditi ultrazvučni pregled penisa ili pregled magnetnom rezonancom [1,14,15]. Iako se u velikom broju studija navodi da je klinička dijagnoza dovoljna u većini slučajeva, primena „imidžing“ metoda može doprineti boljem planiranju hirurške intervencije, manjoj inciziji, kao i manjem hirurškom morbiditetu [1,6,14,15]. Praksa u našoj ustanovi je da se kod svake sumnje na frakturu penisa obavi ultrazvučni pregled penisa. Pregled magnetnom rezonancom se u našoj ustanovi indikuje kada ni klinički ni ultrazvučno nije jasno postojanje frakture penisa, ili kada se pacijent odloženo javi na pregled urologa. Kod datog pacijenta, ultrazvučni pregled je pokazao postojanje prekida kontinuiteta tunike albuginee desnog kavernoznog tela, ventralno sa vidljivom ek-

and not associated with urethral injury in approximately 80% of cases [3], whereas urethral rupture occurs in approximately 10%–21% of cases [4,5] and is often associated with bilateral cavernous rupture [3].

In Western countries, penile fracture most commonly occurs during vigorous sexual intercourse (over 80% of cases), and much less frequently during masturbation or trauma to the erect penis [3]. In Middle Eastern countries, the predominant cause is “taghaandan,” or forced detumescence of the erect penis [9]. The sexual positions most commonly associated with penile fracture are the so-called “doggy style” and “missionary” positions [10,11], when the rigid penis slips out of the vagina and strikes the perineum or pubic bone [1]. Among men who have sex with other men, the most common position associated with penile fracture is also “doggy style” [12]. Penile fracture most often occurs during intercourse in “stressful situations,” such as extramarital intercourse, intercourse at the workplace, or in unusual locations [13]. In our case, the patient reported intercourse with an extramarital partner in her apartment. A study from the United States (2021) reported increased use of psychoactive substances among patients hospitalized for penile fracture [2].

As to anamnesis, patients often report hearing a “cracking” sound accompanied by pain, followed by sudden detumescence. Clinically, a penile fracture presents with hematoma, swelling, and deformity, with the hematoma causing deviation of the penis to the contralateral side. This characteristic appearance is referred to as the “eggplant deformity” or “aubergine sign”. In cases of Buck’s fascia rupture, the hematoma may extend to the scrotum, perineum, and suprapubic region [1,3,8]. When urethral injury is present, urethrorrhagia from the urethral meatus may occur [1]. In our case, the patient reported all the characteristic symptoms, and all the above-described clinical signs were confirmed on examination.

The diagnosis of penile fracture is primarily based on history and clinical findings, while imaging – ultrasound or magnetic resonance imaging – is usually employed in equivocal cases [1,14,15]. Although many studies suggest that clinical diagnosis is sufficient in most cases, imaging modalities may facilitate better surgical planning, smaller incisions, and reduced surgical morbidity [1,6,14,15]. In our hospital, ultrasound examinations are routinely performed in all suspected cases of penile rupture. Magnetic resonance imaging is reserved for cases where diagnosis remains unclear or when patients present late. In our patient, ultrasound imaging revealed disruption of the tunica albuginea of the right corpus cavernosum ventrally, with visible blood extravasation (“blush”) and penile hematoma. When urethral injury is

stravazacijom (engl. *extravasation*, i.e., *blush*) krvi i prisutnim penilnim hematomom. U slučaju kada postoji sumnja na povredu uretre, u vidu prisutne uretroragije, hematurije ili nemogućnosti mokrenja, potrebno je preoperativno uraditi retrogradnu uretrocistografiju [1,3,16] ili fleksibilnu uretroskopiju [1,16]. Retrogradna uretrocistografija je u našem slučaju pokazala isticanje kontrasta iz penilne uretre što je potvrdilo rupturu penilne uretre.

Fraktura penisa se leči hirurški. Rezultati istraživanja koje su sprovedi Gamal i saradnici, pokazali su da, u slučaju konzervativnog lečenja, erektilna funkcija bude zadovoljavajuća kod svega 50%, za razliku od hirurškog lečenja, gde erektilna funkcija bude zadovoljavajuća kod 96% pacijenata [17]. Ovi podaci idu u prilog činjenici da je hirurško lečenje metod izbora kod pacijenata sa frakturom penisa [3]. Podaci iz literature ukazuju da se hirurško lečenje može odložiti i do sedam dana uz zadovoljavajuće postoperativne rezultate u pogledu erektilne funkcije [1,18]. S druge strane, retrospektivna multicentrična studija, koja je obuhvatila 137 pacijenata sa frakturom penisa, pokazala je da odlaganje hirurške reparacije duže od osam sati dovodi do lošije erektilne funkcije [3]. Mišljenje autora je da hirurškom lečenju treba pristupiti što je ranije moguće da bi se postigli bolji rezultati, ali bez bespotrebne žurbe. U našem slučaju, pacijent je uveden u operacionu salu četiri sata nakon inicijalnog pregleda od strane urologa.

Najčešći hirurški pristup kod lečenja frakture penisa je cirkumcizijska subkoronalna incizija [1,5,6,8]. Nakon ove incizije, načini se *degloving* penisa i pristupi se svim trima komponentama penisa. Ukoliko pacijent nije cirkumciziran, po završetku reparacije kavernoznih tela, potrebno je načiniti cirkumciziju, čime se izbegava postoperativni edem i eventualna ishemija prepućijuma [1,8]. Ovaj pristup je pogodan kada preoperativno nije poznato mesto laceracije kavernoznog tela, jer se njime postiže bolji pristup kavernoznim telima i spongioznom telu [1,19]. Takođe, *degloving* tehnika ima prednosti kada je prisutno veliko oticanje penisa i ekstenzivan hematom [20]. Međutim, kada je preoperativnim snimanjem utvrđeno mesto laceracije kavernoznog tela, pristup može biti vertikalna penoskrotalna incizija, ili manja lokalna longitudinalna incizija, čime se takođe postižu dobri rezultati [19,21]. U našem slučaju, s obzirom da je na ultrazvučnom pregledu uočena ventralna ruptura kavernoznog tela proksimalno, kao i ruptura uretre na istom nivou na uretrocistografiji, odlučili smo se za središnju vertikalnu penoskrotalnu inciziju. Središnja ventralna i longitudinalna lateralna incizije, za razliku od *degloving* procedura, manje traumatizuju tkivo i manje dodatno povređuju krvne sudove i nerve [19,21]. Takođe, later-

suspected – based on urethrorrhagia, hematuria, or urinary retention – preoperative retrograde urethrocytography [1,3,16] or flexible urethroscopy [1,16] is indicated. In our case, retrograde urethrocytography confirmed urethral rupture, revealing contrast extravasation.

Penile fracture is treated surgically. A study by Gamal et al. demonstrated that erectile function was preserved in only 50% of patients treated conservatively, compared to 96% of those treated surgically [17]. These findings support surgical repair as the treatment of choice [3]. Some studies suggest that surgery may be delayed for up to seven days with acceptable outcomes [1,18]. However, a retrospective multicenter study of 137 patients showed that delays longer than eight hours were associated with worse erectile function [3]. The authors advocate that surgical intervention should be performed as early as possible, but without unnecessary haste. In our case, surgery was performed four hours after initial evaluation.

The most common surgical approach is a circumferential subcoronal incision [1,5,6,8]. Upon incision, penile degloving is performed and all three components of the penis are made accessible. If the patient is uncircumcised, circumcision is recommended at the end of the procedure, i.e., after cavernous body reparation, to prevent postoperative edema and potential preputial ischemia [1,8]. This approach is particularly useful when the location of the cavernous body laceration is unknown preoperatively, as it enables better access to the cavernous bodies and the corpus spongiosum [1,19]. Also, the degloving technique has its advantages when the penis is excessively swollen with extensive hematoma [20]. However, when the site of cavernous body laceration is identified with preoperative imaging, a targeted approach such as a penoscrotal or localized longitudinal incision may be applied, which also yields good outcomes [19,21]. In our case, since preoperative ultrasound imaging revealed a ventral rupture of the cavernous body, proximally, and preoperative urethrocytography showed a urethral rupture at the same level, the midline vertical penoscrotal incision was chosen. Compared to degloving techniques, the midline ventral and longitudinal lateral incisions are less traumatic for the tissue and reduce the risk of additional neurovascular injury [19,21]. Additionally, lateral incisions are applicable in circumcised men in whom there is not enough skin for adequate healing [19]. Penoscrotal access also provides better exposure of the urethra [21].

Intraoperative injection of saline solution can contribute to identifying the site of laceration of the corpus cavernosum and the urethra, as well as enable verification of the success of the suture [1,8]. When the site of laceration of the corpus cavernosum is identified, sutur-

alne incizije pogodne su i kod cirkumciziranih muškaraca kod kojih nema dovoljno kože za adekvatno zarastanje [19]. Penoskrotalna incizija, takođe, pruža i bolji pristup penilnoj uretri [21].

Intraoperativno ubrizgavanje fiziološkog rastvora može da doprinese identifikaciji mesta laceracije kavernoznog tela i uretre, kao i da omogući proveru uspešnosti suture [1,8]. Kada se identifikuje mesto laceracije kavernoznog tela, preporučuje se sutura 2-0 ili 3-0 resorptivnim šavovima [1,5,8]. U slučaju povrede uretre, preporučuje se sutura uretre preko pažljivo plasiranog urinarnog katetera finim resorptivnim 4-0 ili 5-0 šavovima [1,3,22]. Aćimović i saradnici su opisali slučaj reparacije uretre udružene sa frakturom penisa pomoću grafta bukalne mukoze [23]. U našem slučaju, reparacija kavernoznog tela učinjena je pomoću 3-0 polifilamentnog resorptivnog šava, a reparacija uretre pomoću 5-0 resorptivnog monofilamentnog šava preko pažljivo plasiranog Folijeveg katetera.

Kod našeg pacijenta, postoperativni tok je protekao uredno. Devetnaestog postoperativnog dana je izvađen urinarni kateter. Savetovana je apstinencija od seksualnih odnosa narednih mesec dana, što je u skladu sa preporukama da kateter ostane dve do tri nedelje od operacije [1] i da pacijent apstinira od seksualnih odnosa najmanje dve nedelje [24], pri čemu većina urologa savetuje seksualnu apstinenciju šest do osam nedelja od operacije [25]. Tokom osam meseci praćenja, pacijent je navodio da je zadovoljan izgledom penisa, da ima potpune erekcije, kao i da uredno mokri. Na uroflowmetriji, nakon osam meseci od operacije, opisana je normalna, zvonasta kriva sa $Q_{\max}$ 29 ml/s.

Udaljene postoperativne komplikacije frakture penisa najčešće su erektilna disfunkcija i nastanak kurvature penisa. Većina studija ukazuje na očuvanje erektilne funkcije u preko 90% slučajeva nakon hirurškog lečenja [8,24,26]. S obzirom da je fraktura penisa traumatičan događaj, erektilna disfunkcija može nastati i kao posledica psihogenog faktora [25]. Prisustvo kurvature penisa procenjuje se na oko 5% slučajeva nakon hirurškog lečenja frakture penisa, pri čemu su kurvature obično blage i u većini slučajeva ne zahtevaju hirurški tretman [3,25]. Aktuelne studije pokazuju da je procenat dugoročnih komplikacija veći u slučaju odlaganja hirurškog lečenja [3,27], bilo da je u pitanju kasno javljanje u referentni centar [27], bilo da je u pitanju produženo vreme od prijema do hirurškog lečenja [3].

ZAKLJUČAK

Fraktura penisa je retko urgentno urološko stanje, pri čemu je relativno retko udružena sa lezijom uretre. Prikaz našeg slučaja ukazuje na značaj inicijalne ultrazvučne i radiografske dijagnostike u detekciji ruptur kaver-

ing with 2-0 or 3-0 absorbable sutures is recommended [1,5,8]. In the case of urethral injury, urethral suturing over a carefully placed urinary catheter using fine 4-0 or 5-0 absorbable sutures is recommended [1,3,22]. Aćimović et al. described a case of urethral repair associated with penile fracture using a buccal mucosa graft [23]. In our case, repair of the corpus cavernosum was performed using a 3-0 polyfilament absorbable suture, while urethral repair was performed using a 5-0 absorbable monofilament suture over a carefully placed Foley catheter.

In our patient, the postoperative course was uneventful. The urinary catheter was removed on the nineteenth postoperative day. Abstinence from sexual intercourse for the following month was advised, which is in accordance with recommendations that the catheter remain in place for two to three weeks after surgery [1] and that the patient abstain from sexual intercourse for at least two weeks [24], while most urologists advise sexual abstinence for six to eight weeks after surgery [25]. During eight months of follow-up, the patient reported satisfaction with the appearance of the penis, full erections, as well as normal urination. On uroflowmetry, eight months after surgery, a normal, bell-shaped curve with $Q_{\max}$ 29 ml/s was described.

Late postoperative complications of penile fracture are most commonly erectile dysfunction and the development of penile curvature. Most studies indicate preservation of erectile function in over 90% of cases after surgical treatment [8,24,26]. Given that penile fracture is a traumatic event, erectile dysfunction may also occur as a result of psychogenic factors [25]. The presence of penile curvature is estimated at around 5% of cases after surgical treatment of penile fracture, with curvatures usually being mild and in most cases not requiring surgical treatment [3,25]. Current studies show that the rate of long-term complications is higher in cases of delayed surgical treatment [3,27], whether due to late presentation to a referral center [27] or prolonged time from admission to surgical treatment [3].

CONCLUSION

Penile fracture is a rare urologic emergency and is relatively infrequently associated with urethral injury. This case highlights the importance of initial ultrasonographic and radiographic evaluation in detecting both cavernosal and urethral rupture. When the site of injury is identified preoperatively, a ventral penoscrotal approach may be an appropriate surgical option. Early recognition and prompt surgical management result in excellent functional outcomes in terms of erectile function, urination, and penile appearance.

Conflict of interest: None declared.

noznog tela i uretre. U slučaju kada je preoperativno prisutno mesto lezije, ventralna penoskrotalna incizija može biti pogodan hirurški pristup. Pravovremeno prepoznavanje i hirurško lečenje frakture penisa udružene sa lezijom uretre daje odlične funkcionalne rezultate u pogledu erektilne funkcije, mokrenja i izgleda penisa.

Sukob interesa: Nije prijavljen.

LITERATURA / REFERENCES

1. Morey A, Simhan J. Genital and Lower Urinary Tract Trauma. In: Partin A, Dmochowski R, Kavoussi L, Peters C, editors. Campbell-Walsh-Wein Urology. Philadelphia: Elsevier; 2021. p. 3048-61.
2. Christian-Miller N, Lenis AT, Fero KE, Madrigal J, Eleswarapu SV, Chamie K, et al. Risk factors for penile fracture compared with a surgical control cohort in the United States: the role of substance abuse. *Asian J Androl*. 2021 May-Jun;23(3):236-9. doi: 10.4103/aja.aja_70_20.
3. Bozzini G, Albersen M, Otero JR, Margreiter M, Cruz EG, Mueller A, et al.; European Association of Urology Young Academic Urologists Men's Health working party. Delaying Surgical Treatment of Penile Fracture Results in Poor Functional Outcomes: Results from a Large Retrospective Multi-center European Study. *Eur Urol Focus*. 2018 Jan;4(1):106-10. doi: 10.1016/j.euf.2016.02.012.
4. Arikan MG, Akgul B, Turk S, Tantekin ÖO, Çakiroğlu B, Arda E. Beyond conventional wisdom: unexplored risk factors for penile fracture. *Sex Med*. 2024 Oct 1;12(5):qfae068. doi: 10.1093/sexmed/qfae068.
5. Ory J, Bailly G. Management of penile fracture. *Can Urol Assoc J*. 2019 Jun;13(6 Suppl4):S72-4. doi: 10.5489/auaj.5932.
6. Hardesty J, Burns RT, Soyster ME, Mellon M, Bernie HL. A review of the literature and proposed algorithm for penile fracture management. *Sex Med Rev*. 2023 Dec 23;12(1):100-5. doi: 10.1093/sxmrev/qead041.
7. Brock G, Hsu GL, Nunes L, von Heyden B, Lue TF. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. *J Urol*. 1997 Jan;157(1):276-81. doi: 10.1016/S0022-5347(01)65359-X.
8. Mydlo JH. Surgeon experience with penile fracture. *J Urol*. 2001 Aug;166(2):526-9. doi: 10.1016/S0022-5347(05)65975-7.
9. Zargooshi J. Penile fracture in Kermanshah, Iran: report of 172 cases. *J Urol*. 2000 Aug;164(2):364-6. doi: 10.1016/S0022-5347(05)67361-2.
10. Barros R, Schulze L, Ornellas AA, Koifman L, Favorito LA. Relationship between sexual position and severity of penile fracture. *Int J Impot Res*. 2017 Sep;29(5):207-9. doi: 10.1038/ijir.2017.24.
11. Syarif S, Azis A, Natsir AS, Putra MZDA. What is the most dangerous sexual position that caused the penile fracture? A systematic review and meta-analysis. *Int Braz J Urol*. 2024 Jan-Feb;50(1):28-36. doi: 10.1590/S1677-5538.IBJU.2023.0419.
12. Barros R, Lacerda G, Schul A, Ornellas P, Koifman L, Favorito LA. Sexual complications of penile fracture in men who have sex with men. *Int Braz J Urol*. 2018 May-Jun;44(3):550-4. doi: 10.1590/S1677-5538.IBJU.2017.0520.
13. Kramer AC. Penile fracture seems more likely during sex under stressful situations. *J Sex Med*. 2011 Dec;8(12):3414-7. doi: 10.1111/j.1743-6109.2011.02461.x.
14. Spieseeck P, Mang J, Fischer T, Hamm B, Lerchbaumer MH. Diagnostic performance of MRI and US in suspicion of penile fracture. *Transl Androl Urol*. 2022 Mar;11(3):377-85. doi: 10.21037/tau-21-957.
15. Zare Mehrjardi M, Darabi M, Bagheri SM, Kamali K, Bijan B. The role of ultrasound (US) and magnetic resonance imaging (MRI) in penile fracture mapping for modified surgical repair. *Int Urol Nephrol*. 2017 Jun;49(6):937-45. doi: 10.1007/s11255-017-1550-x.
16. Morey AF, Brandes S, Dugi DD 3rd, Armstrong JH, Breyer BN, Broghammer JA, et al.; American Urological Association. Urotrauma: AUA guideline. *J Urol*. 2014 Aug;192(2):327-35. doi: 10.1016/j.juro.2014.05.004.
17. Gamal WM, Osman MM, Hammady A, Aldahshoury MZ, Hussein MM, Saleem M. Penile fracture: long-term results of surgical and conservative management. *J Trauma*. 2011 Aug;71(2):491-3. doi: 10.1097/TA.0b013e3182093113.
18. el-Assmy A, el-Tholoth HS, Mohsen T, Ibrahim el-HI. Does timing of presentation of penile fracture affect outcome of surgical intervention? *Urology*. 2011 Jun;77(6):1388-91. doi: 10.1016/j.urol.2010.12.070.
19. Xu MX, Zhou Z, Yao HJ, Zhang K, Da J, Zhang M, et al. Comparison of different approaches to the surgical treatment of penile fractures: quicker return to sexual function with longitudinal incisions. *Int J Impot Res*. 2016 Jul;28(4):155-9. doi: 10.1038/ijir.2016.13.
20. Minor TX, Brant WO, Rahman NU, Lue TF. Approach to management of penile fracture in men with underlying Peyronie's disease. *Urology*. 2006 Oct;68(4):858-61. doi: 10.1016/j.urol.2006.05.022.
21. Mazari EM, Livadas K, Chalikopoulos D, Bisas A, Deliveliotis C, Skolarikos A. Penile fractures: immediate surgical approach with a midline ventral incision. *BJU Int*. 2009 Aug;104(4):520-3. doi: 10.1111/j.1464-410X.2009.08455.x.
22. Nale D, Bojanić N, Nikić P. Penile fracture: a rare case of simultaneous rupture of the one corpus cavernosum and complete urethral rupture. *Vojnosanit Pregl*. 2015 Jan;72(1):60-2. doi: 10.2298/vsp1501060n.
23. Acimovic M, Zivkovic M, Georgescu AV, Matei IR, Bumbasirevic U. Repair of urethral injury associated with penile fracture using buccal mucosa graft: A novel therapeutic approach for complex cases. *Injury*. 2020 Dec;51 Suppl 4:S114-6. doi: 10.1016/j.injury.2020.02.116.
24. Uygun MC, Gülerkaya B, Altuğ U, Germiyanoglu C, Erol D. 13 years' experience of penile fracture. *Scand J Urol Nephrol*. 1997 Jun;31(3):265-6. doi: 10.3109/00365599709070345.
25. McElroy K, Ramsden P, Pickard R. Penile fracture. *Nat Clin Pract Urol*. 2006 Mar;3(3):170-4; quiz 175. doi: 10.1038/ncpuro0433.
26. De Luca F, Garaffa G, Falcone M, Raheem A, Zacharakis E, Shabbir M, et al. Functional outcomes following immediate repair of penile fracture: a tertiary referral centre experience with 76 consecutive patients. *Scand J Urol*. 2017 Apr;51(2):170-5. doi: 10.1080/21681805.2017.1280532.
27. Naouar S, Boussaffa H, Braiek S, El Kamel R. Management of penile fracture: Can it wait? *African J Urol*. 2018 Mar;24(1):56-9. doi: 10.1016/j.afju.2017.07.006.

FORMIRANJE ARTERIOVENSKE FISTULE U AKSILARNOM BLOKU I SEDACIJI KOD DETETA SA TERMINALNOM BUBREŽNOM INSUFICIJENCIJOM – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

AXILLARY BRACHIAL PLEXUS BLOCK UNDER PROCEDURAL SEDATION FOR ARTERIOVENOUS FISTULA FORMATION IN A CHILD WITH END-STAGE RENAL DISEASE – A CASE REPORT

Lazar Jakšić¹, Emil Bosinci¹, Velja Milačić²

¹ Univerzitetska dečja klinika, Beograd, Srbija

¹ University Children's Hospital, Belgrade, Serbia

² Institut za kardiovaskularne bolesti „Dedinje“, Beograd, Srbija

² Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia

SAŽETAK

Uvod/Cilj: Formiranje arteriovenske (AV) fistule predstavlja zlatni standard vaskularnog pristupa za hemodijalizu. Kod odraslih, primenom blokova brahijalnog plexusa (BBP) za formiranje podlaktne AV fistule obezbeđujemo ne samo adekvatnu analgeziju već i pozitivno dejstvo na primarnu patentnost fistule. Takođe, usled ostvarenih uslova hirurške anestezije, intervenciju je moguće obaviti u uslovima proceduralne sedacije.

Prikaz slučaja: Pacijentkinja stara 12 godina primljena je zbog formiranja AV fistule radi izvođenja hemodijalize, a zbog terminalne bubrežne insuficijencije. Kifoskolioza torakalnog dela kičmenog stuba kao i kratak vrat ograničene pokretljivosti, te niski rast pacijentkinje, upućivali su na moguću otežanu intubaciju. Uprkos nedavno preležanoj infekciji gornjih disajnih puteva, koja je budila sumnju na njihovu pojačanu osetljivost, doneta je odluka o potrebi za hirurškim lečenjem. Odlučili smo se za aksilarni BBP u uslovima proceduralne sedacije. Primenjeno je osnovno praćenje vitalnih funkcija i data je kiseonička potpora od 3 l/min, putem maske. Blok je izveden pod kontrolom ultrazvuka, primenom 8 ml 0,5% levobupivakaina (1,4 mg/kg) i 5 ml 2% lidokaina (3,33 mg/kg). Tokom intervencije u trajanju od 100 minuta, pacijentkinja je bila u potpunosti hemodinamski i respiratorno stabilna, neometanog spontanog disanja. Buđenje je proteklo bez komplikacija, nakon čega je pacijentkinja upućena na odeljenje gde je analgezija održavana acetaminofenom, po potrebi. Ukupna perioperativna potrošnja opioda svedena je na uvodnu dozu fentanila od 0,83 µg/kg.

Zaključak: U ovom pedijatrijskom slučaju, aksilarni BBP obezbedio je adekvatnu analgeziju uz minimalnu upotrebu opioda prilikom formiranja AV fistule, kao i izbegavanje očekivane otežane intubacije. Neophodno je imati na umu maksimalne dozvoljene doze lokalnih anestetika, specifičnosti njihove primene kod dece sa komorbiditetima, kao i moguće komplikacije, među kojima je najznačajnija sistemska toksičnost lokalnih anestetika.

Glavne reči: anestezija, aksilarni blok brahijalnog plexusa, pedijatrijski slučaj, hemodijaliza, terminalna bubrežna insuficijencija

ABSTRACT

Introduction/Objective: Arteriovenous (AV) fistula formation has become the gold standard for hemodialysis vascular access. The use of brachial plexus blocks (BPB) for antebrachial AV fistula formation in adults provides not just adequate analgesia but a potentially positive effect on primary fistula patency. Additionally, the resultant state of surgical anesthesia may enable the surgery to be performed under procedural sedation.

Case report: A 12-year-old patient was admitted for AV fistula formation for the purpose of hemodialysis due to end-stage renal disease. Kyphoscoliosis of the thoracic spine, the patient's short neck with limited mobility, and her short stature posed a potential difficulty for intubation. Despite a recently resolved upper respiratory tract infection, which raised suspicion of airway hyperreactivity, the decision was made to proceed with surgical treatment and perform an axillary BPB under procedural sedation. Basic monitoring of vital functions was applied, with oxygen support at 3 l/min via mask. The ultrasound-guided block was performed using 8 ml of 0.5% levobupivacaine (1.4 mg/kg) and 5 ml of 2% lidocaine (3.33 mg/kg). During the one-hundred-minute surgical procedure, the patient maintained hemodynamic and respiratory stability and spontaneous breathing. The patient awoke without complications and was referred to the hospital ward. Her pain was managed with acetaminophen, as needed. The total perioperative opioid consumption was limited to the induction dose of 0.83 µg/kg of fentanyl.

Conclusion: In this pediatric case, the use of axillary BPB provided adequate analgesia with minimal opioid administration for the formation of an AV fistula. It also enabled the surgical team to avoid an expectedly difficult intubation. One needs to keep in mind the maximum safe dose of local anesthetics, the nuances of their use in children with comorbidities, as well as the potential complications, among which local anesthetic systemic toxicity is the most important.

Keywords: anesthesia, axillary brachial plexus block, pediatric case, hemodialysis, end-stage renal disease

Autor za korespondenciju:
Lazar Jakšić
Univerzitetska dečja klinika
Tiršova 10, 11000 Beograd, Srbija
Elektronska adresa: lazar.jaksic@udk.bg.ac.rs

Corresponding author:
Lazar Jakšić
University Children's Hospital
10 Tiršova Street, 11000 Belgrade, Serbia
E-mail: lazar.jaksic@udk.bg.ac.rs

Primljeno • Received: January 24, 2026; Revidirano • Revised: March 9, 2026; Prihvaćeno • Accepted: March 10, 2026; Online first: March 25, 2026

DOI: 10.5937/smcl7-64342

UVOD

Vaskularni pristup za hemodijalizu moguće je ostvariti formiranjem arteriovenske fistule ili grafta, plasiranjem venskog ili intraperitonealnog katetera. Zbog niže stope infekcije i tromboze, kao i boljeg protoka krvi, formiranje arteriovenske (AV) fistule predstavlja zlatni standard vaskularnog pristupa za dijalizu kod odraslih pacijenata [1], pri čemu je dobrobit navedene metode prepoznata i u pedijatrijskoj populaciji [2,3]. Kod odraslih pacijenata, jasno je opisan pozitivan efekat vazodilatacije izazvane blokom brahijalnog pleksusa (BBP) na primarnu patentnost podlaktne AV fistule [4–6]. Kod dece, isti efekat nije do sada ispitivan, te samo može biti pretpostavljen. Iako je aksilarni BBP prethodno primenjivan kod određenih pedijatrijskih pacijenata u kombinaciji sa opštom anestezijom, slučajevi izvođenja intervencije u uslovima bloka i proceduralne sedacije nisu opisani. Kako BBP, a konkretno aksilarni BBP, obezbeđuje hiruršku anesteziju za intervencije ispod nivoa lakta [7], pacijenti pod povišenim rizikom od komplikacija izazvanih endotrahealnom intubacijom (mehaničke povrede, bronhospazam, nemogućnost intubacije, i dr.) i opštom anestezijom mogli bi da budu kandidati za izvođenje intervencije u uslovima regionalne anestezije. Izvođenje aksilarnog bloka brahijalnog pleksusa takođe može biti praćeno komplikacijama, kao što su neuspeli blok, oštećenje nerava, akcidentalna intravaskularna primena lokalnog anestetika i sledstvena sistemska toksičnost.

PRIKAZ SLUČAJA

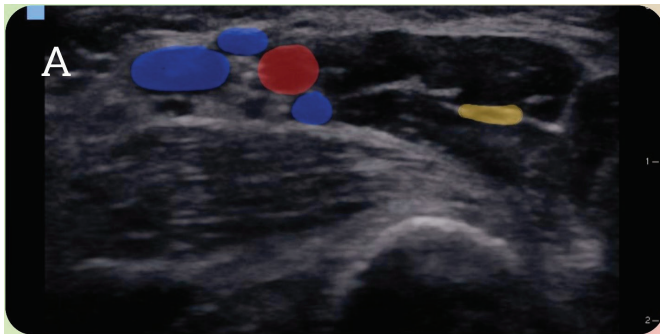
Devojčica stara 12 godina, visoka 110 cm i teška 36 kg, primljena je na Odeljenje nefrologije Univerzitetske dečje klinike, radi formiranja podlaktne arteriovenske fistule. Prethodno je podvrgnuta operativnom lečenju mijelomeningocele. Takođe je praćena zbog dobro kontrolisane epilepsije, hipotireoze, anemije, i arterijske hipertenzije. Klasifikovana je kao ASA (engl. *American Society of Anesthesiology*) status 3. Pacijentkinji je preoperativno bio ograničen unos hrane i vode, bez anamnestičkih podataka ili kliničkih pokazatelja povraćanja. Usled renalne osteodistrofije, pacijentkinja je imala značajnu kifoskoliozu torakalnog dela kičmenog stuba, kao i nizak rast, a uočena je i umereno ograničena pokretljivost vrata u svim pravcima. Ordinirajući anesteziolog procenio je da bi endotrahealna intubacija mogla biti otežana. Uz Mekintoš i Miler špatule različitih veličina za direktnu laringoskopiju, na raspolaganju nam je bio i fiberoptički bronhoskop. Dodatni faktor rizika predstavljala je infekcija gornjih disajnih puteva preležana dve nedelje pred intervenciju. Uprkos sledstveno povećanom riziku od pojave

INTRODUCTION

Vascular access for hemodialysis can be established by forming an arteriovenous fistula or graft, or by placing a venous or intraperitoneal catheter. Due to lower rates of infection and thrombosis, as well as better blood flow, formation of an arteriovenous (AV) fistula is the gold standard for hemodialysis vascular access in adult patients [1], with the benefits of this method also recognized in the pediatric population [2,3]. In adults, the positive effect of vasodilation induced by brachial plexus block (BPB) on the primary patency of forearm AV fistulas has been clearly described [4–6]. In children, this effect has not yet been investigated and can only be hypothesized. Although axillary BPB has previously been applied in certain pediatric patients in combination with general anesthesia, cases of performing the procedure under regional block and procedural sedation have not as yet been reported. As BPB, and more specifically axillary BPB, provides surgical anesthesia for procedures below the level of the elbow [7], patients at increased risk of complications associated with endotracheal intubation (mechanical injury, bronchospasm, failed intubation, etc.) and general anesthesia may be candidates for undergoing the procedure under regional anesthesia. However, an axillary brachial plexus block may also be associated with complications, such as block failure, nerve injury, accidental intravascular administration of local anesthetic, and consequent systemic toxicity.

CASE REPORT

A 12-year-old girl, 110 cm in height and weighing 36 kg, was admitted to the University Children's Hospital Department of Nephrology for the formation of a forearm arteriovenous fistula. She had previously undergone surgical treatment for myelomeningocele. She was also being monitored for well-controlled epilepsy, hypothyroidism, anemia, and arterial hypertension. She was classified as American Society of Anesthesiologists (ASA) physical status III. Preoperatively, oral intake of food and fluids was restricted, with no anamnestic data or clinical signs of vomiting. Due to renal osteodystrophy, the patient had marked thoracic kyphoscoliosis, as well as short stature, and moderately limited neck mobility in all directions was also observed. The attending anesthesiologist assessed that endotracheal intubation might prove difficult. In addition to Macintosh and Miller laryngoscope blades of various sizes for direct laryngoscopy, a fiberoptic bronchoscope was also available. An additional risk factor was an upper respiratory tract infection that had resolved two weeks prior to the procedure. Despite the consequently increased risk of complications associated with endotra-



Slika 1.

A. Aksilarna arterija (crveno), aksilarne vene (plavo), mišićno-kožni živac (žuto).
B. Aksilarna arterija (crveno), aksilarne vene (plavo), lokalni anestetik (zeleno), igla (žuta strelica).

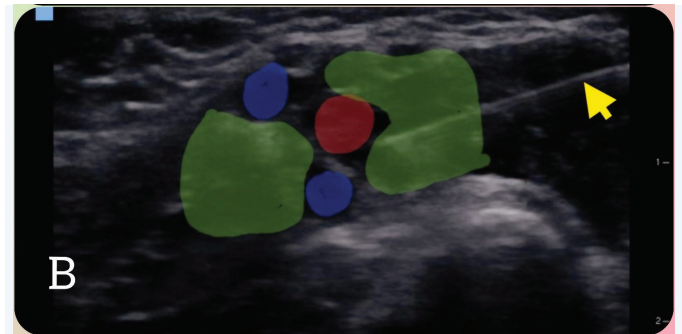


Figure 1.

A. Axillary artery (red), axillary veins (blue), musculocutaneous nerve (yellow).
B. Axillary artery (red), axillary veins (blue), local anesthetic (green), needle (yellow arrow)

komplikacija izazvanih endotrahealnom intubacijom, zbog progresije primarne bolesti doneta je odluka o operativnom lečenju.

Odlučeno je da su u uslovima proceduralne sedacije izvede aksilarni BBP. Neposredno pre uvođenja u anesteziju, izmeren je neinvazivni krvni pritisak od 125/87 mmHg. Pri uvođenju u anesteziju, pacijentkinji je venskim putem dato 1 mg midazolama i 30 µg fentanila, a sedacija je održavana infuzijom propofola u dozi od 6–8 mg/kg/h. Aksilarni BBP (Slika 1) izveden je u uslovima asepse pod kontrolom ultrazvuka (aparatus eZono 4000, igla veličine 22G/50mm, *in-plane* tehnika). Oko nerava samog plexusa dato je 8 ml 0,5% levobupivakaina i 5 ml 2% lidokaina, dok je oko mišićno-kožnog živca čije grane inervišu kožu spoljašnje strane podlaktice dat po 1 ml navedenih lokalnih anestetika. Ukupno je dato 1,4 mg/kg levobupivakaina i 3,33 mg/kg lidokaina. Primenjeno je osnovno praćenje vitalnih funkcija.

Tokom intervencije, pacijentkinja je bila u potpunosti hemodinamski i respiratorno stabilna uz kiseoničku potporu od 3 l/min, putem maske, sa vrednostima srednjeg arterijskog pritiska između 85 i 90 mmHg.

Buđenje je proteklo bez komplikacija koje bi zahvalele intervenciju, odmah nakon čega je pacijentkinja prevedena na odeljenje. Postoperativna analgezija bila je zadovoljavajuća, uz uvođenje 500 mg intravenskog acetaminofena tek 8 sati nakon intervencije. Postoperativni bol praćen je uz pomoć NRS skale (engl. *Numeric Rating Scale*), a ponavljane doze analgetika davane su u slučaju prijavljenog intenziteta bola od tri ili više. Ukupna doza acetaminofena u prvom postoperativnom danu iznosila je 1 g. Kako opioidi nisu davani postoperativno, ukupna primena opioda svela se na uvodnu dozu fentanila od 0,83 µg/kg. U postoperativnom toku nisu uočene komplikacije po tipu oštećenja nerava, infekcije ubodnog mesta, kao ni toksičnih efekata lokalnih anestetika.

cheal intubation, surgical treatment was indicated due to progression of the primary disease.

It was decided to perform an axillary BPB under procedural sedation. Immediately prior to induction of anesthesia, noninvasive blood pressure was registered at 125/87 mmHg. At induction, the patient received 1 mg of midazolam and 30 µg of fentanyl intravenously, and sedation was maintained with a propofol infusion at a dose of 6–8 mg/kg/h. The axillary BPB (Figure 1) was performed under aseptic conditions with ultrasound guidance (eZono 4000 device, 22G/50 mm needle, *in-plane* technique). A total of 8 ml of 0.5% levobupivacaine and 5 ml of 2% lidocaine was administered around the nerves of the plexus, while 1 mL of each of the aforementioned local anesthetics was administered around the musculocutaneous nerve, whose branches innervate the skin of the lateral forearm. The total administered doses were 1.4 mg/kg of levobupivacaine and 3.33 mg/kg of lidocaine. Standard monitoring of vital signs was applied.

During the procedure, the patient remained completely hemodynamically and respiratorily stable, with oxygen support at 3 l/min via face mask and with mean arterial pressure readings between 85 and 90 mmHg.

Emergence from anesthesia was uneventful and without complications requiring intervention, upon which the patient was transferred to the hospital ward. Postoperative analgesia was satisfactory, and 500 mg of intravenous acetaminophen was administered only after eight hours since the procedure had passed. Postoperative pain was monitored using the Numeric Rating Scale (NRS), and repeated doses of analgesics were administered in cases of reported pain intensity of three or higher. The total dose of acetaminophen during the first postoperative day was 1 g. As no opioids were administered postoperatively, total opioid use was limited to the induction dose of fentanyl (0.83 µg/kg). No postoperative complications were observed, including nerve injury, puncture-site infection, or toxic effects of local anesthetics.

DISKUSIJA

Formiranje pouzdanog i dugotrajnog vaskularnog pristupa za dijalizu kod pedijatrijskih pacijenata sa terminalnom bubrežnom insuficijencijom je od ključnog značaja. Iako postoje alternativna rešenja, kao što su venski i peritonealni kateteri, formiranje AV fistule predstavlja zlatni standard [1]. Prethodno su takvi pacijenti podvrgavani isključivo opštoj anesteziji, pri čemu je učinjen pomak ka primeni različitih metoda regionalne anestezije u odrasloj populaciji [4–6]. Inicijalno je primenjivana infiltracija lokalnim anestetikom, međutim blokovi brahijalnog pleksusa su se, zbog obezbeđivanja uslova hirurške anestezije, nametnuli kao primarno rešenje za podlaktne fistule [7]. Kod odraslih pacijenata, formiranje fistule uz BBP uveliko se sprovodi u budnom stanju ili u uslovima sedacije, dok kod dece to još uvek nije slučaj, te se i dalje mahom sprovodi u obaveznoj opštoj anesteziji. Primena perifernih nervnih blokova u budnom stanju, proceduralnoj sedaciji ili u opštoj anesteziji kod dece nije povezana sa povišenom incidencijom komplikacija [8]. Tome doprinosi činjenica da je kod pacijenata koji se podvrgavaju elektivnim intervencijama neophodno potvrditi striktno poštovanje preoperativnog ograničenja unosa na usta, te jasno utvrditi faktore koji bi mogli doprineti regurgitaciji i sledstvenoj aspiraciji želudačnog sadržaja (npr. gastroezofagealni refluks, nedavno povraćanje bilo koje prirode, emetogene hirurške intervencije, primena emetogenih lekova) [9].

Adekvatna kontrola bola u postoperativnom periodu je od izuzetnog značaja i može da spreči prenaplašene odgovore na bol u starijem uzrastu [10]. Kako bi to bilo ostvareno, uz što manju upotrebu opioda, periferni nervni blokovi su predloženi kao jedan od efektivnih modaliteta [11]. Dobrobit primene ovog bloka takođe je uočena kada je u pitanju primarna patentnost fistule. Naime, kod odraslih pacijenata su opisani bolji i dugotrajniji rezultati po pitanju patentnosti fistule u odnosu na pacijente koji nisu dobili blok [4,5].

U pedijatrijskoj populaciji taj efekat nije do sada ispitivan, te samo može biti pretpostavljen. Nažalost, BBP se i dalje ne primenjuju rutinski kod dece podvrgnute formiranju podlaktne AV fistule. Deca su kao populacija sklonija otežanoj intubaciji i hiperreaktivnosti disajnog puta, što kod njih dovodi do učestalije pojave respiratornih komplikacija, kao što su laringospazam i bronhospazam, naročito kada istovremeno postoje faktori koji doprinose navedenoj hiperreaktivnosti [12–14]. Pacijenti prepoznati kao visokorizični bi mogli biti podvrgnuti formiranju fistule u uslovima sedacije i aksilarnog bloka brahijalnog pleksusa, te na taj način pošteđeni mogućih komplikacija izazvanih endotrahealnom intubacijom. Dobra klinička praksa nalaže da

DISCUSSION

Establishing reliable and long-lasting vascular access for dialysis in pediatric patients with end-stage renal disease is of critical importance. Although alternative options exist, such as venous and peritoneal catheters, AV fistula formation remains the gold standard [1]. Historically, such patients have been managed exclusively under general anesthesia. However, there has been a shift towards the use of various regional anesthesia techniques in the adult population [4–6]. Initially, local anesthetic infiltration was used. However, brachial plexus blocks have emerged as the primary modality for forearm fistula formation due to their ability to provide surgical anesthesia [7]. In adults, fistula formation under BPB is widely performed in awake patients or under sedation, whereas in children, this is still not the case, and procedures are predominantly performed under mandatory general anesthesia. In children, the use of peripheral nerve blocks in awake patients, patients under procedural sedation, or under general anesthesia has not been associated with an increased incidence of complications [8]. This is supported by the requirement that patients undergoing elective procedures must demonstrate strict adherence to preoperative fasting guidelines, and that factors possibly contributing to regurgitation and subsequent aspiration of gastric contents (e.g., gastroesophageal reflux, recent vomiting of any etiology, emetogenic surgical procedures, administration of emetogenic drugs) must be clearly identified [9].

Adequate postoperative pain control is of paramount importance and may prevent exaggerated pain responses later in life [10]. To achieve this while minimizing opioid use, peripheral nerve blocks have been proposed as an effective modality [11]. The benefit of this block has also been observed in terms of primary fistula patency. Specifically, in adult patients, better and more durable fistula patency outcomes have been reported compared with patients who did not receive a block [4,5].

In the pediatric population, this effect has not yet been investigated and can only be hypothesized. Unfortunately, BPBs are still not routinely used in children undergoing forearm AV fistula formation. Children, as a population, are more prone to difficult intubation and airway hyperreactivity, which leads to a higher incidence of respiratory complications such as laryngospasm and bronchospasm, particularly in the presence of concomitant risk factors that contribute to such hyperreactivity [12–14]. Patients identified as high risk could undergo fistula formation under sedation combined with an axillary brachial plexus block, thereby avoiding potential complications associated with endotracheal intubation. Good clinical practice dictates

je u ovakvim slučajevima i dalje neophodno biti u pripravnosti za hitnu intubaciju kao i za zbrinjavanje eventualnog nastalog laringospazma i/ili bronhospazma.

Kombinovana primena kratkododelujućih i dugododelujućih lokalnih anestetika je i dalje predmet rasprave [15,16]. Kliničko iskustvo naše ustanove podudarno je sa istraživanjima koja upućuju na brže ostvarene uslove hirurške anestezije [17]. Takođe, nije jasno dokazano da kombinovana primena lokalnih anestetika neće dovesti do bržeg nastanka hirurške anestezije od izolovane primene dugododelujućih lokalnih anestetika [18].

Iako terminalna bubrežna insuficijencija nema značajniji uticaj na farmakokinetiku amidnih lokalnih anestetika [19,20], neophodno je preduzeti mere predostrožnosti po pitanju komplikacija izazvanih primenom lokalnih anestetika, a prevashodno po pitanju njihove sistemske toksičnosti. Sistemska toksičnost lokalnih anestetika (engl. *local anesthetic systemic toxicity* – LAST) predstavlja retku i najtežu sistemsku komplikaciju u regionalnoj anesteziji. Nastaje kao rezultat osnovnog mehanizma dejstva lokalnih anestetika, odnosno blokade natrijumskih kanala. Zbog gotovo univerzalnog prisustva natrijumskih kanala u tkivima, klinička slika je izuzetno varijabilna (trnjenje usana, osećaj metalnog ukusa u ustima, zujanje u ušima, vrtoglavica, arterijska hipertenzija ili hipotenzija, tahikardični ili bradikardični poremećaji srčanog ritma do asistolije, konvulzije, poremećaji stanja svesti do kome) i zavisi od količine leka koja je dospela u krvotok, kao i od organskog sistema koji je dominantno zahvaćen [21].

U prikazanom pedijatrijskom slučaju, primena aksilarnog bloka brahijalnog pleksusa obezbedila je adekvatnu intraoperativnu analgeziju i smanjila perioperativnu potrošnju opioida prilikom formiranja podlaktne AV fistule. Ovakav pristup pružio je uslove za izvođenje intervencije u uslovima proceduralne sedacije, čime je izbegnuta očekivana otežana intubacija, kao i potencijalne komplikacije izazvane takvom intubacijom. U eventualnoj rutinskoj primeni, neophodno je imati na umu maksimalne dozvoljene doze lokalnih anestetika, specifičnosti njihove primene kod dece sa komorbiditetima, kao i moguće komplikacije, među kojima je najznačajnija sistemska toksičnost lokalnih anestetika.

Sukob interesa: Nije prijavljen.

that, even in such cases, preparedness for emergency intubation and management of potential laryngospasm and/or bronchospasm remains essential.

The combined use of short-acting and long-acting local anesthetics remains a subject of debate [15,16]. The clinical experience in our hospital is consistent with studies suggesting more rapid achievement of surgical anesthesia conditions [17]. However, it has not been clearly demonstrated that combined administration of local anesthetics will not result in a faster onset of surgical anesthesia compared with the use of long-acting local anesthetics alone [18].

Although end-stage renal disease does not significantly affect the pharmacokinetics of amide local anesthetics [19,20], precautionary measures regarding complications associated with their use are necessary, particularly with respect to systemic toxicity. Local anesthetic systemic toxicity (LAST) is rare but is also the most severe systemic complication in regional anesthesia. It results from the primary mechanism of local anesthetics action, namely, sodium channel blockade. Given the near-universal presence of sodium channels in tissues, the clinical presentation is highly variable (perioral numbness, metallic taste, tinnitus, dizziness, arterial hypertension or hypotension, tachyarrhythmia or bradyarrhythmia, which may escalate to asystole, seizures, altered consciousness, which may escalate to a coma) and depends on the amount of drug that has entered the circulation, as well as the organ system predominantly affected [21].

In the presented pediatric case, the use of an axillary brachial plexus block provided adequate intraoperative analgesia and reduced perioperative opioid consumption during the formation of a forearm AV fistula. This approach enabled the procedure to be performed under procedural sedation, thereby avoiding anticipated difficult intubation and potential complications associated with it. In potential routine application, it is essential to consider the maximum allowable doses of local anesthetics, the specifics of their use in children with comorbidities, as well as possible complications, among which local anesthetic systemic toxicity is the most significant.

Conflict of interest: None declared.

LITERATURA / REFERENCES

1. Preka E, Shroff R, Stronach L, Calder F, Stefanidis CJ. Update on the creation and maintenance of arteriovenous fistulas for haemodialysis in children. *Pediatr Nephrol*. 2021 Jul;36(7):1739-49. doi: 10.1007/s00467-020-04746-6.
2. Raina R, Joshi H, Chakraborty R, Sethi SK. Challenges of long-term vascular access in pediatric hemodialysis: Recommendations for practitioners. *Hemodial Int*. 2021 Jan;25(1):3-11. doi: 10.1111/hdi.12868.
3. Ahmed OF, Hamodat OM, Kakamad FH, Abduljabbar RS, Salih AM, Omar DA, et al. Outcomes of arteriovenous fistula for hemodialysis in pediatric age group. *Ann Med Surg (Lond)*. 2021 Nov 23;72:103100. doi: 10.1016/j.amsu.2021.103100.
4. Montelongo S, Brooks DE, Klopfenstein J, Peden EK. Surgical creation of upper extremity arteriovenous fistula and grafts: a narrative review. *Cardiovasc Diagn Ther*. 2023 Feb 28;13(1):147-55. doi: 10.21037/cdt-21-565.
5. Tomas VG, Hollis N, Ouanes JP. Regional Anesthesia for Vascular Surgery and Pain Management. *Anesthesiol Clin*. 2022 Dec;40(4):751-73. doi: 10.1016/j.anclin.2022.08.016.
6. Weeks JJ, Johnson PA, Garcia-Tomas V. Regional anesthesia for peripheral vascular surgery: what does the evidence tell us? *Curr Opin Anaesthesiol*. 2025 Oct 1;38(5):645-51. doi: 10.1097/ACO.0000000000001551.
7. Nijs K, Hertogen P, Buelens S, Coppens M, Teunkens A, Jalil H, et al. Axillary Brachial Plexus Block Compared with Other Regional Anesthesia Techniques in Distal Upper Limb Surgery: A Systematic Review and Meta-Analysis. *J Clin Med*. 2024 May 29;13(11):3185. doi: 10.3390/jcm13113185.
8. Pinto N, Sawardekar A, Suresh S. Regional Anesthesia: Options for the Pediatric Patient. *Anesthesiol Clin*. 2020 Sep;38(3):559-75. doi: 10.1016/j.anclin.2020.05.005.
9. He Y, Wang R, Wang F, Chen L, Shang T, Zheng L. The clinical effect and safety of new preoperative fasting time guidelines for elective surgery: a systematic review and meta-analysis. *Gland Surg*. 2022 Mar;11(3):563-75. doi: 10.21037/gs-22-49.
10. Eccleston C, Fisher E, Howard RF, Slater R, Forgeron P, Palermo TM, et al. Delivering transformative action in paediatric pain: a Lancet Child & Adolescent Health Commission. *Lancet Child Adolesc Health*. 2021 Jan;5(1):47-87. doi: 10.1016/S2352-4642(20)30277-7.
11. Raney EM, van Bosse HJP, Shea KG, Abzug JM, Schwend RM. Current State of the Opioid Epidemic as it Pertains to Pediatric Orthopaedics from the Advocacy Committee of the Pediatric Orthopaedic Society of North America. *J Pediatr Orthop*. 2018 May/Jun;38(5):e238-44. doi: 10.1097/BPO.0000000000001143.
12. Kenth J, Walker R. Assessment and management of the predicted difficult airway in neonates, infants and children. *Anaesth Intensive Care Med*. 2024 Oct;25(10):685-702. doi: 10.1016/j.mpaic.2024.07.006.
13. Kim HS, Kim YS, Lim BG, Lee JH, Song J, Kim H. Risk Assessment of Perioperative Respiratory Adverse Events and Validation of the COLDS Score in Children with Upper Respiratory Tract Infection. *Medicina (Kaunas)*. 2022 Sep 23;58(10):1340. doi: 10.3390/medicina58101340.
14. Hii J, Templeton TW, Sommerfield D, Sommerfield A, Matava CT, von Ungern-Sternberg BS. Risk assessment and optimization strategies to reduce perioperative respiratory adverse events in pediatric anesthesia-Part 1 patient and surgical factors. *Paediatr Anaesth*. 2022 Feb;32(2):209-16. doi: 10.1111/pan.14377.
15. Lin C, Guerrero AL, Jesin J, Tangri R, Luginaah NA, Kumar K, et al. Comparing block characteristics of mixtures of short/intermediate- and long-acting local anesthetics for peripheral nerve block: a systematic review and meta-analysis. *Braz J Anesthesiol*. 2025 May-Jun;75(3):844617. doi: 10.1016/j.bjane.2025.844617.
16. Almasi R, Rezman B, Kriszta Z, Patczai B, Wiegand N, Bogar L. Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks. *Heliyon*. 2020 Sep 2;6(9):e04718. doi: 10.1016/j.heliyon.2020.e04718.
17. Aguilera G, Tabilo C, Jara Á, Aliste J. 0.25% bupivacaine-1% lidocaine vs 0.5% bupivacaine for ultrasound-guided infraclavicular brachial plexus block: a randomized controlled trial. *Reg Anesth Pain Med*. 2025 Aug 5;50(8):627-34. doi: 10.1136/rapm-2024-105511.
18. Pietroski Dos Santos N, Silva VP, Oliveira GS, Musacchio VC, Carvalho VH. Efficacy of long-acting local anesthetics versus their mixture with shorter-acting local anesthetics for peripheral nerve blocks guided by ultrasound: a systematic review with meta-analysis of randomized controlled trials. *Reg Anesth Pain Med*. 2026 Feb 5;51(2):132-41. doi: 10.1136/rapm-2024-106104.
19. Heppollette CAA, Brunnen D, Bampoe S, Odor PM. Clinical Pharmacokinetics and Pharmacodynamics of Levobupivacaine. *Clin Pharmacokinet*. 2020 Jun;59(6):715-45. doi: 10.1007/s40262-020-00868-0.
20. Uppal NN, Jhaveri M, Hong S, Shore-Lesserson L, Jhaveri KD, Izzedine H. Local anesthetics for the Nephrologist. *Clin Kidney J*. 2021 Jul 2;15(2):186-93. doi: 10.1093/ckj/sfab121. Erratum in: *Clin Kidney J*. 2021 Oct 05;15(1):182. doi: 10.1093/ckj/sfab144.
21. Schweitzer-Chaput A, Callot D, Bouazza N, Lesage F, Oualha M, Paret N, et al. Local anesthetics systemic toxicity in children: analysis of the French pharmacovigilance database. *BMC Pediatr*. 2023 Jun 24;23(1):321. doi: 10.1186/s12887-023-04126-7.

PERIBULBARNANESTEZIJA UZ CILJANU INTRAVENSKU ANALGOSEDACIJU ESKETAMINOM TOKOM ENUKLEACIJE: SAVREMENI REVIJALNI PRIKAZ

OSTALI ČLANCI

OTHER ARTICLES

PERIBULBAR ANESTHESIA WITH TARGETED INTRAVENOUS ESKETAMINE ANALGOSEDATION DURING ENUCLEATION: A CONTEMPORARY NARRATIVE REVIEW

Margita Lučić^{1,2}, Dolika D. Vasović¹

¹ Univerzitetski klinički centar Srbije, Klinika za očne bolesti, Beograd, Srbija

² Univerzitetski klinički centar Srbije, Centar za anesteziju, reanimaciju, intenzivnu terapiju i terapiju bola, Beograd, Srbija

¹ University Clinical Centre of Serbia, Clinic for Eye Diseases, Belgrade, Serbia

² University Clinical Center of Serbia, Center for Anesthesia and Resuscitation, Belgrade, Serbia

SAŽETAK

Uvod: Enukleacija je invazivna oftalmološka procedura praćena izraženim nociceptivnim i refleksnim stimulusom, što predstavlja značajan anesteziološki izazov, naročito kod starijih i komorbidnih pacijenata. Savremeni anesteziološki trendovi sve više favorizuju primenu regionalne anestezije u kombinaciji sa ciljanom analgoosedacijom kao bezbedniju alternativu opštoj anesteziji.

Cilj: Prikazati savremene koncepte primene peribulbarne anestezije u kombinaciji sa ciljanom intravenskom analgoosedacijom esketaminom tokom enukleacije, sa posebnim osvrtom na hemodinamsku stabilnost, prevenciju okulokardijalnog refleksa, kontrolu perioperativnog bola, postoperativnu mučninu i povraćanje, kao i mogućnost uklanjanja ove tehnike u principe jednodnevne hirurgije.

Metod: U radu je sprovedena narativna analiza dostupne savremene literature iz oblasti oftalmološke i regionalne anestezije, sa fokusom na farmakološka svojstva esketamina, mehanizme dejstva peribulbarnog bloka i kliničke aspekte njihove kombinovane primene tokom enukleacije.

Zaključak: Peribulbarna anestezija u kombinaciji sa esketaminom vođenom ciljanom analgoosedacijom predstavlja bezbedan i efikasan savremeni anesteziološki pristup za izvođenje enukleacije, naročito kod starije i komorbidne populacije. Ovaj pristup omogućava stabilnu hemodinamiku, očuvano spontano disanje, adekvatnu kontrolu bola, nisku incidencu postoperativne mučnine i povraćanja i brz funkcionalni oporavak, uz mogućnost primene u okviru jednodnevne hirurgije.

Ključne reči: enukleacija, peribulbarna anestezija, esketamin, analgoosedacija, okulokardijalni refleks

ABSTRACT

Introduction: Enucleation is an invasive ophthalmic procedure accompanied by pronounced nociceptive and reflex stimuli, representing a significant anesthesiological challenge, particularly in elderly and comorbid patients. Contemporary anesthesiology trends increasingly favor the use of regional anesthesia combined with targeted analgoosedation as a safer alternative to general anesthesia.

Aim: To present current concepts of peribulbar anesthesia combined with targeted intravenous esketamine-guided analgoosedation during enucleation, with special emphasis on hemodynamic stability, prevention of the oculocardiac reflex, control of perioperative pain, postoperative nausea and vomiting, and the feasibility of integrating this technique into day-surgery protocols.

Methods: A narrative review of contemporary literature in the fields of ophthalmic and regional anesthesia was conducted, focusing on the pharmacological properties of esketamine, the mechanisms of action of the peribulbar block, and the clinical aspects of their combined use during enucleation.

Conclusion: Peribulbar anesthesia combined with esketamine-guided targeted analgoosedation represents a safe and effective contemporary anesthesiological approach for performing enucleation, particularly in elderly and comorbid patients. This approach provides stable hemodynamics, preserved spontaneous respiration, adequate pain control, a low incidence of postoperative nausea and vomiting, and rapid functional recovery, with the potential for application within a day-surgery setting.

Keywords: enucleation, peribulbar anesthesia, esketamine, analgoosedation, oculocardiac reflex

Autor za korespondenciju:

Dolika D. Vasović

Klinika za očne bolesti, Univerzitetski klinički centar Srbije

Pasterova 2, 11000 Beograd, Srbija

Elektronska adresa: jdolika.vasovic@gmail.com

Corresponding author:

Dolika D. Vasović

Clinic for Eye Diseases, University Clinical Centre of Serbia

2 Pasterova Street, 11000 Belgrade, Serbia

E-mail: dolika.vasovic@gmail.com

Primljeno • Received: January 5, 2026; **Revidirano • Revised:** February 11, 2026; **Prihvaćeno • Accepted:** February 12, 2026; **Online first:** March 25, 2026

DOI: 10.5937/smcl7-63921

UVOD

Enukleacija predstavlja jednu od najinvazivnijih procedura u očnoj hirurgiji [1]. Iako je hirurški relativno kratkotrajna, ova intervencija je praćena izrazito snažnim nociceptivnim stimulusom i značajnim hemodinamskim i autonomnim reakcijama, uključujući trigeminokardijalni, odnosno okulokardijalni refleks (OKR), što je čini posebnim anesteziološkim izazovom [2]. Klinička manifestacija ovih refleksnih odgovora može uključivati bradikardiju, hipotenziju, poremećaje srčanog ritma, a u najtežim slučajevima i asistoliju [2,3].

Tradicionalno, enukleacija se izvodila u uslovima opšte endotrahealne anestezije. Međutim, ovaj pristup je povezan sa povećanim rizikom od respiratornih, kardiovaskularnih i neurokognitivnih komplikacija, naročito kod starije i komorbidne populacije [4]. U skladu sa savremenim anesteziološkim principima, sve veći značaj pridaje se primeni regionalnih anestezioloških tehnika u kombinaciji sa analgosedacijom, sa ciljem smanjenja perioperativnog rizika, ubrzanog postoperativnog oporavka i unapređenja ukupne bezbednosti pacijenata [2,5].

Peribulbarna anestezija predstavlja pouzdanu regionalnu tehniku koja obezbeđuje adekvatnu senzornu blokadu i akineziju oka, uz značajno povoljniji bezbednosni profil u poređenju sa retrobulbarnim blokom [2,6]. U kombinaciji sa kontinuiranom intravenskom analgosedacijom esketaminom u subanestetičkim dozama, ovaj pristup omogućava stabilan perioperativni tok uz očuvano spontano disanje, minimalne hemodinamske oscilacije i povoljan postoperativni oporavak [5,6].

Cilj ovog revijalnog rada je da prikaže savremene koncepte primene peribulbarne anestezije u kombinaciji sa esketaminom tokom enukleacije, sa posebnim osvrtom na hemodinamsku stabilnost, kontrolu perioperativnog bola, prevenciju okulokardijalnog refleksa, smanjenje incidence postoperativne mučnine i povraćanja, kao i mogućnost uklapanja ovog anesteziološkog pristupa u principe jednodnevne hirurgije.

Regionalna anestezija u očnoj hirurgiji – savremeni koncept

Razvoj lokalnih anestetika, uz kontinuirano unapređenje tehnika regionalne i lokalne anestezije, značajno je doprineo razvoju savremene očne hirurgije [1]. Ove tehnike omogućavaju adekvatnu analgeziju i, u određenim slučajevima, pouzdanu akineziju oka uz minimalno sistemsko opterećenje, što je od posebnog značaja kod starijih i komorbidnih pacijenata [2].

Najčešće primenjivane anesteziološke tehnike u oftalmološkoj hirurgiji uključuju topikalnu anesteziju,

INTRODUCTION

Enucleation represents one of the most invasive procedures in ophthalmic surgery [1]. Although surgically relatively short in duration, this intervention is accompanied by an extremely strong nociceptive stimulus and significant hemodynamic and autonomic responses, including the trigeminocardiac reflex, i.e., the oculocardiac reflex (OCR), which makes it a particular anesthesiological challenge [2]. The clinical manifestation of these reflex responses may include bradycardia, hypotension, cardiac arrhythmias, and in the most severe cases, asystole [2,3].

Traditionally, enucleation has been performed under general endotracheal anesthesia. However, this approach is associated with an increased risk of respiratory, cardiovascular, and neurocognitive complications, particularly in elderly and comorbid patients [4]. In accordance with contemporary anesthesiology principles, increasing importance is being given to the use of regional anesthesia techniques combined with analgosedation, with the aim of reducing perioperative risk, accelerating postoperative recovery, and improving overall patient safety [2,5].

Peribulbar anesthesia represents a reliable regional technique that provides adequate sensory block and ocular akinesia, with a significantly more favorable safety profile compared to the retrobulbar block [2,6]. In combination with continuous intravenous analgosedation using esketamine in subanesthetic doses, this approach enables a stable perioperative course with preserved spontaneous respiration, minimal hemodynamic fluctuations, and favorable postoperative recovery [5,6].

The aim of this review article is to present contemporary concepts in the application of peribulbar anesthesia combined with esketamine during enucleation, with particular emphasis on hemodynamic stability, perioperative pain control, prevention of the oculocardiac reflex, reduction in the incidence of postoperative nausea and vomiting, as well as the potential integration of this anesthetic approach into the principles of day-case surgery.

Regional Anesthesia in Ophthalmic Surgery – Contemporary Concept

The development of local anesthetics, along with the continuous improvement of regional and local anesthesia techniques, has significantly contributed to the advancement of modern ophthalmic surgery [1]. These techniques provide adequate analgesia and, in certain cases, reliable ocular akinesia with minimal systemic burden, which is particularly important in elderly and comorbid patients [2].

subkonjunktivalnu i subtenonsku anesteziju, kao i retrobulbarni i peribulbarni blok [2,3]. Topikalna anestezija ne obezbeđuje akinezijsku oku i stoga nije pogodna za duboke orbitalne zahvate, ali predstavlja standardnu metodu u minimalno invazivnim procedurama. Subtenonska anestezija omogućava pouzdanu analgeziju prednjeg segmenta oka uz delimičnu akinezijsku i povoljan bezbednosni profil, zbog čega se često koristi u svakodnevnoj kliničkoj praksi [3].

Retrobulbarni blok obezbeđuje brzu i efikasnu analgeziju i akinezijsku oku i orbite, ali je povezan sa povećanim rizikom od ozbiljnih komplikacija, uključujući perforaciju bulbusa, povredu optičkog živca, intravaskularnu aplikaciju anestetika i intratekalno širenje sa potencijalno životno ugrožavajućom anestezijom moždanog stabla („brainstem anesthesia“) [4].

Peribulbarni blok je razvijen sa ciljem smanjenja navedenih rizika uz očuvanje visoke efikasnosti regionalne anestezije [1,4]. Izvodi se jednom ili dvema punkcijama, najčešće inferotemporalnim pristupom, uz ekstrakonalnu aplikaciju lokalnog anestetika, samostalno u obliku 2% lidokaina ili u kombinaciji sa 0,5% levobupivakainom radi produženog dejstva. Difuzijom lokalnog anestetika postiže se blokada senzornih i motornih vlakana n. ophthalmicus (V1), n. maxillaris (V2), kao i III, IV i VI kranijalnog živca do nivoa ciliarnog gangliona [2,4]. U poređenju sa retrobulbarnim blokom, peribulbarni pristup ima značajno povoljniji bezbednosni profil, uz stabilniju kontrolu intraokularnog pritiska (IOP) i okularnog perfuzionog pritiska (OPP), kao i nižu incidencu okulokardijalnog refleksa (OKR) [1,5].

Esketamin u ciljanoj analgo sedaciji – farmakološki profil i klinička primena

Esketamin je potentni antagonist NMDA receptora sa izraženim analgetskim i sedativnim dejstvom, uz minimalan uticaj na respiratorni centar [6]. Kao S-enantiomer ketamina, odlikuje se približno dvostruko većom afinitetnom i analgetskom potentnošću, što omogućava pouzdanu analgeziju u subanestetičkim dozama uz manju učestalost psihomimetskih neželjenih efekata u poređenju sa racemskim ketaminom [6,7]. Pored primarnog delovanja na NMDA receptore, esketamin ostvaruje i dodatne efekte putem opioidnih receptora, monoaminskih puteva i voltažno-zavisnih kalcijumskih kanala, čime se postiže multimodalni analgetski efekat bez klinički značajne respiratorne depresije [6–8].

Farmakokinetički profil esketamina karakterišu brz početak dejstva (30–60 sekundi nakon intravenske primene), kratak kontekst-zavisni poluživot i predviđiva eliminacija, što omogućava preciznu titraciju infuzije i brz oporavak nakon prekida primene [7,8]. Njegov

The most commonly used anesthetic techniques in ophthalmic surgery include topical anesthesia, subconjunctival and sub-Tenon's anesthesia, as well as retrobulbar and peribulbar blocks [2,3]. Topical anesthesia does not provide ocular akinesia and is therefore not suitable for deep orbital procedures, but it represents the standard method in minimally invasive interventions. Sub-Tenon's anesthesia provides reliable analgesia of the anterior segment of the eye with partial akinesia and a favorable safety profile, which is why it is frequently used in routine clinical practice [3].

The retrobulbar block provides rapid and effective analgesia and akinesia of the eye and orbit but is associated with an increased risk of serious complications, including globe perforation, optic nerve injury, intravascular injection of the anesthetic, and intrathecal spread with potentially life-threatening brainstem anesthesia [4].

The peribulbar block was developed with the aim of reducing the aforementioned risks while maintaining high efficacy of regional anesthesia [1,4]. It is performed using one or two injections, most commonly via an inferotemporal approach, with extraconal administration of the local anesthetic, either as 2% lidocaine alone or in combination with 0.5% levobupivacaine to prolong the duration of action. Through diffusion of the local anesthetic, sensory and motor fibers of the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve, as well as cranial nerves III, IV, and VI up to the level of the ciliary ganglion, are blocked [2,4]. Compared to the retrobulbar block, the peribulbar approach has a significantly more favorable safety profile, with more stable control of intraocular pressure (IOP) and ocular perfusion pressure (OPP), as well as a lower incidence of the oculocardiac reflex (OCR) [1,5].

Esketamine in Targeted Analgo sedation – Pharmacological Profile and Clinical Application

Esketamine is a potent NMDA receptor antagonist with pronounced analgesic and sedative properties, exerting minimal influence on the respiratory center [6]. As the S-enantiomer of ketamine, it demonstrates approximately twice the receptor affinity and analgesic potency, enabling reliable analgesia at subanesthetic doses with a lower incidence of psychomimetic adverse effects compared to racemic ketamine [6,7]. In addition to its primary action on NMDA receptors, esketamine exerts supplementary effects via opioid receptors, monoaminergic pathways, and voltage-gated calcium channels, thereby producing a multimodal analgesic effect without clinically significant respiratory depression [6–8].

umereni simpatikomimetski efekat doprinosi održavanju srčane frekvence i srednjeg arterijskog pritiska u fiziološkim granicama, čime se smanjuje rizik od perioperativne hipotenzije, koja se često javlja tokom duboke sedacije ili opšte anestezije [6,9].

U kontekstu enukleacije, procedure koju karakteriše intenzivan nociceptivni stimulus, trakcija ekstraokularnih mišića i manipulacija optičkim nervom, neophodni su očuvani respiratorni refleksi, hemodinamska stabilnost i adekvatna analgezija. U tom smislu, esketamin predstavlja racionalan izbor za kontinuiranu analgosedaciju [5,9].

U poređenju sa propofolom, esketamin omogućava stabilnije održavanje hemodinamskih parametara, uz ograničene fiziološke fluktuacije arterijskog pritiska i srčane frekvence [5,10]. Midazolam, iako efikasan anksiolitik, ne poseduje analgetska svojstva i često zahteva dodatnu primenu opioda, dok deksmedetomidin, uprkos očuvanoj respiratornoj funkciji, može dovesti do bradikardije i hipotenzije, uz potencijalno nedovoljnu analgeziju tokom izrazito bolnih faza enukleacije [3,5].

Prednosti peribulbarne anestezije uz esketamin tokom enukleacije

Većina pacijenata podvrgnutih enukleaciji pripada starijoj populaciji i često ima pridružena kardiovaskularna, respiratorna i metabolička oboljenja, što značajno povećava perioperativni rizik u uslovima opšte anestezije [11]. Prednosti regionalnog anesteziološkog pristupa ogledaju se u izbegavanju manipulacije disajnim putem, smanjenju hemodinamskih oscilacija, minimalnom sistemskom opterećenju i bržem postoperativnom oporavku [2,11].

U tom kontekstu, peribulbarna anestezija u kombinaciji sa ciljanom analgosedacijom esketaminom omogućava stabilnije vrednosti arterijskog pritiska i srčane frekvence, uz očuvano spontano disanje i zaštitne refleksne mehanizme [5,9].

Enukleacija predstavlja jedan od najizraženijih refleksogenih zahvata u očnoj hirurgiji. Aktivacija trigemino-vagalnog refleksnog luka tokom trakcije ekstraokularnih mišića i manipulacije optičkim nervom može dovesti do pojave okulkardijalnog refleksa (OKR), sa potencijalno ozbiljnim hemodinamskim posledicama [2,4]. Kombinacija peribulbarne anestezije i analgosedacije esketaminom doprinosi smanjenju incidence ovog refleksa kroz efikasnu blokadu aferentnih refleksnih puteva i modulaciju autonomnog odgovora [5]. Smanjena potreba za opiodnim analgeticima dodatno rezultuje nižom učestalošću postoperativne mučnine i povraćanja, bržim funkcionalnim oporavkom i većim komforom pacijenata [1,8].

The pharmacokinetic profile of esketamine is characterized by a rapid onset of action (30–60 seconds following intravenous administration), a short context-sensitive half-life, and predictable elimination, allowing precise infusion titration and rapid recovery after discontinuation [7,8]. Its moderate sympathomimetic effect helps maintain heart rate and mean arterial pressure within physiological ranges, thereby reducing the risk of perioperative hypotension, a common complication of deep sedation or general anesthesia [6,9].

In the context of enucleation, a procedure characterized by intense nociceptive stimulation, traction of the extraocular muscles, and manipulation of the optic nerve, preservation of respiratory reflexes, hemodynamic stability, and adequate analgesia are essential. In this regard, esketamine represents a rational choice for continuous analgosedation [5,9].

Compared with propofol, esketamine enables more stable maintenance of hemodynamic parameters, with limited physiological fluctuations in arterial pressure and heart rate [5,10]. Midazolam, although an effective anxiolytic, lacks intrinsic analgesic properties and often necessitates adjunctive opioid administration, whereas dexmedetomidine, despite preserving respiratory function, may induce bradycardia and hypotension, with potentially insufficient analgesia during highly painful phases of enucleation [3,5].

Advantages of Peribulbar Anesthesia with Esketamine During Enucleation

The majority of patients undergoing enucleation belong to the elderly population and frequently present with concomitant cardiovascular, respiratory, and metabolic comorbidities, significantly increasing perioperative risk under general anesthesia [11]. The advantages of a regional anesthetic approach include avoiding airway manipulation, reducing hemodynamic fluctuations, minimizing systemic burden, and accelerating postoperative recovery [2,11].

In this context, peribulbar anesthesia combined with targeted analgosedation using esketamine provides more stable arterial pressure and heart rate values while preserving spontaneous ventilation and protective reflex mechanisms [5,9].

Enucleation represents one of the most pronounced reflexogenic procedures in ophthalmic surgery. Activation of the trigemino-vagal reflex arc during traction of the extraocular muscles and manipulation of the optic nerve may provoke the oculocardiac reflex (OCR), potentially leading to serious hemodynamic consequences [2,4]. The combination of peribulbar anesthesia and analgosedation with esketamine reduces the incidence of this reflex by effectively blocking afferent reflex pathways

DISKUSIJA

Primena peribulbarne anestezije u kombinaciji sa ciljanom intravenskom analgosedacijom esketaminom predstavlja racionalan i savremen odgovor na specifične anesteziološke zahteve koje nameće enukleacija [1,2]. Ovaj multimodalni pristup objedinjuje prednosti stabilne regionalne analgezije i akinezije oka sa centralnom analgezijom i sedacijom uz očuvano spontano disanje, čime se izbegavaju hemodinamske i respiratorne oscilacije karakteristične za opštu anesteziju [2–4].

Poseban značaj ovog koncepta ogleda se u njegovoj primeni kod starije i komorbidne populacije, kod koje su kardiopulmonalne i neurokognitivne rezerve često ograničene [5,6]. Stabilna hemodinamika, efikasna prevencija okulokardijalnog refleksa i smanjena potreba za opioidima doprinose boljoj kontroli postoperativnog bola, nižoj incidenci postoperativne mučnine i povraćanja i bržem funkcionalnom oporavku pacijenata [1,3,7]. U tom kontekstu, kombinacija peribulbarne blokade i esketaminom vođene ciljane analgosedacije pokazuje visok stepen bezbednosti i dobru kliničku toleranciju [2,8].

U skladu sa savremenim *fast-track* anesteziološkim protokolima, ovakav pristup omogućava raniju mobilizaciju, kraći boravak u sobi za oporavak i, kod pažljivo selektovanih pacijenata, bezbedno uklapanje enukleacije u principe jednodnevne hirurgije [4,6]. Iako su potrebna dalja prospektivna i multicentrična istraživanja radi dodatne standardizacije protokola i procene dugoročnih ishoda, dostupni podaci iz literature dosledno ukazuju na kliničku opravdanost ovog pristupa [2,5,9]. Na osnovu postojećih dokaza, peribulbarna anestezija u kombinaciji sa ciljanom analgosedacijom esketaminom može se smatrati metodom izbora kod pažljivo selektovanih pacijenata koji se podvrgavaju enukleaciji, uz povoljan balans između bezbednosti, efikasnosti i komfora pacijenata [1,2].

Ograničenja dostupne literature

Dostupni dokazi o primeni regionalne anestezije uz esketamin tokom enukleacije ograničeni su nedostatkom velikih, randomizovanih i kontrolisanih studija [2,5]. Većina publikovanih radova odnosi se na manje invazivne oftalmološke procedure, dok su podaci specifični za enukleaciju retki i metodološki heterogeni, sa varijacijama u anesteziološkim tehnikama, režimima sedacije i kriterijumima procene ishoda [3,7,8]. Dodatna ograničenja proizilaze iz etičkih i kliničkih izazova sprovođenja randomizovanih studija kod starijih i komorbidnih pacijenata [5,6].

Uprkos tome, postojeći podaci ukazuju na povoljan trend ka boljoj hemodinamskoj stabilnosti, smanjenju

and modulating the autonomic response [5]. Reduced reliance on opioid analgesics further results in a lower incidence of postoperative nausea and vomiting, faster functional recovery, and improved patient comfort [1,8].

DISCUSSION

The use of peribulbar anesthesia in combination with targeted intravenous analgo-sedation using esketamine represents a rational and contemporary response to the specific anesthetic demands imposed by enucleation [1,2]. This multimodal approach integrates the benefits of stable regional analgesia and ocular akinesia with central analgesia and sedation while preserving spontaneous respiration, thereby avoiding the hemodynamic and respiratory fluctuations characteristic of general anesthesia [2–4].

The particular relevance of this concept is reflected in its application in elderly and comorbid patients, whose cardiopulmonary and neurocognitive reserves are often limited [5,6]. Stable hemodynamics, effective prevention of the oculocardiac reflex, and reduced opioid requirements contribute to improved postoperative pain control, a lower incidence of postoperative nausea and vomiting, and faster functional recovery [1,3,7]. In this context, the combination of peribulbar block and esketamine-guided targeted analgo-sedation demonstrates high safety and good clinical tolerability [2,8].

In accordance with contemporary fast-track anesthetic protocols, this approach enables earlier mobilization, shorter stay in the recovery unit, and among carefully selected patients—the safe integration of enucleation into the principles of day-case surgery [4,6]. Although further prospective and multicenter studies are required to standardize protocols and evaluate long-term outcomes, the available literature consistently supports the clinical justification of this approach [2,5,9]. Based on current evidence, peribulbar anesthesia combined with targeted analgo-sedation using esketamine may be considered a method of choice in carefully selected patients undergoing enucleation, offering a favorable balance between safety, efficacy, and patient comfort [1,2].

Limitations of the Available Literature

The available evidence regarding the use of regional anesthesia with esketamine during enucleation is limited by the lack of large, randomized controlled trials [2,5]. Most published studies concern less invasive ophthalmic procedures, whereas data specific to enucleation are scarce and methodologically heterogeneous, with variations in anesthetic techniques, sedation regimens, and outcome assessment criteria [3,7,8]. Additional limitations arise from the ethical and clinical

perioperativnog rizika i bržem oporavku pri primeni regionalne anestezije uz analgozaciju u poređenju sa opštom anestezijom, što opravdava dalja istraživanja i kliničko razmatranje ovog pristupa [1,2,4,9].

Sukob interesa: Nije prijavljen.

challenges of conducting randomized studies in elderly and comorbid populations [5,6].

Nevertheless, existing data indicate a favorable trend toward improved hemodynamic stability, reduced perioperative risk, and faster recovery with regional anesthesia combined with analgozedation compared to general anesthesia, thereby supporting further research and clinical consideration of this approach [1,2,4,9].

Conflict of interest: None declared.

LITERATURA / REFERENCES

1. Calenda E, Benzerroug M, Retout A, Genevois O. Duration of pain after a combination of peribulbar anesthesia and local anesthetic in the ball after enucleation or evisceration: 115 cases. *J Clin Anesth*. 2010 Sep;22(6):485-6. doi: 10.1016/j.jclinane.2009.12.008.
2. Adewara BA, Badmus SA, Adegbehingbe BO, Awe OO, Onakpoya OH, Adeoye AO. Trends in Eye Removal Surgeries at a Tertiary Care Hospital Over Three Decades. *West Afr J Med*. 2022 Oct 20;39(10):1068-74.
3. Ali HM, Elbadawy AM. Comparative Study of Retrobulbar Block versus Ketamine Infusion during Eye Enucleation/Evisceration (Randomized Controlled Trial). *Anesth Essays Res*. 2020 Jan-Mar;14(1):92-9. doi: 10.4103/aer.AER_146_19.
4. Ye W, Hu Z, Jin X, Wang P. Effects of dexmedetomidine for retrobulbar anesthesia in orbital ball implants after enucleation surgery. *Indian J Ophthalmol*. 2015 Sep;63(9):704-9. doi: 10.4103/0301-4738.170981. Erratum in: *Indian J Ophthalmol*. 2015 Nov;63(11):876. doi: 10.4103/0301-4738.171983.
5. Nagy AA, El-Sayd SH, Ahmed AA, Rajab GZ. Optimal Dose of Dexmedetomidine Retrobulbar Anesthesia during Phacoemulsification Cataract Surgery. *Anesth Essays Res*. 2017 Oct-Dec;11(4):1046-50. doi: 10.4103/aer.AER_116_17.
6. Zhu Y, Li Z, Chen W, Fan P, Yang S, Liu X, et al. Incidence and Risk Factors of Moderate to Severe Postoperative Pain Following the Placement of Primary and Secondary Orbital Implants: A Prospective Observational Study. *Ophthalmic Plast Reconstr Surg*. 2021 Jan-Feb 01;37(1):27-32. doi: 10.1097/IOP.0000000000001664.
7. Ang MJ, Silkiss RZ. The Use of Long-Acting Liposomal Bupivacaine (Exparel) for Postoperative Pain Control Following Enucleation or Evisceration. *Ophthalmic Plast Reconstr Surg*. 2018 Nov/Dec;34(6):599. doi: 10.1097/IOP.0000000000001218.
8. Ye H, Chen R, Lian X, Huang J, Mao Y, Lu R, et al. Risk factors associated with postoperative pain and discomfort in oculoplastic surgery with general anesthesia: a prospective study. *J Pain Res*. 2018 Feb 21;11:407-15. doi: 10.2147/JPR.S156104.
9. Rodolico A, Cutrufelli P, Di Francesco A, Aguglia A, Catania G, Concerto C, et al. Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: an overview of systematic reviews with meta-analysis. *Front Psychiatry*. 2024 Feb 1;15:1325399. doi: 10.3389/fpsyt.2024.1325399.
10. Han D, Du X, Li Y, Wang Y, Wei L, Zhang L, et al. Supplemental low-dose esketamine to propofol versus propofol alone on perioperative characteristics in children undergoing surgery: a prospective randomized controlled trial. *Minerva Anestesiol*. 2024 Mar;90(3):162-71. doi: 10.23736/S0375-9393.23.17550-X.
11. Pai V, Parra-Fariñas C, Shaikh F, Mallipatna A, Zaarour C, Muthusami P. An updated review of intra-arterial chemotherapy for retinoblastoma. *Radiologia (Engl Ed)*. 2025 Mar-Apr;67(2):162-75. doi: 10.1016/j.rxeng.2025.02.001.

UPUTSTVO AUTORIMA ZA PRIPREMU RADOVA

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

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

Radovi se šalju elektronski. Adresa za prijavljivanje rada za časopis je <https://aseestant.ceon.rs/index.php/smdlk>. Časopis koristi otvoren sistem pristupa koji omogućava automatsko proveravanje plagijarizma i autoplagijarizma. Uz rad se šalju i odgovarajuće potvrde (videti na kraju ovog uputstva).

OPŠTA UPUTSTVA

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

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

PRIPREMA RADA

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

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

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

INSTRUCTIONS FOR AUTHORS

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

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

Papers are submitted electronically. The web address for submitting papers is <https://aseestant.ceon.rs/index.php/smdlk>. The Journal uses an open access system that allows automatic checking for plagiarism and autoplagiarism. Appropriate certificates should be provided with the paper (see at the end of these instructions).

GENERAL INSTRUCTIONS

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

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

PREPARING THE PAPER

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

COVER PAGE (first page) should include the title of the paper, without acronyms, a suggested short title of the paper, the full names of the authors (without titles) indexed using numbers, the official name of the institutions where the authors work, place and country (in the order corresponding to the indexed numbers of the authors). At the bottom of the page, provide the name, contact address, phone number, fax number and email address of the corresponding author. The cover page should be in Serbian and English language (second page).

ABSTRACT should be up to 250 words, including acronyms (third page). For original papers, preliminary and short communications, meta-analyses and review papers, the abstract should have the following structure: Introduction, Aim, Methods, Results, Conclusion. Each of these segments should be written as a separate paragraph. For case report, the summary should have the following sections: Introduction, Case Report, Conclusion; each part should be written as a separate paragraph. For other types of papers, the abstract does not have a special structure. List three to six key words or phrases below the abstract. Words from the

ba da se ponavljaju reči iz naslova, a ključne reči treba da budu relevantne i opisne. U izboru ključnih reči koristiti *Medical Subject Headings* – MeSH (<http://www.nlm.nih.gov/mesh>). Sažetak treba da bude napisan na srpskom i engleskom jeziku.

Na **četvrtoj strani** treba da se nalazi prevod teksta koji je na trećoj strani (sažetak). Ova strana mora da ima identičnu strukturu trećoj strani.

Od pete strane broji se broj strana predviđen za odgovarajuću strukturu rada.

STRUKTURA RADA. Svi podnaslovi se pišu velikim masnim slovima (**bold**). Originalni rad, meta-analiza, prethodno i kratko saopštenje obavezno treba da imaju sledeće podnaslove: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Metode rada, Rezultati, Diskusija (koncizna, jasna, predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi), Zaključak (mora proisteci isključivo iz rezultata istraživanja rada, Spisak skraćenica (ukoliko su korišćene u tekstu), Zahvalnica, Literatura (navodi se arapskim brojevima redosledom kojim je u tekstu navedena u uglastim zagradama, vidi dalje). Struktura rada kod pregleda literature sastoji se od Uvoda, Većeg broja podnaslova, Zaključka, Literature. Autori preglednog rada treba da navedu bar tri rada (kao autori ili koautori) publikovanih u časopisima s recenzijom. Struktura rada kod prikaza jednog ili više slučajeva čine: Uvod (Cilj rada navesti kao poslednji pasus Uvoda), Prikaz bolesnika, Diskusija, Literatura. Ne treba koristiti imena bolesnika, inicijale, niti brojeve istorija bolesti, naročito u ilustracijama. Prikazi slučajeva ne smeju imati više od pet autora.

STATISTIČKE METODE, PRIKAZ I INTERPRETACIJA REZULTATA

Ukoliko je moguće, sve numeričke vrednosti zaokružiti na jedno decimalno mesto. Ne duplirati prikaz rezultata u tabelama i grafikonima. Za prikaz rezultata u tabelama i tekstu preporuka je da se: numerički podaci sa normalnom raspodelom i bez ekstremnih vrednosti prikazuju kao aritmetička sredina $\pm$ standardna devijacija; numerički podaci čija raspodela odstupa od normalnosti ili kada postoje ekstremne vrednosti, i ordinalni podaci prikazuju kao medijana i opseg (minimalna – maksimalna vrednost); nominalni podaci i ordinalni podaci sa malim brojem kategorija prikazuju kao n (%).

Prilikom opisa primenjenih statističkih metoda, prikaza i interpretacije rezultata u radu pridržavati se *SAMPL Guidelines* (Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: the "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines*. *Int J Nurs Stud* 2015;52(1):5-9.). Primenjene statističke metode treba opisati dovoljno detaljno da ih čitalac može ponoviti na svojim podacima. Navesti korišćeni statistički test i nivo značajnosti. Saopštiti tačnu *p*-vrednost na 3 decimalna mesta.

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

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

DECIMALNI BROJEVI. U tekstu rada na engleskom jeziku, u tabelama, na grafikonima i drugim prilogima decimalne brojeve pisati sa tačkom (npr. 12.5 ± 3.8), a u tekstu na srpskom jeziku sa zarezom (npr. $12,5 \pm 3,8$). Kad god je to moguće, broj zaokružiti na jednu decimalu.

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

title should not be repeated, and the key words should be relevant and descriptive. The Medical Subject Headings – MeSH thesaurus (<http://www.nlm.nih.gov/mesh>) should be used for selecting the key word. The abstract should be submitted in both Serbian and English language.

The **fourth page** should contain the translation of the text from the third page (abstract). This page must have the identical structure as the third page.

The number of pages provided for the appropriate structure of the paper is counted from the fifth page.

STRUCTURE OF THE PAPER. Capital bold letters should be used for all sub-headings. Original papers, meta-analyses, preliminary and short communications must have the following subheadings: Introduction (the objective of the paper should be stated in the last paragraph of the Introduction), Methodologies, Results, Discussion (concise and clear, it represents the interpretation and comparison of study results with relevant studies published in domestic and international literature), Conclusion (it must derived solely from the results of the research), List of acronyms (if used in the text), Acknowledgment, and Literature (listed using Arabic numerals, in the order in which they appear in the text, in square brackets, see below). The structure of literature review papers should be: Introduction, a number of subheadings, Conclusion, and Literature. The authors of the reviews should list at least three papers (as authors or co-authors) published in peer-reviewed journals. The structure of the paper presenting one or more cases should consists of: Introduction (the objective of the paper should be given as the last paragraph of the Introduction), Case Report, Discussion, and Literature. Patient names, initials, and medical history numbers should not be used, especially in illustrations. Case reviews should not have more than five authors.

STATISTICAL METHODS, PRESENTATION AND INTERPRETATION OF RESULTS

If possible, all numbers should be rounded to one decimal place. The display of results in tables and graphs should not be repeated. When presenting results in tables and text, it is recommended that numerical data with normal distribution and without extreme values be presented as arithmetic mean $\pm$ standard deviation; that numerical data whose distribution deviates from normal distribution or when there are extreme values, and ordinal data, be presented as the median and range (minimum–maximum value); that nominal data and ordinal data with a small number of categories be displayed as n (%).

When describing the applied statistical methods, presentation and interpretation of results in the paper, follow the *SAMPL Guidelines* (Lang TA, Altman DG. *Basic statistical reporting for articles published in biomedical journals: The "Statistical Analyses and Methods in the Published Literature" or the SAMPL Guidelines*. *Int J Nurs Stud* 2015; 52(1):5-9.). The applied statistical methods should be described in sufficient detail so that the reader may repeat them using own data. Indicate the statistical test used and the level of significance. Report the correct *p*-value to the third decimal place.

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

ACRONYMS should be used only when necessary, i.e. for very long names of chemical compounds and names that are already commonly used as acronyms (standard acronyms, such as DNA, AIDS, HIV). For each acronym, the full term should be given at the first appearance in the text, unless it is a standard unit of measure. Acronym should not be used in the title. Avoid using acronyms in the abstract, but if necessary, explain each acronym at the first appearance in the text.

DECIMAL NUMBERS. In the English text of the paper, in tables, graphs and other appendices decimal numbers are written with a point (e.g. 12.5 ± 3.8), and in the text in Serbian with a comma (e.g. $12,5 \pm 3,8$). Whenever possible, round the number to one decimal place.

(mol), a pritisak krvi u milimetrima živinog stuba (mm Hg). Sve rezultate hematoloških, kliničkih i biohemijskih merenja navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).

PRILOZI su tabele, slike (fotografije, crteži, sheme, grafikoni), do šest po radu. Svaki prilog se dostavlja kao poseban dokument, obeležen na isti način kao u tekstu. Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje

TABELE. Svaka tabela treba da bude sama po sebi lako razumljiva. Naslov treba otkucati iznad tabele, a objašnjenja ispod nje. Tabele se označavaju arapskim brojevima prema redosledu navođenja u tekstu. Tabele crtati isključivo u programu *Word*, kroz meni *Table–Insert–Table*, uz definisanje tačnog broja kolona i redova koji će činiti mrežu tabele. Desnim klikom na mišu – pomoću opcija *Merge Cells* i *Split Cells* – spajati, odnosno deliti ćelije. Kucati fontom *Times New Roman*, veličinom slova 12 pt, s jednostrukim proredom i bez uvlačenja teksta. Korišćene skraćenice u tabeli treba objasniti u legendi ispod tabele. Ukoliko je rukopis na srpskom jeziku, priložiti nazive tabela i legendu na oba jezika. Takođe, u jednu tabelu, u okviru iste ćelije, uneti i tekst na srpskom i tekst na engleskom jeziku (nikako ne praviti dve tabele na dva jezika!).

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

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

HEME I CRTEŽI. Crteži i sheme se dostavljaju u *jpg* ili *tiff* formatu. Svi podaci na shemi kucaju se u fontu *Times New Roman*, veličina slova 10 pt. Korišćene skraćenice na shemi treba objasniti u legendi ispod sheme. Ukoliko je rukopis na srpskom jeziku, priložiti nazive shema i legendu na oba jezika.

ZAHVALNICA. Navesti sve saradnike koji su doprineli stvaranju rada a ne ispunjavaju kriterijume za autorstvo, kao što su osobe koje obezbeđuju tehničku pomoć, pomoć u pisanju rada ili rukovode odeljenjem koje obezbeđuje opštu podršku. Finansijska i materijalna pomoć, u obliku sponzorstva, stipendija, poklona, opreme, lekova i drugo, treba takođe da budu navedene.

LITERATURA. Spisak referenci je odgovornost autora, a citirani članci treba da budu lako pristupačni čitaocima časopisa. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50, a u meta-analizi do 100.

Broj citiranih originalnih radova mora biti najmanje 80% od ukupnog broja referenci, odnosno broj citiranih knjiga, poglavlja u knjigama i preglednih članaka manji od 20%. Nije dozvoljeno citiranje apstrakata. Ukoliko je bitno komentarisati rezultate koji su publikovani samo u vidu apstrakta, neophodno je to navesti u samom tekstu rada. Reference članaka koji su prihvaćeni za štampu,

UNITS OF MEASURE. Express length, weight and volume in metric units (meter – m, kilogram (gram) – kg (g), liter – l) or their parts. Express temperature in degrees Celsius (°C), amount of substance in moles (mol), and blood pressure in millimeters of mercury (mmHg). All results of hematological, clinical and biochemical measurements should be reported using the metric system, according to the International System of Units (SI).

ATTACHMENTS are tables, pictures (photographs, drawings, diagrams, graphs), up to six per paper. Each attachment is submitted as a separate document, labeled the same way as it appears in the text. If tables, graphs, charts or figures have already been published, the original source should be indicated, and written consent for their use attached.

TABLES. Tables should be easily comprehensible. The caption should be typed above the table, with an explanation below it. Tables are labeled with Arabic numerals, according to the order of appearance in the text. Tables should be drawn only in MS Word, using the Insert Table function, defining the exact number of columns and rows that will form the table grid. Use Merge Cells and Split Cells options to merge or split cells. Use Times New Roman font, size 12 pt, with single spacing and no indentation. The acronyms used in the table should be explained in the legend below the table. If the manuscript is in Serbian, attach the names of the tables and the legend in both languages. Also, enter the Serbian text and English text in the same table, within a single cell (never make two tables in two languages).

IMAGES. All forms of graphic attachments are images. Photographs, drawings, diagrams and graphs can be published. Images are labeled using Arabic numerals, according to the order of appearance in the text. Only digital photos (black-and-white or color) of at least 300 dpi resolution, in TIFF or JPG format are accepted (small, blurry and poor-quality images will not be accepted for print). If the authors do not have or are not able to submit digital photos, then the original images should be scanned at a resolution of 300 dpi and in original size. If the paper requires multiple images for illustration, several will be published in the paper, and the rest will be included in the e-version of the article, as a MS PowerPoint presentation (each image must be numbered and include a legend). The used microscope magnification should be noted in the image legend. Each photo should include the scale. The image names and the legend should be provided in both Serbian and English language.

GRAPHS. Graphs should be provided and submitted in MS Excel, in order to show the accompanying values arranged by cell. The same graphs should be copied into a MS Word document. Graphs are labeled with Arabic numerals, according to the order of appearance in the text. All data in the graphs should be displayed using the Times New Roman font. Acronyms used on the graph should be explained in the legend below the graph. Include the names of the graphs and the legend in both Serbian and English language.

DIAGRAMS AND DRAWINGS. Diagrams and drawings can be submitted in JPG or TIFF format. All data in the diagram should be displayed using the Times New Roman font, size 10 pt. The acronyms used in the diagram should be explained in the legend below the diagram. If the manuscript is submitted in Serbian, the names of the diagrams and the legends should be provided in both Serbian and English language.

ACKNOWLEDGEMENTS. List all associates who contributed to the production of the paper but do not meet the authorship criteria, such as persons providing technical assistance, assistance in writing the paper, or managing the department that provided general support. Financial and material assistance, in the form of sponsorships, scholarships, donations, equipment, medicine, etc., should also be listed.

LITERATURE. The list of references is the responsibility of the author, and the cited articles should be easily accessible to the readers of the Journal. References should be numbered using Arabic numerals, according to the order of appearance in the text. The number of references should not exceed 30, except in the case of literature reviews, in which case it may be up to 50, and up to 100 in the case of meta-analyses.

ali još nisu objavljeni, treba označiti sa *in press* i priložiti dokaz o prihvatanju rada za objavljivanje.

Podaci o korišćenju literaturi u tekstu označavaju se arapskim brojevima u uglastim zagrada – npr. [1,2], i to redosledom kojim se pojavljuju u tekstu. Reference se citiraju prema **Vankuverskom stilu** (uniformisanim zahtevima za rukopise koji se predaju biomedicinskim časopisima), koji je uspostavio Međunarodni komitet urednika medicinskih časopisa (<http://www.icmje.org>), čiji format koriste U.S. National Library of Medicine i baze naučnih publikacija. Primeri navođenja publikacija (članaka, knjiga i drugih monografija, elektronskog, neobjavljenog i drugog objavljenog materijala) mogu se pronaći na internet-stranici http://www.nlm.nih.gov/bsd/uniform_requirements.html. Prilikom navođenja literature veoma je važno pridržavati se pomenutog standarda, jer je to jedan od najbitnijih faktora za indeksiranje prilikom klasifikacije naučnih časopisa. Podaci sa interneta citiraju se uz navođenje datuma pristupa tim podacima.

PREDVIĐEN BROJ STRANICA ZA RAD SA SVIM PRILOZIMA

1. **Uvodnici** – do 5 strana: mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.
2. **Originalni članci** – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.
3. **Pregledni članci** – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 3 rada autora članka iz uže naučne oblasti koja je opisana u radu.
4. **Prethodna ili kratka saopštenja** – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.
5. **Stručni članci** – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.
6. **Prikazi slučajeva** – do 6 strana. Opisuje retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.
7. **Članci iz istorije medicine** – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.
8. **Ostali članci** – prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i naučne vesti i članci napisani u znak sećanja (*In memoriam*).

Original papers must account for at least 80% of the total number of references, i.e. the number of cited books, book chapters, and reviews must be less than 20%. Citing abstracts is not permitted. If it is important to comment on results that have been published only in the form of an abstract, it is necessary to cite this in the text of the paper. References to articles that have been accepted for publication but have not yet been published should be marked "in press" and proof of acceptance of the paper for publication should be attached.

Information about the literature used in the paper is indicated in the text by Arabic numerals in square brackets, e.g. [1,2], in the order in which they appear in the text. References are cited according to the **Vancouver style** (Uniform Requirements for Manuscripts Submitted to Biomedical Journals), established by the International Committee of Medical Journal Editors (<http://www.icmje.org>), whose format is used by the U.S. National Library of Medicine and scientific publication databases. Examples of citations of publications (articles, books and other monographs, electronic, unpublished and other published material) are available at http://www.nlm.nih.gov/bsd/uniform_requirements.html. When citing literature, it is very important to abide by the mentioned standard, because it is one of the most important indexing factors when classifying scientific journals. Online data is cited with the date of access to that data.

NUMBER OF PAGES FOR THE PAPER (WITH ALL ATTACHMENTS)

1. **Editorials** (up to 5 pages) present opinions or discussions on a particularly relevant topic for the Journal, as well as on data published in this or other journals. They are usually written by one author, by invitation.
2. **Original articles** (up to 12 pages) present the results of the research of the authors of the paper and their interpretation. The research should be processed and presented in a way that can be repeated, and the analysis of results and conclusions should be clear so that they can be verified.
3. **Reviews** (up to 10 pages) represent the systematic, comprehensive and critical presentation of a problem on the basis of analyzed and discussed data from literature, which reflect the state of the science in a particular area of research. The literature used in the paper must contain at least 3 papers by the author of the article from the specific scientific field addressed in the paper.
4. **Preliminary and short communications** (up to 4 pages) contain extremely important scientific results that should be published as soon as possible. They do not have to contain a detailed description of the methodology and results, but they must contain all the same sections as original articles, in a concise form.
5. **Professional articles** (up to 10 pages) refer to the verification or presentation of previous research; they represent a useful means of disseminating knowledge and adapting original research to the needs of existing science and practice.
6. **Case report** (up to 6 pages) describe rare cases from practice and are similar to professional articles. These papers present unusual forms and courses of disease, unexpected reactions to the applied therapy, application of new diagnostic procedures, or rare and new diseases.
7. **History of medicine articles** (up to 10 pages) describe developments from the past, with the aim of preserving medical and health culture. They have the same form as professional articles.
8. **Other articles** – book reviews, excerpts from foreign literature, reports from congresses and professional conferences, statements on the operation of health organizations, branches and sections, editorial statements, letters to the editorial board, medical news, questions and answers, professional and scientific news and articles written in commemoration (*in memoriam*).

U POSTUPKU PRIJAVE

U postupku prijave neophodno je da se naglasi kojoj kategoriji rad pripada: uvodnik, stručni rad, originalni rad, prethodna ili kratka saopštenja, pregledni članak, prikaz slučaja, prikaz serije slučajeva, članak iz istorije medicine i drugo.

Uz rad neophodno je da se pošalje:

- 1) saglasnost svih autora, da rad nije delimično ili u celini objavljen, poslat ili prihvaćen za štampu u drugom časopisu,
- 2) potpisana izjava svih autora da su rukopis pročitali i odobrili za objavljivanje u časopisu sa navođenjem njihovog doprinosa u realizaciji istraživanja i pisanja rada,
- 3) izjava o nepostojanju sukoba interesa.

Autori su dužni da se pridržavaju etičkih standarda koji se odnose na naučnoistraživački rad. (*The Declaration of Helsinki, The Basel Declaration, Good Laboratory Practice, Good Clinical Practice, ICMJE guidelines*).

IN THE SUBMISSION PROCEDURE

in the submission procedure it is necessary to point out which category the paper belongs to: editorial, professional paper, original paper, preliminary or short communications, review article, case review, case series review, paper on the history of medicine, or other.

Together with the paper, it is necessary to include:

- 1) signed statements of all the authors that the work has not been partially or entirely published, sent or accepted for publication in another journal;
- 2) signed statements of all authors that they have read the manuscript and approved it for publication in the Journal, stating their contribution to the study or the writing of the paper,
- 3) a declaration on absence of conflict of interest.

It is the responsibility of each author to ensure that manuscripts submitted to Srpski medicinski časopis Lekarske komore are written in accordance with ethical standards (*The Declaration of Helsinki, The Basel Declaration, Good Laboratory Practice, Good Clinical Practice, ICMJE guidelines*).

CIP - Каталогизacija у публикацији
Народна библиотека Србије, Београд

61

SRPSKI medicinski časopis Lekarske komore

= Serbian journal of the Medical chamber / glavni i odgovorni urednik Milena Šantrić-Milićević. - [Štampano izd.]. - Vol. 1, br. 1 (sep. 2020)- . - Beograd : Lekarska komora Srbije, 2020- (Beograd : Birograf Comp). - 30 cm

Tromesečno. - Drugo izdanje na drugom medijumu:

Srpski medicinski časopis Lekarske komore (Online) = ISSN 2737-9752

ISSN 2737-971X = Srpski medicinski časopis Lekarske komore (Štampano izd.)

COBISS.SR-ID 19685641

