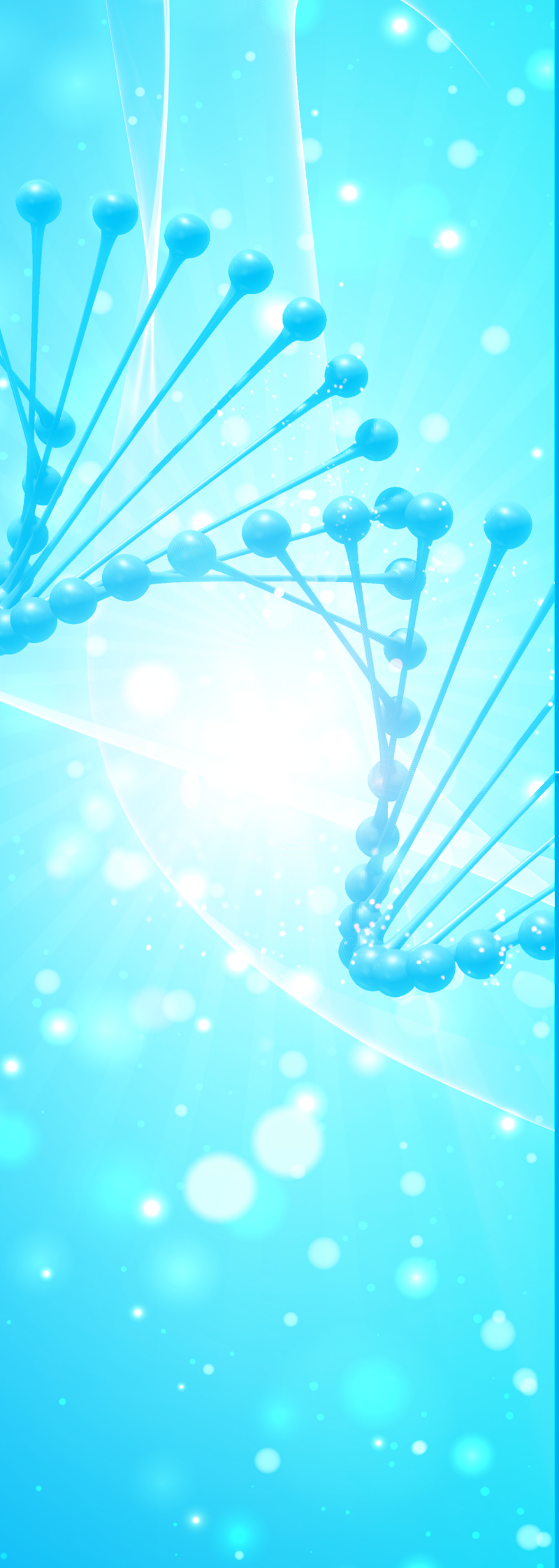


ISSN 0350-3208
eISSN 2683-4286

KOMORA ZDRAVSTVENIH
USTANOVA SRBIJE - BEOGRAD

GODIŠTE 52 · SVESKA 4 · DECEMBAR 2023

# ZDRAVSTVENA ZAŠTITA

# HEALTH CARE

VOLUME 52 · ISSUE 4 · DECEMBER 2023

THE CHAMBER OF HEALTHCARE
INSTITUTIONS OF SERBIA - BELGRADE

Stručni časopis **Zdravstvena zaštita**, koji Komora zdravstvenih ustanova Srbije izdaje od 1972. godine, objavljuje neobjavljene originalne stručne i naučne radove, pregledne članke, kratka saopštenja, uvodnike, pisma uredniku, meta-analize, prikaze bolesnika, aktuelne teme, prikaze stručnih knjiga i skupova, i drugo, iz oblasti medicine, farmacije, biohemije, stomatologije i menadžmenta u zdravstvu, čime doprinosi promociji i razvoju nauke, struke i naučno-istraživačkog rada.

Naučne i stručne radove u časopisu objavljuju vrhunski stručnjaci različitih profila sa naučnim i drugim zvanjima, akademici. Prenoseći u proteklom periodu odabrane tekstove do svojih čitalaca, stranice **Zdravstvene zaštite** istovremeno predstavljaju svedočanstvo, kako pionirskog rada Komore, tako i svojevrsne istorije zdravstva Srbije.

Od januara 2019. godine sprovodi se elektronsko uređivanje časopisa **Zdravstvena zaštita** (engl. *Health Care*), a od septembra 2019. dostupan je u režimu otvorenog pristupa (engl. *Open Access*). Otvoren pristup obezbeđuje besplatno čitanje, preuzimanje, čuvanje, štampanje i korišćenje objavljenih rukopisa u časopisu svakom korisniku koji ima pristup internetu. Svi članci objavljeni u časopisu **Zdravstvena zaštita** mogu se besplatno preuzeti sa sajta časopisa: http://scindeks.ceon.rs/journaldetails.aspx?issn=0350-3208. Časopis se objavljuje četiri puta godišnje.

Svi rukopisi pre objavljivanja u časopisu **Zdravstvena zaštita** prolaze internu (preliminarni pregled rukopisa od strane urednika i/ili uređivačkog odbora) i eksternu recenziju (dve nezavisne recenzije od strane stručnjaka u datoj oblasti pri čemu se poštuje anonimnost i autora recenzije i autora rukopisa). Konačna odluka o objavljivanju rukopisa donosi se na osnovu stručne, etičke i statističke recenzije. Pre objavljivanja rukopisa, vrši se kontrola plagijarizma, odnosno rukopis se upoređuje sa svim originalnim tekstovima u dostupnim bazama podataka.

Radovi mogu biti napisani na srpskom ili engleskom jeziku, sa rezimeima na srpskom i engleskom jeziku.

Radove objavljene u časopisu **Zdravstvena zaštita** indeksiraju: SCIndeks - *Serbian Citation Index*, COBISS.SR – ID 3033858 i doiSerbia.

Scientific journal **Zdravstvena zaštita** (The Journal of **Health Care**), which has been published by the Chamber of health institutions of Serbia since 1972, publishes unpublished original expert and scientific papers, review articles, short communications, introductions, letters to the editor, meta – analyses, case reports of the patients, actual topics, depictions of scientific books and conferences, among other things related to the field of medicine, stomatology, pharmacology, biochemistry and health management. In this way, the magazine contributes to the promotion and development of science, as well as expertise and scientific research work.

Preeminent experts of different profiles and with different scientific titles publish their scientific and research papers in the journal. By means of conveying the selected texts, the pages of **Health Care** represent the testimony, of both the pioneering work of the Chamber, and a kind of history of health care in Serbia alike.

The Journal of **Health Care** has been edited electronically since January 2019, and it has been in Open Access Mode since September 2019. Open access enables reading free of charge, downloading, saving, printing and using writings published in the journal to any user that has an internet access. All papers published in **Health Care** can be downloaded for free on the journal's website: http://scindeks.ceon.rs/journaldetails.aspx?issn=0350-3208. The journal is published four times a year.

Prior to publishing in **Health Care**, all writings go through an internal review (preliminary review of the manuscript by the editor and/or editorial board) as well as an external review (independent reviews by the experts form the given field, while respecting the anonymity of the author of the review and the author of the paper). Final decision on whether the paper is going to be published is reached on the basis of expertly, ethical, and statistical review. Control for plagiarism is performed before the paper is published, which implies comparing the manuscript to all original texts in the available databases.

Papers could be written in the Serbian or English language, with summaries in both Serbian and English.

Papers published in The Journal **Health Care** are indexed by: SCIndeks - Serbian Citation Index, COBISS.SR – ID 3033858 and doiSerbia.

KOMORA ZDRAVSTVENIH USTANOVA SRBIJE

ISSN 0350-3208
eISSN 2683-4286
COBISS.SR-ID 3033858
UDK 613/614


**Zvanični časopis Komore zdravstvenih ustanova Srbije za medicinu, farmaciju, biohemiju, stomatologiju i menadžment u zdravstvu**

**GODINA 52** **BROJ 4** **DECEMBAR** **2023. GODINA**

**VLASNIK I IZDAVAČ:**
Komora zdravstvenih ustanova Srbija

**ZA IZDAVAČA:**
Snežana Rašić Đorđević



**ADRESA UREDNIŠTVA:**
11000 Beograd, Hajduk Veljkov venac 4-6
Tel/faks: +381 11 3622 523 ili +381 11 3622 524
E-mail: urednik@komorazus.org.rs
Žiro račun: 205-4707-32

**Menadžer časopisa:**
Đorđe Nikodinović

**Tehnički urednik i lektor za srpski jezik:**
Asist. dr Aleksandra Nikolić

**Prevodilac i lektor za engleski jezik:**
Prof. Milica Matić

**Štampa:**
Cakum Pakum, Beograd

**Tiraž:** 50 primeraka

Članci u celosti dostupni su na internet stranici:
http://scindeks.ceon.rs/journaldetails.aspx?issn=0350-3208

ISSN 0350-3208
eISSN 2683-4286
COBISS.SR-ID 3033858
UDK 613/614


THE CHAMBER OF HEALTHCARE INSTITUTIONS OF SERBIA

**Official journal of the Chamber of Healthcare Institutions of Serbia for medicine, pharmacy, biochemistry, stomatology and healthcare management**

**YEAR 52** **ISSUE NO. 4** **DECEMBER** **YEAR 2023**

**THE OWNER AND PUBLISHER:**
Serbian Chamber of Health Institutions

**FOR THE PUBLISHER:**
Snezana Rasic Djordjevic



**EDITORIAL BOARD ADDRESS:**
11000 Belgrade, Hajduk Veljkov venac 4-6
Tel/fax: +381 11 3622 523 or +381 11 3622 524
E-mail: urednik@komorazus.org.rs
Account number: 205-4707-32

**Journal manager:**
Djorđe Nikodinovic

**Technical editor and Serbian language editor :**
Asst. Aleksandra Nikolic, MD

**Translator and English language editor:**
Milica Matic, PhD

**Press:**
Cakum Pakum, Beograd

**Circulation:** 50 copies

Articles are available in their integral versions on the webpage:
http://scindeks.ceon.rs/journaldetails.aspx?issn=0350-3208

# SADRŽAJ

# CONTENTS

PRIKAZ IZLOŽBE

UDK BROJEVI: 929:61 Костић А.
61(497.11)"2023"(062.5)
DOI: https://www.doi.org/10.5937/zdravzast52-47449

# 130 GODINA OD ROĐENJA I 40 GODINA OD SMRTI PROF. DR ALEKSANDRA Đ. KOSTIĆA

**Nela Puškaš**[1]

[1] institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić," Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija

[*] Korespondencija: Nela Puškaš, Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić," Medicinski fakultet, Univerzitet u Beogradu, Višegraska 26a, Beograd, Republika Srbija; e-mail: nela.puskas@med.bg.ac.rs

Ove godine navršava se 130 godina od rođenja i 40 godina od smrti prof. dr Aleksandra Đ. Kostića, osnivača Instituta za histologiju i embriologiju Medicinskog fakulteta u Beogradu, koji je u tri mandata bio i na poziciji dekana. Pored toga, učestvovao je u osnivanju Farmaceutskog fakulteta i Fakulteta veterinarske medicine Univerziteta u Beogradu (1,2). Autor je jedinstvenog višejezičnog medicinskog rečnika i urednik brojnih stručnih i naučnih izdanja. Bio je pionir medicinske fotografije i filma na našim prostorima, bio je i prvi lekar koji se na našim prostorima bavio seksologijom, ali i pisac i pesnik, kompozitor i pijanista, arheolog i paleontolog, čime je zadužio našu medicinu, druge oblasti nauke i umetnosti, ali i društvo u celini (2,3). Tim povodom, na Medicinskom fakultetu Univerziteta u Beogradu, u okviru tradicionalnog simpozijuma pod nazivom „Stremljenja i novine u medicini" biće organizovan simpozijum pod nazivom „Delo prof. dr Aleksandra Đ. Kostića". Simpozijum je planiran za 7. decembar 2023. godine, a organizator je autor ovog teksta.

U okviru simpozijuma biće predstavljen jedan deo bogatog stručnog, naučnog, umetničkog i kulturnog rada prof. Aleksandra Kostića. Nakon uvodnog predavanja prof. dr Nele Puškaš koje ima za cilj da sublimira radni opus prof. Kostića, koji ga svrstava u istorijsku ličnost srpske medicine, akademik Vladimir Bumbaširević će govoriti o njegovim istraživanjima u oblasti histologije i embriologije. Rad u oblasti medicinske terminologije i krunu njegovog rada u toj oblasti – višejezični Medicinski rečnik, predstaviće dr. Zoran Vacić, predsednik Sekcije za istoriju medicine Srpskog lekarskog društva. Osvrt i kritiku pripovedačkog dela prof. Kostića će izložiti književni kritičar Jasmina Ahmetagić, dok će osvrt na njegov kompozitorski opus i pijanističke sposobnosti predstaviti muzikolog Snežana Nikolajević. Biće to i jedinstvena prilika da publika čuje neke od Kostićevih interpretacije Šopenovih klavirskih kompozicija, koje je njegov sin Vojislav Voki Kostić snimio 1969. godine, a početkom dve hiljaditih uradio njihovu postprodukciju i ostavio 50 numerisanih CD primeraka. Presek arheoloških iskopavanja koje je vršio prof. Kostić i značaj otkrivenih artefakata će predstaviti Miloš Spasić, muzejski savetnik u Muzeju grada Beograda, dok će o njegovom radu i angažovanju na formiranju muzejske postavke u Grockoj, gde je najveći broj predmeta i pronađen, govoriti Zorica Atić, direktorka Centra za kulturu Grocka. Ona će govoriti o sudbini prve izložbene postavke, koja je bila u Rančićevoj kući, ali i o formiranju Legata dr Aleksandra Kostića u biblioteci „Ilija Garašanin" u Grockoj, gde je bogata arheološka i paleontološka zaostavština prof. Kostića danas smeštena. Ovaj simpozijum je i prilika da se prvi put pod okriljem Medicinskog fakulteta u Beogradu govori o političkim dešavanjima koja su prethodila udaljavanju prof. Kostića sa fakulteta 1952. godine, a koja su imala snažan uticaj na njegov profesionalni, umetnički i društveni angažman. Ovu intrigantnu temu, praćenu i brojnim kontroverzama, predstaviće Dragomir Bondžić, naučni savetnik u Institutu za savremenu istoriju i autor više publikacija koje detaljno obrađuju odnos komunističke vlasti prema profesorima Beogradskog univerziteta u periodu od 1945. do 1954. godine.

Simpozijum će pratiti izložba „Tajne iz zaboravljene arhive", koja će biti postavljena u holu deka-

REVIEW OF AN EXHIBITION

UDK NUMBERS: 929:61 Костић А.
61(497.11)"2023"(062.532)
DOI: https://www.doi.org/10.5937/zdravzast52-47449

# MARKING THE 130th ANNIVERSARY OF PROFESSOR ALEKSANDAR Đ. KOSTIĆ'S BIRTH AND THE 40th ANNIVERSARY OF HIS DEATH

**Nela Puškaš**[1]

[1] Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić," Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia

[*] Correspondence: Prof. Nela Puškaš, Institute of Histology and Embryology "Prof. dr Aleksandar Đ. Kostić", Faculty of Medicine, University of Belgrade, 26a Višegradska street, 11000 Belgrade, Republic of Serbia; e-mail: nela.puskas@med.bg.ac.rs

This year marks the 130th anniversary of Prof. Aleksandar Đ. Kostić's death and the 40th anniversary of his death. Professor Kostić was the founder of the Institute of Histology and Embryology of the Faculty of Medicine in Belgrade and held the position of Dean for three terms. In addition, he participated in the founding of the Faculty of Pharmacy and the Faculty of Veterinary Medicine of the University of Belgrade (1,2). He is the author of a unique multilingual Medical dictionary and editor of numerous professional and research publications. He was a pioneer of medical photography and film, as well as the first doctor who dealt with sexology in this region, but also a writer and poet, composer and pianist, archaeologist and paleontologist. As such, he has left a lasting mark in Serbian medicine, but also in other areas of science and art, and in Serbian society as a whole (2, 3). On this occasion, at the Faculty of Medicine of the University of Belgrade, within the symposium *Trends and Innovations in Medicine*, which is traditionally organized every year, a symposium *The Work of Professor Aleksandar Đ. Kostić* will be held. The symposium is planned for December 7, 2023, and the organizer is the author of this text.

As part of the symposium, a part of the rich professional, scientific, artistic and cultural work of Prof. Aleksandar Kostić will be presented. After the opening lecture by Prof. Dr. Nela Puškaš, which aims to present a summary of the body of work of Professor Kostić, which makes him a historical figure of Serbian Medicine, Academician Vladimir Bumbaširević will talk about Professor Kostić's research in the field of histology and embryology. The Professor's work in the field of medical terminology and the pinnacle of his efforts in this area – the multilingual Medical Dictionary, will be presented by Dr Zoran Vacić, President of the Section for the History of Medicine of the Serbian Medical Society. A critical review of the literary work of Prof. Kostić will be presented by literary critic Jasmina Ahmetagić, while musicologist Snežana Nikolajević will present an overview of his work as a composer and his skill as a pianist. This will also be a unique opportunity for the audience to hear some of Kostić's interpretations of Chopin's piano compositions, which his son Vojislav Voki Kostić recorded in 1969, and in the early 2000s carried out their post-production leaving 50 numbered CD copies. An overview of the archaeological excavations carried out by Prof. Kostić and the significance of the uncovered artifacts will be presented by Miloš Spasić, Senior curator at the Belgrade City Museum, while Zorica Atić, Director of the Grocka Culture Center, will talk about the Professor's work and involvement in the creation of the permanent exhibit in Grocka, where the largest number of the artefacts were found. She will talk about the fate of the first permanent exhibit at the Gallery *Rančić's House*, but also about the forming of the *Legacy of Dr. Aleksandar Kostić* within the *Ilija Garašanin* library in Grocka, where the abundant archaeological and paleontological legacy of Prof. Kostić is housed today. This symposium is also an opportunity to talk, for the first time under the auspices of the Faculty of Medicine in Belgrade, about the political events that preceded the removal of Prof. Kostić from the Faculty in 1952,

nata Medicinskog fakulteta u Beogradu. Izložbeni panoi će biti deo panoa predstavljenih u galeriji Rančićeva kuća, a zatim i u Galeriji nauke i tehnike SANU, tokom oktobra i novembra 2022. godine, kada je prvi put i predstavljena bogata fotografska zaostavština prof. Kostića za koju se decenijama nije znalo da postoji i koja je otkrivena tek nedavno (4). U ulozi stručnih vodiča će se naći studenti medicine, inače, članovi Centra za stručni i naučno-istraživački rad studenata, koji su bili izuzetni domaćini i vodiči publici tokom trajanja izložbe u Galeriji nauke i tehnike SANU.

Sam datum simpozijuma nosi još jednu simboliku. Naime, pre trideset godina, 7. decembra 1993. godine, prof. Obren Popović je organizovao prvi i do danas jedini skup posvećen delu prof. Kostića. Radno predsedništvo tadašnjeg skupa su činili profesori Medicinskog fakulteta u Beogradu: prof. dr Slobodan Đorđević, akademik Vladimir Kajuh, akademik Vojin Šulović, prof. dr Radivoje Grbić, prof. dr Slavko Simeunović, prof. dr Obren Popović, akademik Veselinka Šušić, akademik Miroslav Simić i prof. dr Milovan Krstić. Na skupu su govorili: prof. dr Obren Popović, akademik Vojin Šulović, dr Budimir Pavlović, prof. dr Milorad Japundžić, prof. dr Ljubomir Erić, prof. dr Slobodan Đorđević, gospodin Mile Đorđević, tadašnji upravnik Fotografskog odeljenja i akademik Dragoslav Srejović.

Imajući u vidu vreme predviđeno programom, kao i broj planiranih tema, može se reći i da je ovaj skup osvrt na samo jedan deo bogatog opusa rada prof. Kostića i da otvara prostor i predstavlja najavu bar još jednog sličnog, a slobodno se može reći i neophodnog skupa. Naime, o radu i doprinosu prof. Kostića se nakon njegovog udaljavanja sa Medicinskog fakulteta, 1952. godine, nije mnogo govorilo. Razlog za to je upravo politička pozadina odluke o udaljavanju. Značajan deo njegove zostavštine u tim okolnostima je uništen ili sklonjen od očiju javnosti i prepušten zaboravu. Na fakultetu je organizovan samo jedan, prethodno pomenuti simpozijum. Međutim, nedavno otkrivena zaostavština na Institutu za histologiju i embriologiju, otvorila je priliku da mnoge istine i činjenice vezane za rad prof. Kostića i njegovih saradnika u međuratnom periodu ugledaju svetlost dana, ali i da delo ove značajne ličnosti srpske medicine ponovo oživi i bude predstavljeno i intrepretirano naučnoj i stručnoj javnosti u svetlu vremena u kome živimo. Prethodno organizovane izložbe, kao i planirani skup u okviru simpozijuma „Stremljenja i novine u medicini" predstavljaju samo početak i jedan su u nizu koraka koji se preduzimaju ka povratku prof. Kostića na javnu scenu i pokušaj su da se višedecenijska nepravda prema njemu delimično ublaži.

Svojim dolaskom na ovaj jedinstven skup pod nazivom „Delo prof. dr Aleksandra Đ. Kostića" povodom 130 godina od rođenja i 40 godina od smrti, u okviru simpozijuma „Stremljenja i novine u medicini", 7. decembra u 14 časova u svečanu Salu dekanata Medicinskog fakulteta u Beogradu, doprinećete očuvanju sećanja i odati priznanje i poštovanje prema prof. dr Aleksandru Đ. Kostiću, ali i generacijama nastavnika koji su iz temelja gradili i stvarali Medicinski fakultet u Beogradu.

## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

## Reference


1. Puškaš N. Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" kroz prizmu sudbine njegovog osnivača. Zdravstvena zaštita 2021; 50(4):55-76. doi: 10.5937/zdravzast50-35011
2. Puškaš N. Institut za histologiju i embriologiju u najmodernijoj zgradi Medicinskog fakulteta u Beogradu između dva svetska rata. Medicinska istraživanja 2023; 56(2):31-7.doi: 10.5937/medi56-44482
3. Puškaš N, Arađan I. Fotografsko odeljenje profesora Aleksandra Kostića – osnivanje, dometi i značaj. Zdravstvena zaštita 2022;51(4):16-31.doi: 10.5937/zdravzast51-41664
4. Labudović Borović M. Izložba „Tajne iz zaboravljene arhive" u Galeriji nauke i tehnike SANU – autor: prof. dr Nela Puškaš, Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" Medicinski fakultet Univerziteta u Beogradu. Zdravstvena zaštita 2022;51(4):8-15. doi: 10.5937/zdravzast51-41973

which had a strong influence on his professional, artistic and social involvement. This intriguing topic, filled with numerous controversies, will be presented by Dragomir Bondžić, Principal Research Fellow at the Institute for Contemporary History and author of several publications which present a detailed analysis of the relationship of the communist authorities towards the professors of the University of Belgrade in the period from 1945 to 1954.

The symposium will be accompanied by the exhibition "Secrets from the Forgotten Archive", which will be set up in the atrium of the Dean's Office of the Faculty of Medicine in Belgrade. The exhibition panels are some of the panels originally presented at the Gallery Rančić's House, and then in the Gallery of Science and Technology of the Serbian Academy of Sciences and Arts (SASA), during October and November 2022, when Prof. Kostić's rich photography legacy, which was not known to exist for decades and was discovered only recently, was presented (4). Students of medicine, members of the Center for Student's Professional and Scientific Research will perform the role of guides during the exhibition. These students have proven to be exceptionally good hosts and guides at the exhibition held at the SASA Gallery of Science and Technology.

The date of the symposium itself is additionally symbolic. Namely, thirty years ago, on December 7, 1993, Prof. Obren Popović organized the first, and to date the only symposium dedicated to the work of Prof. Kostić. The following professors of the Faculty of Medicine in Belgrade were chairmen: Prof. Slobodan Đorđević, Academician Vladimir Kajuh, Academician Vojin Šulović, Prof. Radivoje Grbić, Prof. Slavko Simeunović, Prof. Obren Popović, Academician Veselinka Šušić, Academician Miroslav Simić, and Prof. Milovan Krstić.

The speakers at this symposium were: Prof. Obren Popović, Academician Vojin Šulović, Dr Budimir Pavlović, Prof. Milorad Japundžić, Prof. Ljubomir Erić, Prof. Slobodan Đorđević, Mr. Mile Đorđević, who was at the time the Director of the Photography Department of the Faculty of Medicine, and Academician Dragoslav Srejović.

Bearing in mind the time provided for in the program, as well as the number of planned topics, it can be said that this symposium is an overview of only a part of Prof. Kostić's rich body of work which opens the door to at least one more similar, and one can safely say, necessary symposium or conference. Namely, not much has been said about the Professor's work and impact after his removal from the Faculty of Medicine, in 1952. The reason for this lies in the political motivation that drove the decision to dismiss the Professor from the Faculty. In such circumstances, a significant part of his legacy was destroyed or hidden from the public and left forgotten. The symposium described above was the only symposium dedicated to his work held at the Faculty of Medicine. However, the body of work left by the Professor which was recently discovered at the Institute of Histology and Embryology has provided the opportunity for many truths and facts related to the work of Prof. Kostić and his associates in the interwar period to come to light. This discovery has also provided an opportunity for the work of this important figure of Serbian medicine to come back to life and be presented and interpreted in the scientific and professional circles in the context of the time we live in. The exhibitions previously organized, as well as the symposium that is to be held as a part of the Trends and Innovations in Medicine, represent merely the initial step in a series of steps that need to be taken towards publicly reestablishing the significance of Prof. Kostić's work and attempting to right the decades of injustice against him.

By coming to the unique symposium *The Work of Professor Aleksandar Đ. Kostić* on the 130$^{th}$ anniversary of his birth and the 40$^{th}$ anniversary of his death, which will be held as a part of the symposium *Trends and Innovations in Medicine*, on December 7, 2023, at 2 p.m. in the assembly hall of the Dean's Office of the Faculty of Medicine in Belgrade, you will contribute to the preservation of his memory and to the recognition and respect that Professor Aleksandr Đ. Kostić rightly deserves, as do the generations of teachers who have built and developed the Faculty of Medicine in Belgrade from the ground up.

## Competing interests

The author declared no competing interests.

## References

1. Puškaš N. Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" kroz prizmu sudbine njegovog osnivača. Zdravstvena zaštita 2021;50(4):55-76. doi: 10.5937/zdravzast50-35011

**Primljen:** 31.10.2023. **Revizija:** 29.11.2023. **Prihvaćen:** 02.12.2023.

2. Puškaš N. Institut za histologiju i embriologiju u najmodernijoj zgradi Medicinskog fakulteta u Beogradu između dva svetska rata. Medicinska istraživanja 2023; 56(2):31-7.doi: 10.5937/medi56-44482
3. Puškaš N, Arađan I. Fotografsko odeljenje profesora Aleksandra Kostića – osnivanje, dometi i značaj. Zdravstvena zaštita 2022;51(4):16-31.doi: 10.5937/zdravzast51-41664
4. Labudović Borović M. Izložba „Tajne iz zaboravljene arhive" u Galeriji nauke i tehnike SANU – autor: prof. dr Nela Puškaš, Institut za histologiju i embriologiju „Prof. dr Aleksandar Đ. Kostić" Medicinski fakultet Univerziteta u Beogradu. Zdravstvena zaštita 2022;51(4):8-15. doi: 10.5937/zdravzast51-41973



**Received:** 10/31/2023 **Revised:** 11/29/2023 **Accepted:** 12/02/2023

PRIKAZ IZLOŽBE

UDK BROJEVI: 61:929 Миловановић М.
340.6:069.9(497.11)"2023"
DOI: https://www.doi.org/10.5937/zdravzast52-47453

# KATALOG IZLOŽBE „*MORTUI VIVOS DOCENT* – KAD MRTVI UČE ŽIVE“ AUTORA JELENE JOVANOVIĆ SIMIĆ I SLOBODANA NIKOLIĆA

**Aleksa Leković**[1]

[1] Institut za sudsku medicinu „Milovan Milovanović“, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija

[*] Korespondencija: dr Aleksa Leković, Institut za sudsku medicinu „Milovan Milovanović“, Medicinski fakultet, Univerzitet u Beogradu, Deligradska 31a, 11000 Beograd, Republika Srbija; e-mail: aleksa.lekovic@med.bg.ac.rs; aleksa.lekovic@gmail.com


**Slika 1.** Naslovna korica kataloga izložbe „*Mortui vivos docent* – Kad mrtvi uče žive: Milovan Milovanović i njegovo doba“

Ove se godine proslavlja sto godina od kako je Milovan Milovanović postavljen za vanrednog profesora sudske medicine na Medicinskom fakultetu Univerziteta u Beogradu, čime je osnovana Katedra za sudsku medicinu (1,2). Povodom toga, u Muzeju nauke i tehnike organizovana je izložba „*Mortui vivos docent* – Kad mrtvi uče žive: Milovan Milovanović i njegovo doba“, autora dr Jelene Jovanović Simić, višeg kustosa Muzeja nauke i tehnike, i dr Slobodana Nikolića, profesora sudske medicine Medicinskog fakulteta u Beogradu. Ovu izložbu prati i istoimeni katalog, čiji su izdavači Muzej nauke i tehnike i Medicinski fakultet Univerziteta u Beogradu (Slika 1). Autor grafičkog dizajna kataloga bio je Miloš Janković, a lektor Katarina Spasić. Recenzenti kataloga bili su Slobodan Savić i Dragomir Bondžić (3).

REVIEW OF AN EXHIBITION

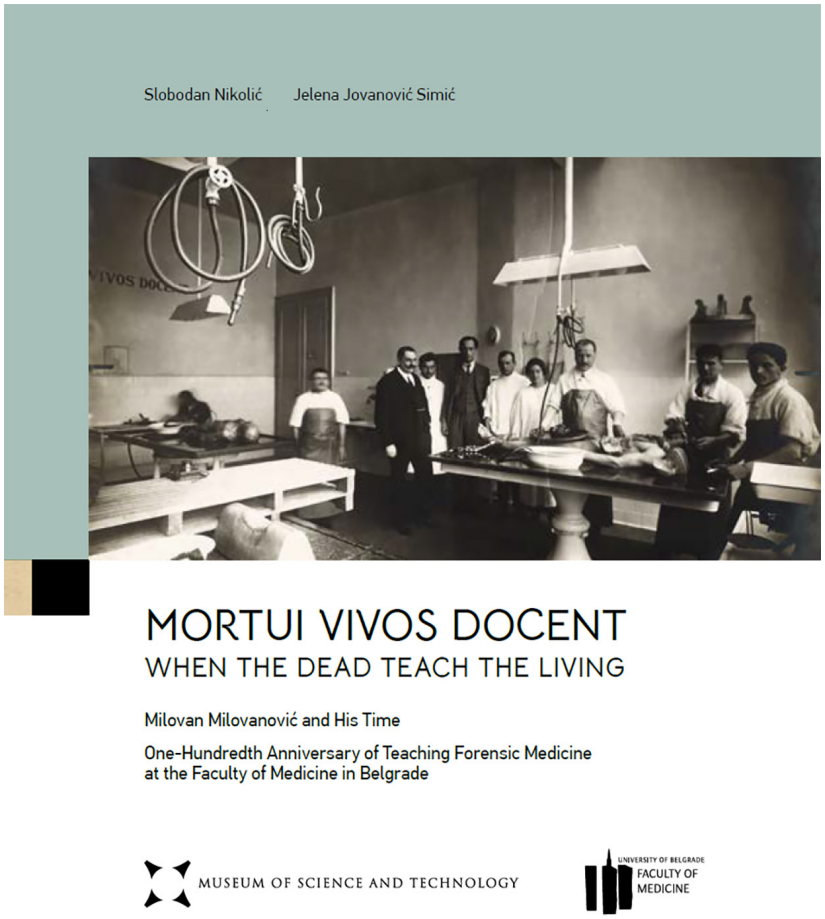
UDK NUMBERS: 61:929 Милованović М.
340.6:069.9(497.11)"2023"
DOI: https://www.doi.org/10.5937/zdravzast52-47453

# THE EXHIBITION CATALOG "*MORTUI VIVOS DOCENT* – WHEN THE DEAD TEACH THE LIVING" AUTHORED BY JELENA JOVANOVIĆ SIMIĆ AND SLOBODAN NIKOLIĆ

**Aleksa Leković**[1]

[1] Institute of Forensic Medicine "Milovan Milovanović," Faculty of Medicine, University of Belgrade, Republic of Serbia

[*] Correspondence: Aleksa Leković, MD, Institute of Forensic Medicine "Milovan Milovanović," University of Belgrade, Faculty of Medicine, 31a Deligradska Str., 11000 Belgrade, Republic of Serbia; e-mail: aleksa.lekovic@med.bg.ac.rs; aleksa.lekovic@gmail.com




**Picture 1.** Front cover of the Exhibition Catalog "*Mortui vivos docent* – When the Dead Teach the Living: Milovan Milovanović and His Time"

This year marks the hundredth anniversary since Milovan Milovanović was appointed as the Associate Professor of Forensic Medicine at the Faculty of Medicine, University of Belgrade, and thus, the Department of Forensic Medicine was established (1, 2). On this occasion, the Museum of Science and Technology organized the Exhibition "*Mortui vivos docent* – When the Dead Teach the Living: Milovan Milovanović and His Time," authored by dr Jelena Jovanović Simić, senior curator of the Museum of Science and Technology and dr Slobodan Nikolić, professor of forensic medicine at the Faculty of Medicine in Belgrade. This exhibition is accompanied by the Catalog with the same title, published by the Museum of Science and Technology and the

Katalog ima 105 stranica i sastoji se iz pet poglavlja, sa spiskom literature na kraju. U prvom delu kataloga „Iz istorije sudske medicine u Srbiji“ dat je sažet pregled razvoja ove medicinske specijalističke grane u Srbiji, sa posebnim akcentom na život i rad Edvarda Mihela (1864-1915), prvog specijaliste sudske medicine u Srbiji (4). U drugom delu „Milovan Milovanović i njegovo doba“, koji je glavni deo kataloga, kroz devet hronološki raspoređenih celina prikazani su život i rad Milovana Milovanovića (1884-1948): od ranog školovanja u Negotinu i Zaječaru i kasnije u Beču, preko učešća u oslobodilačkim ratovima i Prvom svetskom ratu, rada u Prosekturi Opšte državne bolnice, osnivanja Sudskomedicinskog zavoda, rada na Medicinskom fakultetu i života posle Drugog svetskog rata. Posebno su prikazani i opisani njegov pedagoški i naučni rad, privatni život i okolnosti njegove smrti, odnosno samoubistva. U trećem delu prikazana je Forenzička zbirka Instituta za sudsku medicinu, njen nastanak i razvoj. U četvrtom delu „Iz arhive Instituta“ prikazana su manje poznata dokumenta iz vremena Drugog svetskog rata. I na kraju, u kratkom petom delu navedeni su najznačajniji datumi u jednom veku postojanja Katedre i Instituta – „Institut kroz vreme“.

Katalog je ilustrovan velikim brojem fotografija, pre svega fotografija eksponata prikazanih na izložbi, koji su skoro svi sa Instituta.

Katalog je tako koncipiran da čitalac vrlo lako prati razvoj sudske medicine u Srbiji i u Beogradu, a posebno razvoj Sudskomedicinskog zavoda, odnosno Instituta za sudsku medicinu. Iako je Milovan Milovanović, iz razumljivih razloga, centralna ličnost u katalogu, u tekstu je jasno istaknuto i ko su njegovi prethodnici, ali i ko su nastavljači njegove škole sudske medicine: pre svega Julijana Bogićević (1990-1977), njegova najvernija saradnica, kasnije prva žena u zvanju redovnog profesora i prva žena na mestu dekana nekog fakulteta Univerziteta u Beogradu i to u periodu 1959/60. i 1962-64. godine (4). Tekst je praćen mnogim citatima iz knjiga i zapisa kako Milovana Milovanovića, tako i njegovih savremenika, koji, zajedno sa eksponatima i dokumentima, daju odličan uvid u to kako se razvijao Sudskomedicinski zavod između dva svetska rata.

Koji i kakvi su bili sudskomedicinski slučajevi i kako su oni rešavani u Milovanovićevo doba, predstavljeno je u trećem delu kataloga, kroz prikaz konkretnih preparata i predmeta iz Forenzičke zbirke Instituta (5). Svaki od ovih preparata i predmeta stavljen je u konkretni onovremeni kontekst, koliko je to bilo moguće. Sami preparati i predmeti, ali i obdukcioni protokoli, fotografije sa policijskih uviđaja, sheme sa povredama crtane tokom obdukcija, povredna sredstva, oruđa i oružja, članci iz dnevnih novina, prateća dokumenta – sve nam ovo daje skoro potpunu rekonstrukciju konkretnih događaja i dočarava način onovremenog rešavanja svakog predstavljenog sudskomedicinskog slučaja. Ali ne samo to: poneke staklene stojnice tzv. mokrih preparata koji su opisani u katalogu, tokom priprema za prikazivanje na izložbi bile su otvorene i preparati dodatno analizirani. Od nekih su tom prilikom uzeti isečci za mikroskopski pregled, te su ovi nalazi omogućili dodatna razjašnjenja datih slučajeva. Takođe, u tekstu kataloga pravljene su i paralele između ondašnjih povreda, bolesti ili porekla smrti, koje su određeni prikazani preparati ilustrovali, sa onim šta možemo danas da vidimo u sudskomedicinskoj praksi: to je posebno dobro prikazao tekst o sifilisu, kao i urađeni savremeni snimak kompjuterizovanom tomografijom preparata srca i kičmenog stuba preparata iz Forenzičke zbirke. Ovaj deo kataloga ne bavi se, dakle, samo istorijskim činjenicama i istorijskim pregledom rada u Prosekturi, već ima i dodatnu didaktičku vrednost.

U četvrtoj celini kataloga, prikazana su manje poznata dokumenta koja imaju posebnu vrednost. Autori u delu „Iz arhive Instituta“ navode devetnaest imena osoba umrlih u Opštoj državnoj bolnici u Beogradu i obdukovanih u Zavodu, a koje su bile žrtve eksplozije municije u Smederevskoj tvrđavi 5. juna 1941. Tu je i Zapisnik o ekshumaciji tela rodoljuba, žrtava okupacione i kolaboracionističke vlasti u Srbiji, streljanih i sahranjenih od 27. aprila do 2. oktobra 1944, a sam Zapisnik je sastavljen aprila 1945. Takođe, predstavljen je i Zapisnik o pregledu tela žrtava ustaške vlasti u Nezavisnoj državi Hrvatskoj, nađenih na obalama Dunava i Save kod Beograda tokom leta 1942. godine.

U katalogu se nalaze i tri vrlo vredne fotografije, koje su ovom prilikom prvi put objavljene. Sve tri su iz Arhive Instituta za histologiju i embriologiju Medicinskog fakulteta „Prof. dr Aleksandar Đ. Kostić“ u Beogradu, i to iz fotografske zaostavštine profesora Aleksandra Đ. Kostića, a autori kataloga i izložbe dobili su ih zahvaljujući profesorki Neli Puškaš. Na jednoj je obdukciona sala Sudskomedicinskog zavoda, pre nego što su in-

Faculty of Medicine University of Belgrade (Picture 1). The author of the graphic design of the Catalog was Miloš Janković, and the proofreader was Katarina Spasić. The reviewers of the Catalog were Slobodan Savić and Dragomir Bondžić (3).

The Catalog has 105 pages and five chapters, with a bibliography at the end. In the first section of the catalog, "From the History of Forensic Medicine in Serbia," a brief review of the development of this field of medicine is given, with a special accent put on the life and work of Edvard Mihel (1864-1915), the first Forensic Medicine specialist in Serbia (4). In the second section, "Milovan Milovanović and His Time," which is the main part of the catalog, the life and work of Milovan Milovanović (1884-1948) are presented through nine chronologically arranged units: from his early school days in Negotin and Zaječar and later in Vienna, through his participation in liberation wars and the World War I, work in the Autopsy Department – Prosecture of the General State Hospital, the establishment of the Institute of Forensic Medicine, work at the Faculty of Medicine and life after the World War II. His pedagogical and scientific work, private life, and the circumstances of his death, that is, suicide, are especially presented and described. The third section, the Forensic Collection of the Institute of Forensic Medicine, presents its creation and development. In the fourth section, "From the Institute's Archives," less-known documents from the period of World War II are presented. Finally, in the short fifth section, "The Institute through Time," the most significant dates of the first century of the Department and Institute are listed.

The Catalog is illustrated with many photographs, primarily of specimens presented at the Exhibition, most of which are from the Institute.

The concept is arranged so that a reader can easily follow the development of Forensic Medicine in Serbia and Belgrade, especially the development of the Institute of Forensic Medicine. Although Milovan Milovanović is understandably the central figure of the Catalog, it is clearly stated in the text who his predecessors were, as well as who the successors of his school of forensic medicine are: first of all, Julijana Bogićević (1890-1977), his most loyal associate, later to become the first woman with the title of a Full Professor and the first woman appointed as a Dean of any faculty of the University of Belgrade, in the periods of 1959-60 and 1962-64 (4). The text is accompanied by numerous quotations from books and writings of Milovan Milovanović, as well as his contemporaries, which, alongside the specimens and documents, provide an excellent insight into the development of the Institute of Forensic Medicine between the two World Wars.

What were the forensic cases like and how they were solved in Milanovic's time is presented in the third section of the Catalog, through the presentation of specific specimens and objects from the Forensic Collection of the Institute (5). Each of these specimens and objects was put as much as possible into a particular context of that time. The specimens and objects, as well as autopsy protocols, photo-documentation of police investigations, schemes with injuries drawn during autopsies, injury-causing objects, tools and weapons, articles from daily newspapers, and accompanying documents – all this provides almost the reconstruction of specific events and evokes the ways of solving the each presented forensic case of that time. Moreover, some glass stands of the so-called "wet" specimens (preparations) described in the catalog were opened, and specimens were additionally analyzed during the preparations for the exhibition. Samples were obtained from some of the specimens for further microscopic examination, and these findings enabled the additional clarification of presented cases. Additionally, in the text of the catalog, parallels were made between injuries, diseases, or the cause of death illustrated by some specimens, and what we can see in contemporary forensic practice: this was well shown in the text regarding syphilis, as well as by the modern computerized tomography (CT)-imaging of the heart and spinal column specimen from the Forensic Collection. This section of the Catalog does not only consider historical facts and historical review of work in the Autopsy Department – *Prosecture* but also has additional, didactic value.

Less-known documents of exceptional value are presented in the fourth section of the Catalog. In the section "From the Institute's Archives," the authors list names of nineteen persons who died in the General State Hospital in Belgrade and were autopsied at the Institute and who were the victims of the ammunition explosion in the Smederevo Fortress on June 5, 1941. Additionally, there is documentation of the exhumation of patriots' bodies, victims of the belligerent occupation, and

stalirana sva tri stola za obdukcije. Druga je jedina do sada poznata privatna fotografije profesora Milovanovića: snimljen je na brodu, na Dunavu, u opuštenoj atmosferi, nasmejan. Treća je fotografija, čini se, najvrednija i najinteresantnija: na njoj je amfiteatar Sudskomedicinskog zavoda, inače prvi sagrađeni amfiteatar Medicinskog fakulteta, pun studenata, spremnih da odslušaju predavanje. Kako je ova fotografija iz 1924. godine, može se pretpostaviti da su snimljeni studenti iz prve generacija studenata medicine, možda baš na predavanju iz sudske medicine. Šteta što na njoj nije i profesor Milovanović!

Tekst kataloga i prateći materijal na vrlo dobar način čitaocu predstavljaju razvoj sudske medicine u Beogradu i Srbiji, daju istorijske činjenice o životu i radu osnivača Katedre za sudsku medicinu profesora Milovana Milovanovića, ali, takođe, rekonstruišu i epohu – vreme u kojem je živeo i radio Milovan Milovanović.

Katalog je odlično svedočanstvo jedne dobre i vrlo interesantne izložbe!

## Konflikt interesa

Autori je izjavio da nema konflikta interesa.

## Reference


1. Nikolić S, Živković V. Milovan Milovanović. U: Đorđević V, ured. Život i delo srpskih naučnika, Biografije i bibliografije, Knjiga XVIII. Srpska akademija nauka i umetnosti: Beograd; 2022; 33-75.
2. Nikolić S. Sekcija za sudsku medicinu. U: Čolović R, ured. 150 godina Srpskog lekarskog društva. Srpsko lekarsko društvo: Beograd; 2022.
3. Nikolić S, Jovanović Simić J. Mortui vivos docent – Kad mrtvi uče žive: Milovan Milovanović i njegovo doba – povodom sto godina nastave sudske medicine na Medicinskom fakultet u Beogradu. Muzej za nauku i tehniku, Medicinski fakultet Univerziteta u Beogradu: Beograd; 2023.
4. Veljković S. Hronika sudske medicine u Beogradu. Beograd: CIBIF Medicinski fakultet u Beogradu; 2009.
5. Nikolić S, Cvetković D, Živković V. Regarding "The ongoing loss of historical material from institutions". Forensic Sci Med Pathol. 2021;17:375.




**Primljen:** 31.10.2023. **Revizija:** 12.11.2023. **Prihvaćen:** 24.11.2023.

collaborationist authorities in Serbia, who were shot and buried between April 27 and October 2, 1944, while the Record itself was written in April 1945. Also, the Record of the body examination of the victims of the Ustasha organization of the Independent State of Croatia found on the riverbanks of the Sava and Danube near Belgrade during the summer of 1942 was presented.

The Catalog also includes three valuable, first-time published photos. All three are from the Archives of the Institute of Histology and Embryology "Prof. Dr Aleksandar Đ. Kostić" of the Faculty of Medicine in Belgrade, the legacy of Professor Aleksandar Đ. Kostić, and the authors of the Exhibition and the Catalog received them as a courtesy of Professor Nela Puškaš. One of the photos shows the autopsy room of the Institute of Forensic Medicine before the three autopsy tables were installed. The second is the only private photo of Professor Milovanović taken on a boat on the Danube in a relaxed atmosphere, with him smiling. The third is, it seems, the most valuable and interesting: it shows the Amphitheater of the Institute of Forensic Medicine, the first amphitheater of the Faculty of Medicine, full of students ready to listen to the lecture. Since this photo dates from 1924, it can be assumed that this was the first generation of medical students, possibly during the lecture in Forensic Medicine. Sadly, Professor Milovanović is not in this photo.

The text of the Catalog and the accompanying material well demonstrate to readers the development of Forensic Medicine in Belgrade and Serbia and provide historical facts regarding the life and work of the founder of the Department of Forensic Medicine, Professor Milovan Milovanović, also reconstructing the epoch – the time in which Milovan Milovanović lived and worked.

The Catalog is an excellent testimony of a good and very interesting exhibition.

## Competing interests

The author declared no competing interests.

## References


1. Nikolić S, Živković V. Milovan Milovanović. In: Đorđević V, Ed. Život i delo srpskih naučnika, Biografije i bibliografije, Knjiga XVIII. Srpska akademija nauka i umetnosti: Beograd; 2022; 33-75.
2. Nikolić S. Sekcija za sudsku medicinu. In: Čolović R, Ed. 150 godina Srpskog lekarskog društva. Srpsko lekarsko društvo: Beograd; 2022.
3. Nikolić S, Jovanović Simić J. Mortui vivos docent – When the Dead Teach the Living: Milovan Milovanović and his Time – One–Hundredth Anniversary of Teaching Forensic Medicine at the Faculty of Medicine in Belgrade. Museum of Science and Technology, University of Belgrade – Faculty of Medicine: Belgrade; 2023.
4. Veljković S. Hronika sudske medicine u Beogradu. Beograd: CIBIF Medicinski fakultet u Beogradu; 2009.
5. Nikolić S, Cvetković D, Živković V. Regarding "The ongoing loss of historical material from institutions". Forensic Sci Med Pathol. 2021;17:375.




**Received:** 10/31/2023 **Revised:** 11/12/2023 **Accepted:** 11/24/2023

UDK BROJ: 616-089.168
DOI: https://www.doi.org/10.5937/zdravzast52-47258

PREGLEDNI RAD

# FAKTORI RIZIKA ZA NASTANAK POSTOPERATIVNOG DELIRIJUMA

**Vesna Jovanović[1,2], Nebojša Lađević[1,2], Sandra Šipetić Grujičić[3]**

[1] Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija
[2] Centar za anesteziologiju i reanimatologiju, Univerzitetski klinički centar Srbije, Beograd, Republika Srbija
[3] Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija

[*] Korespondencija: Vesna Jovanović, Centar za anesteziologiju i reanimatologiju Univerzitetskog kliničkog centra Srbije, Resavska 51, 11000 Beograd, Republika Srbija; e-mail: vantonijevicjov@gmail.com

**SAŽETAK**

Pojava postoperativnog delirijuma (POD) prepoznata je poslednjih decenija kao važan klinički sindrom, naročito kod starijih bolesnika koji se podvrgavaju hirurškom lečenju. Cilj ovog preglednog rada se odnosio na ispitivanje preoperativnih, intraoperativnih i postoperativnih faktora koji mogu da dovedu do nastanka POD. Faktori rizika za nastanak POD su brojni, a što je najznačajnije, mnogi se mogu modifikovati. Neki od najznačajnijih faktora rizika za nastanak POD su starije životno doba, zloupotreba alkohola, preoperativno lošiji funkcionalni i kognitivni status, prisustvo depresije i demencije. Veća učestalost javljanja POD zabeležena je kod pacijenata podvrgnutih kompleksnijim operativnim zahvatima kao što su kardiohirurške, vaskularne i ortopedske operacije frakture kuka. Uočeno je da nakon hitnih operativnih zahvata POD se 1,5 do 3 puta češće javlja nego kod elektivnih planiranih operativnih procedura. Takođe, intraoperativno krvavljenje i primena transfuzije su identifikovani kao značajni faktori rizika za nastanak POD. Da bi se izbegli kognitivni deficiti uzrokovani dužom ekspozicijom anesteziji, istraživanja su pokazala da titracija anestetika praćenjem bispektralnog indeksa, kao i evociranih auditivnih potencijala, može smanjiti prekomernu izloženost anesteticima i samim tim smanjiti rizik od postoperativne kognitivne disfunkcije. Poznavanje faktora rizika i identifikacija pacijenata sa povećanim rizikom predstavljaju osnovu strategije za prevenciju ovog sindroma. Trenutni dokazi sugerišu da perioperativno izbegavanje upotrebe benzodijazepina, kao i adekvatna perioperativna kontrola bola, predstavljaju ključne mere za redukciju rizika od POD.

**Ključne reči:** postoperativni delirijum, kognitivni deficit, faktori rizika, starije osobe

## Uvod

Delirijum se prema Međunarodnoj klasifikaciji bolesti (MKB-10, F 05) definiše kao etiološki nespecifičan organski cerebralni sindrom koji karakterišu istovremeni poremećaji svesti i pažnje, percepcije, razmišljanja, pamćenja, psihomotornog ponašanja, emocija i ritma budnost-spavanje (1). Pojava postoperativnog delirijuma (POD) prepoznata je poslednjih decenija kao važan klinički sindrom, naročito kod starijih bolesnika koji se podvrgavaju hirurškom lečenju (2). Klinička prezentacija ovog sindroma veoma je varijabilna. Najčešće se klasifikuje na osnovu motornih i pridruženih psihomotornih karakteristika. Pacijent može imati hiperaktivni oblik delirijuma, koga karakterišu nemir, konstantni pokreti i agitacija, ili hipoaktivni delirijum koga karakterišu usporenost ili nedostatak pokreta, nereagovanje i oskudne govorne sposobnosti. Kod nekih pacijenata može se javiti mešoviti tip poremećaja, odnosno javlja se hiperaktivna i hipoaktivna faza u kratkom vremenskom periodu (2). U većini do sada objavljenih istraživanja POD najčešće nastaje prvog postoperativnog dana, ređe drugog ili trećeg, a simptomi najčešće traju od 1 do 3 dana (2,3). Ovaj sindrom je čest problem kod bolesnika u jedinicama intenzivnog lečenja (JIL) i udružen je sa važnim kliničkim ishodima, uključujući povećan broj dana provedenih na mehaničkoj ventilaciji, produženu hospitalizaciju, veće troškove lečenja i smrtnost (4,5).

*Health Care 52(4), 2023*

UDK NUMBER: 616-089.168

**REVIEW ARTICLE**

DOI: https://www.doi.org/10.5937/zdravzast52-47258

# RISK FACTORS FOR THE OCCURRENCE OF POSTOPERATIVE DELIRIUM

**Vesna Jovanović[1,2], Nebojsa Lađević[1,2], Sandra Šipetić Grujičić[3]**

[1] Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[2] Center for Anesthesiology and Reanimation, University Clinical Center of Serbia, Belgrade, Republic of Serbia
3 Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia

[*] Correspondence: Vesna Jovanović, Center for Anesthesiology and Reanimation of the University Clinical Center of Serbia, Resavska 51, 11000 Belgrade, Republic of Serbia; e-mail: vantonijevicjov@gmail.com

**SUMMARY**

The occurrence of postoperative delirium (POD) has been recognized in recent decades as an important clinical syndrome, especially in elderly patients undergoing surgical treatment. The aim of this review was to examine the preoperative, intraoperative and postoperative factors that can lead to the occurrence of POD. The risk factors for developing POD are numerous, and most importantly, many can be modified. Some of the most significant risk factors for the occurrence of POD are older age, alcohol abuse, preoperatively worse functional and cognitive status, presence of depression and dementia. A higher incidence of POD was observed in patients undergoing more complex surgical procedures such as cardiac, vascular and orthopedic hip fracture operations. It was observed that after emergency surgical procedures POD occurs 1.5 to 3 times more often than during elective planned surgical procedures. Also, intraoperative bleeding and the application of transfusion were identified as significant risk factors for the occurrence of POD. In order to avoid cognitive deficits caused by longer exposure to anesthesia, research has shown that anesthetic titration by monitoring the bispectral index, as well as evoked auditory potentials, can reduce excessive exposure to anesthetics and thus reduce the risk of postoperative cognitive dysfunction. Knowledge of risk factors and identification of patients at increased risk are the basis of a strategy for the prevention of this syndrome. Current evidence suggests that perioperative avoidance of benzodiazepine use as well as adequate perioperative pain control are key measures to reduce the risk of POD.

**Keywords:** postoperative delirium, cognitive dysfunction, risk factors, older age

## Introduction

According to the International Classification of Diseases (ICD-10, F 05), postoperative delirium is defined as an etiologically non-specific organic cerebral syndrome characterized by the simultaneous disorders of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotions and the sleep-wake cycle (1). In recent decades, postoperative delirium (POD) has been recognized as an important clinical syndrome, especially in older patients undergoing surgical treatment (2). The clinical presentation of this syndrome is highly variable. It is most often classified based on the motor symptoms and associated psychomotor characteristics. A patient may have a hyperactive form of delirium characterized by restlessness, constant movements and agitation, or a hypoactive delirium which is characterized by sluggishness, or lack of movement, unresponsiveness, and poor speech abilities. In some patients, a mixed form may occur, that is, both the hyperactive and hypoactive forms occur in a short period of time (2). In the majority of studies, which have been published so far, POD most often occurs on the first postoperative day, less often on the second or third, and the symptoms usually last from 1 to 3 days (2,3). This syndrome is a common problem in patients in intensive care units (ICUs) and it is associated with important clinical outcomes, including the increased number of days spent on

Prema dosadašnjim istraživanjima učestalost javljanja POD kod hirurških pacijenata veoma je varijabilna i zavisi od dijagnostičkih kriterijuma, ispitivane populacije, kao i vrste hirurške procedure. Prema podacima vodiča za klasifikaciju mentalnih poremećaja DSM-5 (engl. *Diagnostic and Statistical Manual for Mental Disorders, fifth edition*) delirijum se javlja kod 15-53% starijih pacijenata nakon operacije i kod čak 70-87% bolesnika smeštenih u JIL (4). Veća prevalencija POD zabeležena je kod pacijenata podvrgnutih kompleksnijim operativnim zahvatima kao što su kardiohirurške, vaskularne i ortopedske operacije frakture kuka (4).

Patofiziologija ovog sindroma i dalje nije u potpunosti razjašnjena, ali je očigledno da nastaje kao rezultat interakcije više činilaca koji se u literaturi najčešće opisuju kao predisponirajući i precipitirajući faktori. Faktori rizika za njegov nastanak su brojni, vezani su kako za samog bolesnika tako i za operativnu proceduru, i što je najznačajnije mnogi od njih se mogu modifikovati. Najčešće se u literaturi klasifikuju kao faktori vezani za pacijenta i faktori vezani za operativnu proceduru ili kao preoperativni, intraoperativni i postoperativni faktori. Iako je prevalencija javljanja POD-a visoka, veliki broj kliničkih slučajeva je nedijagnostikovan, smatra se da se jedan broj slučajeva može prevenirati (5).

Cilj ovog preglednog rada je ispitivanje preoperativnih, intraoperativnih i postoperativnih faktora koji mogu da dovedu do nastanka POD.

## Metode

U okviru ovog preglednog rada za pretraživanje literature korišćene su tri bibliografske baze podataka: PubMed, WoS, i Scopus. Pretraživanje literature je sprovedeno za period 2010-2023. godine, a korišćene ključne reči su bile: POD, faktori rizika, preoperativni, operativni i postoperativni. U radu su prikazani rezultati samo onih istraživanja koja su bila objavljena na engleskom jeziku.

## Preoperativni faktori rizika

### *Starost i pol*

Starost bolesnika predstavlja jedan od najviše ispitivanih i najznačajnijih sociodemografskih faktora rizika za nastanak POD-a, a pokazano je da uzrast iznad 65 godina predstavlja nezavistan faktor rizika za nastanak ovog sindroma (6). Meta-analiza, koja je ispitivala faktore rizika za nastanak POD-a nakon kardiohirurških operacija, obuhvatila je četrnaest studija sa ukupno 13.286 pacijenata (7). U devet studija starost bolesnika predstavljala je faktor rizika za nastanak POD-a. Sedam od njih pokazalo je da rizik od nastanka POD-a raste sa povećanjem starosti bolesnika za svaku godinu, dok su dva istraživanja pokazala da je starost preko 65 godina značajno udružena sa povećanim rizikom od nastanka POD-a (7).

Sistematski pregled literature i meta-analiza podataka koji su ispitivali faktore rizika za nastanak POD-a nakon operacije frakture kuka uključili su 44 studije sa ukupno 104.572 pacijenta (8). Dvadeset studija pokazalo je značaj starosti u nastanku POD-a, a rezultati meta-analize ovih studija sugerišu da je starije životno doba značajan faktor rizika kod bolesnika posle operacije preloma kuka. Što se tiče pola, u ovom istraživanju 32 studije su pokazale povezanost pola i nastanka POD-a, a objedinjeni rezultati pokazali su da su osobe ženskog pola manje podložne nastanku POD-a. Ipak, rezultati ispitivanja pola kao faktora rizika rezlikuju se u drugim istraživanjima. U sistematskom pregledu literature faktora rizika kod starijih bolesnika koji su podvrgnuti gastrointestinalnim operativnim zahvatima, pol nije bio povezan sa nastankom POD-a (9), a meta-analiza podataka o faktorima rizika kod bolesnika nakon operacije kičme pokazala je da osobe muškog pola imaju manji rizik od nastanka ovog sindroma (10).

### *Nivo obrazovanja*

Važnost kapaciteta kognitivne rezerve pacijenata kao faktora rizika za nastanak postoperativnih kognitivnih deficita prepoznata je u mnogim dosadašnjim istraživanjima (11,12). Najčešće korišćen indikator kognitivne rezerve jeste nivo obrazovanja, zbog izloženosti mozga mentalnim aktivnostima koje mogu uticati na to da se proces nastanka demencije odloži.

*Feinkohl* i sar. su sproveli meta-analizu podataka iz literature da bi ispitali povezanost kognitivne rezerve pacijenata i nastanka postoperativne kognitivne disfunkcije (11). Petnaest studija, sa ukupno 5.104 pacijenta uključeno je u istraživanje. Rezultati su pokazali da je viši nivo edukacije, odnosno duže vreme provedeno u obrazovanju, povezano sa smanjenim rizikom od nastanka postoperativnih kognitivnih deficita. Svaka godina provedena duže u obrazovanju bila je udružena sa smanjenjem rizika

mechanical ventilation, prolonged hospitalization, higher medical costs and mortality (4,5).

According to previous research, the incidence of POD in surgical patients is highly variable and depends on the diagnostic criteria, the examined population, and the type of surgical procedure. According to the Manual for the classification of mental disorders DSM-5 (Diagnostic and Statistical Manual for Mental Disorders, fifth edition), delirium occurs in 15-53% of elderly patients after surgery and even in 70-87% of patients hospitalized in the ICUs (4). A higher prevalence of POD has been reported in patients undergoing more complex surgical procedures, such as cardiac, vascular surgeries and hip fracture surgeries (4).

The pathophysiology of this syndrome has not been completely elucidated, but it is obvious that it occurs as a result of the interaction of several factors that are most often described in the literature as predisposing and precipitating factors. The risk factors for its occurrence are numerous, and they are related both to the patient himself and to the surgical procedure, and most importantly, many of them can be modified. They are most often classified in the literature as factors related to the patient and factors related to the surgical procedure, or as preoperative, intraoperative and postoperative. Although the prevalence of POD is high, and a large number of clinical cases are not diagnosed, it is believed that a number of cases can be prevented (5).

The aim of this review was to examine the preoperative, intraoperative and postoperative factors that can lead to the occurrence of POD.

## Methods

In this review, three bibliographic databases PubMed, WoS, and Scopus were used for literature search. The literature search was conducted for the period 2010-2023, and the following keywords were used: POD, risk factors, preoperative, operative and postoperative. The review presents only the results of those studies published in the English language.

## Preoperative risk factor

### *Age and gender*

The patient's age is one of the most studied and most important socio-demographic risk factors for the occurrence of POD, and it has been shown that age over 65 years is an independent risk factor for the occurrence of this syndrome (6). A meta-analysis that examined the risk factors for the occurrence of POD after cardiac surgery included fourteen studies with a total of 13.286 patients (7). In nine studies, the patient's age was a risk factor for the occurrence of POD. Seven of them showed that the risk of developing POD increased with the patient's age for each year, while two studies showed that the age over 65 years was significantly associated with the increased risk of developing POD (7).

A systematic literature review and meta-analysis of data that examined the risk factors for POD after hip fracture surgery included 44 studies with a total of 104,572 patients (8). Twenty studies showed the importance of age for the occurrence of POD, and the results of meta-analysis of these studies suggested that older age was a significant risk factor in patients after hip fracture surgery. As far as the gender variable is concerned, in this research, 32 studies showed a connection between gender and the occurrence of POD, while the pooled results showed that women were less susceptible to the occurrence of POD. However, the results of examining gender as a risk factor were different in other studies. In a systematic literature review of risk factors in elderly patients undergoing gastrointestinal surgery, gender was not associated with the occurrence of POD (9), while a meta-analysis of data on risk factors in patients after spine surgery showed that males had a lower risk of developing this syndrome (10).

### *Level of education*

The importance of the patient's cognitive reserve capacity as a risk factor for the occurrence of postoperative cognitive deficits has been recognized in many previous studies (11,12). The most commonly used indicator of cognitive reserve is the level of education, due to the exposure of the brain to mental activities that can influence the process of dementia occurrence to be postponed.

Feinkohl et al. conducted a meta-analysis of literature data in order to examine the connectedness between the patient's cognitive reserve and the occurrence of postoperative cognitive dysfunction (11). Fifteen studies, with a total of 5104 patients were included in the research. The results showed that a higher level of education, that is, longer time spent in

nastanka za 10%. U istraživanju *Alvarez-Bastidas* i sar. koje je uključilo pacijente podvrgnute različitim operativnim procedurama, POD je zabeležen kod čak 44% pacijenata koji su bili neobrazovani, sa oko 2 puta većom šansom da dobiju POD u odnosu na one sa bilo kakvim obrazovanjem (12).

### *Bračni status*

Prema nekim istraživanjima, i bračni status predstavlja značajan faktor rizika za razvoj postoperativnog delirijuma. Ispitivanjem preoperativnih faktora rizika kod pacijenata nakon transuretralne resekcije prostate, procenat pacijenata koji su u braku bio je značajno manji u grupi koja je razvila POD nego u grupi bez POD-a, što je sugerisalo da status samca, razvedenog ili udovca može predstavljati faktor rizika za nastanak POD-a (13). Za razliku od ovog istraživanja, studija koja je uključila 358 uroloških bolesnika pokazala je da bračni status ne korelira značajno sa nastankom POD-a nakon transuretralne resekcije prostate (14). Međutim, u sistematskom pregledu literature, koji je takođe uključio populaciju uroloških pacijenata, status neoženjen/neudata predstavljao je faktor rizika za nastanak POD-a, pored dužeg vremena trajanja operacije, muškog pola i starijeg životnog doba (15). Takođe, u navedenoj studiji *Alvarez-Bastidas* i sar., 66% pacijenata koji nisu imali stabilan partnerski odnos iskusilo je pojavu POD-a (12).

### *Komorbiditeti*

Ispitivanjem skora Američkog udruženja anesteziologa (engl. *American Society of Anesthesiologists score* - ASA) kao faktora rizika za nastanak POD-a, došlo se do oprečnih rezultata, mada većina istraživanja ukazuje na njego značaj. U meta-analizi *Lee* i sar., koja je uključila 12 istraživanja koja su ispitivala faktore rizika nakon kolorektalne hirurgije, ASA skor nije bio značajno različit kod pacijenata koji su imali POD i onih koji ga nisu imali (15). Međutim, meta-analiza podataka iz literature o faktorima rizika za POD među starijim bolesnicima podvrgnutih hitnim ili elektivnim gastrointestinalnim operacijama, pokazala je značaj ovog parametra. Istraživanje je obuhvatilo 11 studija sa ukupno 1427 pacijenata a značajno veći rizik od nastanka POD-a imali su pacijenti sa ASA skorom 3 i više (9). Meta-analiza *Wu* i sar., pokazala je da pacijenti ASA statusa 1 i 2 imaju manji rizik za razvoj POD-a nakon operacije preloma kuka (8).

Prema nekim autorima i hronična opstruktivna bolest pluća (HOBP) predstavlja važan faktor rizika za nastanak POD-a. Patofiziološki mehanizam dejstva objašnjava se hroničnom hipoksijom koja kod ovih bolesnika dovodi do disfunkcije mozga i opadanja kognitivnih funkcija. Testiranjem ovih funkcija pokazano je da su one značajno snižene kod bolesnika sa HOBP (16).

Velika meta-analiza, koja je uključila 43 istraživanja i ukupno 13.179 hirurških pacijenata, isključujući kardiohirurške operacije, pokazala je da su kardiovaskularne bolesti, u prvom redu hipertenzija, najčešći komorbiditet bolesnika koji su razvili POD (17). Slično istraživanje među pacijentima nakon operacije kičme, koje je obuhvatilo 40 studija, pokazalo je da prisustvo komorbiditeta uopšte kod pacijenata značajno povećava rizik od nastanka POD (17). Meta-analizom 13 studija pokazano je da hipertenzija predstavlja značajan faktor rizika za nastanak ovog sindroma nakon hirurgije kičme (10).

Dobro je poznato da hiperglikemija predstavlja značajan faktor rizika udružen sa lošijim ishodom operativnog lečenja. Većina istraživanja sugeriše da postoji veza između dijabetes melitusa i nastanka postoperativnih kognitivnih deficita. Bolesnici sa dijabetes melitusom (DM), naročito oni sa lošom dugoročnom kontrolom glikemije, mogu biti u povećanom riziku od nastanka POD-a usled mikrovaskularnih promena na mozgu koje mogu dovesti i do kognitivnih disfunkcija. Opservaciona kohortna studija u koju je uključeno 3178 pacijenata nakon kardiohirurške operacije, pokazala je da su pacijenti koji su razvili POD češće bili dijabetičari (18). U univarijantnoj analizi podataka dijagnoza DM-a bila je udružena sa povećanim rizikom od nastanka POD-a, dok je multivarijantnom analizom pokazano da su preoperativno povišene vrednosti glikoiziliranog hemoglobina (HbA1c) faktor rizika za nastanak POD-a, bez obzira na dijagnozu dijabetes melitusa (18). Meta-analizom faktora rizika nakon kardiohirurških operacija utvrđeno je, takođe, da DM predstavlja značajan faktor rizika (7). Ispitujući uticaj perioperativne hiperglikemije na neurokognitivne ishode nakon operacije *Hermanides* i sar. su, u svom sistematskom pregledu literature, pokazali da DM predstavlja faktor rizika za razvoj POD, i da je akutna perioperativna hiperglikemija udružena sa nastankom POD i postoperativnih kognitivnih deficita nezavisno od dijagnoze DM (19).

education, was associated with a reduced risk of postoperative cognitive deficits. Each year spent longer in education was associated with a 10% risk reduction. In the study by Alvarez-Bastidas et al. that included patients who were exposed to different surgical procedures, POD was noted in as many as 44% of patients who were not educated, with about two times higher chance of developing POD compared to those who were educated (12).

### *Marital status*

According to some studies, marital status is also a significant risk factor for the development of postoperative delirium. Examining preoperative risk factors in patients after transurethral resection of the prostate, the percentage of married patients was significantly lower in the group that developed POD than in the group without POD, which suggested that single, divorced or widowed status may be a risk factor for the development of POD (13). In contrast to this research, a study that included 358 patients showed that marital status did not significantly correlate with the occurrence of POD after transurethral resection of the prostate (14). However, in a systematic literature review that also included the population of urological patients, single status represented a risk factor for the occurrence of POD in addition to the longer duration of surgery, male gender and older age (15). Also, in the above mentioned study by Alvarez-Bastides and associates, 66% of patients who did not have a stable partner relationship experienced the occurrence of POD (12).

### *Comorbidities*

Conflicting results were obtained when the American Society of Anesthesiologists score (ASA score) was examined as a risk factor for the occurrence of POD, although the majority of studies indicate its importance. In a meta-analysis by Lee and associates, which included 12 studies that examined risk factors after colorectal surgery, the ASA score was not significantly different in patients who had POD and those who did not have it (15). However, a meta-analysis of literature data on risk factors for POD among elderly patients undergoing emergency or elective gastrointestinal surgeries, showed the importance of this parameter. The research included 11 studies with a total of 1427 patients, and patients with the ASA score 3 and higher than 3 had a significantly higher risk of developing POD (9). A meta-analysis by Wu and associates showed that patients with the ASA status 1 and 2 had a lower risk of developing POD after hip fracture surgery (8).

According to some authors, chronic obstructive pulmonary disease (COPD) is also an important risk factor for the development of POD. The pathophysiological mechanism of action is explained by chronic hypoxia, which in these patients leads to brain dysfunction and decline in cognitive functions. Testing of these functions showed that they were significantly reduced in patients with COPD (16).

A large meta-analysis that included 43 studies and a total of 13,179 surgical patients, excluding cardiac surgeries, showed that cardiovascular diseases, primarily hypertension, were the most common comorbidities in patients who developed POD (17). A similar study among patients after spine surgery, which included 40 studies, showed that the presence of comorbidities in general significantly increased the risk of developing POD (17). A meta-analysis of 13 studies showed that hypertension was a significant risk factor for the development of this syndrome after spine surgery (10).

It is well-known that hyperglycemia is a significant risk factor associated with a worse outcome of surgical treatment. The majority of studies suggest that there is a relationship between diabetes mellitus and the occurrence of postoperative cognitive deficits. Patients with diabetes mellitus, especially those with a poor long-term control of glycemia may be at increased risk of developing POD due to microvascular changes in the brain that may also lead to cognitive dysfunctions. An observational cohort study, which included 3178 patients after cardiac surgery, showed that patients who developed POD had diabetes more frequently (18). In the univariate data analysis, the diagnosis of DM was associated with the increased risk of developing POD, while the multivariate analysis showed that the elevated values of glycosylated hemoglobin (HbA1c) before surgery were the risk factor for developing POD regardless of the diagnosis of diabetes mellitus (18). A meta-analysis of risk factors after cardiac surgeries also found that DM was a significant risk factor (7). In their systematic literature review, Hermanides and associates examined the influence of perioperative hyperglycemia on neurocognitive outcomes after surgery and they showed that DM

Pshijatrijski i neurodegenerativni komorbiditeti takođe su udruženi sa povećanim rizikom od nastanka POD. Ova činjenica naročito se odnosi na bolesnike koji preoperativno imaju demenciju ili depresiju. Naime, smatra se da hirurški stres dovodi do nastanka neuroinflamacije, a preoperativno smanjen kapacitet bolesnika da prevaziđe ovo inflamatorno stanje može doprineti nastanku perioperativnih neurokognitivnih poremećaja. Preoperativno prisutna demencija kod bolesnika predstavljala je najjači faktor rizika za nastanak POD-a u istraživanju *Iamaroon* i sar. (20). U studiju je uključeno 249 pacijenata iz svih oblasti hirurgije osim kardiohirurgije. Multivarijantnom analizom pokazano je da jedino demencija i starost bolesnika preko 75 godina predstavljaju nezavisne faktore rizika za nastanak POD (20). Interesantna je i studija *Sprung* i sar. koja se bavila ispitivanjem rizika za nastanak POD-a kod pacijenata sa preoperativno prisutnim blagim kognitivnim oštećenjem ili demencijom, kao i povezanost između nastalog POD-a i naknadnog razvoja blagog kognitivnog oštećenja ili demencije kod preoperativno kognitivno normalnih starijih pacijenata (21). U studiji su potvrđeni raniji nalazi da u opštoj hirurškoj populaciji stariji bolesnici sa blagim kognitivnim oštećenjem imaju veći rizik za razvoj POD-a u poređenju sa bolesnicima bez kognitivnog oštećenja. Takođe, kod starijih bolesnika koji su prethodno imali normalan kognitivni status, a koji su razvili POD nakon operacije, veća je verovatnoća da će se naknadno dijagnostikovati demencija ili blaži kognitivni poremećaji (21).

Depresija predstavlja najznačajniji psihijatrijski komorbiditet koji je dokazani faktor rizika za nastanak POD-a. Prisustvo depresije na više načina može da ugrozi postoperativni tok i odloži oporavak bolesnika, a mnoge studije su pokazale da ona predstavlja nezavistan faktor rizika za nastanak POD-a. Velika meta-analiza sprovedena na kardiohirurškim bolesnicima uključila je 97 studija, koje su obuhvatale podatke od 60.479 pacijenata podvrgnutih operaciji aortokoronarnog bajpasa (22). Značajni preoperativni faktori rizika za razvoj POD-a, koji su imali najveću veličinu efekta na njegov nastanak, bili su prisustvo kognitivnog oštećenja, prethodni moždani udar, depresija, aritmija, periferna vaskularna bolest, bubrežna slabost, indeks telesne mase >30 kg/m$^2$, diabetes melitus, hipertenzija i starija životna dob (22). Prisustvo depresije predstavljalo je takođe i umereni faktor rizika za razvoj kognitivnog deficita u prvih 1 do 6 meseci nakon ove operacije (22). Preoperativno prisutna depresija identifikovana je kao faktor rizika za nastanak POD-a i u prethodno navedenoj velikoj meta-analizi *Chen* i sar. (7). Takođe je, analizom podataka o POD'u, nakon operacije kičme kao jedan od 18 faktora rizika za nastanak POD-a identifikovano prisustvo depresije kod bolesnika (10).

### *Prekomerna upotreba alkohola*

Mnoga istraživanja pokazala su negativni uticaj prekomerne upotrebe alkohola na kognitivne funkcije starijih osoba. Prekomerna upotreba alkohola prema mnogim istraživanjima predstavlja nezavisan faktor rizika za nastanak delirijuma nakon hirurških procedura, a meta-analiza *Abate* i sar. je pokazala da je nastanak POD-a dva puta češći kod pacijenata koji hronično koriste alkohol (17). Takođe, u meta-analizi koja je obuhvatila istraživanja faktora rizika za nastanak POD-a nakon operacija na gastrointestinalnom traktu, anamnestički podatak o prekomernoj upotrebi alkohola je identifikovan kao značajan (9). U velikoj meta-analizi, nakon operacija zgloba kuka i kolena, korišćenje alkohola je predstavljalo jedan od značajnih faktora rizika za POD (23). Međutim, za razliku od ovih istraživanja, sistematskim pregledom literature ispitujući faktore rizika među urološkim bolesnicima, upotreba alkohola nije identifikovana kao značajni faktor rizika za nastanak POD (24).

### *Vrednosti serumskih albumina*

Najveći broj studija ispitivao je uticaj poremećaja elektrolita, prvenstveno natrijuma i kalijuma, anemije i niske vrednosti albumina na nastanak POD-a. Meta-analiza o faktorima rizika za POD nakon kolorektalne hirurgije pokazala je da, pored starosti bolesnika i pozitivne anamneze za prethodni delirijum, niske vrednosti serumskih albumina predstavljaju faktor rizika za nastanak ovog sindroma (15). U sistematskom pregledu literature koji su sproveli *Sholc* i sar. ispitivan je veliki broj laboratorijskih parametara kao potencijalnih faktora rizika za nastanak POD-a, ali je samo nivo albumina pokazao značajnost (9). Grupa bolesnika kod kojih se razvio POD imala je značajno niže vrednosti ovog parametra (9). Rezultati skorašnje velike meta-anlize pokazuju da kod bolesnika nakon totalne artroplastike kuka ili kolena faktore rizika za razvoj POD-a predstavljaju nizak nivo albumina i hemoglobina (23).

was a risk factor for the development of POD, as well as that acute perioperative hyperglycemia was associated with the development of POD and postoperative cognitive deficits independently of the diagnosis (19).

Psychiatric and neurodegenerative comorbidities are also associated with the increased risk of developing POD. This fact especially refers to patients who have dementia or depression preoperatively. Namely, it is believed that surgical stress leads to neuroinflammation, and the preoperatively reduced capacity of the patient to overcome this inflammatory state can contribute to the emergence of perioperative neurocognitive disorders. The preoperatively present dementia in the patient was the strongest risk factor for the occurrence of POD in the study by Iamaroon and associates (20). The study included 249 patients from all field of surgery except cardiac surgery. A multivariate analysis showed that only dementia and the patient's age over 75 years were independent risk factors for the development of POD (20). The study by Sprung et al. is also interesting and it examined the risk of developing POD in patients with preoperatively present mild cognitive impairment or dementia, as well as the association between emerging POD and the subsequent development of mild cognitive impairment or dementia in elderly patients with preoperatively normal cognitive functions (21). Earlier findings that in the general surgical population, older patients with mild cognitive impairment had a higher risk of developing POD compared to patients without cognitive impairment were confirmed in the study. Also, in elderly patients who previously had a normal cognitive status and who developed POD after surgery, dementia or mild cognitive disorders were more likely to be diagnosed subsequently (21).

Depression represents the most significant psychiatric comorbidity, which is a proven risk factor for the occurrence of POD. The presence of depression can endanger the postoperative course and postpone the patient's recovery in several ways, while many studies have shown that it is an independent risk factor for the development of POD. A large meta-analysis, which was conducted on cardiac surgical patients, included 97 studies with the data on 60,479 patients undergoing coronary artery bypass graft surgery (22). Significant preoperative risk factors for the development of POD, which had the greatest influence on its onset, included the presence of cognitive impairment, previous stroke, depression, arrhythmia, peripheral vascular disease, renal insufficiency, body mass index > 30 kg/m$^2$, diabetes mellitus, hypertension and older age (22). The presence of depression was also a moderate risk factor for the development of cognitive deficit in the first 1 to 6 months after this operation (22). The preoperatively present depression was identified as a risk factor for the occurrence of POD in the above mentioned large meta-analysis by Chen and associates (7). Also, the analysis of data on POD after spine surgery showed the presence of depression in these patients as one of the 18 risk factors for the occurrence of POD (10).

### *Alcohol abuse*

Many studies have shown the negative influence of alcohol abuse on the cognitive functions of the elderly. According to many studies, alcohol abuse is an independent risk factor for the occurrence of delirium after surgical procedures, and a meta-analysis by Abate et al. showed that the occurrence of POD was two times more frequent in patients who used alcohol chronically (17). Also, in a meta-analysis that included research on risk factors for the occurrence of POD after gastrointestinal surgeries, anamnestic data on alcohol abuse was identified as significant (9). In a large meta-analysis, after hip and knee surgeries, alcohol use was one of significant risk factors for POD (23). However, in contrast to these studies, a systematic literature review, which examined the risk factors among urological patients, alcohol use was not identified as a significant risk factor for the development of POD (24).

### *The values of serum albumin*

The largest number of studies examined the influence of electrolyte imbalance, primarily sodium and potassium, anemia and low values of albumin on the development of POD. A meta-analysis of risk factors for POD after colorectal surgery showed that, in addition to the patient's age and a positive history of previous delirium, a lower albumin level was a risk factor for the occurrence of this syndrome (15). In a systematic literature review conducted by Scholz and associates, a large number of laboratory parameters were examined as potential risk factors for the occurrence of POD,

## Intraoperativni faktori rizika

Intraoperativni faktori rizika najčešće su klasifikovani kao faktori vezani za anestezju i faktori vezani za operaciju.

### *Faktori vezani za anesteziju*

Dosadašnja istraživanja su pokazala da češće podvrgavanje opštoj anesteziji može da dovede do pojave kognitivne disfunkcije kod pacijenata. Intraoperativne vrednosti srednjeg arterijskog pritiska i parcijalnog pritiska ugljen dioksida predstavljaju fiziološke varijable koje su usko povezane sa nastankom POD-a. Zato je prilikom primene opšte anestezije neophodno prevenirati nastanak intraoperativne hipotenzije i hipokapnije naročito kod starijih bolesnika zbog njihovog uticaja na redukciju cerebralnog krvnog protoka. Sistematski pregled literature koji je istraživao globalnu prevalenciju i faktore rizika POD-a među hirurškim pacijentima isključujući kardiohirurške operacije, pokazao je da se POD javlja oko 3 puta češće nakon operacija koje se izvode u opštoj anesteziji u odnosu na one koje se izvode u uslovima regionalne anestezije (17).

Randomizovana multicentrična studija poredila je efekte primene regionalne anestezije (spinalne, epiduralne, kombinovane spinalne i epiduralne) i opšte anestezije (intravenske, inhalacione) kod 950 pacijenata starijih od 65 godina kod kojih je urađena operacija frakture kuka (25). Regionalna anestezija bez sedacije nije značajno smanjila nastanak POD-a u odnosu na opštu anesteziju. POD je zabeležen kod 6,2% pacijenata kod kojih je primenjena regionalna anestezija i kod 5,1% pacijenata kod kojih je primenjena opšta anestezija (25). Nasuprot tome, meta-analiza podataka je pokazala da primena opšte anestezije za totalnu artroplastiku zgloba kuka ili kolena predstavlja faktor rizika za nastanak POD-a i da primena spinalne anestezije može smanjiti ovaj rizik (23).

U meta-analizi uticaja različite tehnike anestezije kod operacija kuka na nastanak POD-a rezultati su bili različiti kod uključenih studija (8). Pet studija uključenih u analizu pokazalo je povezanost između primene regionalne anestezije i nastanka POD-a. Rezultati meta-analize pokazuju da ova vrsta anestezije predstavlja potencijalni faktor rizika i da će pacijenti kod kojih je za ovu vrstu operacije primenjena regionalna anestezija verovatno razviti POD u postoperativnom toku. Isto tako, u ovoj analizi utvrđen je i značajan uticaj primene opšte anestezije na nastanak POD-a, nakon isključenja dve studije da bi se rešila heterogenost (8). Analizom podataka među urološkim operacijama nije utvrđena značajnost primene ni opšte ni regionalne anestezije na razvoj POD-a (24).

Mnoga istraživanja sprovedena su sa ciljem da se ispitaju efekti dubine anestezije na nastanak POD-a, ali su rezultati kontroverzni i dalje predstavljaju predmet debate. Da bi se izbegli kognitivni deficiti uzrokovani dužom ekspozicijom anesteziji, istraživanja su pokazala da titracija anestetika praćenjem bispektralnog indeksa (BIS), kao i evociranih auditivnih potencijala, može smanjiti prekomernu izloženost anesteticima i samim tim smanjiti rizik od postoperativne kognitivne disfunkcije (26). Multicentrična randomizovana klinička studija pratila je pojavu POD-a kod 655 pacijenata, koji su podvrgnuti velikim operativnim zahvatima u prvih pet dana postoperativno (27). Pokazano je da smanjena dubina anestezije smanjuje i rizik od nastanka POD-a. Incidencija POD-a u grupi sa vrednostima BIS 50 (plića anestezija) bila je 19%, a u grupi sa vrednostima BIS 35 (dublja anestezija) 28%. Nakon godinu dana praćenja pacijenti iz grupe koja je dobila pliću anesteziju pokazali su značajno bolje kognitivne funkcije u odnosu na one koji su za vreme operacije bili u duboljoj anesteziji (27). Zato i internacionalni vodiči za postoperativni delirijum preporučuju intraoperativnu upotrebu kontinuiranog EEG monitoringa, naročito kod starijih bolesnika, radi praćenja dubine opšte anestezije odnosno izbegavanja preterano duboke anestezije u cilju smanjenja njegove incidencije (28).

Sistematski pregled literature upoređivao je efekte inhalacione i totalne intravenske anestezije na nastanak kognitivnih deficita kod starijih bolesnika u nekardiohirurškim granama hirurgije. Istraživanje je uključilo 28 randomizovano kontrolisanih studija sa ukupno 4507 ispitanika a rezultati nisu pokazali jasne dokaze prednosti jedne ili druge vrste anestezije u smanjenju nastanka POD-a (29). Analizom efekata upotrebe različitih inhalacionih anestetika sevoflurana, izoflurana i desflurana na nastanak POD, takođe nije utvrđena razlika u njihovom uticaju na nastanak POD (29). (29).

Vrsta anestetika koji se primenjuje tokom operacije nije bila značajan faktor rizika za POD, ali je dosta istraživanja pokazalo da perioperativna upotreba opioida može biti uzrok njegovog nastanka (30). Takođe, premedikacija benzodijazepin-

however, only the level of albumin proved to be significant (9). The group of patients, in whom POD developed, had significantly lower values of this parameter (9). The results of a recent large meta-analysis have shown that in patients after total hip or knee arthroplasty, risk factors for the development of POD are low levels of albumin and hemoglobin (23).

## Intraoperative risk factors

Intraoperative risk factors are most commonly classified as factors related to anesthesia and factors related to surgery.

### *Factors related to anesthesia*

Earlier studies have shown that frequent general anesthesia can lead to can lead to the occurrence of cognitive dysfunction in patients. Intraoperative values of mean arterial pressure and partial pressure of carbon dioxide are physiological variables that are closely related to the occurrence of POD. Therefore, when general anesthesia is applied, it is necessary to prevent the appearance of intraoperative hypotension and hypocapnia, especially in older patients due to their influence on the reduction of cerebral blood flow. A systematic literature review, which examined the global prevalence and risk factors for POD among surgical patients excluding cardiac surgeries, showed that POD occurred about 3 times more often after surgeries performed under general anesthesia in comparison to those performed in the conditions of regional anesthesia (17).

A randomized multicentric study compared the effects of regional anesthesia (spinal, epidural, combined spinal and epidural) and general anesthesia (intravenous, inhalation) in 950 patients older than 65 years who underwent hip fracture surgery (25). Regional anesthesia without sedation did not significantly reduce the occurrence of POD compared to general anesthesia. POD was reported in 6.2% of patients who received regional anesthesia and in 5.1% of patients who received general anesthesia (25). In contrast, a meta-analysis of data showed that the use of general anesthesia for total hip or knee arthroplasty was a risk factor for the occurrence of POD and that the use of spinal anesthesia could reduce this risk (23).

In a meta-analysis of the influence of different techniques of anesthesia in hip surgery on the occurrence of POD, the results were different in included studies (8). Five studies included in the analysis showed the connectedness between the application of regional anesthesia and the occurrence of POD. The results of meta-analysis showed that this kind of anesthesia was a potential risk factor and that patients who received regional anesthesia for this type of operation would probably experience the occurrence of POD. In addition, in this analysis, a significant influence of general anesthesia on the occurrence of POD was found, after two studies had been excluded in order to solve the heterogeneity (8). The analysis of data related to urological surgeries did not show the significance of the application of either general or regional anesthesia on the development of POD (24).

Many studies have been conducted with the aim of examining the effects of the depth of anesthesia on the occurrence of POD, but the results are controversial and are still the subject of debate. In order to avoid cognitive deficits caused by longer exposure to anesthesia, research has shown that anesthetic titration by monitoring the bispectral index (BIS), as well as auditory evoked potentials, can reduce the excessive exposure to anesthetics and thus reduce the risk of postoperative cognitive dysfunction (26). A multicentric randomized clinical trial has observed the occurrence of POD in 655 patients who underwent major surgeries in the first five days postoperatively (27). It has been shown that that the reduced depth of anesthesia also reduces the risk of POD occurrence. The incidence of POD in the group with the target values of BIS 50 (shallow anesthesia) was 19% and in the group with the values of BIS 35 (deeper anesthesia) 28%. After one year of follow-up, the patients from the group that received shallow anesthesia showed significantly better cognitive functions compared to those who received deeper anesthesia (27). Therefore, international guidelines for postoperative delirium recommend the intraoperative use of continuous EEG monitoring, especially in elderly patients, in order to monitor the depth of general anesthesia, i.e. to avoid excessively deep anesthesia in order to reduce its incidence (28).

A systematic literature review compared the effects of inhalational and total intravenous anesthesia on the occurrence of cognitive deficits in elderly patients in non-cardiac branches of surgery. The research included 28 randomized

ima predstavlja značajan faktor rizika za nastanak POD-a pa vodič Evropskog udruženja anesteziologa za postoperativni delirijum sugeriše perioperativno izbegavanje upotrebe benzodijazepina osim kod veoma anksioznih bolesnika (28).

### *Faktori vezani za operaciju*

Faktori rizika vezani za operaciju odnose se najviše na vrstu hirurške procedure i povezani su sa stepenom operativnog stresa. Kardiohirurške operacije, operacije aneurizme abdominalne aorte kao i ortopedska operacija frakture kuka predstavljaju zahvate sa povišenim rizikom za nastanak POD-a (7,8). Ovaj sindrom predstavlja jednu od najčešćih komplikacija nakon kardiohirurgije, a prema rezultatima meta-alnalize *Chen* i sar. učestalost varira od 4.1% do 54.9% (7). Treba naglasiti da nisu sve vrste kardiohirurških operacija podjednako povezane sa pojavom ovog sindroma. Nakon operacije srčanih valvula učestalost javljanja POD je veća u odnosu na operacije aortokoronarnog bajpasa. Isto tako, nisu sve ortopedske operacije podjednako visoko rizične za razvoj POD-a. Među njima, operacija preloma vrata butne kosti predstavlja najrizičniju operaciju za nastanak ovog sindroma jer se najčešće radi o starijim pacijentima koji su lošijeg opšteg stanja, operacija se češće izvodi kao hitna procedura, a intenzitet postoperativnog bola je značajan (7,8,17,22,23).

Još jedan bitan faktor vezan za operaciju jeste hitnost procedure. Pokazano je da je nakon hitnih operativnih zahvata POD 1,5 do 3 puta češći nego kod elektivnih planiranih operativnih procedura (8,31). Takođe, intraoperativno krvavljenje i primena transfuzije predstavljali su značajan faktor rizika za nastanak POD u više sistematskih pregleda literature (8,9,23).

## Postoperativni faktori rizika

U postoperativnom periodu, intenzitet postoperativnog bola i primena pojedinih lekova, prvenstveno opioida, utvrđeni su kao faktori rizika za nastanak POD-a zbog njihovog efekta na centralni nervni sistem. U prospektivnoj kohortnoj studiji koja je uključila 581 pacijenta predviđenih za velike nekardijalne operativne zahvate, utvrđeno je da jak intenzitet postoperativnog bola, kao i upotreba visokih doza opioida, povećavaju rizik za nastanak POD-a kod svih pacijenata (32). U vodiču Evropskog udruženja anesteziologa za postoperativni delirijum jedna od preporuka za njegovu prevenciju jeste redovna adekvatna procena intenziteta i blagovremeno kupiranje postoperativnog bola. Posebno je naglašena važnost redovne procene intenziteta postoperativnog bola kod dementnih bolesnika upotrebom različitih validnih skala za njegovo merenje kod ove populacije. Preporučuje se pacijent kontrolisana analgezija (engl. *Patient-controlled analgesia*, PCA) kao najbolja vrsta analgezije ukoliko je pacijent u stanju da njenom upotrebom sam pronađe pravi balans između adekvatne analgezije i minimalne doze opioida. Pažljiva titracija dubine anestezije vođena neuromonitoringom i adekvatna perioperativna kontrola bola predstavljaju najefikasnije strategije zasnovane na dokazima koje smanjuju rizike nastanka POD-a (28). Pored navedenih, značajni postoperativni faktori rizika jesu i produžen boravak na mehaničkoj ventilaciji kao i produžen boravak u JIL prema rezultatima meta analize koja je ispitivala faktore rizika za nastank POD nakon kardiohirurških operacija (7).

## Zaključak

Često javljanje POD-a u različitim hirurškim granama ukazuje na značaj ovog problema, a identifikacija brojnih faktora rizika za njegov nastanak doprinosi redukciji ili eliminaciji njegovog javljanja. Identifikacija pacijenata sa povećanim rizikom predstavlja osnovu strategije za prevenciju ovog sindroma. Trenutni dokazi sugerišu da perioperativno izbegavanje upotrebe benzodijazepina, pažljiva titracija dubine anestezije vođena monitoringom i adekvatna perioperativna kontrola bola kod rizičnih bolesnika predstavljaju najefikasnije strategije koje minimiziraju rizike nastanka POD-a.

## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

## Reference


1. World Health Organization: International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Version 2019. http://apps.who.int/classifications/apps/icd/icd10online/
2. Luzius A. Steiner. Postoperative delirium. Part 1: pathophysiology and risk factors. Eur J Anaesthesiol 2011;28:628–36. doi: 10.1097/EJA.0b013e328349b7f5
3. Leotsakos I, Katafigiotis I, Gofrit ON, Duvdevani M, Mitropoulos D. Postoperative Delirium after Urological Surgery: A Literature Review. Curr Urol. 2019;13(3):133-140 doi: 10.1159/000499280
4. American Psychiatric Association, DSM-5 Task

controlled studies with a total of 4507 participants, and the results did not show clear evidence of the advantages of one or the other type of anesthesia in reducing the occurrence of POD (29). The analysis of the effects of the use of different inhalational anesthetics sevoflurane, isoflurane and desflurane on the occurrence of POD also no difference was found in their influence on the occurrence of POD (29).

The type of anesthetic, which is administered during operation, was not a significant risk factor for POD, but many studies have shown that the perioperative use of opioids may cause its occurrence (30). Also, premedication with benzodiazepines is a significant risk factor for the occurrence of POD, and therefore, the Guideline of the European Society of Anesthesiology for Postoperative Delirium suggests the perioperative avoidance of the use of benzodiazepine except in very anxious patients (28).

### *Factors related to surgery*

Risk factors related to surgery refer mostly to the type of surgical procedure and they are associated with the degree of operative stress. Cardiac surgeries, abdominal aortic aneurysm surgery, as well as hip fracture surgery are procedures with the increased risk of POD (7,8). This syndrome presents one of the most common complications after cardiac surgery, and according to the results of one meta-analysis conducted by Chen and associates, the incidence varies from 4.1 to 54.9% (7). It should be emphasized that not all types of cardiac surgeries are equally associated with the occurrence of this syndrome. After heart valve surgery, the incidence of POD is higher in comparison to coronary artery bypass surgery. Likewise, not all orthopedic surgeries have equally high risk for the development of POD. Among them, femoral neck fracture surgery represents the most risky operation for the occurrence of this syndrome, because it is mostly performed in older patients with a poor general condition, as an emergency procedure, while the intensity of postoperative pain is significant (7,8,17,22,23).

Another important factor related to the surgery is the emergency of the procedure. It has been shown that after emergency surgical procedures, POD was 1.5 to 3 times more common than during elective planned surgical procedures (8,31). Also, intraoperative bleeding and the use of transfusion were significant risk factors for the occurrence of POD in several systematic reviews of literature (8,9,23).

## Postoperative risk factors

In the postoperative period, the intensity of postoperative pain and the use of certain drugs, primarily opioids, have been established as risk factors for the occurrence of POD due to their effect on the central nervous system. In a prospective cohort study, which included 581 patients planned for major non-cardiac surgeries, it was found that the strong intensity of postoperative pain, as well as the use of high doses of opioids increased the risk of POD in all patients (32). In the guide of the European Association of Anesthesiologists for postoperative delirium, one of the recommendations for its prevention is regular adequate assessment of the intensity and timely relief of postoperative pain. The importance of regular assessment of postoperative pain intensity in demented patients using different valid scales for its measurement in this population is particularly emphasized. Patient-controlled analgesia (PCA) is recommended as the best type of analgesia if the patient is able to use it to find the right balance between adequate analgesia and the minimum dose of opioids. Careful titration of the depth of anesthesia guided by neuromonitoring and adequate perioperative pain control are the most effective evidence-based strategies to reduce the risks of POD (28). In addition to the above, significant postoperative risk factors are a prolonged stay on mechanical ventilation and a prolonged stay in the ICU according to the results of a meta-analysis that examined risk factors for the onset of POD after cardiac surgery (7).

## Conclusion

The frequent occurrence of POD in various surgical branches indicates the importance of this problem, while the identification of numerous risk factors for its occurrence contributes to the reduction or elimination of its occurrence. The identification of patients at increased risk is the basis of the strategy for the prevention of this syndrome. Current evidence suggests that perioperative avoidance of benzodiazepines, the careful titration of the depth of anesthesia guided by monitoring, and adequate perioperative pain control in high-risk patients are the most efficient strategies that minimize the risk of POD development.

Force. Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc; 2013. https://doi.org/10.1176/appi.books.9780890425596

5. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. J Am Geriatr Soc 2015;63:142–150. doi: 10.1111/jgs.13281.
6. Pinho C, Cruz S, Santos A, Abelha FJ. Postoperative delirium: age and low functional reserve as independent risk factors. J Clin Anesth. 2016;33:507-13. doi: 10.1016/j.jclinane.2015.09.002.
7. Chen H, Mo L, Hu H, Ou Y, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. J Cardiothorac Surg. 2021;16(1):113. doi: 10.1186/s13019-021-01496-w.
8. Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2021;36(1):3-14. doi: 10.1002/gps.5408.
9. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. Br J Surg. 2016;103(2):e21-8. doi: 10.1002/bjs.10062.
10. Wu X, Sun W, Tan M. Incidence and risk factors for postoperative delirium in patients undergoing spine surgery: a systematic review and meta-analysis. Biomed Res Int. 2019;2019:2139834. doi: 10.1155/2019/2139834.
11. Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive reserve and the risk of postoperative cognitive dysfunction. Dtsch Arztebl Int. 2017;114(7):110-7. doi: 10.3238/arztebl.2017.0110.
12. Alvarez-Bastidas L, Morales-Vera E, Valle-Leal JG, Marroquín-González J. Delirium in the elderly patient after anesthesia: associated factors. Colomb J Anesthesiol. 2018; 46(4):273-8, doi: 10.1097/CJ9.0000000000000077
13. Tai S, Xu L, Zhang L, Fan S, Liang C. Preoperative risk factors of postoperative delirium after transurethral prostatectomy for benign prostatic hyperplasia. Int J Clin Exp Med. 2015;8:4569–74.
14. Xue P, Wu Z, Wang K, Tu C, Wang X. Incidence and risk factors of postoperative delirium in elderly patients undergoing transurethral resection of prostate: a prospective cohort study. Neuropsychiatr Dis Treat. 2016;12:137-42. doi: 10.2147/NDT.S97249.
15. Stoddard MD, Cho A, Chen SA, Dunphy C, Wright DN, Chughtai B. A systematic review of postoperative delirium in the urologic patient. Curr Urol Rep. 2020;21(12):60. doi: 10.1007/s11934-020-01010-0.
16. De Carolis A, Giubilei F, Caselli G, Casolla B, Cavallari M, Vanacore N, et al. Chronic obstructive pulmonary disease is associated with altered neuropsychological performance in young adults. Dement Geriatr Cogn Dis Extra. 2011;1(1):402-8. doi: 10.1159/000333079.
17. Abate SM, Checkole YA, Mantedafro B, Basu B, Aynalem AE. Global prevalence and predictors of postoperative delirium among non-cardiac surgical patients: A systematic review and meta-analysis. Int J Surg Open. 2021;32:100334, https://doi.org/10.1016/j.ijso.2021.100334.
18. Kotfis K, Szylińska A, Listewnik M, Brykczyński M, Ely EW, Rotter I. Diabetes and elevated preoperative HbA1c level as risk factors for postoperative delirium after cardiac surgery: an observational cohort study. Neuropsychiatr Dis Treat. 2019;15:511-21. doi: 10.2147/NDT.S196973.
19. Hermanides J, Qeva E, Preckel B, Bilotta F. Perioperative hyperglycemia and neurocognitive outcome after surgery: a systematic review. Minerva Anestesiol. 2018;84(10):1178-88. doi: 10.23736/s0375-9393.18.12400-x.
20. Iamaroon A, Wongviriyawong T, Sura-Arunsumrit P, Wiwatnodom N, Rewuri N, Chaiwat O. Incidence of and risk factors for postoperative delirium in older adult patients undergoing noncardiac surgery: a prospective study. BMC Geriatr. 2020;20(1):40. doi: 10.1186/s12877-020-1449-8.
21. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth. 2017;119(2):316-23. doi: 10.1093/bja/aex130.
22. Greaves D, Psaltis PJ, Davis DHJ, Ross TJ, Ghezzi ES, Lampit A, et al. Risk factors for delirium and cognitive decline following coronary artery bypass grafting surgery: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(22):e017275. doi: 10.1161/JAHA.120.017275.
23. Zhao J, Liang G, Hong K, Pan J, Luo M, Liu J, Huang B. Risk factors for postoperative delirium following total hip or knee arthroplasty: A meta-analysis. Front Psychol. 2022;13:993136. doi: 10.3389/fpsyg.2022.993136.
24. Sanyaolu L, Scholz AFM, Mayo I, Coode-Bate J, Oldroyd C, Carter B, Quinn T, Hewitt J. Risk factors for incident delirium among urological patients: a systematic review and meta-analysis with GRADE summary of findings. BMC Urol. 2020;20(1):169. doi: 10.1186/s12894-020-00743-x.
25. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, et al. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. JAMA. 2022;327(1):50-8. doi: 10.1001/jama.2021.22647.
26. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013;110(Suppl 1):i98–i105. doi: 10.1093/bja/aet055
27. Evered LA, Chan MTV, Han R, Chu MHM, Cheng BP, Scott DA, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. Br J Anaesth. 2021;127(5):704-12. doi: 10.1016/j.bja.2021.07.021
28. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol. 2017;34(4):192-214. doi: 10.1097/EJA.0000000000000594.
29. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF. Intravenous

## Competing interests

The authors declared no competing interests.

## References


1. World Health Organization: International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Version 2019. http://apps.who.int/classifications/apps/icd/icd10online/
2. Luzius A. Steiner. Postoperative delirium. Part 1: pathophysiology and risk factors. Eur J Anaesthesiol 2011;28:628–36. doi: 10.1097/EJA.0b013e328349b7f5
3. Leotsakos I, Katafigiotis I, Gofrit ON, Duvdevani M, Mitropoulos D. Postoperative Delirium after Urological Surgery: A Literature Review. Curr Urol. 2019;13(3):133-140 doi: 10.1159/000499280
4. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc; 2013. https://doi.org/10.1176/appi.books.9780890425596
5. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. J Am Geriatr Soc 2015;63:142–150. doi: 10.1111/jgs.13281.
6. Pinho C, Cruz S, Santos A, Abelha FJ. Postoperative delirium: age and low functional reserve as independent risk factors. J Clin Anesth. 2016;33:507-13. doi: 10.1016/j.jclinane.2015.09.002.
7. Chen H, Mo L, Hu H, Ou Y, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. J Cardiothorac Surg. 2021;16(1):113. doi: 10.1186/s13019-021-01496-w.
8. Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2021;36(1):3-14. doi: 10.1002/gps.5408.
9. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. Br J Surg. 2016;103(2):e21-8. doi: 10.1002/bjs.10062.
10. Wu X, Sun W, Tan M. Incidence and risk factors for postoperative delirium in patients undergoing spine surgery: a systematic review and meta-analysis. Biomed Res Int. 2019;2019:2139834. doi: 10.1155/2019/2139834.
11. Feinkohl I, Winterer G, Spies CD, Pischon T. Cognitive reserve and the risk of postoperative cognitive dysfunction. Dtsch Arztebl Int. 2017;114(7):110-7. doi: 10.3238/arztebl.2017.0110.
12. Alvarez-Bastidas L, Morales-Vera E, Valle-Leal JG, Marroquín-González J. Delirium in the elderly patient after anesthesia: associated factors. Colomb J Anesthesiol. 2018; 46(4):273-8, doi: 10.1097/CJ9.0000000000000077
13. Tai S, Xu L, Zhang L, Fan S, Liang C. Preoperative risk factors of postoperative delirium after transurethral prostatectomy for benign prostatic hyperplasia. Int J Clin Exp Med 2015;8:4569–74.
14. Xue P, Wu Z, Wang K, Tu C, Wang X. Incidence and risk factors of postoperative delirium in elderly patients undergoing transurethral resection of prostate: a prospective cohort study. Neuropsychiatr Dis Treat. 2016;12:137-42. doi: 10.2147/NDT.S97249.
15. Stoddard MD, Cho A, Chen SA, Dunphy C, Wright DN, Chughtai B. A systematic review of postoperative delirium in the urologic patient. Curr Urol Rep. 2020;21(12):60. doi: 10.1007/s11934-020-01010-0.
16. De Carolis A, Giubilei F, Caselli G, Casolla B, Cavallari M, Vanacore N, et al. Chronic obstructive pulmonary disease is associated with altered neuropsychological performance in young adults. Dement Geriatr Cogn Dis Extra. 2011;1(1):402-8. doi: 10.1159/000333079.
17. Abate SM, Checkole YA, Mantedafro B, Basu B, Aynalem AE. Global prevalence and predictors of postoperative delirium among non-cardiac surgical patients: A systematic review and meta-analysis. Int J Surg Open. 2021;32:100334, https://doi.org/10.1016/j.ijso.2021.100334.
18. Kotfis K, Szylińska A, Listewnik M, Brykczyński M, Ely EW, Rotter I. Diabetes and elevated preoperative HbA1c level as risk factors for postoperative delirium after cardiac surgery: an observational cohort study. Neuropsychiatr Dis Treat. 2019;15:511-21. doi: 10.2147/NDT.S196973.
19. Hermanides J, Qeva E, Preckel B, Bilotta F. Perioperative hyperglycemia and neurocognitive outcome after surgery: a systematic review. Minerva Anestesiol. 2018;84(10):1178-88. doi: 10.23736/s0375-9393.18.12400-x.
20. Iamaroon A, Wongviriyawong T, Sura-Arunsumrit P, Wiwatnodom N, Rewuri N, Chaiwat O. Incidence of and risk factors for postoperative delirium in older adult patients undergoing noncardiac surgery: a prospective study. BMC Geriatr. 2020;20(1):40. doi: 10.1186/s12877-020-1449-8.
21. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth. 2017;119(2):316-23. doi: 10.1093/bja/aex130.
22. Greaves D, Psaltis PJ, Davis DHJ, Ross TJ, Ghezzi ES, Lampit A, et al. Risk factors for delirium and cognitive decline following coronary artery bypass grafting surgery: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(22):e017275. doi: 10.1161/JAHA.120.017275.
23. Zhao J, Liang G, Hong K, Pan J, Luo M, Liu J, Huang B. Risk factors for postoperative delirium following total hip or knee arthroplasty: A meta-analysis. Front Psychol. 2022;13:993136. doi: 10.3389/fpsyg.2022.993136.
24. Sanyaolu L, Scholz AFM, Mayo I, Coode-Bate J, Oldroyd C, Carter B, Quinn T, Hewitt J. Risk factors for incident delirium among urological patients: a systematic review and meta-analysis with GRADE summary of findings. BMC Urol. 2020;20(1):169. doi: 10.1186/s12894-020-00743-x.
25. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, et al. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. JAMA.

versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2018;8(8):CD012317. doi: 10.1002/14651858.CD012317.pub2.

30. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011;40(1):23-9. doi: 10.1093/ageing/afq140.
31. Ansaloni L, Catena F, Chattat R, Fortuna D, Franceschi C, Mascitti P, Melotti RM. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery, British Journal of Surgery, 2010;97(2):273–80, https://doi.org/10.1002/bjs.6843
32. Leung JM, Sands LP, Lim E, Tsai TL, Kinjo S. Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? Am J Geriatr Psychiatry. 2013;21(10):946-56. doi: 10.1016/j.jagp.2013.01.069.



**Primljen:** 21.10.2023. **Revizija:** 2.12.2023. **Prihvaćen:** 2.12.2023.

2022;327(1):50-8. doi: 10.1001/jama.2021.22647.

26. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013;110(Suppl 1):i98–i105. doi: 10.1093/bja/aet055
27. Evered LA, Chan MTV, Han R, Chu MHM, Cheng BP, Scott DA, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. Br J Anaesth. 2021;127(5):704-12. doi: 10.1016/j.bja.2021.07.021
28. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperativedelirium.EurJAnaesthesiol.2017;34(4):192-214. doi: 10.1097/EJA.0000000000000594.
29. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2018;8(8):CD012317. doi: 10.1002/14651858.CD012317.pub2.
30. Clegg A, Young JB. Which medications to avoid in people at risk of delirium: a systematic review. Age Ageing. 2011;40(1):23-9. doi: 10.1093/ageing/afq140.
31. Ansaloni L, Catena F, Chattat R, Fortuna D, Franceschi C, Mascitti P, Melotti RM. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery, British Journal of Surgery, 2010;97(2):273–80, https://doi.org/10.1002/bjs.6843
32. Leung JM, Sands LP, Lim E, Tsai TL, Kinjo S. Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? Am J Geriatr Psychiatry. 2013;21(10):946-56. doi: 10.1016/j.jagp.2013.01.069.



**Received:** 10/21/2023 **Revised:** 12/02/2023 **Accepted:** 12/02/2023

UDK BROJ: 616.37-006.6-036.22
DOI: https://www.doi.org/10.5937/zdravzast52-47366

PREGLEDNI RAD

# EPIDEMIOLOGIJA RAKA PANKREASA

**Belma Muratović[1], Aleksandra Nikolić[2]**

[1] Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija
[2] Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu, Beograd, Republika Srbija

[*] Korespondencija: Aleksandra Nikolić, Institut za epidemiologiju, Medicinski fakultet, Univerzitet u Beogradu, Višegradska 26a, 11000 Beograd, Republika Srbija; e-mail: aleksandra.m.nikolic@med.bg.ac.rs

**SAŽETAK**

U svetu, rak pankreasa je sedmi vodeći uzrok umiranja i dvanaesti vodeći uzrok obolevanja medju svim malignim tumorima. Stope incidencije i mortaliteta variraraju od zemlje do zemlje, što je posledica izloženosti različitim faktorima rizika, mogućnostima ranog dijagnostikovanja i pravovremenog i adekvatnog lečenja. Procenjuje se da će do 2040. godine doći do daljeg porasta broja obolelih (npr. za 27,4% u Evropi) i umrlih (npr. za 28,5% u Evropi) od karcinoma pankreasa. Prema Nacionalnom institutu za karcinome u Sjedinjenim Američkim Državama prosečno petogodišnje preživljavanje za rak pankreasa iznosi 12%. Promenljivi i nepromenljivi faktori doprinose nastanku ovog tumora. Rak pankreasa se češće javlja kod starijih, muškaraca, korisnika duvana i alkohola, osoba sa dijabetesom, preležanim pankreatitisom, fizički neaktivnih i gojaznih, kao i kod osoba sa pozitivnom porodičnom anamnezom za ovaj maligni tumor. Neophodno je raditi na edukaciji stanovništva o faktorima rizika za nastanak raka pankreasa, mogućnostima prevencije i načinu ranog dijagnostikovanja ove bolesti.

**Ključne reči:** rak pankreasa, incidencija, mortalitet, faktori rizika, preživljavanje, prevencija

## Uvod

Rak pankreasa je maligni tumor koji je sedmi vodeći uzrok smrti u svetu od malignih bolesti (1). Prema GLOBOCAN 2020, rak pankreasa je bio na 12. mestu kao najčešći karcinom. (1). U 2020. godini u svetu je dijagnostikovano 495.773 slučajeva raka pankreasa, a kao posledica istog zabeleženo je 466.003 slučajeva smrti (1). Sa starenjem raste broj novoobolelih i umrlih od raka pankreasa, a stope incidencije su veće kod muškaraca nego kod žena (2).

Etiologija karcinoma pankreasa je multifaktorijalna i kompleksna. Kao dominantni faktori rizika za nastanak raka pankreasa navode se pušenje i pozitivna porodična anamneza za ovaj maligni tumor (3,4). Rak pankreasa se uglavnom deli na dva tipa: adenokarcinom pankreasa, koji je najčešći (85% slučajeva) koji nastaje u egzokrinim žlezdama pankreasa, i neuroendokrini tumor pankreasa (PanNET), koji je ređi (manje od 5%) i javlja se u endokrinom tkivu pankreasa (5). Karcinom pankreasa ima veoma lošu prognozu, petogodišnje preživljavanje u visoko razvijenoj zemlji kao što je SAD iznosi svega 12,5% (6).

Dijagnoza se postavlja na osnovu imidžing metoda, kao što su kompjuterizovana tomografija, magnetna rezonanca, pozitronska emisiona tomografija i endoskopski ultrazvuk i biopsija iglom (7). Međutim, uglavnom se dijagnoza postavlja tek u uznapredovalom stadijumu (7). U procesu lečenja koriste se hirurške procedure, hemioterapija i biološka terapija, ali su prognoza i preživljavanje kod ovog tumora niski (8).

Cilj ovog preglednog rada je da se sagledaju učestalost i rasprostranjenost ovog malignog tumora, kao i da se identifikuju potencijalni faktori za nastanak ovog oboljenja radi predlaganja odgovarajućih preventivnih mera.

## Metode

U okviru ovog preglednog rada za pretraživanje literature korišćena je jedna bibliografska baza podataka PubMed. Pretraživanje literature je spro-

UDK NUMBER: 616.37-006.6-036.22
DOI: https://www.doi.org/10.5937/zdravzast52-47366

REVIEW ARTICLE

# EPIDEMIOLOGY OF PANCREATIC CANCER

**Belma Muratović[1], Aleksandra Nikolić[2]**

[1] Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia
[2] Institute of epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Republic of Serbia

[*] Correspondence: Aleksandra Nikolić, Institute of epidemiology, Faculty of Medicine, University of Belgrade, 26a Višegradska street, 11000 Belgrade, Republic of Serbia; e-mail: aleksandra.m.nikolic@med.bg.ac.rs

**SUMMARY**

Pancreatic cancer is the seventh leading cause of cancer-related deaths and the twelfth most common cancer worldwide. Incidence and mortality rates vary from country to country, which is a consequence of exposure to different risk factors, the possibilities of early diagnosis and timely and adequate treatment. It is estimated that by 2040, there will be a further increase in the number of patients (e.g. by 27.4% in Europe) and deaths (e.g. by 28.5% in Europe) caused by pancreatic cancer. According to the National Cancer Institute of the United States of America, the average five-year survival rate for pancreatic cancer is 12%. Modifiable and non-modifiable factors contribute to the occurrence of this tumor. Pancreatic cancer occurs more often in the elderly, men, tobacco and alcohol users, people with diabetes, chronic pancreatitis, physically inactive and obese people, as well as in people with a positive family history of this malignant tumor. It is necessary to work on educating the population about the risk factors for pancreatic cancer, the possibilities of prevention and ways of early diagnosis of this disease.

**Key words:** pancreatic cancer, incidence, mortality, risk factors, survival, prevention

## Introduction

Pancreatic cancer is a malignant tumor that is the seventh leading cause of cancer-related deaths in the world (1). According to GLOBOCAN 2020, pancreatic cancer was the twelfth most common cancer (1). In 2020, 495,773 cases of pancreatic cancer were diagnosed worldwide, and there were 466,003 deaths caused by this tumor (1). The number of new cases and deaths caused by pancreatic cancer increases with age, and the incidence rates are higher in men than in women (2).

The etiology of pancreatic cancer is multifactorial and complex. The dominant risk factors for pancreatic cancer are smoking and a positive family history of this malignant tumor (3,4). Pancreatic cancer is mainly divided into two types: pancreatic adenocarcinoma, which is the most common (85% of cases) and occurs in the exocrine glands of the pancreas, and pancreatic neuroendocrine tumor (PanNET), which is rarer (less than 5%) and occurs in the endocrine tissue of the pancreas (5). Pancreatic cancer has a very poor prognosis, and the five-year survival rate in the highly developed country such as the USA is only 12.5% (6).

The diagnosis is based on imaging methods, such as computed tomography, magnetic resonance, positron emission tomography and endoscopic ultrasound and needle biopsy (7). However, the diagnosis is usually established only at an advanced stage (7). In the treatment process, surgical procedures, chemotherapy and biological therapy are used, but the prognosis and survival of this tumor are low (8).

The aim of this review article is to assess the incidence and prevalence of this malignant tumor, as well as to identify potential factors for the occurrence of this disease in order to propose appropriate preventive measures.

## Methods

Within the scope of this review article, the bibliographic database PubMed was used for the

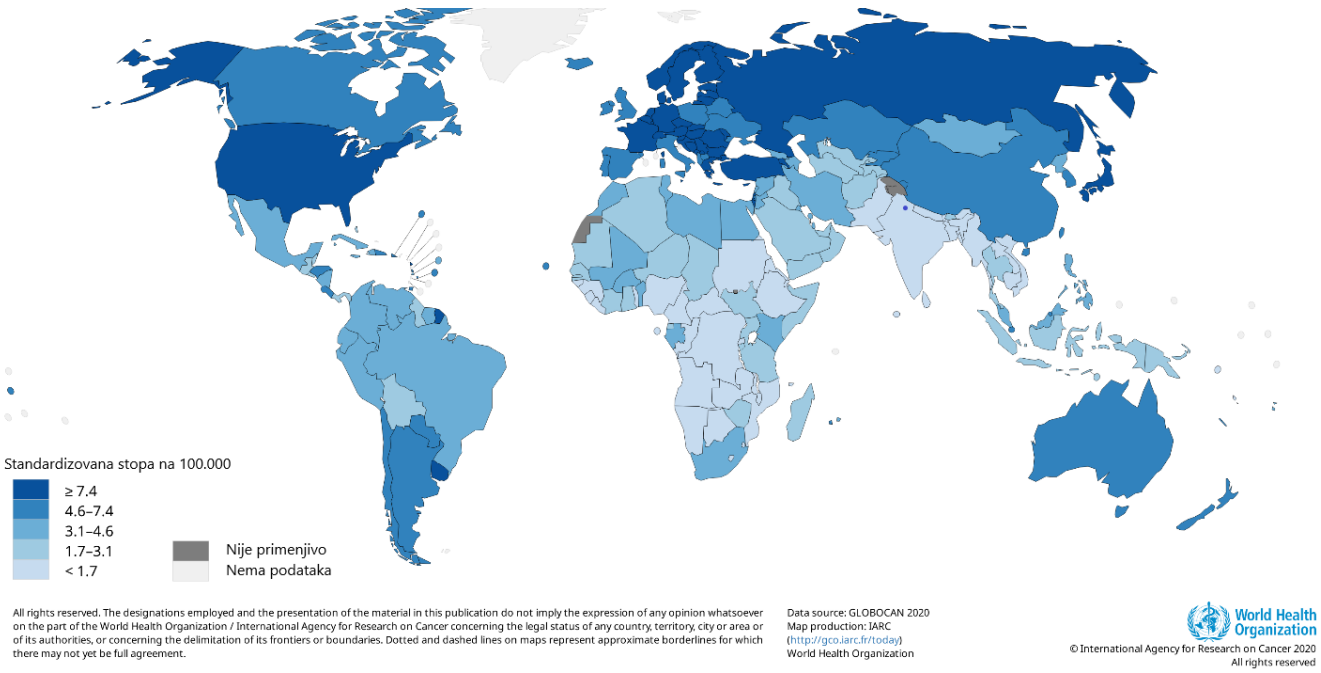
vedeno za poslednjih petnaest godina korišćenjem ključnih reči. U radu su prikazani rezultati samo onih istraživanja koja su bila objavljena na engleskom jeziku.

## Incidencija

Incidencija raka pankreasa varira od regiona, pola i godina starosti (1). U 2020. godini, zabeležena su 495.773 nova slučaja karcinoma pankreasa (1). Skoro polovina obolelih (47,1%) bila je iz Azije, 28,3% iz Evrope, 12,6% iz Severne Amerike, dok su oboleli iz Latinske Amerike činili 7,5% obolelih, a iz Afrike 3,4% obolelih (1). Standardizovana stopa incidencije za oba pola u svetu iznosila je 4,9 na 100.000 stanovnika (1). Najniže stope incidncije za rak pankreasa su zabeležene u Južno-Centralnom delu Azije (1,2 na 100.000), i u Srednjoj Africi (1,5 na 100.000), a najveće u Zapadnoj Evropi (8,6 na 100.000) i Severnoj Americi (8,0 na 100.000) (Slika 1). Zemlje sa najvećom stopom incidencije na svetu su Mađarska (11,2 na 100.000), Urugvaj (10,7 na 100.000), i Japan (9,9 na 100.000), a sa najnižom su Bocvana (0,66 na 100.000), Vanuatu (0,64 na 100.000), i Malavi (0,63 na 100.000). Globalno, stope incidencije su veće kod muškaraca (5,7 na 100.000) nego kod žena (4,1 na 100.000) (1). Ova bolest se skoro ne dijagnostikuje pre 55. godine života, a potom incidencija raste i najveća je posle 70. godine (2).

U Republici Srbiji, rak pankreasa je na 7. mestu na osnovu broja obolelih od svih malignih bolesti i čini 3,5% svih novotkrivenih slučajeva karcinoma, sa incidencijom od 8,5 na 100.000 (1,9). U Republici Srbiji je u 2020. godini broj novoobolelih od raka pankreasa iznosio 1.453, i to 791 kod muškaraca, i 662 kod žena. Standardizovana stopa incidencije je bila veća kod muškaraca i iznosila je 11,3 na 100.000, dok je kod žena bila 7,9 na 100.000 (9). Najviše uzrasno-specifične stope incidencije bile su kod starijih od 70 godina (9).

Još uvek nije jasno zašto toliko varira stopa incidencije raka pankreasa u različitim regionima i po polu. Pretpostavlja se da je to zato što je u svetu različita izloženost faktorima rizika. Žene su manje izložene faktorima rizika iz okruženja odgovornim za njihov nastanak ili manje sklone ovakvim malignim tumorima, kao na primer korišćenje cigareta. Cigarete češće konzumiraju muškarci i češće obolevaju od karcinoma pankreasa (10). Još jedna stvar koju treba uzeti u obzir je da dostupnostdijagnostičkih mrtoda varira između razvijenih i nerazvijenih geografskih područja. Štaviše, neke razlike u procenjenoj incidenciji mogu se pripisati kvalitetu registara, jer se obuhvat, potpunost i tačnost razlikuju od zemlje do zemlje (11).




**Slika 1.** Procenjena standardizovana stopa incidencije (prema populaciji sveta) za 2020. godinu za rak pankreasa za oba pola i sve uzraste (Izvor: GLOBOCAN 2020; https://gco.iarc.fr/today)

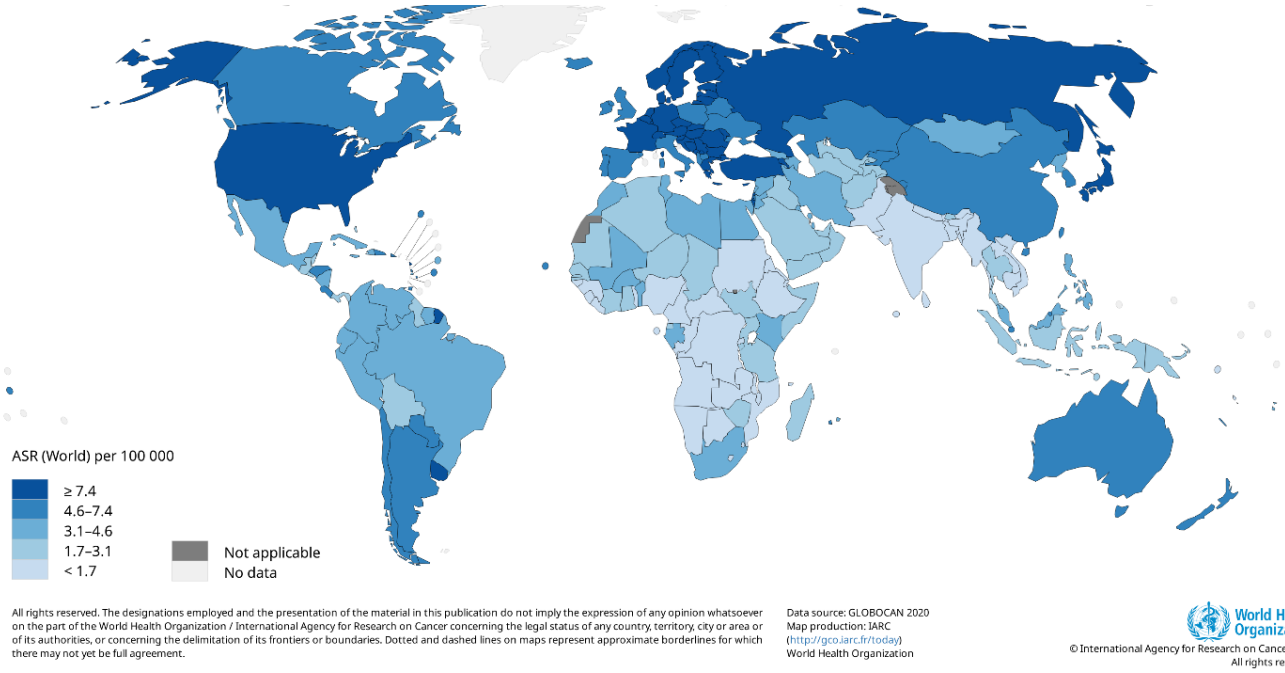
search of literature. The literature search was conducted for the last fifteen years using the key words. Only the results of studies that were published in the English language were included in this article.

## Incidence

The incidence of pancreatic cancer varies by region, gender and age (1). In 2020, 495,773 new cases of pancreatic cancer were recorded (1). Almost half of the patients (47.1%) were from Asia, 28.3% were from Europe, 12.6% from North America, while 7.5% of patients were from Latin America, and 3.4% of patients from Africa (1). In the world, the standardized incidence rate for both sexes was 4.9 per 100,000 inhabitants (1). The lowest incidence rates for pancreatic cancer were registered in the South-Central part of Asia (1.2 per 100,000), and in Central Africa (1.5 per 100,000), while the highest rates were in Western Europe (8.6 per 100,000) and North America (8.0 per 100,000) (Picture 1). The countries with the highest incidence rate in the world are Hungary (11.2 per 100,000), Uruguay (10.7 per 100,000), and Japan (9.9 per 100,000), while the lowest rates are in Botswana (0.66 per 100,000), Vanuatu (0.64 per 100,000), and Malawi (0.63 per 100,000). Globally, the incidence rates are higher in men (5.7 per 100,000) than in women (4.1 per 100,000) (1). This disease is almost never diagnosed before the age of 55, and then the incidence increases and is the highest after the age of 70 (2).

In the Republic of Serbia, pancreatic cancer is the 7th most common malignant tumor and it accounts for 3.5% of all newly diagnosed cancer cases, with the incidence of 8.5 per 100,000 (1,9). In 2020, in the Republic of Serbia, the number of new cases of pancreatic cancer amounted to 1,453, that is, 791 of men and 662 of women. The standardized incidence rate was higher in men and it was 11.3 per 100,000, while in women it was 7.9 per 100,000 (9). The highest age-specific incidence rates were in people older than 70 (9).

It is still not clear why the incidence rate of pancreatic cancer varies so much by gender and in different regions. It is assumed that it is the case because exposure to risk factors is different across the world. Women are less exposed to environmental risk factors responsible for its occurrence, such as smoking, or less prone to these malignant tumors. Cigarettes are more often used by men and they are more likely to get pancreatic cancer (10). Another thing that should be considered is that the availability of diagnostic tools varies between developed and underdeveloped geographic regions. Furthermore,




**Picture 1.** Estimated standardized incidence rate (according to the world population) for the year 2020 for pancreatic cancer, both sexes, all ages (Source: GLOBOCAN 2020; https://gco.iarc.fr/today)

## Mortalitet

Mortalitet raka pankreasa varira od regiona, pola i godina starosti (1). U 2020. godini, zabeleženo je 466.003 smrti od karcinoma pankreasa, sa standardizovanom stopom mortaliteta od 4,5 na 100.000 stanovnika (1). U Južno-Centralnoj Aziji zabeležena je najmanja stopa mortaliteta za rak pankreasa (1,1 na 100.000), i u Srednjoj Africi (1,5 na 100.000), a najveća u Zapadnoj Evropi (7,8 na 100.000) i Severnoj Americi (6,5 na 100.000). Mađarska i Urugvaj su zemlje sa najvećom stopom mortaliteta u svetu (10,2 na 100.000), a Malavi sa najmanjom (0,62 na 100.000) (Slika 2). Stope mortaliteta su veće kod muškaraca (5,3 na 100.000) u odnosu na žene (3,8 na 100.000) (1).

U Republici Srbiji, rak pankreasa je na 4. mestu prema broju umrlih od malignih bolesti i čini 5,6% svih umrlih usled malignih bolesti, sa standardizovanom stopom mortaliteta od 8 na 100.000 (1,9). U 2020. godini, u Republici Srbiji je broj umrlih od raka pankreasa iznosio 1169 (625 muškaraca i 544 žena). Standardizovana stopa mortaliteta za rak pankreasa je bila veća kod muškaraca i iznosila je 8,5 na 100.000, dok je kod žena bila 5,4 na 100.000 (9). U periodu 1999-2019. godine, u Centralnoj Srbiji stopa mortaliteta je bila najveća kod starijih od 70 godina i to kod oba pola (12).

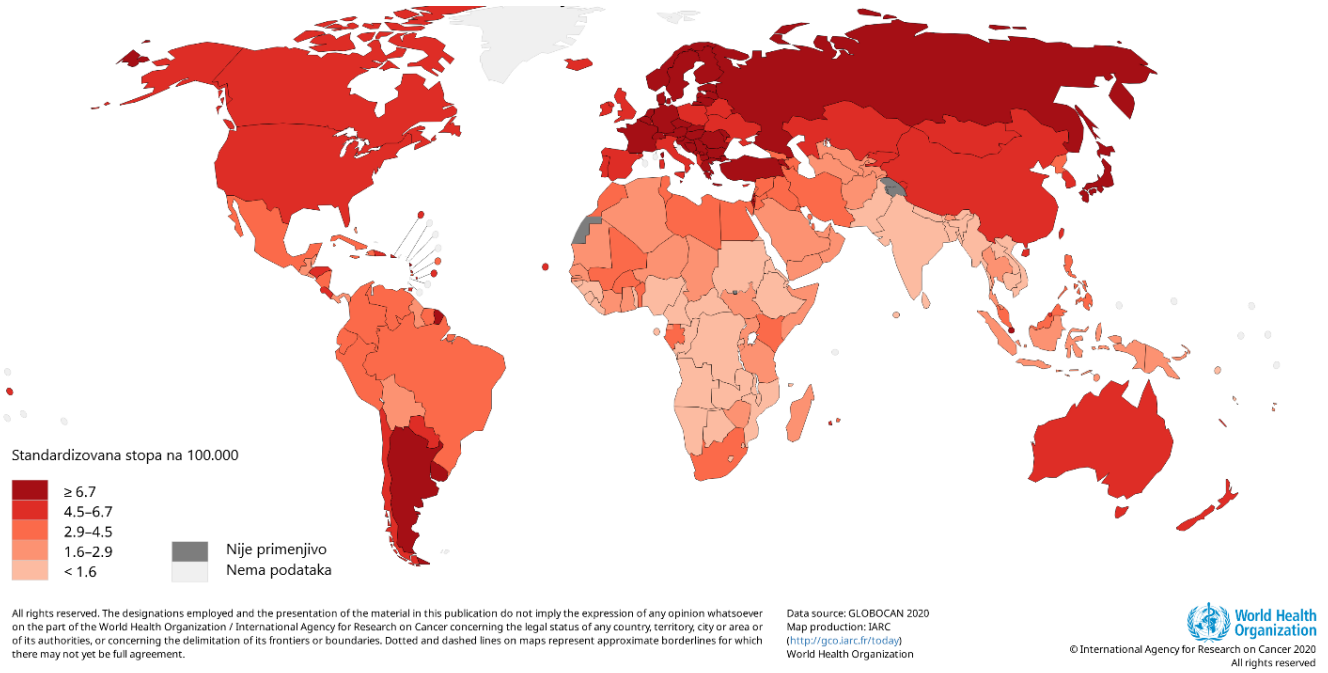
Primećuje se da su stope incidencije i mortaliteta slične. To ide u prilog činjenici da se ova bolest teško leči, otkriva se u kasnijim stadijumima zbog nespecifičnih simptoma, pacijenti su većinom stariji i sa narušenim zdravljem (13).

## Kretanje obolevanja i umiranja od raka pankreasa

U poslednje dve decenije primećen je rast stopa incidencije i mortaliteta raka pankeasa i on je različit po regionima sveta. U SAD, standardizovane stope incidencije su bile u blagom porastu od 0,9% godišnje u periodu 2010-2019, dok su stope mortaliteta rasle prosečno 0,1% godišnje u periodu 2011-2020. godine (6).

Predviđanje opterećenja karcinomom pankreasa u sveta govori da će broj obolelih i umrlih biti znatno veći u 2040. godini (Slike 3 i 4). Najveći rast broja obolelih u 2040. godini, u odnosu na 2020. godinu, očekuje se u Africi (+100,1%), zatim u Latinskoj Americi i karibima (+81,6%) i u Aziji (+81,5%), a najmanji u Evropi (+27,4%). Najveći rast broja umrlih u 2040. godini, u odnosu na 2020. godinu, očekuje se u Africi (+100,7%), a najmanji u Evropi (+28,5%) (14).

U Centralnoj Srbiji, u periodu od 1999-2019. godine, stope incidencije i mortaliteta za rak pankreasa su bile u porastu. Kod muškaraca stopa incidencije za rak pankreasa je prosečno rasla za 2,9% godišnje, a kod žena za 3,7%. Stope mortaliteta za rak pankreasa su prosečno rasle za +1,2% godišnje




**Slika 2.** Procenjena standardizovana stopa mortaliteta (prema populaciji sveta) za 2020. godinu za rak pankreasa za oba pola i sve uzraste (Izvor: GLOBOCAN 2020; https://gco.iarc.fr/today)

some differences in the estimated incidence may be attributed to the quality of registries, because coverage, completeness and accuracy vary between different countries (11).

## Mortality

The mortality of pancreatic cancer varies by region, sex and age (1). In 2020, 466,003 deaths caused by pancreatic cancer were registered, with the standardized mortality rate of 4.5 per 100,000 (1). The lowest mortality rate of pancreatic cancer was registered in South-Central Asia (1.1 per 100,000), and in Central Africa (1.5 per 100,000), while the highest was in Western Europe (7.8 per 100,000) and North America (6.5 per 100,000). Hungary and Uruguay are the countries with the highest mortality rate in the world (10.2 per 100,000), while the lowest rate is in Malawi (0.62 per 100,000) (Picture 2). Mortality rates are higher in men (5.3 per 100,000) in comparison to women (3.8 per 100,000) (1).

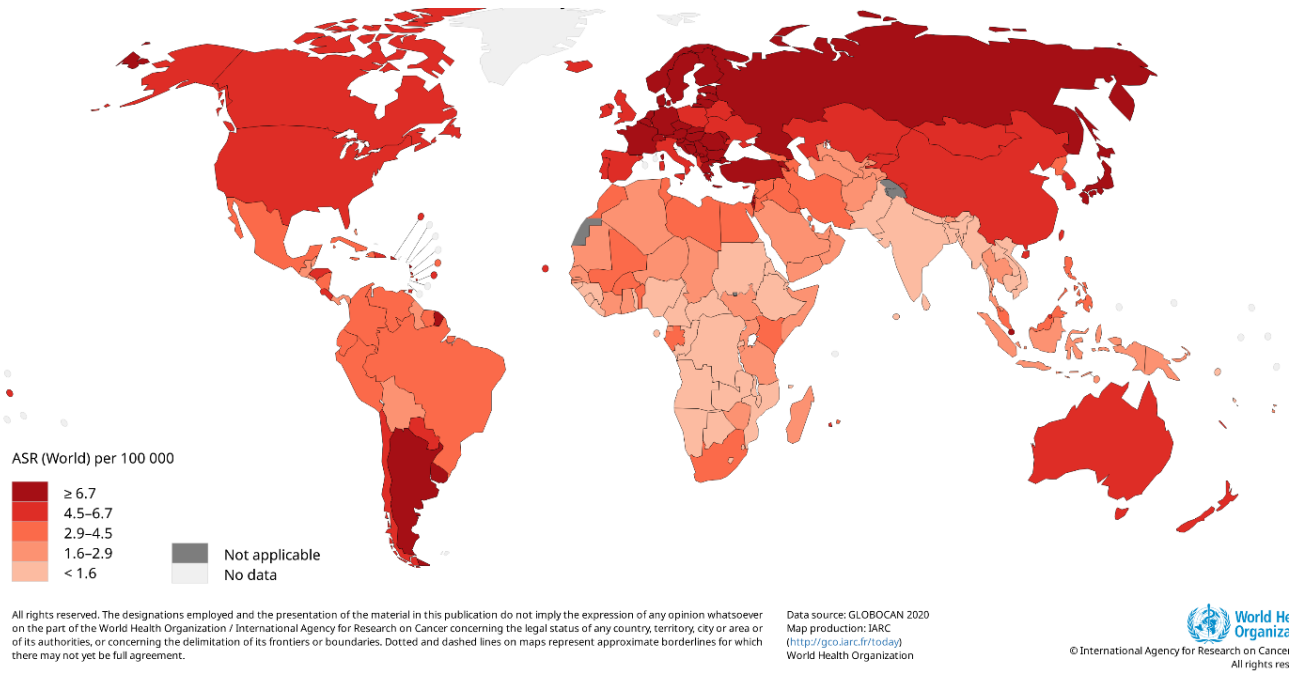
In the Republic of Serbia, pancreatic cancer ranks 4th in terms of the number of deaths caused by malignant diseases, and it accounts for 5.6% of all cancer-related deaths, with the standardized mortality rate of 8 per 100,000 (1,9). In 2020, in the Republic of Serbia, the number of deaths caused by pancreatic cancer was 1169 (625 men and 544 women). The standardized mortality rate of pancreatic cancer was higher in men and it amounted to 8.5 per 100,000, while in women it was 5.4 per 100,000 (9). In the period 1999-2019, in Central Serbia, the mortality rate was the highest in persons older than 70 years in both sexes (12).

It has been noticed that incidence and mortality rates are similar. This is in favor of the fact that this disease is hard to cure, it is discovered in later stages due to non-specific symptoms, and patients are mostly the elderly with the impaired health (13).

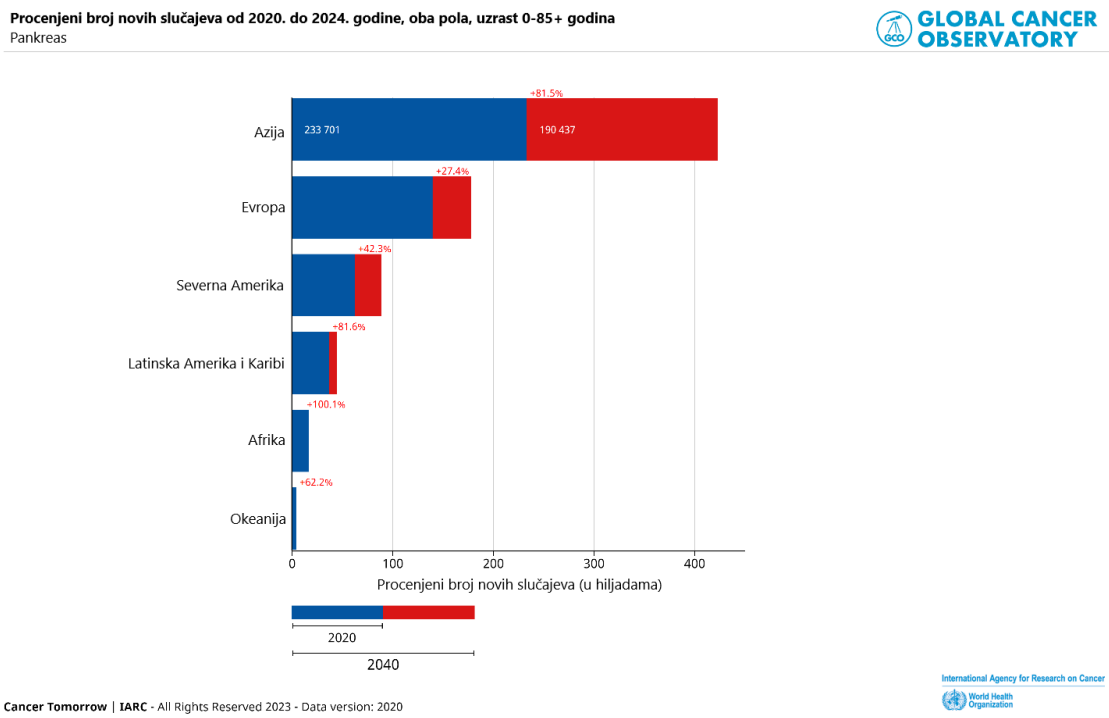
## Trends in pancreatic cancer incidence and mortality

An increase in incidence and mortality rates of pancreatic cancer has been noticed in the last two decades, and it varies by regions of the world. In the USA, standardized incidence rates increased slightly, that is, 0.9% per year in the period 2010-2019, while mortality rates increased, on average, by 0.1% per year in the period 2011-2020 (6).

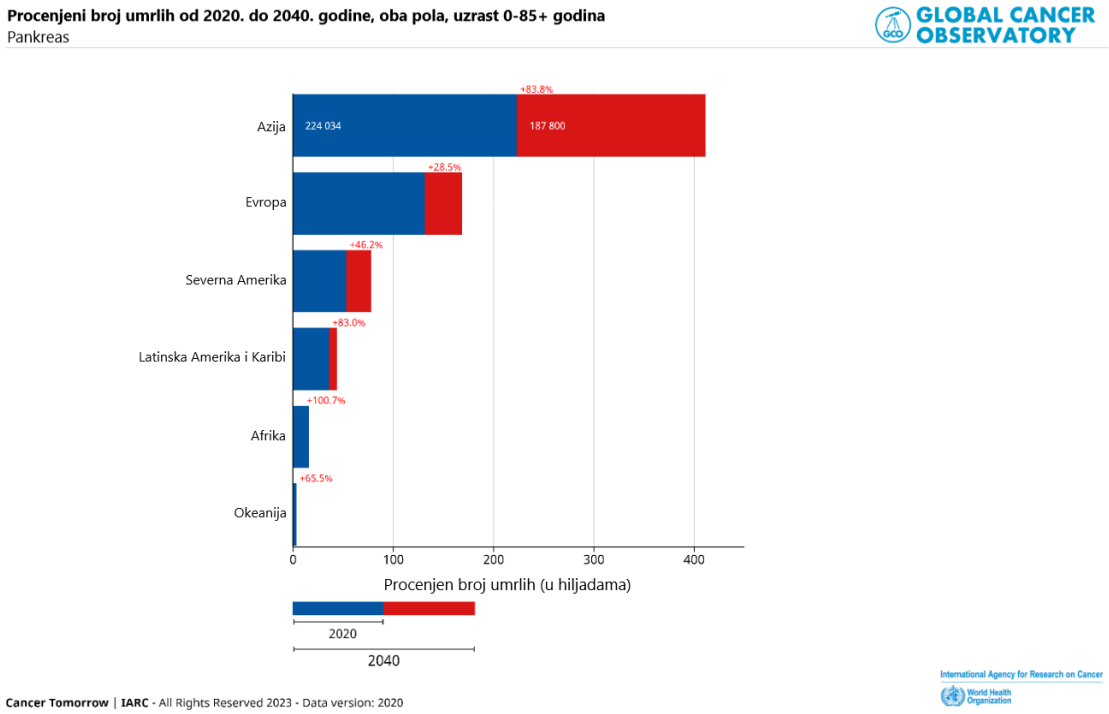
Estimates of the burden of pancreatic cancer in the world predict that the number of new cases and deaths will be significantly higher in 2040 (Pictures 3 and 4). The highest increase in the number of new cases in 2040 in comparison to 2020 is expected in Africa (+100.1%), followed by Latin America and the Caribbean (+81.6%) and Asia (+81.5%), while the lowest is expected in Europe (+27.4%). The largest increase in the number of




**Picture 2.** Estimated standardized mortality rate (by the world population) in 2020 for pancreatic cancer, for both sexes, all ages (Source: GLOBOCAN 2020; https://gco.iarc.fr/today)



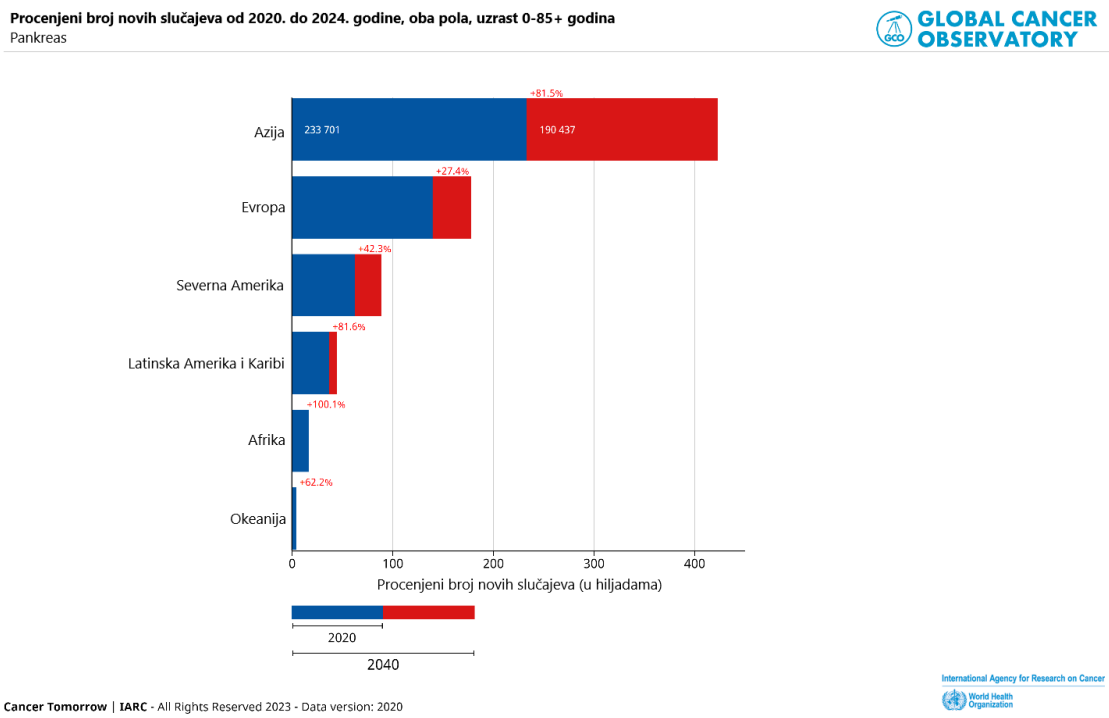

**Slika 3.** Trend porasta broja obolelih od raka pankreasa po regionima sveta od 2020. do 2040. godine (Izvor: IARC - Cancer tomorrow; https://gco.iarc.fr/tomorrow)



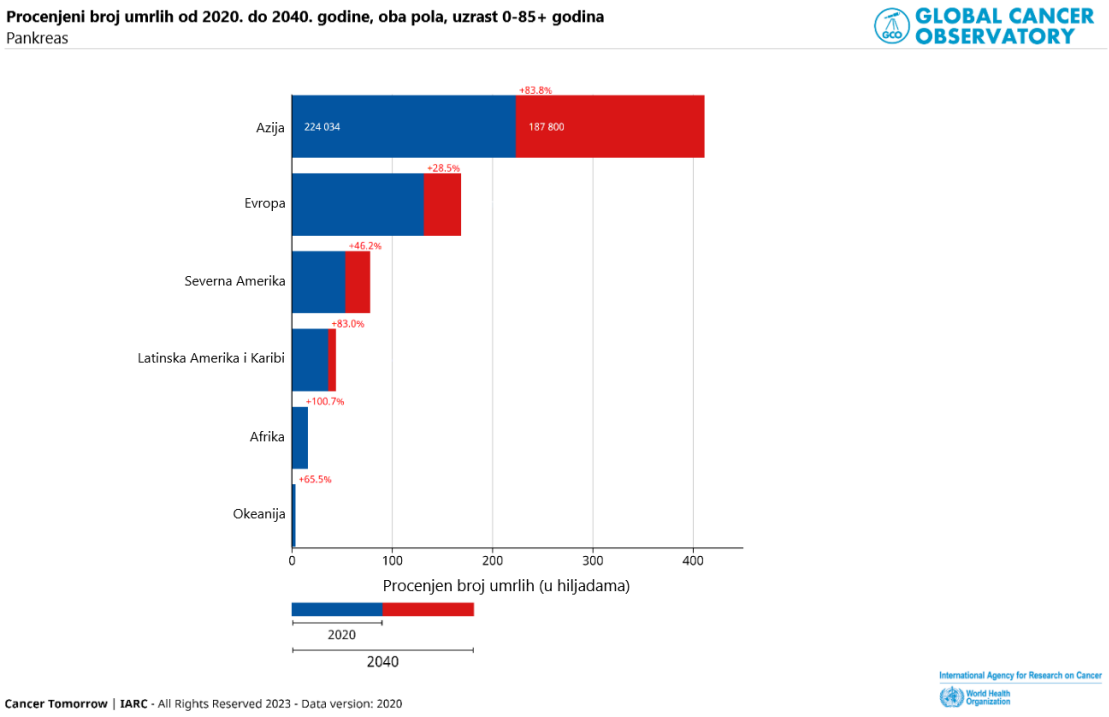

**Slika 4.** Trend porasta broja umrlih od raka pankreasa po regionima sveta od 2020. do 2040. godine (Izvor: IARC - Cancer tomorrow; https://gco.iarc.fr/tomorrow)

kod muškaraca, a za +0,6% kod žena, ali je samo kod muškaraca utvrđen značajan porast (12). Procenjuje se da će se u Republici Srbiji broj obolelih povećati za 8,9%, a broj umrlih za 9,5% do 2040. godine, u odnosu na 2020. godinu (14).

Različit trend rasta broja obolelih i umrlih od raka pankreasa objašnjava se različitom distribucijom faktora rizika. Konzumiranje cigareta je prepoznato kao najznačajniji faktor rizika za nastanak ovog karcinoma i smatra se da se smanjenjem prevalencije korisnika cigareta može prevenirati i karcinom pankreasa. Pored pušenja cigareta, alkohol, ishrana bogata zasićenim masnim kiselinama i nedovoljno sprovođenje fizičke aktivnosti utiču na oboljevanje. Zanimljivo je da se procenjuje najveći porast obolevanja i umiranja u Africi, koja je u fazi




**Picture 3.** Rising trends in pancreatic cancer incidence by world regions from 2020 to 2040 (Source: IARC - Cancer tomorrow; https://gco.iarc.fr/tomorrow)




**Picture 4.** Rising trends in pancreatic cancer mortality by world regions from 2020 to 2040 (Source: IARC - Cancer tomorrow; https://gco.iarc.fr/tomorrow)

deaths in 2040, in comparison to 2020, is expected in Africa (+100.7%), while the lowest is expected in Europe (+28.5%) (14).

In the period 1999-2019, in Central Serbia, incidence and mortality rates of pancreatic cancer increased. In men, the incidence rate of pancreatic cancer increased, on average, by 2.9% per year, and in women by 3.7%. Mortality rates of pancreatic cancer increased, on average, by +1.2% per year in men, and by +0.6% in women, but a significant increase was found only in men (12). It is estimated that in the Republic of Serbia, the number of new cases will increase by +8.9%, while the number of deaths will increase by 9.5% by 2040, in comparison to 2020 (14).

The different trend of increase in the number

razvoja i tako ima ograničene pristupe dijagnostici i lečenju. Mogući načini da se ovaj trend obolevanja smanji jeste da se prevenira promenom načina života i poboljša svest o bolesti i njenim simptomima, kako bi se dijagnostikovala u ranijim stadijumima (2).

## Preživljavanje

Karcinom pankreasa je oboljenje visoke smrtnosti. Petogodišnje preživljavanje u periodu od 2014-2018. godine je poboljšano sa 6% na 9%, što pokazuje da je napredak moguć i da je postignut (2).

Preživljavaje zavisi od puno faktora, a jedan od najznačajnijih je stadijum u kojem se bolest otkriva. Prema Nacionalnom institutu za karcinome u SAD-u prosečno petogodišnje preživljavanje je 12,5%. Ako je karcinom dijagnostikovan u ranoj fazi, kada je hirurško odstranjivanje moguće, petogodišnje preživljavanje je 44,3%. Ako se karcinom proširio na okolna tkiva i organe, petogodišnje preživljavanje je 16,2%. Međutim, 51% obolelih u trenutku dijagnostikovanja ima udaljene metastaze, i kod njih petogodišnje preživljavanje iznosi oko 3,2% (6).

## Etiologija i faktori rizika

Faktori rizika za nastanak raka pankreasa se mogu podeliti na promenljive i nepromenljive, u odnosu na to da li možemo ili ne da ih preveniramo (2). Pušenje predstavlja najrasprostranjeniji i najvažniji faktor rizika za nastanak karcinoma pankreasa. U meta analizi iz 2012. godine, pokazano je da je rizik od nastanka karcinoma pankreasa 2,2 puta veći kod trenutnih pušača i 1,17 puta kod bivših pušača u odnosu na nepušače (3). Rizik za nastanak karcinoma pankreasa se povećava sa većim brojem popušenih cigareta dnevno i sa dužim pušačkim stažom (3). Nema povezanosti sa godinama života kada je osoba počela sa konzumiranjem cigareta (3).

Konzumiranje alkohola je povezano sa nastankom karcinoma pankreasa. Osobe koje piju više od 4 jedinice alkohola dnevno (jedna jedinica alkohola je 14,8 ml čistog etanola u navedenom piću) su u većem riziku od onih koji piju manje. Rizik je znatno povećan kod osoba koje konzumiraju 9 i više jedinica alkohola dnevno. Što se tiče vrste alkoholnog pića, osobe koje konzumiraju više od 4 jedinice vina su u većem riziku od nastanka karcinoma pankreasa, dok porast rizika nije primećen za konzumaciju piva ili žestokog pića (15).

Povećana telesna težina i veći indeks telesne mase (ITM) povezani su sa većim rizikom od nastanka karcinoma pankreasa za razliku od osoba koje imaju normalne vrednosti ITM. Čak su i veći obim struka i veći odnos obima struka i kukova povezani sa nastankom ovog karcinoma (16).

Povećano konzumiranje crvenog mesa (više od 120 gr dnevno) i prerađenog mesa (više od 50 gr dnevno) su povezani sa nastankom karcinoma pankreasa (17). U Ujedinjenom Kraljevstvu je na osnovu podataka dve velike prospektivne studije (ukupno 60.310 ispitanika) zaključeno da je manji mortalitet od ove bolesti kod osoba koje jedu manje mesa ili su vegeterijanci ili vegani (18).

Ostali promenljivi faktori sa kojima je povezano oboljevanje od raka pankreasa jesu fizička neaktivnost i profesionalna izloženost nekim supstancama (npr. nikl, kadmijum, arsen, hlorisani organski rastvarači, formaldehid) (2,19).

U nepromenljive faktore rizika za nastanak raka pankreasa spadaju pol, uzrast, komorbiditeti, pozitivna porodična anamneza za ovaj maligni tumor, itd. Muškarci češće obolevaju od karcinoma pankreasa nego žene (1,2,20). Smatra se da su muškarci češće izloženi faktorima rizika (pušenju i alkoholu) u odnosu na žene i da je zato kod njih veća stopa incidencije nego kod žena (2). Ova bolest se gotovo i ne javlja kod osoba mlađih od 55. godina, što znači da se sa starenjem povećava mogućnost nastanka ove bolesti (1,2,20,21). Mnoge studije potvrđuju povezanost šećerne bolesti i nastanka karcinoma pankreasa. Ovaj rizik je znatno povećan kod osoba koje duže vreme boluju od dijabetesa melitusa (19). Osobe sa pozitivnom porodičnom istorijom u vezi javljanja karcinoma pankreasa su u većem riziku za nastanak raka pankreasa za razliku od osoba koje nemaju ovu bolest u porodici. Bolest se češće javlja kod srodnika prve linije u odnosu na dalje krvne srodnike (4). Ostali nepromenljivi faktori za nastanak raka pankreasa su pankreatitis, infekcija *H. pylori*, infekcija uzrokovana hepatitis B i C virusom, prisustvo određenih mutacija i dr. (2,19).

## Prevencija

Rana dijagnoza karcinoma pankreasa bi mogla smanjiti mortalitet, poboljšati preživljavanje i kvalitet života osoba sa karcinomom pankreasa. Međutim, skrining opšte populacije ne bi doneo očekivane rezultate i zato bi trebalo izabrati rizičnu grupu koju treba podvrgnuti testiranju, kao što su bliski srodnici obolelih i oni koji su izloženi faktori-

of new cases and deaths caused by pancreatic cancer is explained by different distribution of risk factors. Smoking has been recognized as the most significant risk factor for the occurrence of this cancer, and it is believed that pancreatic cancer can be prevented by reducing the prevalence of tobacco users. In addition to smoking, alcohol, a diet rich in saturated fatty acids and insufficient physical activity influence the occurrence of this disease. It is interesting that the highest increase in morbidity and mortality is estimated in Africa, which is a developing country, and thus has limited access to diagnostics and treatment. Possible ways to reduce this disease trend is to prevent it by changing the lifestyle and by improving the awareness regarding this disease and its symptoms, in order to diagnose it in earlier stages (2).

## Survival

Pancreatic cancer is a disease with high mortality. Five-year survival in the period 2014-2018 improved from 6% to 9%, which shows that improvement is possible and has been achieved (2).

Survival depends on many factors and one of the most important is the stage at which the disease is detected. According to the National Cancer Institute in the USA, the average five-year survival rate is 12.5%. If cancer is diagnosed at an early stage, when surgical removal is possible, the five-year survival rate is 44.3%. If the cancer has spread to surrounding organs and tissues, the five-year survival rate is 16.2%. However, 51% of patients have distant metastases at the moment of diagnosis, and their five-year survival is about 3.2% (6).

## Etiology and risk factors

Risk factors for pancreatic cancer may be divided into modifiable and non-modifiable, in relation to whether we can prevent them or not (2). Smoking is the most common and important risk factor for the occurrence of pancreatic cancer. In one meta-analysis from 2012, it was shown that the risk of developing pancreatic cancer is 2.2 times higher in current smokers and 1.17 times higher in former smokers in comparison to non-smokers (3). The risk of developing pancreatic cancer increases with a greater number of cigarettes smoked per day and with a longer history of smoking (3). It is not associated with the age when a person started smoking cigarettes (3).

Alcohol consumption is associated with the occurrence of pancreatic cancer. Persons who drink more than 4 units of alcohol per day (one unit of alcohol is 14.8 ml of pure ethanol in that drink) are at an increased risk compared to those who drink less. The risk is significantly higher in persons who consume 9 units of alcohol or more per day. As far as the type of alcoholic beverage is concerned, persons who consume more than 4 units of wine are at an increased risk of developing pancreatic cancer, while the increase of this risk was not noted for beer or other spirits (15).

The increased body weight and higher body mass index (BMI) are associated with a higher risk of pancreatic cancer, as opposed to people who have normal BMI values. Even a bigger waist circumference and a higher waist-to-hip ratio are associated with the occurrence of this cancer (16).

The increased consumption of red meat (more than 120 g per day) and processed meat (more than 50 g per day) are associated with the development of pancreatic cancer (17). In the United Kingdom, based on the data from two large prospective studies (60,310 participants), it was concluded that the mortality of this disease is lower in persons who eat less meat or who are vegetarians or vegans (18).

Other modifiable factors associated with pancreatic cancer are physical inactivity and occupational exposure to certain substances (e.g. nickel, cadmium, chlorinated organic solvents, formaldehyde) (2,9).

Non-modifiable risk factors for the occurrence of pancreatic cancer include sex, age, comorbidities, positive family history of this malignant tumor etc. Men are more likely to suffer from pancreatic cancer than women (1,2,20). It is believed that men are more exposed to risk factors (smoking and alcohol) than women, and due to this fact they have a higher incidence rate than women (2). This disease almost does not occur in persons younger than 55, which means that the possibility of the occurrence of this disease increases with age (1,2,20,21). Many studies confirm the connection between diabetes and pancreatic cancer. This risk is significantly increased in people who have suffered from diabetes mellitus for a longer period of time (19). Persons with a positive family history of pancreatic cancer are at an increased risk of developing this disease in contrast to persons who do not have this disease in their family. The

ma rizika (2,22). Bilo bi idealno formirati starostnu granicu kada se treba podvrgnuti testiranju i koliko često kod familijarnog karcinoma, kao i koliko dugo nakon dijagnoze dijabetes melitusa (22).

Međutim, i primarna prevencija ima velikog udela u sprečavanju nastanka bolesti. Najvažniji faktor rizika je pušenje cigareta (3). Prestankom pušenja cigareta se smanjuje i rizik nastanka ove bolesti. Ostali promenljivi faktori se takođe mogu korigovati i smanjiti mogućnost nastanka ove bolesti. Međutim, kod osoba koje imaju genetsku predispoziciju za nastanak ove bolesti, osim menjanja stila života i životnih navika, oni ne mogu značajno uticati na nastanak ove bolesti i za njih bi skrining bio idealan postupak za rano otkrivaje i lečenje (23).

## Zaključak

Karcinom pankreasa je čest maligni tumor i preživljavanje je vrlo nisko. Na osnovu epidemioloških podataka, očekuje se znatan porast obolelih u narednom periodu, ali se smatra da će se poboljšati mogućnosti lečenja i smanjiti smrtnost od ovog karcinoma. Neophodno je raditi na edukaciji stanovništva o faktorima rizika za nastanak raka pankreasa, mogućnostima prevencije i načinu ranog dijagnostikovanja ove bolesti.

## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

## Reference


1. Cancer today [Internet]. [cited 2023 Nov 2]. Available from: http://gco.iarc.fr/today/home
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019;10(1):10–27. doi: 10.14740/wjon1166
3. Bosetti C, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, et al. Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer. 2007;122(5):1118–29. doi: 10.1002/ijc.23232
4. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJA, et al. Prospective Risk of Pancreatic Cancer in Familial Pancreatic Cancer Kindreds. Cancer Research. 2004;64(7):2634–8. doi: 10.1158/0008-5472.can-03-3823.
5. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology. 2015;15(1):8–18. doi: 10.1016/j.pan.2014.10.001
6. SEER [Internet]. [cited 2023 Nov 3]. Cancer of the Pancreas - Cancer Stat Facts. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html
7. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018;24(19):2047–60. doi: 10.3748/wjg.v24.i19.2047
8. Mohammed S, Van Buren II G, Fisher WE. Pancreatic cancer: Advances in treatment. World J Gastroenterol. 2014;20(28):9354–60. doi: 10.3748/wjg.v20.i28.9354.
9. Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut". Malignai tumori u Republici Srbiji 2020. Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut": Belgrade; 2022.[Internet]. [cited 2023 Nov 2]. Available from: https://www.batut.org.rs/download/publikacije/MaligniTumoriuRepubliciSrbiji2020.pdf
10. Ezzati M, Henley SJ, Lopez AD, Thun MJ. Role of smoking in global and regional cancer epidemiology: Current patterns and data needs. International Journal of Cancer. 2005;116(6):963–71. doi: 10.1002/ijc.21100.
11. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005;83(3):171–7.
12. Muratović B, Nikolić A, Šipetić-Grujičić S. Kretanje obolevanja i umiranja od raka pankreasa u Centralnoj Srbiji, u periodu od 1999. do 2019. godine. Zdravstvena zaštita. 2022;51(1):23–38. doi: 10.5937/zdravzast51-36926
13. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? Therap Adv Gastroenterol. 2013;6(4):321–37. doi: 10.1177/1756283X13478680.
14. Cancer Tomorrow [Internet]. [cited 2023 Nov 2]. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/bars?types=0&sexes=0&mode=population&group_populations=0&multiple_populations=1&multiple_populations=903_904_905_908_909_935&single_unit=100
15. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4). Ann Oncol. 2012;23(2):374–82. doi: 10.1093/annonc/mdr120.
16. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric Measures, Body Mass Index and Pancreatic Cancer: a Pooled Analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010;170(9):791–802. doi: 10.1001/archinternmed.2010.63
17. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106(3):603–7. doi: 10.1038/bjc.2011.585.
18. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom123. Am J Clin Nutr. 2016;103(1):218–30. doi: 10.3945/ajcn.115.119461.
19. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. International Journal of Epidemiology. 2015;44(1):186–98. doi: 10.1093/ije/dyu240.
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal

disease occurs more often in the first-line relatives in comparison to more distant relatives (4). Other non-modifiable risk factors for the development of pancreatic cancer are pancreatitis, H. pylori infection, infection caused by hepatitis B and C virus, the presence of certain mutations, etc. (2,19).

## Prevention

Early diagnosis of pancreatic cancer could reduce mortality, improve the survival and quality of life of persons with pancreatic cancer. However, screening the general population would not yield the expected results, and therefore, a risk group should be selected for testing, such as close relatives of the affected and those exposed to risk factors (2,22). It would be ideal to establish the age limit when to do testing and how often in case of hereditary cancer, as well as how long after the diagnosis of diabetes mellitus (22).

However, primary prevention also plays a major role in preventing the onset of disease. The most important risk factor is smoking (3). Stopping smoking reduces the risk of developing this disease. Other modifiable risk factors can also be corrected, thus reducing the possibility of the occurrence of this disease. However, in persons who have a genetic predisposition of this disease, apart from changing their lifestyle and habits, they cannot significantly influence the onset of this disease and for them screening would be an ideal procedure for early detection and treatment (23).

## Conclusion

Pancreatic cancer is a common malignant tumor and survival is very low. Based on the epidemiological data, a significant increase in the number of new cases is expected in the following period, however, it is believed that treatment options will be improved and that mortality will decrease. It is necessary to work on educating the population about risk factors for pancreatic cancer, the possibilities of prevention and ways of early diagnosis of this disease.

## Competing interests

The authors declared no competing interests.

## References


1. Cancer today [Internet]. [cited 2023 Nov 2]. Available from: http://gco.iarc.fr/today/home
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019;10(1):10–27. doi: 10.14740/wjon1166
3. Bosetti C, Levi F, Ferlay J, Garavello W, Lucchini F, Bertuccio P, et al. Trends in oesophageal cancer incidence and mortality in Europe. Int J Cancer. 2007;122(5):1118–29. doi: 10.1002/ijc.23232
4. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJA, et al. Prospective Risk of Pancreatic Cancer in Familial Pancreatic Cancer Kindreds. Cancer Research. 2004;64(7):2634–8. doi: 10.1158/0008-5472.can-03-3823.
5. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhr JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology. 2015;15(1):8–18. doi: 10.1016/j.pan.2014.10.001
6. SEER [Internet]. [cited 2023 Nov 3]. Cancer of the Pancreas - Cancer Stat Facts. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html
7. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018;24(19):2047–60. doi: 10.3748/wjg.v24.i19.2047
8. Mohammed S, Van Buren II G, Fisher WE. Pancreatic cancer: Advances in treatment. World J Gastroenterol. 2014;20(28):9354–60. doi: 10.3748/wjg.v20.i28.9354.
9. Institut of Public Health of Serbia "Dr Milan Jovanović Batut". Malignant tumors in Republic of Serbia 2020. Institut of Public Health of Serbia "Dr Milan Jovanović Batut"Belgrade; 2022. [Internet]. [cited 2023 Nov 2]. Available from: https://www.batut.org.rs/download/publikacije/MaligniTumoriuRepubliciSrbiji2020.pdf
10. Ezzati M, Henley SJ, Lopez AD, Thun MJ. Role of smoking in global and regional cancer epidemiology: Current patterns and data needs. International Journal of Cancer. 2005;116(6):963–71. doi: 10.1002/ijc.21100.
11. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. 2005;83(3):171–7.
12. Muratović B, Nikolić A, Šipetić-Grujičić S. Trends in incidence and mortality from pancreatic cancer in Central Serbia, in the period from 1999 to 2019. Health Care. 2022;51(1):23–38. doi: 10.5937/zdravzast51-36926
13. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? Therap Adv Gastroenterol. 2013;6(4):321–37. doi: 10.1177/1756283X13478680.
14. Cancer Tomorrow [Internet]. [cited 2023 Nov 2]. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/bars?types=0&sexes=0&mode=population&group_populations=0&multiple_populations=1&multiple_populations=903_904_905_908_909_935&single_unit=100
15. Lucenteforte E, La Vecchia C, Silverman D, Petersen GM, Bracci PM, Ji BT, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4). Ann Oncol. 2012;23(2):374–82. doi: 10.1093/annonc/mdr120.

A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394–424. doi: 10.3322/caac.21492

21. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. WJG. 2021;27(27):4298–321. doi: 10.3748/wjg.v27.i27.4298.

22. Lucas AL, Kastrinos F. Screening for Pancreatic Cancer. JAMA. 2019;322(5):407–8. doi: 10.1001/jama.2019.9690

23. Kuroczycki-Saniutycz S, Grzeszczuk A, Zwierz ZW, Kołodziejczyk P, Szczesiul J, Zalewska-Szajda B, et al. Prevention of pancreatic cancer. Contemp Oncol (Pozn). 2017;21(1):30–4. doi: 10.5114/wo.2016.63043.



**Primljen:** 26.10.2023. **Revizija:** 12.11.2023. **Prihvaćen:** 26.11.2023.

16. Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric Measures, Body Mass Index and Pancreatic Cancer: a Pooled Analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med. 2010;170(9):791–802. doi: 10.1001/archinternmed.2010.63
17. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. Br J Cancer. 2012;106(3):603–7. doi: 10.1038/bjc.2011.585.
18. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom123. Am J Clin Nutr. 2016;103(1):218–30. doi: 10.3945/ajcn.115.119461.
19. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. International Journal of Epidemiology. 2015;44(1):186–98. doi: 10.1093/ije/dyu240.
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394–424. doi: 10.3322/caac.21492
21. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. WJG. 2021;27(27):4298–321. doi: 10.3748/wjg.v27.i27.4298.
22. Lucas AL, Kastrinos F. Screening for Pancreatic Cancer. JAMA. 2019;322(5):407–8. doi: 10.1001/jama.2019.9690
23. Kuroczycki-Saniutycz S, Grzeszczuk A, Zwierz ZW, Kołodziejczyk P, Szczesiul J, Zalewska-Szajda B, et al. Prevention of pancreatic cancer. Contemp Oncol (Pozn). 2017;21(1):30–4. doi: 10.5114/wo.2016.63043.



**Received:** 10/26/2023 **Revised:** 11/12/2023 **Accepted:** 11/26/2023

PREGLEDNI RAD

UDK BROJEVI: 615.036
616-071
DOI: https://www.doi.org/10.5937/zdravzast52-47107

# TUMAČENJE REZULTATA KLINIČKIH RANDOMIZOVANIH STUDIJA

**Božana Nikolić**[1]

[1] Katedra za farmaciju, Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Republika Srbija

[*] Korespondencija: doc. dr Božana Nikolić, Katedra za farmaciju, Medicinski fakultet Univerziteta u Novom Sadu, Hajduk Veljkova 3, 21137 Novi Sad, Republika Srbija; e-mail: bozana.nikolic@mf.uns.ac.rs

**SAŽETAK**

Cilj ovog preglednog rada je da kroz primere objasni kako izabrati, računati i tumačiti mere efekta u kliničkim randomizovanim studijama. Kliničke randomizovane studije (engl. *Randomized Control Trials*, RCTs) pripadaju grupi eksperimentalnih studija i sprovode se nad obolelim osobama. U ovim studijama ispitanici se metodom randomizacije raspoređuju u eksperimentalnu grupu, koja dobija ispitivano sredstvo, i kontrolnu, koja prima placebo ili neko do tada korišćeno sredstvo. Rezultati RCTs mogu se prezentovati kroz relativne i apsolutne mere efekta. Relativne mere efekta su relativni rizik (engl. R*elative Risk*, RR) i relativno smanjenje rizika (engl. *Relative Risk Reduction*, RRR), a apsolutne mere efekta su apsolutno smanjenje rizika (engl. *Absolute Risk Reduction*, ARR) i broj pacijenata koje treba lečiti (engl. *Number Needed to Treat*, NNT). Najjači dokaz između uzroka i posledice dobija se u ovim studijama, ali se ove studije retko izvode zbog svoje cene. Mali broj ispitanika u ovim studijama, može se prevazići korišćenjem meta-analize i multicentričnih studija.

**Ključne reči:** epidemiološke studije, kliničke randomizovane studije, mere efekta

## Uvod

Sve epidemiološke studije mogu biti eksperimentalne (interventne) i opservacione (Grafikon 1). U eksperimentalnim studijama istraživač ispituje efikasnost korišćenja leka ili nekog drugog sredstva, dok u opservacionim studijama istraživač ne interveniše, nego posmatra šta se dešava u populaciji (npr. ispitanici koriste lekove nezavisno od istraživača tj. istraživanja, odnosno kao deo rutinske medicinske nege). Nadalje, eksperimentalne studije se prema načinu razvrstavanja ispitanika u grupe dele na randomizovane i nerandomizovane. Randomizacija je proces kojim se ispitanici metodom slučajnog izbora raspoređuju u eksperimentalnu i kontrolnu grupu, da bi ispitanici u obe posmatrane grupe bili što sličniji po svojim karakteristikama.

Opservacione studije mogu biti deskriptivne i analitičke. Tako, deskriptivne studije (prikaz slučaja, serija slučajeva, ekološka studija) nemaju grupu za poređenje, dok analitičke studije (kohortna studija, studija slučajeva i kontrola, studija preseka) karakteriše poređenje dve grupe (1). Opservacionim studijama se ne ispituje efikasnost medicinske intervencije, kao što je lek ili medicinski uređaj, ali mogu pomoći da se identifikuju novi tretmani ili preventivne mere koji bi se potom testirali u kliničkim ispitivanjima.

Prema Uredbi Evropske unije br. 536/2014, kliničke studije se definišu kao istraživanja na ljudima čija je namena da otkriju ili potvrde kliničke, farmakološke i/ili druge farmakodinamske efekte lekova; i/ili utvrde neželjene reakcije na lekove; i/ili prouče apsorpciju, raspodelu, metabolizam i/ili eliminaciju lekova (1,2). Randomizovane kontrolisane studije (engl. *Randomized Controlled Trials*, RCTs) su zlatni standard za izradu smernica za lečenje, dok su sve druge studije komplementarne i korisne za generisanje hipoteza. Njihovi rezultati se izveštavaju kao mere efekta, koje mogu biti relativne (mere odnosa) i apsolutne (mere razlike) (3,4).

Cilj ovog preglednog rada je da kroz primere objasni kako izabrati, računati i tumačiti mere efekta u RCTs.

*Health Care 52(4), 2023*

REVIEW ARTICLE

UDK NUMBERS: 615.036
616-071
DOI: https://www.doi.org/10.5937/zdravzast52-47107

# INTERPRETING THE RESULTS OF RANDOMIZED CONTROLLED TRIALS

**Božana Nikolić**[1]

[1] Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Republic of Serbia

[*] Correspondence: Assoc. professor Božana Nikolić, MD, Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad Hajduk Veljkova 3, 21137 Novi Sad, Republic of Serbia; e-mail: bozana.nikolic@mf.uns.ac.rs

**SUMMARY**

The aim of this review article is to explain, with the help of examples, how to choose, calculate and interpret effect measures in randomized controlled trials. Randomized controlled trials (RCTs) belong to the group of experimental studies and they are conducted on sick persons. In these studies, participants are assigned to the experimental group, which receives the medicine which is being tested, and to the control group, which receives a placebo or a medicine, which has been previously used. The results of RCTs can be presented through relative or absolute effect measures. Relative effect measures include the relative risk (RR) and the relative risk reduction (RRR), while absolute effect measures include the absolute risk reduction (ARR) and the number of patients who should be treated (Number Needed to Treat – NNT). The strongest evidence of cause and effect is obtained in these studies, but these studies are rarely conducted because of their cost. The small number of participants in these studies can be overcome by using meta-analysis and multicenter studies.

**Keywords:** epidemiological studies, randomized controled trial, effect measures

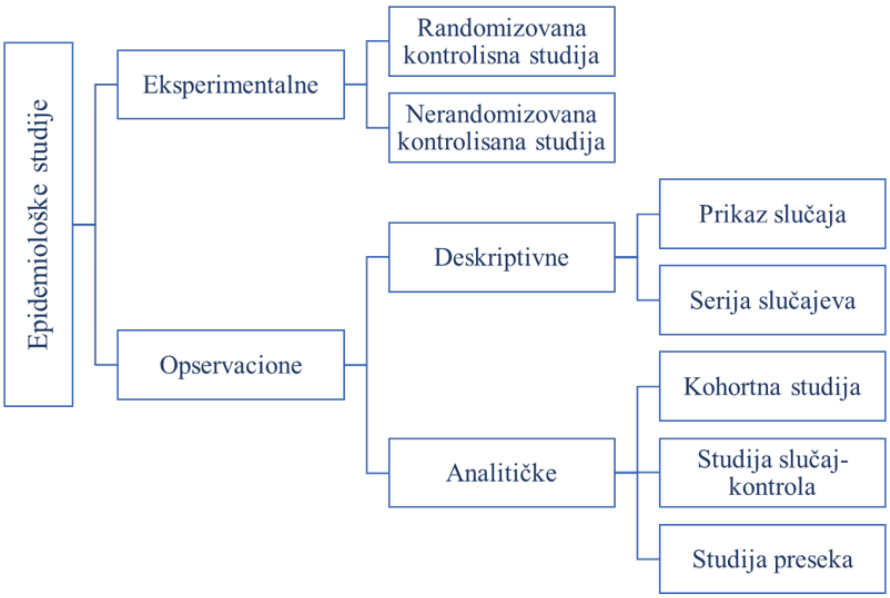
## Introduction

All epidemiological studies can be classified as experimental (interventional) and observational (Figure 1). In experimental studies, the researcher examines the efficacy of using a drug or some other treatment, while in observational studies, the researcher does not intervene, but observes what is happening in that population (e.g. participants use drugs independently of the researcher, that is, as part of routine medical care). Furthermore, experimental studies are classified as randomized and non-randomized according to the ways of assigning the participants to groups. Randomization is the process which refers to a random assignment of participants to the experimental and control group, so that the participants in both observed groups are as similar as possible in terms of their characteristics.

Observational studies can be descriptive and analytical. Thus, descriptive studies (case report, case series, ecological study) do not have a control group, while analytical studies (cohort study, case-control study, cross-sectional study) are characterized by the comparison of two groups (1). Observational studies do not examine the efficacy of a medical intervention, such as a drug or medical device, but they can help identify new treatments or preventive measures that can be tested in clinical trials afterwards.

According to the Regulation of the European Union no. 536/2014, clinical studies are defined as research on humans whose purpose is to discover or verify clinical, pharmacological and/or other pharmacodynamic effects of drugs; and/or identify any adverse reactions; and/or study the absorption, distribution, metabolism and/or excretion of drugs (1,2). Randomized controlled trials (RCTs) are the gold standard for creating guidelines for the treatment, while all other studies are complementary and useful for generating hypotheses. Their results are reported as effect measures, which can be relative (ratio measures) and absolute (difference measures) (3,4).

The aim of this review article is to explain through examples how to choose, calculate and



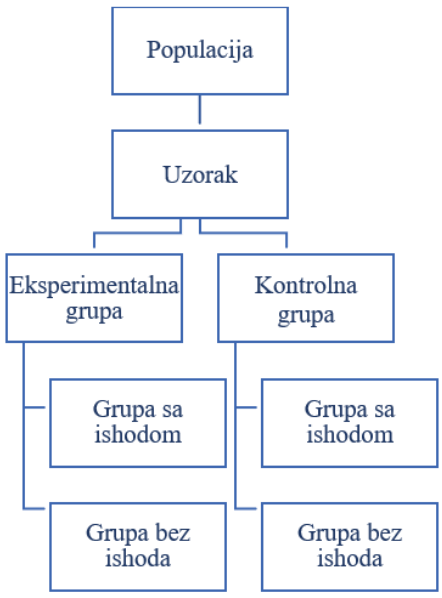

**Grafikon 1.** Podela epidemioloških studija

## Metode

Na osnovu pregleda literature, korišćenjem MEDLINE bibliografske baze podataka, identifikovani su radovi koji se odnose na RCTs u smislu izbora, računanja i tumačenja mera efekata.

## Randomizovani kontrolisani trajali (engl. *Randomized Controlled Trials* – RCTs)

U RCTs (Grafikon 2) ispitanici (obolele osobe) se metodom randomizacije raspoređuju u eksperimentalnu (interventnu) i kontrolnu grupu. Randomizacija može da bude prosta, stratifikovana, blok, itd. Eksperimentalna grupa može da dobije lek ili neko drugo ispitivano sredstvo (npr. novi lek, stari lek ali nova doza, kombinaciju dva ili više lekova i slično), dok kontrolna grupa dobija placebo ili standardno lečenje (lek koji se uobičajeno koristi za ispitivanu indikaciju), pa se prati ishod u obe grupe ispitanika (Grafikon 2). Ishodi, ako se koristi neki lek, mogu da budu: bolest da/ne, relaps bolesti da/ne, ili smrt nastupila/nije nastupila (1,4).




**Grafik 2.** Randomizovana klinička studija

### *Primer RCT u kojima lek smanjuje rizik od neželjenih ishoda*

RCT je sproveden kako bi se ispitali efekti enalaprila na preživljavanje pacijenata sa srčanom insuficijencijom (n=2569) (5). Pacijenti su metodom randomizacije podeljeni u eksperimentalnu i kontrolnu grupu. Eksperimetalna grupa je dobijala enalapril (n=1285), a kontrolna grupa placebo (n=1284). RCT je trajao četiri godine i za to vreme smrt je nastupila kod 452 pacijenta koja su dobijala enalapril i 510 pacijenata koji su dobijali placebo (Tabela 1).

Rezultati RCTs mogu se prezentovati kroz relativne i apsolutne mere efekta. Relativne mere efekta su relativni rizik (engl. *Relative Risk, RR*) i relativno smanjenje rizika (engl. *Relative Risk Reduction*, RRR), a apsolutne mere efekta su apsolutno smanjenje rizika (engl. *Absolute Risk Reduction*, ARR) i broj pacijenata koje treba lečiti (engl. *Number Needed to Treat*, NNT) (4,6).

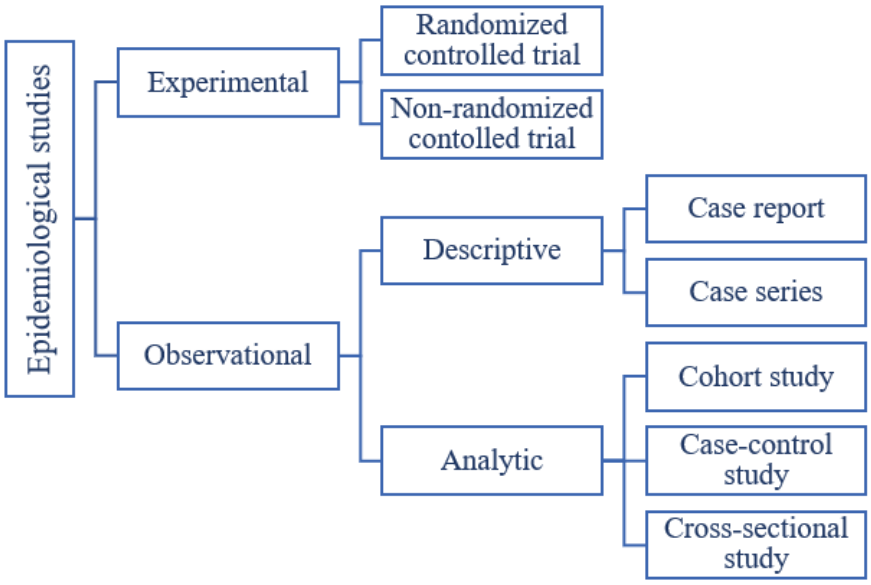



**Figure 1.** Classification of epidemiological studies

interpret effect measures in RCTs.

## Methods

Based on the literature review, using the MEDLINE bibliographic database, studies relating to RTCs in terms of selection, calculation and interpretation of effect measures were identified.

## Randomized controlled trials (RCTs)

In RCTs (Figure 2), participants (patients) are assigned to the experimental (interventional) group and to the control group with the help of the randomization method. Randomization can be simple, stratified, block, etc. The experimental group can receive a drug or some other tested medicinal product (e.g. a new drug, an old drug but a new dose, a combination of two or more drugs, etc.), while the control group receives a placebo or standard treatment (a drug that is commonly used for the examined indication), and then the outcome is observed in both groups of participants (Figure 2). Outcomes, if a drug is used, may be: disease yes/no, disease relapse yes/no, or death occurred/did not occur (1,4).

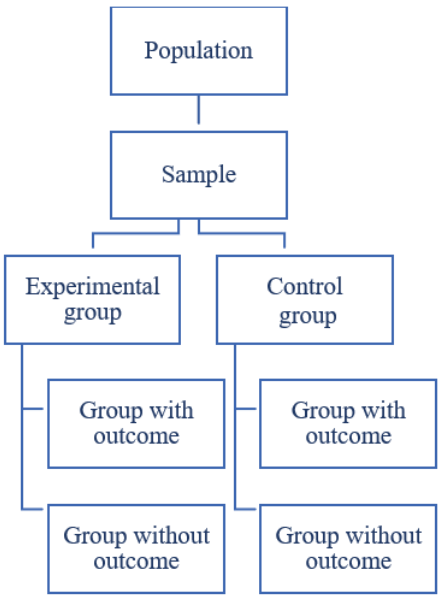



**Figure 2.** Randomized controlled trial

### *An example of RCTs in which a drug reduces the risk of adverse outcomes*

RCT was conducted to examine the effects of enalapril on survival in patients with heart failure (n=2569) (5). The patients were divided into experimental and control groups using the method of randomization. The experimental group received enalapril (n=1285), and the control group received a placebo (n=1284). RCT lasted for four years, and during that period death occurred in 452 patients who received enalapril and 510 patients who received the placebo (Table 1).

The results of RCTs can be presented through relative and absolute effect measures. Relative effect measures are the relative risk (RR) and the relative risk reduction (RRR), while absolute effect measures are the absolute risk reduction (ARR) and the number of patients who need to be treated (NNT) (4,6).

**Tabela 1.** Rezultati četvorogodišnje randomizovane kontrolisane kliničke studije: enalapril (n=1285) naspram placebo (n=1284)

| Grupa | Smrt | | Ukupno |
|---|---|---|---|
| | Da | Ne | |
| **Enalapril** | 452<br>a | 833<br>b | 1285<br>a + b |
| **Placebo** | 510<br>c | 774<br>d | 1284<br>c + d |

$$\text{Rizik od ishoda u eksperimentalnoj grupi}=\frac{a}{a+b}=\frac{452}{1285}=0{,}352$$

$$\text{Rizik od ishoda u kontrolnoj grupi}=\frac{c}{c+d}=\frac{510}{1284}=0{,}397$$

$$RR=\frac{a/(a+b)}{c/(c+d)}=\frac{0{,}352}{0{,}397}=0{,}89$$

$$RRR=\frac{[c/(c+d)-a/(a+b)]}{c/(c+d)}=1-RR=0{,}11$$

$$ARR=c/(c+d)-a/(a+b)=0{,}397-0{,}352=0{,}045$$

$$NNT=\frac{1}{ARR}=22{,}22$$

RR, relativni rizik; RRR, relativno smanjenje rizika; ARR, apsolutno smanjenje rizika; NNT, broj pacijenata koje treba lečiti.

Relativni rizik (RR) je odnos rizika od ishoda u eksperimentalnoj grupi i rizika od ishoda u kontrolnoj grupi (Tabela 1). U ovom primeru, rizik od smrti u eksperimentalnoj grupi je 0,352 ili 35,2%, a rizik od smrti u kontrolnoj grupi je 0,397 ili 39,7%, te je RR=0,89 ili 89% (Tabela 1), što znači da enalapril u odnosu na placebo smanjuje rizik od smrti kod pacijenata sa srčanom insuficijencijom za 11%.

Generalno, kada je RR < 1 to ukazuje da lečenje smanjuje rizik od umiranja (ishoda), a RR > 1 znači da lečenje povećava rizik od umiranja (ishoda). Sa kliničkog aspekta, vrednosti RR manje od 0,5 i veće od 2 se smatraju značajnim. Takođe, vrednosti RR koje su bliže jedinici se mogu smatrati značajnim ukoliko su ishodi ozbiljni ili od izuzetnog javnozdravstvenog interesa (7). Konačno, kada je RR=1, to znači da nema razlike u riziku od ishoda između eksperimentalne i kontrolne grupe.

Relativno smanjenje rizika (RRR) je relativno smanjenje rizika od neželjenog ishoda u eksperimentalnoj grupi u odnosu na rizik od neželjenog ishoda u kontrolnoj grupi (Tabela 1). Što je njegova vrednost veća, to je lečenje efikasnije. RRR u ovom primeru je 0,11 tj. 11% (Tabela 1); to znači da enalapril u odnosu na placebo smanjuje rizik od fatalnog ishoda za 0,11 puta odnosno 11%.

Apsolutno smanjenje rizika (ARR) je apsolutna razlika između rizika od neželjenog ishoda u kontrolnoj i eksperimentalnoj grupi (Tabela 1). Ukoliko je njegova vrednost nula, to ukazuje da između eksperimentalne i kontrolne grupe nema razlike u riziku od ishoda (tj. lečenje ne menja rizik od ishoda - umiranja). ARR u ovom primeru je 0,045 tj. 4,5% (Tabela 1). To znači da je razlika u riziku od smrtnog ishoda između grupe koja je dobijala placebo i grupe koja je dobijala enalapril 4,5%.

Za razliku od RRR, ARR uzima u obzir činjenicu da se neželjeni ishod (npr. smrt) javlja i u populaciji koja nije izložena leku odnosno placebu (3,6).

NNT je broj pacijenata koje treba lečiti u eksperimentalnoj grupi nekim lekom da bi se dobio jedan neželjeni ishod manje u odnosu na kontrolnu grupu koja obično dobija do tada poznato ispitivano sredstvo/placebo. Matematički, predstavlja recipročnu vrednost ARR. NNT u ovom primeru je 22,22 (Tabela 2), što znači da 23 pacijenta treba lečiti enalaprilom da bi se dobio jedan smrtni ishod manje u odnosu na lečenje placebom. Prema konvenciji, NNT se uvek tumači kao ceo broj (leči se ceo, a ne deo pacijenta) uz zaokruživanje na veću vrednost (izbegava se precenjivanje efikasnosti lečenja).

Tumačenje NNT je arbitrarno, i zavisi od kliničkog konteksta. Na primer, za profilkatičke postupke prihvatljiv NNT je između 10 i 100; za hronična stanja, lečenje je vrlo efikasno ako je NNT do 10; dok za akutna stanja (npr. infekcije koje se leče antibioticima), NNT ne bi smeo biti veći od 2. Dakle, poželjno je da NNT ima što manju vrednost (8).

NNT je specifičan za bolest, težinu bolesti, ishod bolesti i trajanje lečenja, pa te varijable treba navesti kako bi se NNT mogao pravilno tumačiti (2). Na primer, pacijenti sa hipertenzijom koriste antihipertenzive kako bi prevenirali kardiovaskularne događaje (infarkt miokarda, moždani udar); i NNT je 141 kada oni sa blagom do umerenom dijastolnom hipertenzijom (90-109 mmHg) koriste antihipertenzive pet godina, a NNT je tri kada oni sa teškom dijastolnom hipertenzijom (110-129 mmHg) koriste antihipertenzive pet godina (8). Dakle, mnogo je više pacijenata sa teškom dijastolnom hipertenzijom koji imaju korist od lečenja. Ili, na primer, duloksetin (60 mg/dan) se koristi u lečenju velikih depresivnih poremećaja i za remisiju je potrebno nekoliko nedelja. Zbog toga je

The relative risk (RR) is the ratio of the risks of an outcome in an experimental group to the risks of an outcome in the control group (Table 1). In this example, the risk of death in the experimental group is 0.352 or 35.2%, while the risk of death in the control group is 0.397 or 39.7%, so RR=0.89 or 89% (Table 1), which means that enalapril compared to placebo reduces the risk of death in patients with heart failure by 11%.

In general, when the RR < 1, it indicates that the treatment reduces the risk of death (outcome), while the RR > 1 means that the treatment increases the risk of death (outcome). From a clinical perspective, the values of RR smaller than 0.5 and greater than 2 are considered to be significant. Also, RR values, which are close to 1, can be considered significant if the outcomes are serious or have the exceptional public health significance (7). Finally, when the RR=1, it means that there is no difference in the risk of an outcome between the experimental and control group.

The RRR is the relative risk reduction in the risk of an adverse outcome in the experimental group compared to the risk of an adverse outcome in the control group (Table 1). The treatment is more efficient when its value is higher. The RRR in this example is 0.11, that is, 11% (Table 1), which means that enalapril reduces the risk of a fatal outcome by 0.11 times or 11% in comparison to placebo.

The ARR is the absolute difference between the risk of an adverse outcome in the control and experimental group (Table 1). If its value is zero, it means that there is no difference in the risk of an outcome between the experimental and control group (the treatment does not change the risk of the outcome – dying). The ARR in this example is 0.045 or 4.5% (Table 1). This means that the difference in the risk of deathly outcome between the group which received placebo and the group which received enalapril is 4.5%.

Unlike the RRR, the ARR takes into consideration the fact that the adverse outcome (e.g. death) occurs in the population that is not exposed to the drug or placebo (3,6).

The NNT is the number of patients who need to be treated in the experimental group with a drug in order to achieve one adverse outcome less compared to the control group that usually receives a previously known tested medicinal product/placebo. Mathematically, it represents a reciprocal value of ARR. The NNT in this example is 22.22 (Table 2), which means that 23 patients need to be treated with enalapril to obtain one deathly outcome less compared to the placebo treatment. According to the Convention, the NNT is always interpreted as a whole number (the whole patient is treated, and not a part of the patient), so the NNT is rounded up to the next higher whole number (overestimation of treatment efficacy is avoided).

The interpretation of the NNT is arbitrary, and it depends on the clinical context. For example, for prophylactic procedures, the acceptable NNT is between 10 and 100; for chronic conditions, the treatment is very efficient is the NNT is up to 10; while for acute conditions (e.g. infections treated with antibiotics), the NNT should not be higher than 2. Therefore, it is desirable that the NNT has the lowest possible value (8).

The NNT is specific for the disease, the severity of the disease, the outcome of the disease and the duration of treatment, and therefore, these variables should be specified so that the NNT could be interpreted correctly (2). For example, patients with hypertension use antihypertensive

**Table 1.** Results of a four-year randomized controlled trial: enalapril (n=1285) vs pacebo (n=1284)

| Group | Death | | Total |
|---|---|---|---|
| | Yes | No | |
| **Enalapril** | 452<br>a | 833<br>b | 1285<br>a + b |
| **Placebo** | 510<br>c | 774<br>d | 1284<br>c + d |

$$\text{Risk of outcome in experimental group} = \frac{a}{a+b} = \frac{452}{1285} = 0.352$$

$$\text{Risk of outcome in control group} = \frac{c}{c+d} = \frac{510}{1284} = 0.397$$

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{0.352}{0.397} = 0.89$$

$$RRR = \frac{[c/(c+d) - a/(a+b)]}{c/(c+d)} = 1 - RR = 0.11$$

$$ARR = c/(c+d) - a/(a+b) = 0.397 - 0.352 = 0.045$$

$$NNT = \frac{1}{ARR} = 22.22$$

RR, relative risk; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat.

NNT u prvoj nedelji lečenja 79, a nakon toga se NNT postepeno smanjuje i u devetoj nedelji lečenja je šest (9).

### *Primer RCTs u kojima lek povećava rizik od neželjenih ishoda*

U hipotetičkom RCT-u su ispitivani efekti antidepresiva venlafaksina na seksualnu funkciju. Pacijenti sa depresijom (n=152) su metodom randomizacije podeljeni u eksperimentalnu i kontrolnu grupu. Eksperimentalna grupa je dobijala venlafaksin (n=80), a kontrolna grupa placebo (n=72). RCT je trajao 12 nedelja i za to vreme seksualna disfunkcija se prvi put javila kod 16 pacijenata koji su dobijali venlafaksin i šest pacijenata koji su dobijali placebo (Tabela 2).

Rezultati RCT-a u kojima lek povećava rizik od neželjenih ishoda se izveštavaju kao relativni rizik (RR), relativno povećanje rizika (engl. *Relative Risk Increase*, RRI), apsolutno povećanje rizika (engl. *Absolute Risk Increase*, ARI) i broj pacijenata koji je potreban za neželjeni ishod (engl. *Number Needed to Harm*, NNH) (1).

**Tabela 2.** Rezultati hipotetičke, dvanaestonedeljne randomizovane kontrolisane studije: venlafaksin (n=80) naspram placebo (n=72)

| Grupa | Seksualna disfunkcija | | Ukupno |
|---|---|---|---|
| | Da | Ne | |
| **Venlafaksin** | 16<br>a | 64<br>b | 80<br>a + b |
| **Placebo** | 6<br>c | 66<br>d | 72<br>c + d |

$$\text{Rizik od ishoda u eksperimentalnoj grupi} = \frac{a}{a+b} = \frac{16}{80} = 0{,}200$$

$$\text{Rizik od ishoda u kontrolnoj grupi} = \frac{c}{c+d} = \frac{6}{72} = 0{,}083$$

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{0{,}200}{0{,}083} = 2{,}41$$

$$RRI = \frac{[a/(a+b) - c/(c+d)]}{c/(c+d)} = RR-1 = 2{,}41-1 = 1{,}41$$

$$ARI = a/(a+b) - c/(c+d) = 0{,}200-0{,}083 = 0{,}117$$

$$NNH = \frac{1}{ARI} = \frac{1}{0{,}117} = 8{,}55$$

RR, relativni rizik; RRI, relativno povećanje rizika; ARI, apsolutno povećanje rizika; NNH, broj pacijenata koji je potreban za neželjeni ishod

Kako je navedeno, RR je odnos rizika od ishoda u eksperimentalnoj grupi i rizika od ishoda u kontrolnoj grupi. U ovom primeru, rizik od seksualne disfunkcije u eksperimentalnoj grupi je 0,200 ili 20,0%, a u kontrolnoj grupi 0,083 ili 8,3%, te je RR=2,41 ili 241% (Tabela 2), što ukazuje da venlafaksin u odnosu na placebo povećava rizik od seksualne disfunkcije kod pacijenata sa depresijom.

Relativno povećanje rizika (RRI) je relativno povećanje rizika od neželjenog ishoda u eksperimentalnoj grupi u odnosu na rizik od neželjenog ishoda u kontrolnoj grupi (Tabela 2). U ovom primeru, RRI = 1,41 tj. 141% (Tabela 2), to znači da venlafaksin u odnosu na placebo povećava rizik od seksualne disfunkcije za 1,41 put odnosno 141%.

Apsolutno povećanje rizika (ARI) je apsolutna razlika između rizika od neželjenog ishoda u eksperimentalnoj i kontrolnoj grupi (Tabela 2). U ovom primeru, ARI = 0,117 tj. 11,7% (Tabela 2); dakle, apsolutna razlika u riziku od seksualne disfunkcije između grupe koja dobija venlafaksin i grupe koja dobija placebo je 11,7%.

Broj pacijenata koji je potreban za neželjeni ishod (NNH) je broj pacijenata koje treba lečiti u eksperimentalnoj grupi da bi se dobio jedan neželjeni ishod više u odnosu na kontrolno lečenje. Matematički, predstavlja recipročnu vrednost ARI -ja (Tabela 2). NNH u ovom primeru je 8,55 (Tabela 2), što znači da osam pacijenata treba lečiti venlafaksinom da bi se dobila jedna seksualna disfunkcija više u odnosu na grupu koja je dobijala placebo. Prema konvenciji, NNH se uvek tumači kao ceo broj (leči se ceo, a ne deo pacijenta) uz zaokruživanje na manju vrednost (izbegava se precenjivanje bezbednosti terapije).

Kao i NNT, tumačenje NNH je arbitrarno i zavisi od kliničkog konteksta. Za neželjene ishode koji ozbiljno kompromituju zdravstveni status pacijenta, prihvatljiv NNH bi trebalo da bude 1000; za neželjene ishode koji nisu ozbiljni, ali zahtevaju prekid lečenja, prihvatljiv NNH bi mogao da bude u opsegu od 10 do 100; konačno, za blage, prolazne neželjene ishode prihvatljiv je NNH ispod 10 (1,8). Dakle, za razliku od NNT, NNH je poželjno da ima što veću vrednost.

### *Relativne naspram apsolutne mere efekta – implikacije za kliničku praksu*

Uprkos tome što je važno da se rezultati RCTs izveštavaju kao relativne i aposolutne mere efekta, oni se uglavnom izveštavaju kao relativne mere

drugs in order to prevent cardiovascular events (myocardial infarction, stroke); and the NNT is 141 when patients with mild to moderate diastolic hypertension (90-109 mmHg) use antihypertensive drugs for five years, while the NNT is three when those with severe diastolic hypertension (110-129 mmHg) use antihypertensive drugs for five years (8). Thus, there are many more patients with severe diastolic hypertension who benefit from the treatment. Or, for example, duloxetine (60 mg/day) is used for the treatment of depressive disorders and remission takes several weeks. Therefore, the NNT is 79 in the first week of treatment, after which the NNT gradually decreases and it amounts to six in the ninth week of treatment (9).

### *An example of RCTs in which a drug increases the risk of adverse outcomes*

In a hypothetical RCT, the effects of the antidepressant venlafaxine on sexual function were examined. The patients with depression (n=152) were randomly divided into the experimental and control group. The experimental group received venlafaxine (n=80), and the control group received placebo (n=72). The RCT lasted for 12 weeks, and during that period sexual dysfunction first occurred in 16 patients who received venlafaxine and in six patients who received placebo (Table 2).

**Table 2.** Results of a hypothetical twelve-week randomized controlled trial: venlafaxine (n=80) vs placebo (n=72)

| Group | Sexual dysfunction | | Ukupno |
|---|---|---|---|
| | Da | Ne | |
| **Venlafaksin** | 16<br>a | 64<br>b | 80<br>a + b |
| **Placebo** | 6<br>c | 66<br>d | 72<br>c + d |

$$\text{Risk of outcome in experimental group} = \frac{a}{a+b} = \frac{452}{1285} = 0.352$$

$$\text{Risk of outcome in control group} = \frac{c}{c+d} = \frac{510}{1284} = 0.397$$

$$RR = \frac{a/(a+b)}{c/(c+d)} = \frac{0.352}{0.397} = 0.89$$

$$RRR = \frac{[c/(c+d) - a/(a+b)]}{c/(c+d)} = 1 - RR = 0.11$$

$$ARR = c/(c+d) - a/(a+b) = 0.397 - 0.352 = 0.045$$

$$NNT = \frac{1}{ARR} = 22.22$$

RR, relative risk; RRI, relative risk increase; ARI, absolute risk increase; NNH, number needed to harm.

The results of RCTs in which a drug increases the risk of adverse outcomes are reported as the relative risk (RR), the relative risk increase (RRI), the absolute risk increase (ARI) and the number needed to harm (NNH) (1).

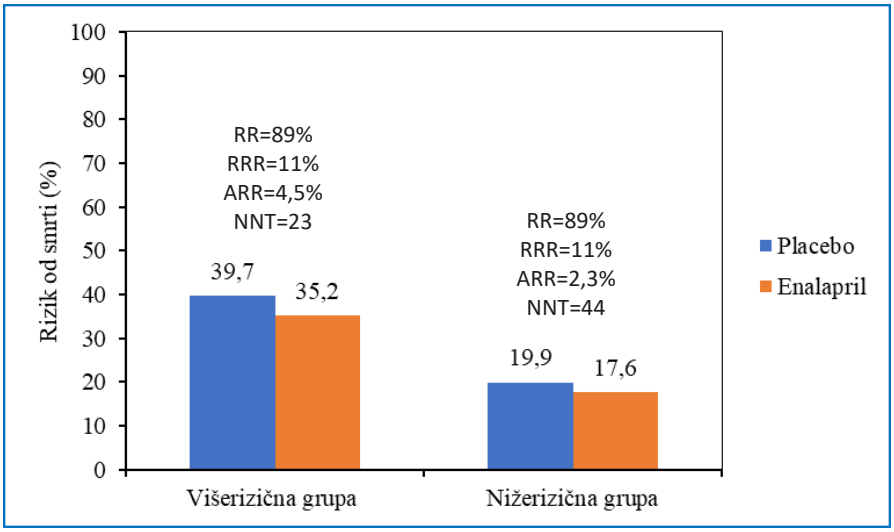
As it has been stated, the RR is the ratio of risk of an outcome in the experimental group to the risk of an outcome in the control group. In this example, the risk of sexual dysfunction in the experimental group is 0.200 or 20%, and in the control group it is 0.083 or 8.3%, so the RR=2.41 or 241% (Table 2), which indicates that venlafaxine in comparison to placebo increases the risk of sexual dysfunction in patients with depression.

The RRI is the relative increase in the risk of an adverse outcome in the experimental group compared to the risk of an adverse outcome in the control group (Table 2). In this example, the RRI=1.41, that is, 141% (Table 2), which means that venlafaxine compared to placebo increases the risk of sexual dysfunction by 1.41 times, or 141%.

The ARI is the absolute difference between the risk of an adverse outcome in the experimental group and control group (Table 2). In this example, the ARI =0.117, that is, 11.7% (Table 2); therefore, the absolute difference regarding the risk of sexual dysfunction between the group which receives venlafaxine and group which receives placebo is 11.7%.

The NNH is the number of patients who need to be treated in the experimental group in order to obtain one more adverse outcome compared to the control treatment. Mathematically, it represents the reciprocal value of ARI (Fiigure 3). The NNH in this example is 8.55 (Figure 3), which means that eight patients need to be treated with venlafaxine to get one more sexual dysfunction compared to the group which receives placebo. According to the convention, the NNH is interpreted as the whole number (the whole patient is treated, not a part of the patient) while it is rounded down to the smaller value (to avoid overestimating the safety of the therapy).

Like the NNT, the interpretation of NNH is arbitrary and depends on the clinical context. For adverse outcomes that seriously compromise the patient's health status, the acceptable NNH should be 1000; for adverse outcomes that are not




**Grafik 3.** Dve grupe pacijenata sa različitim rizikom od ishoda i posledično različitim vrednostima ARR i NNT.

RR, relativni rizik; RRR, relativno smanjenje rizika; ARR, apsolutno smanjenje rizika; NNT, broj pacijenata koje treba lečiti.

efekta (10,11). To za posledicu može imati precenjivanje efekata lečenja (3,6). Ilustracije radi, kada bi rizik od smrti u RCT koji se odnosio na primenu enalaprila (gore navedeni primer) bio manji za pola u obe grupe (226/1285=0,176 tj. 17,6% u grupi koja dobija enalapril i 255/1284=0,199 tj. 19,9% u grupi koja dobija placebo), RR (0,176/0,199=0,89 tj. 89%) i RRR (1–0,89=0,11 tj. 11%) bi ostali nepromenjeni, dok bi se ARR i NNT promenili i iznosili bi 2,3% i 44, redom (Grafikon 3). Promenjene vrednosti ARR i NNT bi mogle promeniti relevantnost i klinički značaj rezultata, te uticati na odluku kliničara da preporuči lečenje.

Navedeni primer ukazuje na činjenicu da se relativne mere efekta ne menjaju, dok se apsolutne mere efekta menjaju kada pacijenti imaju različite bazične rizike od ishoda. Zbog toga, apsolutne mere efekta treba koristiti kada se donose odluke o lečenju (12).

### *Prednosti i nedostaci RCTs*

Kako je navedeno, RCTs daju najjače dokaze između uzroka i posledica pa su zlatni standard za izradu smernica za lečenje. To je njihova glavna prednost, a bazira se na postupcima randomizacije i slepe tehnike (13-14). Ta dva postupka značajno smanjuju pristrasnost istraživača koja bi mogla negativno uticati na dokaze odnosno rezultate istraživanja. Jedna od prednosti je i moguća multicentričnost RCTs što znači da mogu da se sprovode u više kliničkih centara u svetu istovremeno i tako se značajno povećava broj ispitanika te pouzdanost rezultata (13). Sa druge strane, RCTs imaju i određene nedostatake, kao npr. razlika između eksperimentalnih i uslova u kliničkoj praksi, cena, etički problemi (ponekad), te kratko trajanje (13-15). Eksperimentalni uslovi se razlikuju od onih u kliničkoj praksi zbog rigoroznih kriterijuma za uključenje i isključenje što može ograničiti ekstrapolaciju rezultata na širu populaciju. Cena je čest razlog zbog kojeg se određeni RCTs nikada ne sprovedu. Prema podacima koji su dostupni u literaturi, cena jednog RCT je između 0,2 i 611,5 miliona američkih dolara (16). Osim toga, farmaceutske kompanije često finansiraju RCTs što za posledicu može imati pristrasnost istraživača te precenjivanje efekata lečenja (13). Nadalje, dobro je poznato da etički problemi ne opravdavaju upotrebu lekova u trudnoći u svrhu unapređenja medicinskih znanja. Zbog toga za mnoge lekove nedostaju dokazi na osnovu kojih bi kliničari mogli da donesu odluke o njihovoj bezbednoj upotrebi u trudnoći. Konačno, RCTs uglavnom traju između nekoliko nedelja i nekoliko meseci pa odložene neželjene reakcije na lek mogu ostati neotkrivene (14).

## Zaključak

Najjači dokaz između uzroka i posledice dobija se u RVTs, ali se ove studije retko izvode zbog svoje cene. Mali broj ispitanika u ovim studijama, može se prevazići korišćenjem meta-analize i multicentričnih studija. Relativne mere efekta koje se mogu koristiti u RCTs su relativni rizik i relativno smanjenje rizika, a od apsolutnih mera efekta apsolutno smanjenje rizika i broj pacijenata koje treba lečiti.

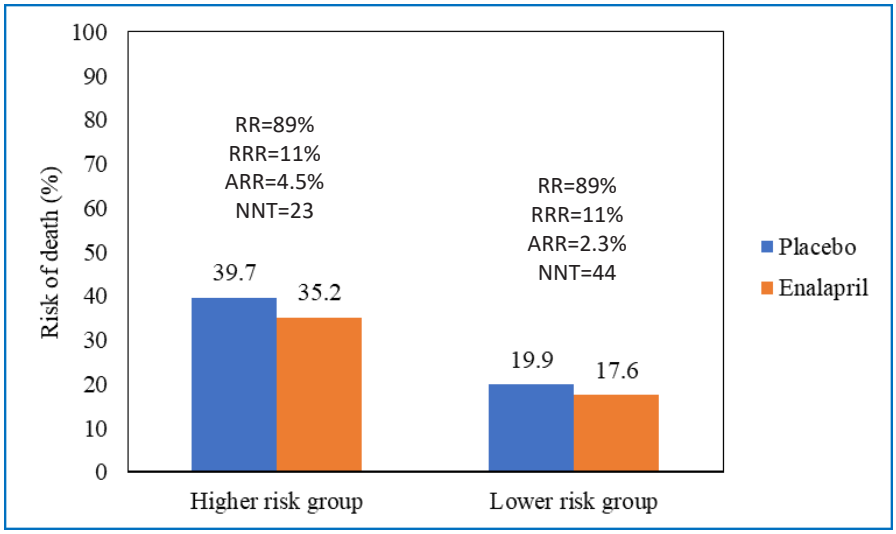



**Figure 3.** Two groups of patients at different risk of outcome and consequently different values of ARR and NNT.

RR, relative risk; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat.

serious but require the termination of treatment, the acceptable NNH could be in the range between 10 and 100; finally, for mild, transient adverse outcomes, the acceptable NNH would be below 10 (1,8). Therefore, in contrast to the NNT, the desirable value of NNH should be as high as possible.

### *Relative versus absolute effect measures – implications for clinical practice*

Although it is important that the results of RCTs are reported as relative and absolute effect measures, they are mostly reported as relative effect measures (10,11). This may result in an overestimation of treatment effects (3,6). For example, if the risk of death in the RCT related to the use of enalapril (the above mentioned example) was reduced by half in both groups (226/1285=0.176, that is 17.6% in the group which received enalapril and 255/1284=0.199, that is, 19.9% in the group which received placebo), the RR (0.176/0.199=0.89 or 89%) and RRR (1-0.89=0.11 or 11%) would remain unchanged and ARR and NNT would change and amount to 2.3% and 44%, respectively (Figure 3). The changed values of ARR and NNT would change the relevance and clinical significance of results, and therefore, influence the clinician's decision to recommend the treatment.

The above mentioned example points to the fact that relative effect measures do not change, while absolute effect measures change when patients have different main risks of an outcome. Therefore, absolute effect measures should be used when decisions about treatment are made (12).

### *The advantages and disadvantages of RCTs*

As it has been stated, RCTs provide the strongest evidence between the cause and effect, and therefore, they are the gold standard for developing treatment guidelines. This is their main advantage, and it is based on the processes of randomization and blinding (13-14). These two procedures significantly reduce the researcher's bias, which could negatively affect the evidence or research results. One of the advantages is the possible multicenter nature of RCTs, which means that they can be simultaneously conducted in several clinical centers in the world, and thus the number of participants significantly increases and consequently the reliability of results, as well (13). On the other hand, RCTs have certain disadvantages, such as the difference between experimental conditions and conditions in clinical practice, cost, ethical problems (sometimes), and short duration (13-15). Experimental conditions are different from those in clinical practice due to rigorous inclusion and exclusion criteria that may limit the extrapolation of results to the wider population. Cost is a common reason why certain RCTs are never conducted. According to the data available in the literature, the cost of one RCT is between 0.2 and 611.5 million US dollars (16). In addition, pharmaceutical companies often finance RCTs, which can, consequently, cause researcher's bias and overestimation of treatment effects (13). Furthermore, it is well-known that ethical problems do not justify the use of drugs in pregnancy for the purpose of improving the medical knowledge.

## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

## Reference


1. Gamulin S. Klinička istraživanja – klinička epidemiologija. Zagreb: Medicinska naklada, 2015. 144 p.
2. European Commission. Clinical trials – Regulation (EU) No 536/2014 [Internet]. [cited August 2023]. Avilable from https://www.health.ec.europa.eu
3. Etminan M, Wright JM, Carleton BC. Evidence-based pharmacotherapy: review of basic concepts and applications in clinical practice. Ann Pharmacother 1998;32(11):1193-200. doi: 10.1345/aph.17333.
4. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook
5. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced ejection fraction and congestive heart failure. N Engl J Med 1991;325(5):293-302. doi: 10.1056/NEJM199108013250501.
6. Darzi AJ, Busse JW, Phillips M, Wykoff CC, Guymer RH, Thabane L, et al. Interpreting results from randomised controlled trials: What measures to focus on in clinical practice. Eye (Lond) 2023; doi: 10.1038/s41433-023-02454-7. Online ahead of print.
7. Andrade C. Understanding realtive risk, odds ratio, and related terms: as simple as it can get. J Clin Psychiatry 2015; 76(7):e857-61. doi: 10.4088/JCP.15f10150.
8. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013;67(5): 407-11. doi: 10.4088/JCP.15f10150.
9. Cookson J, Gilaberte I, Desaiah D, Kajdasz DK. Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat. Int Clin Psychopharmacol 2006;21(5):267-73. doi: 10.1097/00004850-200609000-00004.
10. Agarwal A, Johnston BC, Vernooij RWM, Carrasco-Labra A, Brignardello-Petersen R, Neumann I, et al. Authors seldom report the most patient-important outcomes and absolute effect measures in systematic review abstracts. J Clin Epidemiol 2017;81:3-12. doi: 10.1016/j.jclinepi.2016.08.004.
11. Andersen LW. Absolute vs. Relative effects-implications for subgroup analyses. Trials 2021; 22(1):50 . doi: 10.1186/s13063-020-05005-7.
12. Sormani MP, Bruzzi P. Estimating a treatment effect: chosing between relative and absolute measures. Mult Scler 2017;23(2):197-200.
13. Štimac D, Lackovic A, Poropat G. Važnost provođenja randomiziranih kliničkih istraživanja. Medicina Fluminensis 2017; 53(4):448-53. doi: 10.21860/medflum2017_187364.
14. Saturni S, Bellini F, Braido F, Paggiaro P, Sanduzzi A, Scichilone N, et al. Randomized controlled trials and real-life studies. Approaches and methodologies: a clinical point of view. Pulm Pharmacol Ther 2014;27(2):129-38. doi: 10.1016/j.pupt.2014.01.005.
15. Hariton E, Locascio J. Randomised controlled trials – the gold standard for effectiveness research. BJOG 2018;125(13):1716. doi: 10.1111/1471-0528.15199.
16. Speich B, von Neiderhäusern B, Schur N, Hemkens LG, Fürst T, Bhatnagar N, et al. Systematic review on costs and resource use of randomized clinical trials shows a lack of transparent and comprehensive data. J Clin Epidemiol 2018:96:1-11. doi: 10.1016/j.jclinepi.2017.12.018.




**Primljen:** 14.10.2023. **Revizija:** 26.11.2023. **Prihvaćen:** 26.11.2023.

Therefore, for many drugs, there is a lack of evidence, based on which clinicians could make decisions about their safe use in pregnancy. Finally, RCTs commonly last between several weeks and several months, so delayed adverse drug reactions may remain undiscovered (14).

## Conclusion

The strongest evidence of cause and effect is obtained in RCTs, but these studies are rarely conducted because of their cost. The small number of participants may be overcome by using meta-analysis and multicenter studies. Relative effect measures that can be used in RCTs are the relative risk and relative risk reduction, while absolute effect measures are the absolute risk reduction and the number of patients to be treated.

## Competing interests

The author declared no competing interests.

## References


1. Gamulin S. Klinička istraživanja – klinička epidemiologija. Zagreb: Medicinska naklada, 2015. 144 p.
2. European Commission. Clinical trials – Regulation (EU) No 536/2014 [Internet]. [cited August 2023]. Avilable from https://www.health.ec.europa.eu
3. Etminan M, Wright JM, Carleton BC. Evidence-based pharmacotherapy: review of basic concepts and applications in clinical practice. Ann Pharmacother 1998;32(11):1193-200. doi: 10.1345/aph.17333.
4. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook
5. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced ejection fraction and congestive heart failure. N Engl J Med 1991;325(5):293-302. doi: 10.1056/NEJM199108013250501.
6. Darzi AJ, Busse JW, Phillips M, Wykoff CC, Guymer RH, Thabane L, et al. Interpreting results from randomised controlled trials: What measures to focus on in clinical practice. Eye (Lond) 2023; doi: 10.1038/s41433-023-02454-7. Online ahead of print.
7. Andrade C. Understanding realtive risk, odds ratio, and related terms: as simple as it can get. J Clin Psychiatry 2015; 76(7):e857-61. doi: 10.4088/JCP.15f10150.
8. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013;67(5): 407-11. doi: 10.4088/JCP.15f10150.
9. Cookson J, Gilaberte I, Desaiah D, Kajdasz DK. Treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat. Int Clin Psychopharmacol 2006;21(5):267-73. doi: 10.1097/00004850-200609000-00004.
10. Agarwal A, Johnston BC, Vernooij RWM, Carrasco-Labra A, Brignardello-Petersen R, Neumann I, et al. Authors seldom report the most patient-important outcomes and absolute effect measures in systematic review abstracts. J Clin Epidemiol 2017;81:3-12. doi: 10.1016/j.jclinepi.2016.08.004.
11. Andersen LW. Absolute vs. Relative effects-implications for subgroup analyses. Trials 2021; 22(1):50 . doi: 10.1186/s13063-020-05005-7.
12. Sormani MP, Bruzzi P. Estimating a treatment effect: chosing between relative and absolute measures. Mult Scler 2017;23(2):197-200.
13. Štimac D, Lackovic A, Poropat G. Važnost provođenja randomiziranih kliničkih istraživanja. Medicina Fluminensis 2017; 53(4):448-53. doi: 10.21860/medflum2017_187364.
14. Saturni S, Bellini F, Braido F, Paggiaro P, Sanduzzi A, Scichilone N, et al. Randomized controlled trials and real-life studies. Approaches and methodologies: a clinical point of view. Pulm Pharmacol Ther 2014;27(2):129-38. doi: 10.1016/j.pupt.2014.01.005.
15. Hariton E, Locascio J. Randomised controlled trials – the gold standard for effectiveness research. BJOG 2018;125(13):1716. doi: 10.1111/1471-0528.15199.
16. Speich B, von Neiderhäusern B, Schur N, Hemkens LG, Fürst T, Bhatnagar N, et al. Systematic review on costs and resource use of randomized clinical trials shows a lack of transparent and comprehensive data. J Clin Epidemiol 2018:96:1-11. doi: 10.1016/j.jclinepi.2017.12.018.




**Received:** 10/14/2023 **Revised:** 11/26/2023 **Accepted:** 11/26/2023

ORIGINALNI RAD

UDK BROJ: 616.98:578.834-036.22(497.113)"2021"
DOI: https://www.doi.org/10.5937/zdravzast52-47411

# EPIDEMIOLOŠKE KARAKTERISTIKE KOVID-19 OBOLJENJA U JUŽNOBANATSKOM OKRUGU U 2021. GODINI

**Olivera Stanišić**[1]

[1] Zavod za javno zdravlje Pančevo, Pančevo, Republika Srbija

[*] Korespondencija: dr Olivera Stanišić, Zavod za javno zdravlje Pančevo, Ulica Pasterova 2, 26101 Pančevo, Republika Srbija; e-mail: olivera.r.stanisic@gmail.com

**SAŽETAK**

**Uvod/Cilj:** Novi korona virus ili SARS-CoV-2, se u kratkom periodu nakon svoje pojave, u Vuhanu u Kini, krajem 2019. godine, brzo proširio na ceo svet zbog čega je 11. marta 2020. godine Svetska zdravstvena organizacija proglasila pandemiju kovida 19. Do sada je prijavljeno preko 750 miliona potvrđenih slučajeva kovida 19 i 6,9 miliona umrlih. Cilj ovog istraživanja je da se analiziraju demografske i kliničke karakteristike osoba sa kovid-19 oboljenjem u Južnobanatskom okrugu u 2021. godini.
**Metode:** U radu je primenjena deskriptivna studija koja je obuhvatila 34.912 ispitanika, oba pola i svih uzrasta. U istraživanje su uključeni svi pacijenti kod kojih je u 2021. godini, u Južnobanatskom okrugu, laboratorijski potvrđena SARS-CoV-2 infekcija brzim antigenskim ili RT-PCR testom, bez podatataka da li se infekcija javila prvi put ili ne. Za potrebe ovog israživanja korišćeni su podaci o demografskim i kliničkim karakteristikama obolelih od kovid-19 bolesti. Kao pokazatelj obolevanja koririšćena je incidencija. Kao imenilac stope incidencije korišćen je broj stanovnika za Južnobanatski okrug i osam pripadajućih opština (Alibunar, Bela Crkva, Vršac, Kovačica, Kovin, Opovo, Pančevo i Plandište), prema popisu iz 2011. godine. Svi podaci su obrađeni u I*BM SPSS Statistics 22* (*SPSS Inc., Chicago, IL, USA*) softverskom paketu.
**Rezultati:** U 2021. godini, u Južnobanatskom okrugu je prijavljeno 34.912 obolelih pacijenata sa potvrđenom SARS-CoV-2 infekcijom. Stopa incidencije kovid-19 bolesti je bila 11.885,7/100.000 stanovnika. Najviša stopa incidencije zabeležena je u opštini Kovačica (15.618,7/100.000), kao i u uzrastu 40-49 godina (16.040,9/100.000). U svim uzrasnim grupama stope incidencije za kovid-19 su bile veće za žene nego muškarce, osim u uzrastima 0-14 i 60 i više godina. U oktobru 2021. godine registrovana je najviša stopa incidencije kovid-19 bolesti (2759,3/100.000). Tešku kliničku sliku je imalo 8% obolelih, a 22,8% bar jedan komorbiditet, od kojih je hipertenzija (62,1%) bila najčešća. Najčešće zabeleženi simptom bolesti bila je febrilnost (73,6%). Kompletna vakcinacija sprovedena je kod 17,9% obolelih, a najčešće primenjena vakcina je bila *Sinopharm* (69,9%).
**Zaključak:** Neophodno je stalno raditi na edukaciji stanovništva o važnosti imunizacije, a pogotovo osoba koje imaju veći rizik od razvoja teže forme kovid-19 bolesti.

**Ključne reči:** SARS-CoV-2 infekcija, kovid-19 bolest, težina bolesti, pol, uzrast, komorbiditeti, vakcinalni status

## Uvod

Novi korona virus ili SARS-CoV-2 se u kratkom periodu nakon svoje pojave, u Vuhanu u Kini krajem 2019. godine, brzo proširio na ceo svet zbog čega je 11. marta 2020. godine Svetska zdravstvena organizacija (SZO) proglasila pandemiju kovida 19.

Prema podacima SZO u svetu je prijavljeno preko 750 miliona potvrđenih slučajeva kovid-19 bolesti i 6,9 miliona umrlih (1). Činjenica je da prijavljeni broj obolelih potcenjuje ukupni teret kovid-19 bolesti, obzirom da se veliki broj akutnih infekcija ne dijagnostikuje i ne prijavljuje. Tome u prilog govore istraživanja o seroprevalenciji u Sjedinjenim Američkim Državama (SAD) i Evropi koja ukazuju da stopa incidencije premašuje incidenciju prijavljenih slučajeva za približno 10 ili više puta (2-4).

Studija koja je koristila više izvora podataka, uključujući baze podataka o broju obolelih i umrlih od COVID-19 i seroprevalenciju, procenila je da je do novembra 2021. godine više od 3 milijarde osoba, ili 44 % svetske populacije, bilo zaraženo

ORIGINAL ARTICLE

UDK NUMBER: 616.98:578.834-036.22(497.113)"2021"
DOI: https://www.doi.org/10.5937/zdravzast52-47411

# EPIDEMIOLOGICAL CHARACTERISTICS OF THE COVID-19 DISEASE IN THE SOUTH BANAT DISTRICT IN 2021

**Olivera Stanišić**[1]

[1] Institute for Public Health Pančevo, Pančevo, Republic of Serbia

* Correspondence: Olivera Stanišić, MD, Institute for Public Health Pančevo, Pasterova street 2, 26101 Pančevo, Republic of Serbia; e-mail: olivera.r.stanisic@gmail.com

**SUMMARY**

**Introduction/Aim:** The new coronavirus or SARS- CoV-2, in a short period of time after its appearance in Wuhan, China at the end of 2019, quickly spread throughout the world, which is why on March 11, 2020, the World Health Organization declared a covid pandemic 19. Over 750 million confirmed cases of COVID-19 and 6.9 million deaths have been reported so far. The aim of this research is to analyze the demographic and clinical characteristics of people with COVID-19 in the South Banat District in 2021.
**Methods:** The paper used a descriptive study that included 34,912 subjects of both sexes and all ages. The research included all patients in whom SARS-CoV-2 infection was laboratory-confirmed by a rapid antigen or RT-PCR test in 2021, in the South Banat District, without data on whether the infection occurred for the first time or not. For the purposes of this analysis, data on demographic and clinical characteristics of patients with COVID-19 disease were used. Incidence was used as an indicator of morbidity. As the denominator of the incidence rate, the number of inhabitants was used for the Južno Banat district and eight associated municipalities (Alibunar, Bela Crkva, Vršac, Kovačica, Kovin, Opovo, Pančevo and Plandište), according to the 2011 census. All data were processed in the IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software package.
**Results:** In 2021, 34,912 sick patients with confirmed SARS-CoV-2 infection were reported in the South Banat District. The incidence rate of COVID-19 was 11,885.7/100,000 inhabitants. The highest incidence rate was recorded in the municipality of Kovačica (15,618.7/100,000) and in the 40-49 age group (16,040.9/100,000). In all age groups, the incidence rates for COVID-19 were higher for women than for men, except for ages 0-14 and 60 and over. In October 2021, the highest incidence rate of the COVID-19 disease was registered (2759.3/100,000). 8% of patients had a severe clinical picture, and 22.8% had at least one comorbidity, of which hypertension (62.1%) was the most common. The most frequently recorded symptom of the disease was fever (73.6%). Complete vaccination was carried out in 17.9% of patients, and the most frequently administered vaccine was Sinopharm (69.9%).
**Conclusion:** It is necessary to constantly educate the population about the importance of immunization, especially people with a higher risk of developing a more severe form of the covid-19 disease.

**Keywords:** SARS-CoV-2 infection, COVID-19 disease, disease severity, gender, age, comorbidities, vaccination status

## Introduction

The new corona virus or SARS-CoV-2, shortly after its appearance in Wuhan, China at the end of 2019, quickly spread all around the world, and therefore, the World Health Organization (WHO) declared the pandemic of COVID-19 on the 11th of March, 2020.

According to the WHO data, over 750 million confirmed cases of COVID-19 and 6.9 million deaths have been reported worldwide (1). The fact is that the reported number of patients underestimates the total burden of COVID-19, considering that a large number of acute infections are not diagnosed and reported. This is supported by research on seroprevalence in the United States of America (USA) and Europe, which indicates that the incidence rate exceeds the incidence of reported cases by approximately 10 or more times (2-4).

SARS-CoV-2 najmanje jednom (5). Studija sprovedena u periodu od marta do juna 2022. godine među zdravstvenim radnicima Autonomne pokrajine Vojvodine pokazala je da je 92,96% zdravstvenih radnika i saradnika zaposlenih u zdravstvu bilo SARS-CoV-2 IgG pozitivno pre pojave omikron BA.4/BA.5 podvarijanti (6).

Kada govorimo o broju umrlih od kovida 19, prema Međunarodnim smernicama za potvrđivanje i klasifikaciju (šifriranje), smrt usled kovid-19 oboljenja definisana je, u svrhu nadzora, kao smrt koja potiče od bolesti koja ima klinički odgovarajuće karakteristike, a u verovatnom ili potvrđenom slučaju obolevanja od kovid-19, osim u slučaju kada postoji jasan alternativni uzrok smrti koji ne može biti povezan sa kovid-19 oboljenjem (npr. trauma) (7).

Na osnovu svih dostupnih informacija, SZO je zaključila da je broj prijavljenih umrlih od kovid-19 bolesti potcenjen i da je realnije oslanjati se na višak smrtnosti koji se definiše kao umiranje iznad očekivanja zasnovanog na prepandemijskim stopama mortaliteta u ispitivanoj populaciji. Iako su prijavljeni smrtni slučajevi usled kovid-19 između 1. januara 2020. i 31. decembra 2021. iznosili ukupno 5,94 miliona širom sveta, procenjeno je da je 18,2 miliona ljudi umrlo zbog pandemije kovid-19 (mereno viškom mortaliteta) tokom tog perioda (8-10).

Prema preporukma kojih se drži Evropski centar za sprečavanje i suzbijanje bolesti (ECDC), ključna javnozdravstvene mere za ublažavanje negativnih posledica kovid-19 na nivou pojedinca, zajednice i stanovništva, je sprovođenje imunizacije (11). Vakcine protiv kovid-19 su razvijene i razvijaju se koristeći nekoliko različitih platformi. One su zasnovane na celom virusu, partikuli virusa, virusnom vektoru i nukleinskim kiselinama. Vakcine proizvedene na bazi ovih platformi mogu se podeliti u tri generacije. U vakcine prve generacije spadaju inaktivisane i atenuirane virusne vakcine. Drugu generaciju čine proteinske subjedinične i virusu slične partikule, a treću generaciju vakcina čine virusne vektorske i DNK i RNK vakcine (12). Ukupna korist odobrenih vakcina protiv kovid-19 u prevenciji bolesti prevazilazi rizike od neželjenih efekata. Vremenom nakon vakcinacije, zaštita od infekcije opada kako se postepeno smanjuje titar antitela u serumu, ali se može obnoviti davanjem dodatnih doza. Studije pokazuju da prethodna infekcija virusom SARS-CoV-2 smanjuje rizik od ponovne infekcije virusom SARS-CoV-2. Kako bolest kovid-19 nastavlja da se razvija, sve više pojedinaca na globalnom nivou dobija tzv. „hibridni imunitet“ (imunitet koji se dobija kombinacijom vakcinacije i najmanje jedne prethodne infekcije). Ljudi sa hibridnim imunitetom pokazuju najviši nivo i trajanje zaštite od ponovne infekcije, prijema u bolnicu i teške bolesti (13,14). Efikasnost najznačajnijih vakcina protiv kovid-19 bolesti se kreće od 66,5 - 95%, a za tešku formu bolesti 85,4 - 100%.

U Republici Srbiji je kampanja vakcinacije protiv kovid-19 započela 24. decembra 2020. godine i još uvek se sprovodi kao vanredna, besplatna, preporučena po Programu imunizacije. Agencija za lekove Srbije (ALIMS) odobrila je pet vakcina (plus dve kombinovane-bivalentne revakcine) za zaštitu protiv kovid-19 u R. Srbiji (Pfizer-BioNTech BNT162b2 (Comirnati®); Gamaleia Research Institute Gam-COVID-Vac (Sputnjik V®); Sinopharm BBIBP-CorV (Vero Cell®); Oksford ChAdOk1eneca -S/nCoV-19 AZD1222 (Vakzevria®); Moderna mRNA-1273 (Spikevak®)). Dvovalentna formulacija (Pfizer-BioNTech COVID-19 vakcina, bivalentna [Original i Omicron BA.4/BA.5]) je odobrena kao dodatna doza za osobe od 12 godina ili više, a bivalentna formulacija (Moderna COVID-19 vakcina, bivalentna [Original i Omicron BA.4/BA.5]) je odobrena kao dodatna doza za osobe od 18 godina ili više (15).

Cilj ovog istraživanja je da se analiziraju demografske i kliničke karakteristike osoba sa kovid-19 oboljenjem u Južnobanatskom okrugu u 2021. godini.

## Metode

U radu je primenjena deskriptivna studija koja je obuhvatila 34.912 ispitanika, oba pola i svih uzrasta. U istraživanje su uključeni svi pacijenti kod kojih je tokom 2021. godine, u Južnobanatskom okrugu, laboratorijski potvrđena SARS-CoV-2 infekcija brzim antigenskim ili RT-PCR testom, bez podataka da li se infekcija javila prvi put ili ne.

Izvor podataka bili su nepublikovani podaci iz anketnih upitnika koji su popunjavali lekari Kovid ambulanti osam domova zdravlja, dve opšte i tri specijalne bolnice na teritoriji nadležnosti Zavoda za javno zdravlje Pančevo. Sve popunjene ankete su prosleđivane epidemiološkoj službi Zavoda za javno zdravlje Pančevo gde su naknadno obrađivane i dopunjene nedostajućim podacima, pozivanjem pacijenata ili doktora koji je popunja-

It was estimated in the study, which used multiple data sources, including databases on the number of cases and deaths caused by COVID-19 and seroprevalence, that by November 2021, more than 3 billion people, or 44% of the world's population, were infected with SARS-CoV-2 at least once (5). A study, which was conducted from March to June 2022 among healthcare workers in the Autonomous Province of Vojvodina showed that 92.96% of healthcare workers and their associates had been SARS-CoV-2 IgG positive before the appearance of omicron BA.4/BA.5 variants (6).

As far as the number of deaths caused by COVID-19 is concerned, according to the International Guidelines for the Certification and Classification (coding) of deaths related to COVID-19, it is defined, for the purpose of surveillance, as a death caused by a disease that has certain clinical characteristics, in a probable or confirmed case of COVID-19, except in the case when there is a clear, alternative cause of death that cannot be associated with COVID-19 (e.g. trauma) (7).

Based on all available information, the WHO has concluded that the number of reported deaths due to COVID-19 has been underestimated and that it is more realistic to rely on excess mortality, which is defined as the number of deaths above expectations based on pre-pandemic mortality rates in the study population. Although the number of reported deaths from COVID-19 between January 1st, 2020 and December 31st, 2021 amounted to 5.94 million cases worldwide, it was estimated that 18.2 million people worldwide died due to the COVID-19 pandemic (measured by excess mortality) during that period (8-10).

According to the recommendations of the European Center for Disease Prevention and Control (ECDC), the key public health measure used to mitigate the negative consequences of COVID-19 at the individual, community and population level is the implementation of immunization (11). Vaccines against COVID-19 have been developed with the help of several different platforms. They have been based on the whole virus, virus particle, viral vector and nucleic acids. Vaccines produced on the basis of these platforms can be divided into three generations. The first generation vaccines are inactivated and attenuated viral vaccines. The second generation consists of protein subunits and virus-like particles and the third generation of vaccines consists of viral vector and DNA and RNA vaccines (12). The overall benefit of approved vaccines against COVID-19 in the prevention of disease exceeds the risks related to side effects. Over time, after vaccination, the protection against this infection decreases as the serum antibody titer gradually declines, but it can be restored by administration of additional doses. Studies have shown that the previous infection with the SARS-CoV-2 virus reduces the risk of re-infection with this virus. As the disease COVID-19 continues to develop, more and more individuals globally are getting the so-called "hybrid immunity" (immunity obtained through the combination of vaccination and at least one previous infection). People with hybrid immunity have shown the highest level and duration of protection against re-infection, hospital admission and severe disease (13,14). The effectiveness of the most important vaccines against COVID-19 disease ranges from 66.5-95%, and for severe forms of disease 85.4-100%.

In the Republic of Serbia, the vaccination campaign against COVID-19 began on the 24th of December, 2020 and it is still being carried out as free vaccination recommended for emergency situations within the Immunization Program. The Medicines and Medical Devices Agency of Serbia (ALIMS) has approved five vaccines (plus two combined-bivalent revaccinations) for the protection against COVID-19 in the Republic of Serbia (Pfizer-BioNTech BNT162b2 (Comirnati®); Gamaleia Research Institute Gam-COVID-Vac (Sputnik V®); Sinopharm BBIBP-CorV (Vero Cell®); Oxford ChAdOk1eneca -S/nCoV-19 AZD1222 (Vakzevria®); Moderna mRNA-1273 (Spikevak®)). The bivalent formulation (Pfizer-BioNTech COVID-19 vaccine, bivalent [Original and Omicron BA.4/BA.5]) has been approved as a booster dose for individuals aged 12 and older, while the bivalent formulation (Moderna COVID-19 vaccine, bivalent [Original and Omicron BA.4/BA.5]) has been approved as a booster dose for individuals aged 18 and older (15).

The aim of this study was to analyze the demographic and clinical characteristics of persons with COVID-19 in the South Banat District in 2021.

## Methods

The descriptive study was applied in this paper and it included 34,912 participants of both sexes and all ages. The study included all patients, in whom, during 2021, in the South Banat District, SARS-CoV-2 infection was confirmed by a rapid antigen

vao anketu telefonom, od strane doktora epidemiologa i/ili sanitarnih tehničara službe, a zatim su podaci unošeni u elektronsku bazu Instituta za javno zdravlje Vojvodine - Epidemiološki nadzor Kovid-19. Unos podataka sprovodio se na dnevnom nivou, za sve SARS CoV-2 laboratorijski potvrđene slučajeve na teritoriji Južnobanatskog okruga, u predhodna 24 časa.

Za potrebe ovog istraživanja korišćeni su podaci o demografskim karakteristikama pacijenta (pol, uzrast, prebivalište, zanimanje), kliničkim karakteristikama bolesti (febrilnost, kašalj, bolovi u grlu, bolovi u mišićima, bolovi u zglobovima, glavobolja, mučnina, povraćanje, proliv, gubitak čula ukusa i mirisa, curenje nosa, zapušenost nosa), težini kliničke slike, prisustvu i vrsti komorbiditeta i podaci o vakcinalnom statusu obolelih. Zanimanje pacijenata je obuhvatalo četiri grupe: uslužna delatnost, zdravstvena delatnost, penzioner i ostali. Podaci o težini bolesti odnosili su se na asimptomatske slučajeve, blage, teške i kritične. Zbog malog broja kritičnih i asimptomatskih slučajeva, asimptomatski i blagi su posmatrani kao laki, a teški i kritični kao teži slučajevi bolesti. Kriterijum za blagi oblik bolesti bila je ispunjenost definicije slučaja oboljenja sličnog gripu i asimptomatke forme bolesti, a teški slučajevi bolesti bili su pacijenti sa pneumonijom i/ili kiseoničnom terapijom i pacijenti na respiratoru u jedinici intenzivne nege. Podaci koji se odnose na komorbiditete podrazumevali su prisustvo i odsustvo komorbiditeta kao i njihov broj i vrstu: povišeni krvni pritisak, hronična plućna bolest, dijabetes, maligna bolest, kardiovaskularna bolest, gojaznost i ostale bolesti i stanja.

U odnosu na vakcinalni status pacijenti su podeljeni u dve grupe: neimunizovani (oni koji nisu primili ni jednu dozu vakcine ili su primili jednu dozu vakcine ili dve doze, ali je od poslednje doze vakcine do pojave bolesti prošlo manje od 14 dana) i potpuno imunizovani (oni koji su primili dve doze vakcine pri čemu je od poslednje primljene doze do pojave bolesti prošlo više od 14 dana). U imunizaciji su primenjivane četiri vrste kovid-19 vakcine: Sinopharm, Pfizer-Biontek, Sputnik V i Astra Zeneka.

Kao pokazatelji oboljevanja od SARS CoV-2 infekcije u posmatranom periodu korišćene su opšte i uzrasno specifične stope incidencije. Kao imenilac za izračunavanje stopa incidencije korišćeni su podaci Republičkog zavoda za statistiku o popisu stanovništva iz 2011. godine za Južnobanatski okrug i osam pripadajućih opština: Alibunar, Bela Crkva, Vršac, Kovačica, Kovin, Opovo, Pančevo i Plandište.

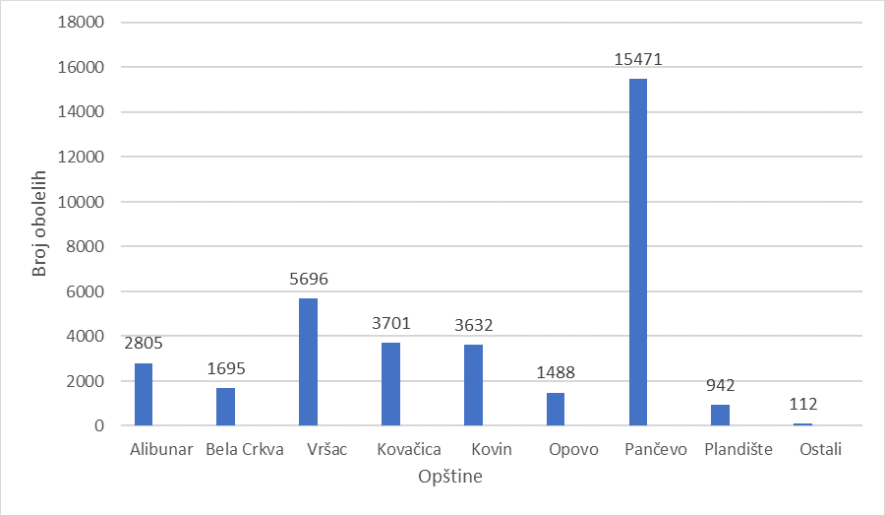
Rezultati su prikazani tabelarno i grafički. Svi podaci su obrađeni u *IBM SPSS Statistics 22* (*SPSS Inc., Chicago, IL, USA*) softverskom paketu.

## Rezultati

U 2021. godini u Južnobanatskom okrugu je prijavljeno 34.912 osoba kod kojih je laboratorijski potvrđena SARS-CoV-2 infekcija, sa stopom incidencije kovid-19 oboljenja od 11.885,7/100.000.

Prosečna starost svih pacijenata obolelih od kovid-19 bolesti je bila 46,21 ± 20,19 godina. Najmlađi oboleli je imao jednu, a najstariji 101 godinu.

Najveći broj obolelih od kovid-19 oboljenja je bio na teritoriji opštine Pančevo (15.474), zatim




**Grafikon 1.** Distribucija obolelih od kovid-19 bolesti po opštinama Južnobanatskog okruga u 2021. godini

test or RT-PCR test, without data on whether the infection occurred for the first time or not.

The source of data included the unpublished data from questionnaires, which had been filled out by doctors from Covid clinics of eight health centers, two general and three special hospitals in the territory of the Public Health Institute Pančevo. All completed questionnaires were sent to the epidemiological department of the Public Health Institute Pančevo, where they were subsequently analyzed and supplemented with missing data, by calling the patients or doctor who filled out the questionnaire by telephone, by the epidemiologist and/or sanitary technicians from the service, and then the data were entered into the electronic database of the Public Health Institute of Vojvodina – Epidemiological surveillance of COVID-19. Data entry was carried out on a daily basis, for all SARS-CoV-2 laboratory-confirmed cases in the territory of the South Banat District in the previous 24 hours.

For the purposes of this research, data on the patient's demographic characteristics were used (gender, age, place of residence, occupation), as well as data on the clinical characteristics of the disease (fever, cough, sore throat, muscle pain, joint pain, headache, nausea, vomiting, diarrhea, loss of senses of taste and smell, rhinorrhea, nasal congestion), the severity of clinical picture, the presence and type of comorbidities and data on the vaccination status of patients. The occupation of patients included four groups: service industry, health care, retired persons and others. Data on the severity of disease referred to asymptomatic cases, mild, severe and critical cases. Due to the small number of critical and asymptomatic cases, asymptomatic and mild cases were observed as mild, while severe and critical were observed as severe cases of disease. The criterion for the mild form of disease was the fulfillment of the case definition of disease with flu-like symptoms and the asymptomatic form of disease, while severe cases were patients with pneumonia and/or oxygen therapy and patients on a respirator in intensive care units. Data related to comorbidities included the presence and absence of comorbidities, as well as their number and type: hypertension, chronic lung disease, diabetes, malignant disease, cardiovascular disease, obesity and other diseases and conditions.

As far as vaccination status is concerned, patients were divided into non-immunized (those who did not receive a single dose of vaccine or received one dose or two doses, but less than 14 days passed from the last dose of vaccine till the onset of disease) and fully immunized (those who received two doses of vaccine, where more than 14 days passed from the last received dose till the onset of disease). Four types of COVID-19 vaccine were administered in the immunization: Sinopharm, Pfizer-Biontek, Sputnik and Astra Zeneca.

General and age-specific incidence rates were used as indicators of SARS-CoV-2 infection in the observed period. The data of the Republic Institute of Statistics on the 2011 census for the South Banat District and its eight municipalities: Alibunar, Bela Crkva, Vršac, Kovačica, Kovin, Opovo, Pančevo and Plandište were used as the denominator for calculating the incidence rates.

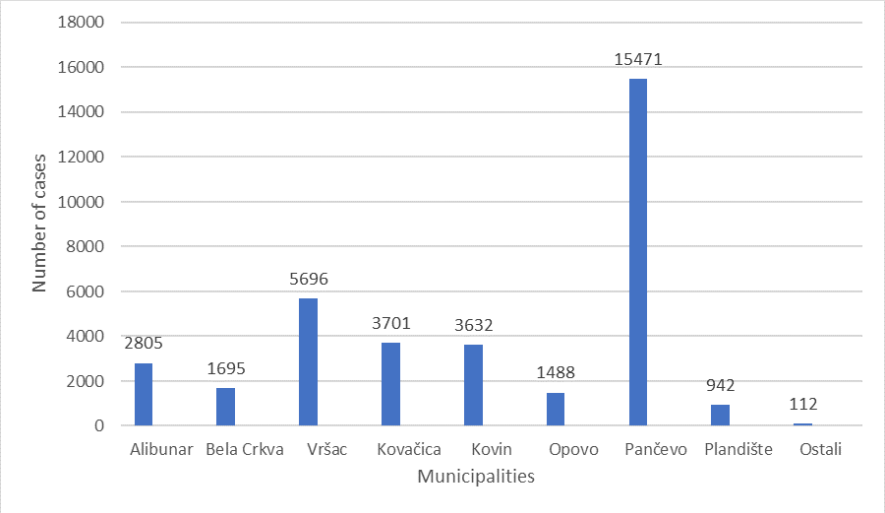
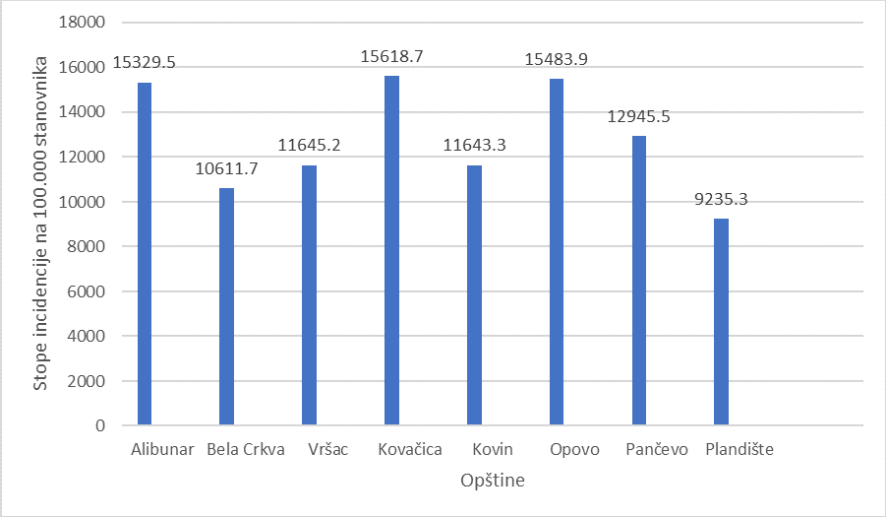



**Figure 1.** Distribution of COVID-19 cases by municipalities in the South Banat District in 2021




**Grafikon 2.** Stope incidencije (na 100.000) kovid-19 bolesti po opštinama Južnobanatskog okruga u 2021. godini

u opštini Vršac (5.696), Kovačica (3.701), Kovin (3.632), Alibunar (2.805), Bela Crkva (1695) i Opovo (1488), a najmanji u opštini Plandište (942) (Grafikon 1).

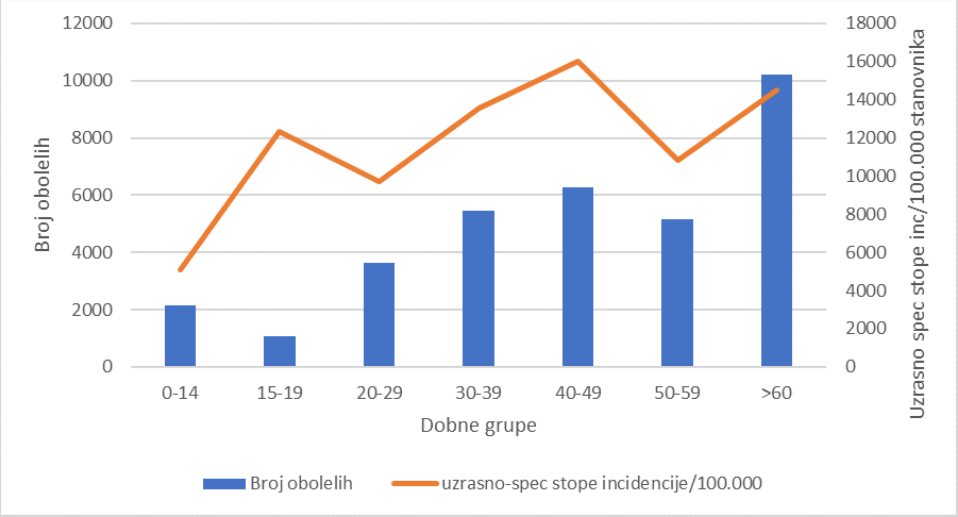
Najviše stope incidencije kovid-19 oboljenja zabeležene su u opštni Kovačica (15.618,7/100.000), Opovo (15.483,9/100.000), Alibunar (15.329,5/100.000), Pančevo (12.954,5/100.000), Vršac (11.645,2/100.000), Kovin (11.643,3/100.000), Beloj Crkvi (10.611,7/100.000), a najniža u opštini Plandište (9.235,3/100.000) (Grafikon 2).

Najviše uzrasno-specifične stope incidencije kovid-19 bolesti su bile u uzrastima 40-49 godina (16.040,9/100.000), 60 i više godina (14.499,8/100.000) i 30-39 godina (13.549,5/100.000), nešto niže u uzrastima 15-19 godina (12.330,9/100.000), 50-59 godina (10.838,9/100.000) i 20-29 godina (9.715,1/100.000), a najniža u uzrastu 1-14 godina (5.064,9/100.000) (Grafikon 3).

Žene su češće obolevale od kovid-19 bolesti (53,6%) nego muškarci 46,4%. Odnos obolelih žena i muškaraca je iznosio 1,16:1. Takođe, u svim uzrasnim gruapama žene su češće obolevale od kovid-19 bolesti nego muškarci, osim u uzrastu 0-14 godina gde je obolevanje bilo slično po polovima (Grafikon 4).

Stope incidencije kovid-19 bolesti su bile veće kod žena nego muškaraca u svim uzrasnim grupama osim u uzrastu 0 do 14 godina i 60 i više godina (Grafikon 5).

Najveća registrovana stopa incidencije kovid-19 bolesti je zabeležena u oktobru mesecu 2021. godine (2759,3/100.000), a najniža u julu mesecu 2021. godine (32,0/100.000) (Grafikon 6).




**Grafikon 3.** Distribucija broja obolelih i uzrasno-specifičnih stopa incidencije (na 100.000) kovid-19 bolesti u Južnobanatskom okrugu u 2021. godini

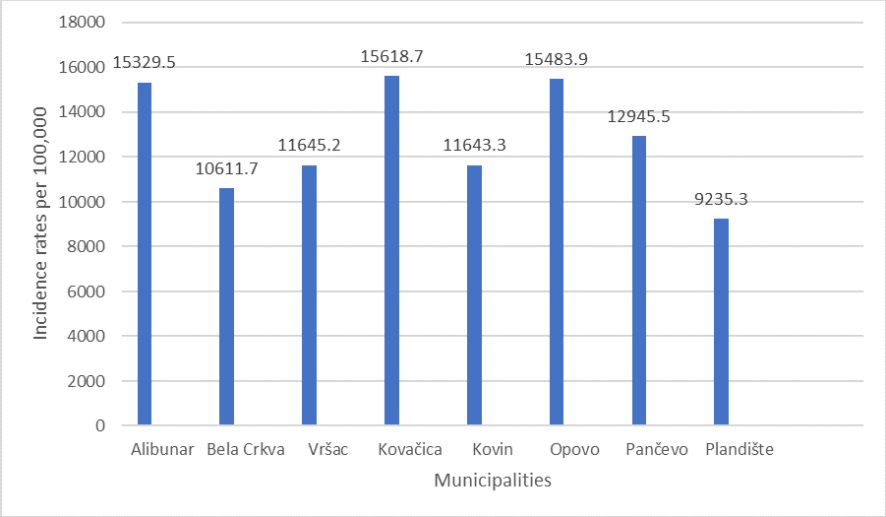



**Figure 2.** Incidence rates (per 100,000) of COVID-19 by municipalities in South Banat District in 2021

The results are presented in tables and graphs. All data were analyzed using the IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) software package.

## Results

In 2021, 34,912 persons were reported in the South Banat District with laboratory-confirmed SARS-CoV-2 infection, with the incidence rate of 11,885.7/100,000.

The average age of all patients suffering from COVID-19 was 46.21+20.19 years. The youngest patient was one, and the oldest was 101 years old.

The largest number of patients with COVID-19 was in the municipality of Pančevo (15,474), followed by the municipalities of Vršac (5,696), Kovačica (3,701), Kovin (3,632), Alibunar (2,805), Bela Crkva (1695) and Opovo (1488), while the smallest number was in the municipality of Plandište (942) (Figure 1).

The highest incidence rates of COVID-19 were recorded in the municipalities of Kovačica (15,618.7/100,000), Opovo (15,483.9/100,000), Alibunar (15,329.5/100.000), Pančevo (12,954.5/100,000), Vršac (11,645.2/100,000), Kovin (11,643.3/100.000), Bela Crkva (10,611.7/100,000), while the lowest rate was in the municipality of Plandište (9,235.3/100,000) (Figure 2).

The highest age-specific incidence rates of COVID-19 were in the age groups 40-49 years (16,040.9/100,000), 60 years and older (14,499.8/100,000) and 30-39 years (13,549.5/100,000), while slightly lower rates were in the age groups 15-19 years (12,330.9/100,000), 50-59 years (10,838.9/ 100,000) and 20-29 years

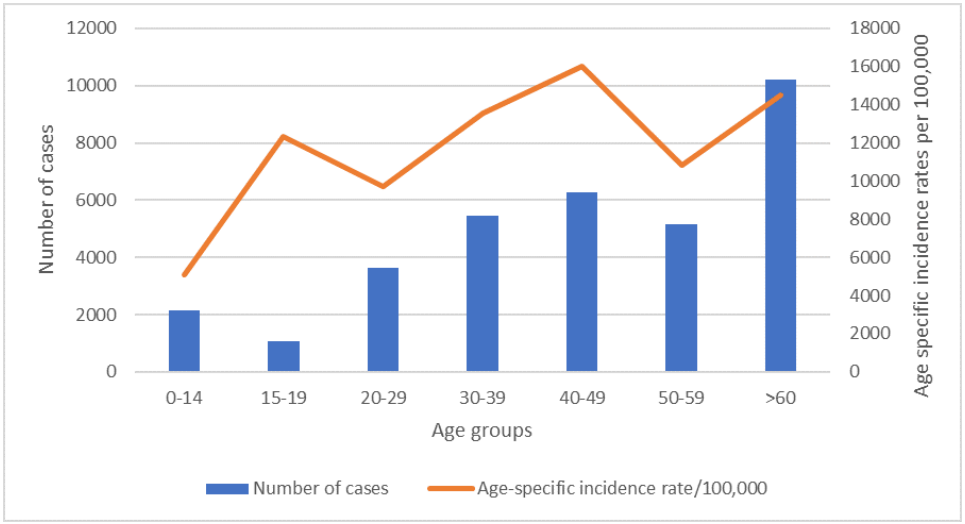
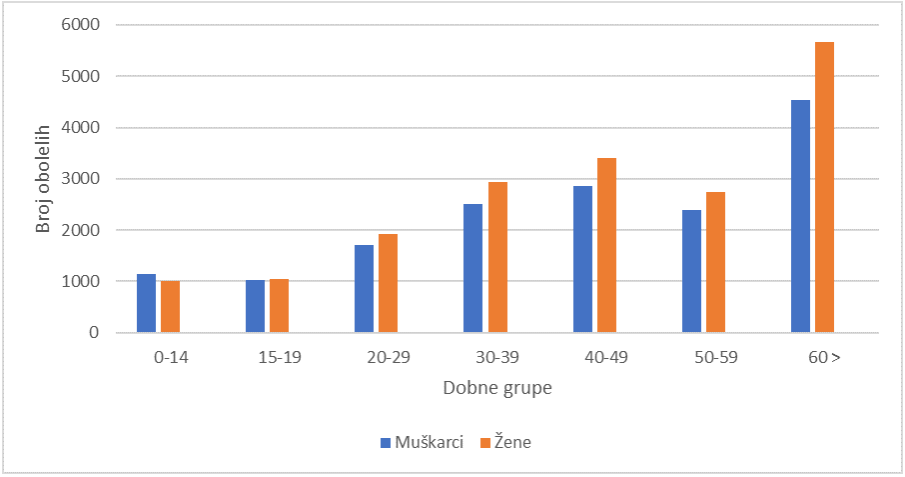
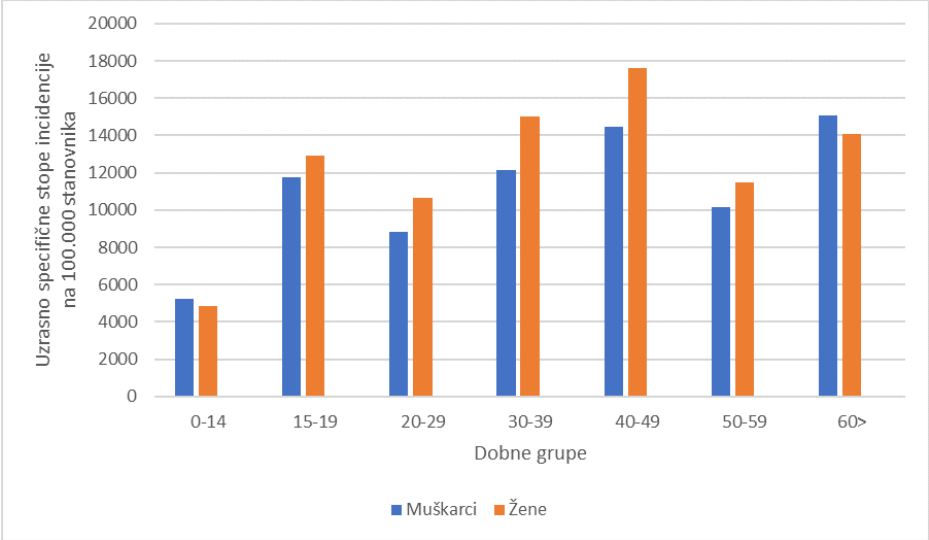


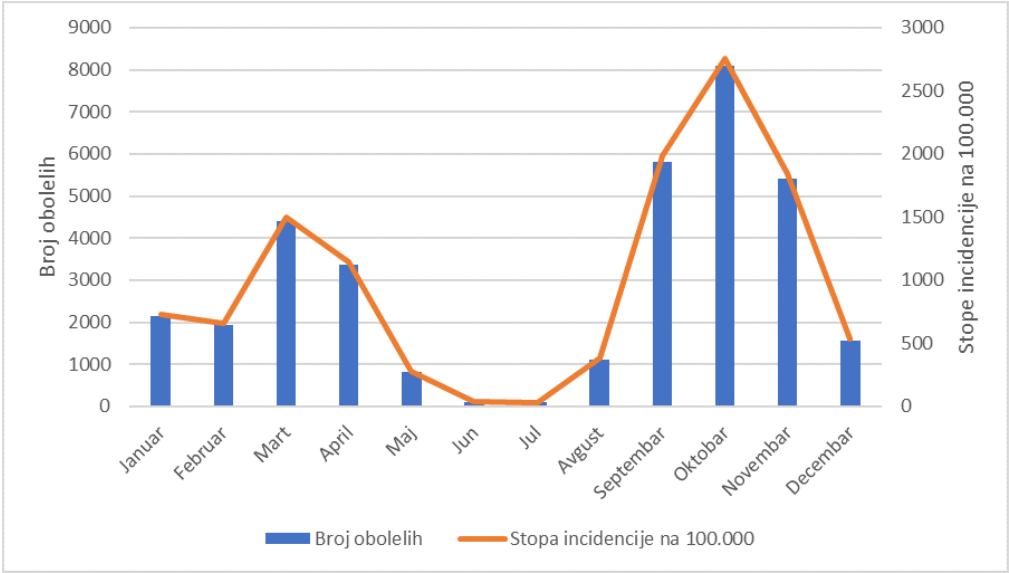

**Figure 3.** Distribution of cases and age-specific incidence rates (per 100,000) of COVID-19 in the South Banat District in 2021




**Grafikon 4.** Distribucija obolelih od kovid-19 bolesti po uzrastu i polu u Južnobanatskom okrugu u 2021. godini




**Grafikon 5.** Stope incidencije (na 100.000) kovid-19 bolesti po polu i uzrastu u Južnobanatskom okrugu u 2021. godini




**Grafikon 6.** Stope incidencije kovid-19 bolesti po mesecima u Južnobanatskom okrugu u 2021. godini

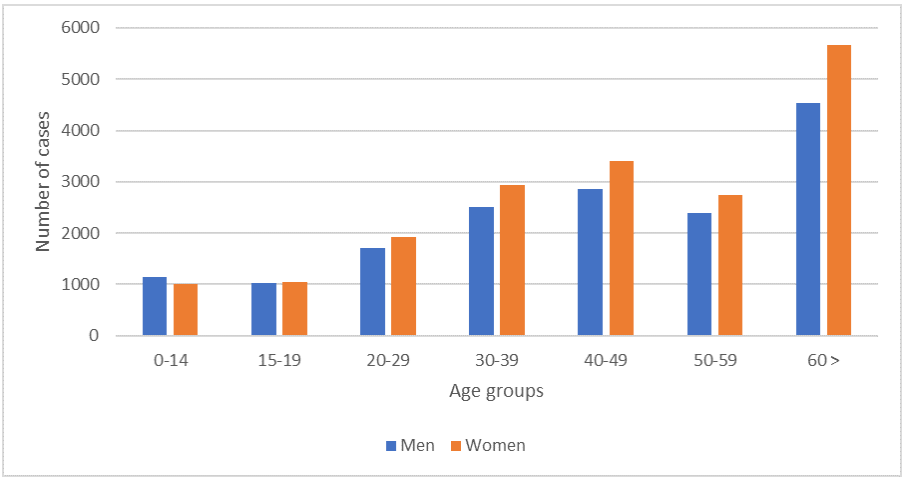



**Figure 4.** Distribution of cases of COVID-19 by age and sex in the South Banat District in 2021

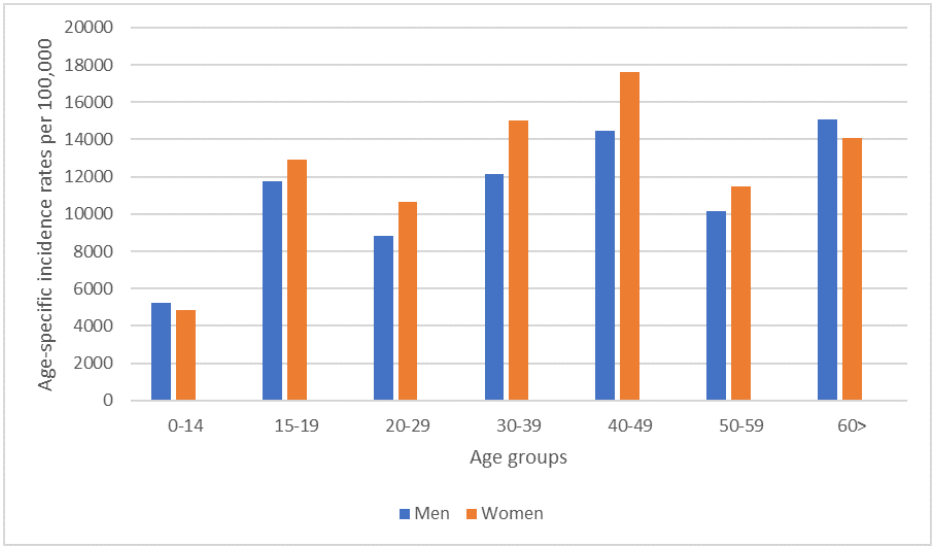



**Figure 5.** Incidence rates (per 100,000) of COVID-19 by sex and age in the South Banat District in 2021

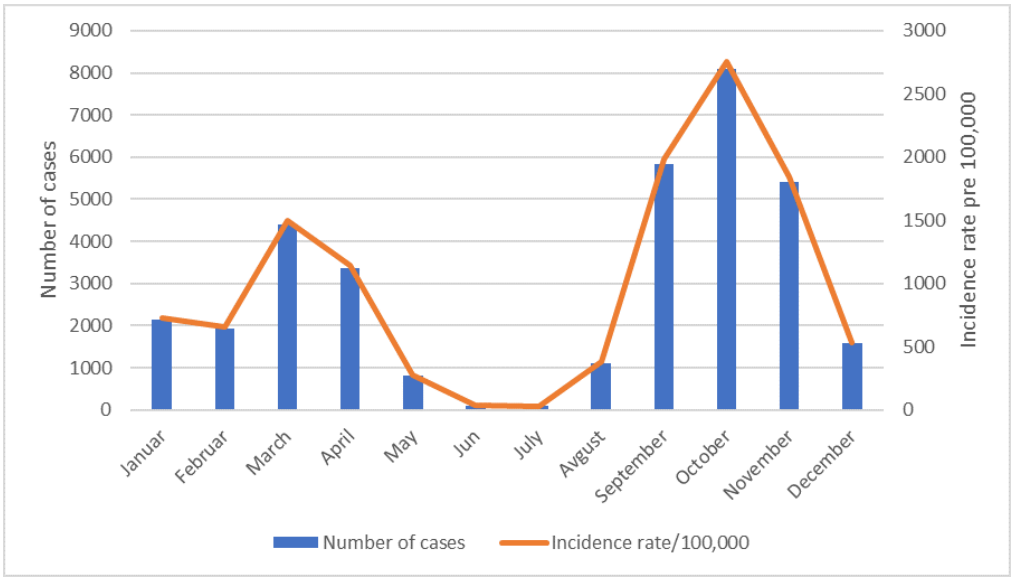



**Figure 6.** Incidence rates of COVID-19 by months in the South Banat District in 2021

Među obolelima od kovid-19 bolesti najviše je bilo penzionera (22%), a zatim radnika uslužnih delatnosti (6,2%) i zdravstvenih radnika (3,0%). Međutim, 68,8% obolelih su pripadali različitim drugim delatnostima. Blagu kliničku sliku je imalo 90,2% obolelih od kovid-19, 8% tešku, a 1,8% nije imalo simptome bolesti.

Najveći broj obolelih (77,2%) je bilo bez komorbiditeta, a 17,3% sa jednim, 4,5% sa dva, 0,9% sa tri, a 0,1% sa više od tri. Najčešći komorbiditi su bili hipertenzija (62,1%), druge hronične bolesti ili stanja (12,6%), dijabetes (11,4%), gojaznost (4,8%), hronična plućna bolest (4,8%), kardiovaskularna (3,4%) i maligna bolest (0,9%).

Prema vodećim simptomima bolesti, febrilnost je bila prisutna kod 73,6% obolelih od SARS-CoV-2 infekcije, kašalj kod 54,4%, malaksalost 56,4%, bolovi u mišićima 24,7%, bolovi u zglobovima 18%, bol u grlu 15,9%, curenje iz nosa 15,9%, gubitak ukusa 7,6%, gubitak mirisa 9,3%, zapušenost nosa 3,2% i proliv 2,9%. Pneumoniju je imalo 2% obolelih od kovid-19 bolesti, a 5,7% je bilo hospitalizovano.

Među obolelima od kovid-19 je bilo 82,1% neimunizovanih, a 17,9% bilo je potpuno imunizovano. Od svih potpuno imunizovanih 69,9% je primilo Sinopharm vakcinu, 16% PfizerBiontek, 10,9% Sputnik V i Astra Zeneku 3,2%.

## Diskusija

U kratkom periodu, nakon svoje pojave, kovid-19 se brzo proširio na ceo svet. Ovo oboljenje i danas, skoro četiri godine nakon što je virus identifikovan, predstavlja veliki javnozdravstveni problem. Još od pojave španske groznice 1918/19 godine, nije u mirnodopskim uslovima bilo događaja koji je jače od ove pandemije uzdrmao čovečanstvo. Pored ogromnih zdravstvenih, ekonomskih i društvenih posledica koje je za sobom ostavila, pandemija je istovremeno pokazala i na koji način se savremeni svet „snašao“ u borbi da kontroliše i zaustavi kovid 19 bolest. Zbog opšte osetljivosti čitave svetske populacije, koja se prvi put susrela sa virusom, brzog širenja virusa koje je doveo do velikog broja obolelih u kratkom vremenskom periodu, velikog opterećenja zdravstvenog sistema na svim nivoima, jasno je bilo da će borba sa virusom biti neizvesna, a tok pandemije na samom njenom početku nepredvidiv.

Prvi potvrđen slučaj zaraznog oboljenja izazvan novim SARS-CoV-2 virusom u našoj zemlji prijavljen je 6. marta 2020. godine, a u Južnobanatskom okrugu, četiri dana kasnije, 10. marta 2020. godine. Epidemija kovida 19 je u Republici Srbiji proglašena 19. marta 2020. godine.

Prema podacima SZO do danas je u svetu prijavljeno preko 770 miliona obolelih od kovida 19, a u Evropi 267 miliona (16). U svetu je najveći broj obolelih prijavljen u Sjedinjenim Američkim Državama (103.436.829), a u Evropi, u Francuskoj (38.997.490), Nemačkoj (38.437.756) i Italiji (26.007.789) (16). U Republici Srbiji oboljenje je potvrđeno kod preko 2,5 miliona stanovnika (16). Prema nepublikovanim podacima Zavoda za javno zdravlje Pančevo do sada je u Južnobanatskom okrugu evidentirano oko 97.000 obolelih od SARS-CoV-2 infekcije.

U Srbiji je početak pandemije kovida 19 obeležio originalni soj virusa iz Vuhana, koji je bio dominantan gotovo do kraja 2020. godine. Naše istraživanje je obuhvatilo 2021. godinu kada je na početku godine dominiro alfa soj virusa. Krajem zime i početkom proleća 2021. alfa soj je potisnuo delta soj, koji je bio odgovoran za petiepidemijski talas, tokom jeseni i na početku zime 2021. godine.

Stopa incidencije obolevanja od kovida 19 u Republici Srbiji je u 2021. godini iznosila 9.919,6/100.000, dok je u AP Vojvodini 11.535/100.000. Na području AP Vojvodine tokom 2021. godine najviše stope incidencije kovid 19 bolesti zabeležene su u Južnobačkom okrugu 13.264,8/100.000, a u Republici Srbiji u Nišavskom okrugu (17.447,7/100.000)(17).

U našem istraživanju, u 2021. godini u Južnobanatskom okrugu je prijavljeno 34.912 obolelih kod kojih je laboratorijski potvrđana SARS-CoV-2 infekcija, sa stopom incidencije 11.885,7/100.000. Zabeležene stope incidencije kovid-19 oboljenja razlikovale su se po opštinama Južnobnatskog okruga. Najviše vrednosti zabeležene su u opštini Kovačica (15.618,7/100.000), Opovo (15.483,9/100.000) i Alibunar (15.329,5/100.000), a najniže u opštini Plandište (9.235,3/100.000). Razlike u učestalosti obolevanja po opštinama delom su rezultat različite organizacije zdravstvene službe i prijavljivanja, a delom rezultat praktikovanja različitih navika (npr. u opštini Kovačica, koju u najvećoj meri čine Slovaci, imaju tendenciju da održe zajedništvo okupljanjem u manjim grupama i dr.).

Broj obolelih i stopa incidencije nisu realne i predstavljaju samo „vrh ledenog brega“ obzirom da je značajan broj slučajeva SARS-CoV-2 infekcija ostao neprijavljen zbog velikog broja osoba koje su

(9,715.1/100,000), and the lowest was in the age group 1-14 years (5,064.9/100,000) (Figure 3).

Women suffered more often from COVID-19 (53.6%) than men (46.4%). The ratio of affected women to men was 1.16:1. Also, in all age groups, women were more likely to suffer from COVID-19 than men, except in the age group 0-14 years where the incidence was similar in relation to gender (Figure 4).

The incidence rates of COVID-19 were higher in women than in men in all age groups, except in the age group 0 to 14 years and 60 and over (Figure 5).

The highest incidence rate of COVID-19 was registered in October 2021 (2759,3/100,000), while the lowest was in July 2021(32,0/100,000) (Figure 6).

The majority of patients were retired persons (22%), followed by healthcare workers (3.0%) and workers in the service industry (6.2%). However, 68.8% of patients belonged to other occupations. 90.2% of patients had a mild clinical picture, 8% severe, while 1.8% had the asymptomatic form of the disease.

The largest number of patients (77.2%) was without comorbidities, while 17.3% were with one, 4.5% with two, 0.9% with three, and 0.1% with more than three comorbidities. The most frequent comorbidity was hypertension (62.1%), other chronic diseases or conditions (12.6%), diabetes (11.4%), obesity (4.8%), chronic lung disease (4.8%), cardiovascular (3.4%) and malignant disease (0.9%).

As far as the leading symptoms of disease are concerned, fever was present in 73.6% of cases of SARS CoV-2 infection, cough in 54.4%, malaise in 56.4%, muscle pain in 24.7%, joint pain in 18%, sore throat in 15.9%, rhinorrhea in 15.9%, loss of taste in 7.6%, loss of smell in 9.3%, nasal congestion in 3.2% and diarrhea in 2.9%. Pneumonia was present in 2% of cases of COVID-19, while 5.7% were hospitalized.

Among the patients affected by COVID-19, 82.1% were not immunized, while 17.9% were completely immunized. Of all the immunized persons, 69.9% received Sinopharm vaccine, 16% Pfizer Biontek, 10.9% Sputnik V and Astra Zeneca 3.2%.

## Discussion

Shortly after its appearance, SARS-CoV-2 quickly spread to the whole world. Today, almost four years after the virus was identified, this disease is still a major public health problem. Ever since the outbreaks of Spanish fever, there have been no events in the conditions of peace that shook humanity more than this pandemic. In addition to the huge health, economic, and social consequences that it left behind, the pandemic at the same time showed how the modern world "managed" in the fight to control and stop COVID-19. Due to the general susceptibility of the whole world population, which encountered the virus for the first time, the rapid spread of the virus which caused the large number of cases in a short period of time, and the heavy burden on the health system at all levels, it was clear that the fight against the virus would be uncertain, and that the course of the pandemic would be unpredictable at its very beginning.

The first confirmed case of an infectious disease caused by the new SARS-CoV-2 virus in our country was reported on the 6$^{th}$ of March, 2020 and four days later, on the 10$^{th}$ of March, 2020 in the South Banat District. The epidemic of COVID-19 was declared in the Republic of Serbia on the 19$^{th}$ of March, 2020.

According to the WHO data, more than 770 million cases of COVID-19 have been reported worldwide so far, while 267 million cases have been reported in Europe (16). In the world, the largest number of cases was reported in the United States of America (103,436,829), then in Europe, in France (38,997,490), Germany (38,437,756) and Italy (26,007,789) (16). In the Republic of Serbia, the disease has been confirmed in over 2.5 million inhabitants (16). According to the unpublished data of the Public Health Institute of Pančevo, about 97,000 cases of SARS-CoV-2 have been recorded in the South Banat District so far.

In Serbia, the beginning of the COVID-19 pandemic was marked by the original strain of the virus from Wuhan, which was dominant almost until the end of 2020. Our study covered the year 2021, when the alpha strain was dominant. In the late winter and early spring of 2021, the alpha strain was suppressed by delta strain, which was responsible for the fifth epidemic wave, during the fall and early winter of 2021.

In 2021, the incidence rate of COVID-19 in the Republic of Serbia was 9,919.6/100,000, while in the Autonomous Province of Vojvodina it was 11,535/100,000. In the territory of AP Vojvodina

imale blagu kliničku sliku ili asimptomatsku bolest i nisu se javljale zdravstvenom sistemu. Tome u prilog govore istraživanja o seroprevalenciji u Sjedinjenim Američkim Državama i Evropi koja ukazuju da stvarna stopa incidencije premašuje incidenciju prijavljenih slučajeva za približno 10 ili više puta (2-4).

Najviša uzrasno-specifična stopa incidencije u 2021. godini u Republici Srbiji zabeležena je u uzrastu 15-19 godina i iznosila je 12.121,1/100.000 stanovnika, dok je u AP Vojvodini bila u uzrastu 40-49 godina i iznosila je 15.236,9/100.000 stanovnika. U našem istraživanju najviše uzrasno-specifične stope incidencije kovid-19 zabeležene su u uzrastu 40-49 godina (16.040,9/100.000). Dobijene vrednosti incidencije bile su više 3,2 puta od najnižih registrovanih u uzrastu 0-14 godina (5.064,9/100.000). Uzrast u kojem su zabeležene najviše stope incidencije odgovara radno aktivnom stanovništvu koje je ostvarilo najveći broj kontakata kako na putu do posla tako i na samom poslu odakle sledi i najveći broj obolelih.

U Južnobanatskom okrugu žene su 1,2 puta češće obolevale nego muškarci, a u Republici Srbiji 1,1 puta češće (17). Zašto više obolevaju žene do 60 godina od kovid 19 bolesti u odnosu na muškrace još uvek nije jasno. Može se pretpostaviti da se žene češće javljaju zdravstvenom sistemu, a takođe u zdravstvu i drugim javnim institucijama veći je broj zaposlenih žena u odnosu na muškarce, pa to može biti razlog i njihove veće izloženosti. Ovi rezultati su slični drugim istraživanjima sprovedenim u Evropi (18,19).

Najviše stope incidencije kovid-19 bolesti, u našoj studiji, odgovaraju jesenjem periodu (septembar, oktobar i novembar), a najmanje u julu 2021. Sve ovo ukazuje na činjenicu da će kovid 19, najverovatnije biti oboljenje sa sezonskim karakterom, tokom hladnijih meseci što odgovara učestalosti pojavljivanja virusa koji se prenose respiratornim putem.

Podaci iz 2020. godine pokazali su da je većina simptomatskih pacijenata razvija samo blagu ili umerenu bolest (80%), tešku bolest sa pneumonijom i kiseoničnom podrškom 15%, a kritičnu sa komplikacijama kao što su respiratorna insuficijencija, ARDS (Akutni respiratorni distres sindrom), sepsa, septični šok, tromboembolija i/ili zatajenje više organa uključujući akutnu renalnu i srčanu insuficijenciju 5% (20). U našem istraživanju blagu kliničku sliku imalo 90,2% obolelih, 8% tešku, a 1,8% nije imalo simptome bolesti.

Prema podacima SZO najčešći simptomi bolesti koji se mogu javiti 5-6 dana nakon izloženosti su: povišena telesna temperatura, kašalj, umor i malaksalost, glavobolja, bolovi u mišićima, gubitak mirisa i ukusa, zapušenost nosa. Teška klinička slika manifestuje se pneumonijom sa otežanim disanjem ili kratakim dahom, konfuzijom i bolovima u grudima i može se komplikovati respiratornom slabošću koja zahteva nadoknadu kiseonika ili mehaničku ventilaciju (21).Treba imati u vidu da ovo nije konačan spisak simptoma kovida i on zavisi od varijante virusa i vakcinalnog statusa pacijenta. Dostupni podaci ukazuju da se povišena telesna temperatura javlja kod 85-90% obolelih, suvi kašalj je prisutan kod dve trećine obolelih. U 15 - 40 % obolelih javljaju se bolovi u mišićima, zglobovima i glavobolja. Proliv, mučnina i povraćanje javljaju se kod 12 % obolelih, dok se gubitak ukusa i mirisa javlja kod 10% obolelih (22). U našem istraživanju, kao i kod drugih istraživanja, febrilnost je bila prisutna kod 73,6% obolelih, malaksalost 56,4%, kašalj kod 54,4%, bolovi u mišićima 24,7%, bolovi u zglobovima 18%, bol u grlu 15,9%, curenje iz nosa 15,9%, gubitak mirisa 9,3%, gubitak ukusa 7,6%, zapušenost nosa 3,2% i proliv 2,9%.

Prema podacima Evropskog centra za prevenciju i kontrolu bolesti rizik od teške bolesti raste sa starenjem i prisustvom komorbiditeta (23,24). Veliki broj stanja je povezan sa teškim kliničkim ishodima u smislu prijema u bolnicu, jedinicu intenzivne nege i mortalitetom. U faktore rizika spadaju hipertenzija, dijabetes, hronična bolest bubrega, koronarna srčana bolest, hronična opstruktivna bolest pluća, cerebrovaskularna bolest i hronična bolest jetre, imunosupresivna terapija, aritmija, ishemijska bolest srca, srčana insuficijencija, rak i gojaznost (25,26). Naše istraživanje je pokazalo da je skoro ¼ obolelih od kovid-19 imalo bar jedan komorbiditet. Najčešći komorbiditeti su bili hipertenzija (62,1%), druge hronične bolesti ili stanja (12,6%), dijabetes (11,4%), gojaznost (4,8%), hronična plućna bolest (4,8%), kardiovaskularna bolest (3,4%) i maligna bolest (0,9%).

Prema nepublikovanim podacima Zavoda za javno zdravlje Pančevo, obuhvat imunizacijom koja podrazumeva najmanje dve doze vakcine protiv kovid-19 u Južnobanatskom okrugu je iznosio 48,4% krajem 2021. godine. Prema podacima Evropskog centra za prevenciju i kontrolu bolesti (ECDC) obuhvat imunizacijom vakcinama protiv kovida 19 razlikovao se značajno od zemlje do

in 2021, the highest incidence rates were recorded in the South Banat District (13,264.8/100,000), and in the Republic of Serbia in the Nišava District (17,447.7/100,000) (17).

In our study, in 2021, 34,912 cases of laboratory-confirmed SARS-CoV-2 infection were reported in the South Banat District, with the incidence rate of 11,885.7/100,000. Recorded incidence rates of COVID-19 differed by municipalities of South Banat District. The highest values were recorded in the municipalities of Kovačica (15,618.7/100,000), Opovo (15,483.9/ 100,000) and Alibunar (15,329.5/ 100,000), and the lowest were in the municipality of Plandište (9,235.3/100,000). These differences in incidence are partly the result of different organization of health service and reporting, and partly the result of different habits (e.g. in the municipality of Kovačica, which is mostly made up of Slovaks, they tend to maintain unity by gathering in smaller groups, etc.).

The number of cases and the incidence rates are not realistic and they are only "the tip of the iceberg", considering that the significant number of SARS-CoV-2 infections remained unreported due to the large number of people who had a mild clinical picture or asymptomatic disease and they were not registered in the health system. This is supported by research on seroprevalence in the United States of America and Europe, which indicates that the incidence rate exceeds the incidence of reported cases by approximately 10 or more times (2-4).

The highest age-specific incidence rate in the Republic of Serbia in 2021 was recorded in the age group 15-19 years and it amounted to 12,121.1/100,000, while in the AP Vojvodina it was in the age group 40-49 years and amounted to 15,236.9/100,000. In our study, the highest age-specific incidence rates of COVID-19 were registered in the age group 40-49 years (16,040.9/100,000). The obtained incidence values were 3.2 times higher than the lowest ones registered in the age group 0-14 years (5,064.9/100,000). The age with the highest incidence rates was among the working population that had the largest number of contacts on the way to work and at work, and therefore there were most cases among this population.

In the South Banat District, women fell ill 1.2 times more often than men, and in the Republic of Serbia, 1.1 times more often (17). It is still not clear why women up to the age of 60 get COVID-19 more often than men. It can be assumed that women report to the health care system more often, and also more women are employed in health care and other public institutions in comparison to men, and therefore, it may be the reason for their greater exposure. These results are similar to the results of other studies conducted in Europe (18,19).

In our study, the highest incidence rates of COVID-19 were recorded in the autumn months (September, October, November), while the lowest rates were in July 2021. All this indicates that COVID-19 will probably be a disease with a seasonal character, which corresponds to the frequency of appearance of respiratory viruses during colder months.

Data from 2020 showed that the majority of symptomatic patients had only mild or moderate disease (80%), while 15% had a severe form of disease with pneumonia and oxygen support, and 5% had a critical form of disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, septic shock, thromboembolism, and/or multiple organ failure, including renal and heart failure (20). In our study, 90.2% of patients had a mild clinical presentation, 8% severe and 1.8% had no symptoms of disease.

According to the WHO data, the most common symptoms that can occur 5-6 days after exposure are the following: elevated body temperature, cough, fatigue and weakness, headache, muscle pain, loss of smell and taste, nasal congestion. The severe clinical presentation is manifested by pneumonia with dyspnea or shortness of breath, confusion and chest pain and it can be complicated by respiratory failure that requires oxygen therapy or mechanical ventilation (21). It should be born in mind that this is not the final list of COVID-19 symptoms and it depends on the variant of the virus and the vaccination status of the patient. Available data indicate that elevated body temperature occurs in 85-90% of patients, while dry cough is present in two thirds of patients. Pain in muscles, joints and headache occur in 15-40% of patients. Diarrhea, nausea and vomiting occur in 12% of patients, while loss of taste and smell appears in 10% of patients (22). In our study, as in other studies, fever was present in 73.6% of patients, malaise in 56.4%, pain in muscles in 24.7%, pain in joints in 18%, sore throat in 15.9%, rhinorrhea in 15.9%, loss of smell in 9.3%, loss of taste in 7.6%, nasal congestion in 3.2% and diarrhea in 2.9%.

zemlje (npr. Bugarska 33,2%, Rumunija 48,6%, Hrvatska 63,1%, Mađarska 69,9%, Italija 84%) (27). Naši podaci su pokazali da je samo 17,9% obolelih od kovid-19 u Južnobanatskom okrugu 2021. godine bilo imunizovano (primili su dve doze kovid-19 vakcine, a bolest je nastala 14 dana nakon druge doze). Od svih potpuno imunizovanih obolelih pacijenata 69,9% njih je primilo Sinopharm vakcinu, 16% PfizerBiontek, 10,9% Sputnik V i 3,2% Astra Zeneku. Ovako visok procenat zastupljenosti Sinopharm vakcine može se objasniti preporukom Stručnog komiteta za imunizaciju - Nacionalnog tela za imunizaciju (NITAG), na osnovu koga je sačinjeno prvo stručno-metodološko uputstvo za sprovođenje vanredne preporučene imunizacije protiv kovid - 19 (SMU) u Republici Srbiji, početkom 2021. godine, kada se starijim osobama preko 60 godina i osobama sa komorbiditetima preporučivala ova vakcina.

## Zaključak

Rezultati dobijeni u ovom istraživanju su značajni za planiranje preventivnih i protivepidemijskih mera za sprečavanje nastanka i širenja kovid-19 bolesti u Južnobanatskom okrugu u budućnosti, kao i u cilju što bolje organizacije zdravstvene službe, a sve radi redukcije obolevanja od SARS CoV-2 infekcije i hospitalizacije. Neophodno je stalno raditi na edukaciji stanovništva o važnosti imunizacije, a pogotovo osoba koje imaju veći rizik od razvoja teže forme bolesti. Neophodna su dalja istraživanja u ovoj oblasti u cilju definisanja prediktora za nastanak teže forme kovid-19 bolesti.

## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

## Reference


1. World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. Table view. Situation by region, Country, Territory & Area. Available from: https://covid19.who.int/table/ (Accessed May 5, 2023)
2. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, at al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396(10247):313. doi: 10.1016/S0140-6736(20)31304-0.
3. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern Med. 2020 Jul 21. doi: 10.1001/jamainternmed.2020.4130. Epub ahead of print.
4. Clarke KEN, Jones JM, Deng Y, Nycz E, Lee A, Iachan R, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep. 2022 Apr 29;71(17):606-608. doi: 10.15585/mmwr.mm7117e3.
5. COVID-19 Cumulative Infection Collaborators. Estimating global, regional, and national daily and cumulative infections with SARS-CoV-2 through Nov 14, 2021: a statistical analysis. Lancet. 2022 Jun 25;399(10344):2351-2380. doi: 10.1016/S0140-6736(22)00484-6.
6. Ristić M, Vuković A, Patić A, Marković M, Petrović V. Seroepidemiology of SARS-CoV-2 Virus in Healthcare Workers before Circulation of the Omicron Sublineages BA.4/BA.5 in Vojvodina, Serbia. Vaccines 2022;10(12):2168. doi: 10.3390/vaccines10122168
7. Institut za javno zdravlje Srbije. WHO. Covid-19 - smernice za potvrđivanje i šifriranje uzroka smrti. Available at: https://www.batut.org.rs/download/Uputstvo_Uzrok_Smrti_COVID-19%20SZO.pdf (Accessed April 16, 2020)
8. World Health Organisation. Global excess deaths associated with COVID-19 (modelled estimates). Available from: https://www.who.int/data/sets/global-excess-deaths-associated-with-covid-19-modelled-estimates (Accessed May 10, 2023).
9. Knutson V, Aleshin-Guendel S, Karlinsky A, Msemburi W. Wakefield J. Estimating Global and Country-Specific Excess Mortality During the COVID-19 Pandemic. Preprint 18 May 2022. Available at: https://arxiv.org/abs/2205.09081. https://doi.org/10.48550/arXiv.2205.09081
10. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet. 2022;399(10334):1513-1536. doi: 10.1016/S0140-6736(21)02796-3
11. Europian Centre for Disease Prevention and Control. Public health control measures for COVID-19. Available at: https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/covid-19/facts/public-health-control-measures-covid-19. (Accessed 26 October 2023)
12. Acosta-Coley I, Cervantes-Ceballos L, Tejeda-Benítez L, Sierra-Márquez L, Cabarcas-Montalvo M, García-Espiñeira M, et al. Vaccines platforms and COVID-19: what you need to know. Trop Dis Travel Med Vaccines. 2022;8(1):20. doi: 10.1186/s40794-022-00176-4.
13. COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023;401(10379):833-842. doi: 10.1016/S0140-6736(22)02465-5.
14. Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. Lancet Infect Dis. 2023;23(5):556-567. doi: 10.1016/S1473-3099(22)00801-5
15. Ministarstvo zdravlja Republike Srbije. Stručno-metodološko uputstvo za sprovođenje vanredne preporučene imunizacije protiv covid-19 u Republici Srbiji vakcinama: PFIZER-BIONTECH COVID-19 VACCINE (Comirnaty), Гам-КОВИД-Вак, SARS-CoV-2 Vaccine

According to the data of the European Center for Disease Prevention and Control, the risk of severe disease increases with age and the presence of comorbidities (23,24). A large number of conditions are associated with severe clinical outcomes in terms of admission to hospital, intensive care unit and mortality. Risk factors include hypertension, diabetes, chronic kidney disease, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease and chronic liver disease, immunosuppressive therapy, arrhythmia, ischemic heart disease, heart failure, cancer and obesity (25,26). Our study showed that almost one fourth of patients with COVID-19 had at least one comorbidity. The most common comorbidities were hypertension (62.1%), other chronic diseases or states (12.6%), diabetes (11.4%), obesity (4.8%), chronic lung disease (4.8%), cardiovascular disease (3.4%) and malignant disease (0.9%).

According to the unpublished data of the Public Health Institute Pančevo, immunization coverage, which includes at least two doses of the vaccine against COVID-19, in the South Banat District was 48.4% at the end of 2021. According to data of the European Center for Disease Prevention and Control (ECDC), the coverage of immunization with vaccines against COVID-19 differed significantly from country to country (e.g. Bulgaria 33.2%, Romania 48.6%, Croatia 63.1%, Hungary 69.9%, Italy 84%) (27). Our data showed that only 17.9% of patients in the South Banat District were immunized (they received two doses of COVID-19 vaccine, and the disease occurred 14 days after the second dose). Of all completely immunized patients, 69.9% of them received the Sinopharm vaccine, 16% Pfizer Biontek, 10.9% Sputnik V, and 3.2% Astra Zeneca. Such a high percentage of Sinopharm vaccine can be explained by the recommendation of the Expert Committee for Immunization – National Immunization Technical Advisory Group (NITAG), based on which the first expert methodological instruction for the implementation of the emergency recommended immunization against COVID-19 in the Republic of Serbia at the beginning of 2021, when this vaccine was recommended to people older than 60 and people with comorbidities.

## Conclusion

The results of this study are important for the planning of anti-epidemic measures for the prevention of occurrence and spreading of COVID-19 in the South Banat District in the future, as well as for the purpose of better organization of health service, which is aimed at reducing the incidence of SARS-Cov-2 infection and hospitalization. It is necessary to constantly work on educating the population about the importance of immunization, especially people who are at increased risk of developing severe forms of disease. Further research in this field is necessary in order to define the predictors for the occurrence of severe forms of COVID-19.

## Competing interests

The authors declared no competing interests.

## References


1. World Health Organisation. WHO Coronavirus (COVID-19) Dashboard. Table view. Situation by region, Country, Territory & Area. Available from: https://covid19.who.int/table/ (Accessed May 5, 2023)
2. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, at al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. 2020;396(10247):313. doi: 10.1016/S0140-6736(20)31304-0.
3. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, et al. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern Med. 2020 Jul 21. doi: 10.1001/jamainternmed.2020.4130. Epub ahead of print.
4. Clarke KEN, Jones JM, Deng Y, Nycz E, Lee A, Iachan R, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep. 2022 Apr 29;71(17):606-608. doi: 10.15585/mmwr.mm7117e3.
5. COVID-19 Cumulative Infection Collaborators. Estimating global, regional, and national daily and cumulative infections with SARS-CoV-2 through Nov 14, 2021: a statistical analysis. Lancet. 2022 Jun 25;399(10344):2351-2380. doi: 10.1016/S0140-6736(22)00484-6.
6. Ristić M, Vuković A, Patić A, Marković M, Petrović V. Seroepidemiology of SARS-CoV-2 Virus in Healthcare Workers before Circulation of the Omicron Sublineages BA.4/BA.5 in Vojvodina, Serbia. Vaccines 2022;10(12):2168. doi: 10.3390/vaccines10122168
7. Institut za javno zdravlje Srbije. WHO. Covid-19 - smernice za potvrđivanje i šifriranje uzroka smrti. Available at: https://www.batut.org.rs/download/Uputstvo_Uzrok_Smrti_COVID-19%20SZO.pdf (Accessed April 16, 2020)
8. World Health Organisation. Global excess deaths associated with COVID-19 (modelled estimates). Available from: https://www.who.int/data/sets/global-excess-deaths-associated-with-covid-19-modelled-estimates (Accessed May 10, 2023).

(Vero Cell), Inactivated, ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) COVISHIELD/AstraZeneca SKBio AZD1222-COVID-19 Vaccine (ChAdOx1-S(recombinant))/ COVID-19 Vaccine AstraZeneca (Vaxzevria) i SPIKEVAX (ranije COVID-19 Vaccine Moderna). Ministarstvo zdravlja Republike Srbije: Beograd, 2022. Available from: https:// SMU za vanrednu preporučenu imunizaciju protiv COVID-19 11.03.2022.pdf

16. World Health Organisation. Table Wiev. Situation by Region, Country, Territory & Area. Available at: https:// covid19.who.int/table
17. Institut za javno zdravlje Srbije dr Milan Jovanović Batut. Izveštaj o zaraznim bolestima u Republici Srbiji za 2021. Institut za javno zdravlje Srbije dr Milan Jovanović Batut: Beograd, 2022. Available at: https://www.batut.org.rs/ index.php?content=2523
18. Goujon A, Natale F, Ghio D, Conte A, Dijkstra L. Age, gender, and territory of COVID-19 infection and fatalities. JRC technical report, 2020. doi:10.2760/642022. Available at: https://op.europa.eu/en/publication-detail/-/ publication/6660b754-a930-11ea-bb7a-01aa75ed71a1/ language-en
19. Disparities in the risk and outcomes from COVID-19. Public Healt England. August 2020 gatteway number: GW-1447. Available at: https://www.gov.uk/government/ publications/covid-19-review-of-disparities-in-risks-and-outcomes
20. WHO. Clinical management of COVID-19: living guideline. Geneva: World Health Organization, 2023 (WHO/2019-nCoV/clinical/2023.2). Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2
21. WHO. Coronavirus desease (COVID 19). Available from: https://www.who.int/news-room/fact-sheets/detail/ coronavirus-disease-%28covid-19%29
22. Radovanović Z. KOVID 19. Klinički aspekti oboljevanja. Smederevo: Heliks, 2022.
23. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, et al. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PLoS One. 2021;16(7):e0254066. doi: 10.1371/journal. pone.0254066.
24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
25. Centers for Disease Control and Prevention. COVID-19. Coronavirus Disease 2019 (COVID-19). Vaccines. Available at. https://www.cdc.gov/coronavirus/2019-ncov/index.html. (Accessed 10 May 2023)
26. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36(7):e3319. doi: 10.1002/dmrr.3319.
27. European Centre for Disease Prevention and Control. Covid-19 vaccine tracker. Available from: https:// commission.europa.eu/strategy-and-policy/coronavirus-response/safe-covid-19-vaccines-europeans_en



**Primljen:** 28.10.2023. **Revizija:** 21.11.2023. **Prihvaćen:** 26.11.2023.

9. Knutson V, Aleshin-Guendel S, Karlinsky A, Msemburi W. Wakefield J. Estimating Global and Country-Specific Excess Mortality During the COVID-19 Pandemic. Preprint 18 May 2022. Available at: https://arxiv.org/abs/2205.09081. https://doi.org/10.48550/arXiv.2205.09081
10. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet. 2022;399(10334):1513-1536. doi: 10.1016/S0140-6736(21)02796-3
11. Europian Centre for Disease Prevention and Control. Public health control measures for COVID-19. Available at: https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/covid-19/facts/public-health-control-measures-covid-19. (Accessed 26 October 2023)
12. Acosta-Coley I, Cervantes-Ceballos L, Tejeda-Benítez L, Sierra-Márquez L, Cabarcas-Montalvo M, García-Espiñeira M, et al. Vaccines platforms and COVID-19: what you need to know. Trop Dis Travel Med Vaccines. 2022;8(1):20. doi: 10.1186/s40794-022-00176-4.
13. COVID-19 Forecasting Team. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023;401(10379):833-842. doi: 10.1016/S0140-6736(22)02465-5.
14. Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. Lancet Infect Dis. 2023;23(5):556-567. doi: 10.1016/S1473-3099(22)00801-5
15. Ministarstvo zdravlja Republike Srbije. Stručno-metodološko uputstvo za sprovođenje vanredne preporučene imunizacije protiv covid-19 u Republici Srbiji vakcinama: PFIZER-BIONTECH COVID-19 VACCINE (Comirnaty), Гам-КОВИД-Вак, SARS-CoV-2 Vaccine (Vero Cell), Inactivated, ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) COVISHIELD/AstraZeneca SKBio AZD1222-COVID-19 Vaccine (ChAdOx1-S(recombinant))/ COVID-19 Vaccine AstraZeneca (Vaxzevria) i SPIKEVAX (ranije COVID-19 Vaccine Moderna). Ministarstvo zdravlja Republike Srbije: Beograd, 2022. Available from: https:// SMU za vanrednu preporučenu imunizaciju protiv COVID-19 11.03.2022.pdf
16. World Health Organisation. Table Wiev. Situation by Region, Country, Territory & Area. Available at: https://covid19.who.int/table
17. Institut za javno zdravlje Srbije dr Milan Jovanović Batut. Izveštaj o zaraznim bolestima u Republici Srbiji za 2021. Institut za javno zdravlje Srbije dr Milan Jovanović Batut: Beograd, 2022. Available at: https://www.batut.org.rs/index.php?content=2523
18. Goujon A, Natale F, Ghio D, Conte A, Dijkstra L. Age, gender, and territory of COVID-19 infection and fatalities. JRC technical report, 2020. doi:10.2760/642022. Available at: https://op.europa.eu/en/publication-detail/-/publication/6660b754-a930-11ea-bb7a-01aa75ed71a1/language-en
19. Disparities in the risk and outcomes from COVID-19. Public Healt England. August 2020 gatteway number: GW-1447. Available at: https://www.gov.uk/government/publications/covid-19-review-of-disparities-in-risks-and-outcomes
20. WHO. Clinical management of COVID-19: living guideline. Geneva: World Health Organization, 2023 (WHO/2019-nCoV/clinical/2023.2). Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2
21. WHO. Coronavirus desease (COVID 19). Available from: https://www.who.int/news-room/fact-sheets/detail/coronavirus-disease-%28covid-19%29
22. Radovanović Z. KOVID 19. Klinički aspekti oboljevanja. Smederevo: Heliks, 2022.
23. Nguyen NT, Chinn J, De Ferrante M, Kirby KA, Hohmann SF, et al. Male gender is a predictor of higher mortality in hospitalized adults with COVID-19. PLoS One. 2021;16(7):e0254066. doi: 10.1371/journal.pone.0254066.
24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
25. Centers for Disease Control and Prevention. COVID-19. Coronavirus Disease 2019 (COVID-19). Vaccines. Available at. https://www.cdc.gov/coronavirus/2019-ncov/index.html. (Accessed 10 May 2023)
26. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;36(7):e3319. doi: 10.1002/dmrr.3319.
27. European Centre for Disease Prevention and Control. Covid-19 vaccine tracker. Available from: https://commission.europa.eu/strategy-and-policy/coronavirus-response/safe-covid-19-vaccines-europeans_en




**Received:** 10/28/2023 **Revised:** 11/21/2023 **Accepted:** 11/26/2023

ORIGINALNI RAD

UDK BROJEVI: 004.762:616.31-06.26/.36-053.2
616.896-053.2
DOI: https://www.doi.org/10.5937/zdravzast52-47345

# UPOTREBA MOBILNE APLIKACIJE ZA POBOLJŠANJE ORALNOG ZDRAVLJA DECE SA AUTIZMOM

**Aleksandra Stamatović[1], Bobana Mitrašinović[2], Anđela Pavlović[3], Dejan Marković[4], Olja Jovanović[5], Jelena Vranješević[5], Julijana Jovanović[6], Dejan Ostojic[7], Jugoslav Ilic[7], Ana Vuković[4]**

[1] Dom zdravlja Požega, Republika Srbija
[2] Dom zdravlja Vršac, Republika Srbija
[3] Stomatološki fakultet, Univerzitet u Beogradu, Republika Srbija
[4] Klinika za dečju i preventivnu stomatologiju, Stomatološki fakultet, Univerzitet u Beogradu, Republika Srbija
[5] Filozofski fakultet, Univerzitet u Beogradu, Republika Srbija
[6] Stomatološki fakultet, Univerzitet u Beogradu, Republika Srbija
[7] Klinika za restaurativnu odontologiju i endodonciju, Stomatološki fakultet, Univerzitet u Beogradu, Republika Srbija

[*] Korespondencija: dr Aleksandra Stamatović, doktor stomatologije, Dom zdravlja Požega, Republika Srbija; DMD, student postdiplomskih studija dečije stomatologije, Jug Bogdanova 1, Požega, Republika Srbija; e-mail: stamatoviceva@gmail.com; telefon: 0641534700

**SAŽETAK**

**Uvod/Cilj:** Osobe iz autističnog spektra (ASD) često se susreću sa značajnim izazovima kada posećuju stomatologa. Mobilne tehnologije pokazale su se obećavajućim kao efikasna pomoćna sredstva u promovisanju zadataka vezanih za oralno zdravlje. Ova studija imala je za cilj da u prvoj fazi ispita dostupnost mobilnih aplikacija za oralno zdravlje na srpskom jeziku i ćiriličnom pismu, a u drugoj da proceni efikasnost aplikacije dizajnirane posebno za posete stomatologu, razvijene na srpskom jeziku i koja koristi ćirilično pismo.
**Metod:** Ova sudija preseka je sprovedena od novembra 2021. do februara 2022. godine na Klinici za dečju i preventivnu stomatologiju Stomatološkog fakulteta u Beogradu, Republika Srbija. Početna faza podrazumevala je pretragu onlajn aplikacija, kako na srpskom tako i na engleskom jeziku, koristeći specifične ključne reči: „mobilne aplikacije“, „autizam“, „stomatologija“ i „oralno zdravlje“. U sledećoj fazi, uključeno je deset porodica koje imaju dete sa ASD-om koje su koristile mobilnu aplikaciju na srpskom jeziku i ćiriličnom pismu koja je posebno razvijena za njihove posete stomatologu. Napredak u saradnji sa stomatologom kod korisnika ove aplikacije je procenjen pomoću strukturisanog protokola posmatranja zasnovanog na TEACCH metodi.
**Rezultati:** Analiza sadržaja mobilnih aplikacija otkriva da je od ukupnog broja aplikacija 64 (70,3%) funkcionalno. Više od polovine (59,4%) ovih aplikacija je dizajnirano za rešavanje poteškoća u razvoju, učenju i govoru. Što se tiče jezika, samo jedna aplikacija za podršku razvoju, učenju i govoru je bila dostupna na srpskom, a tri su bile na hrvatskom jeziku i napisane latiničnim pismom. Međutim, među ovim mobilnim aplikacijama, identifikovana je samo jedna aplikacija za oralno zdravlje, i to na engleskom jeziku. Ovo ukazuje na jasnu potrebu za razvojem aplikacija za oralno zdravlje na srpskom jeziku. Pilot test je pokazao da testirana mobilna aplikacija efikasno podržava decu sa ASD-om u njihovim posetama stomatologu.
**Zaključak:** Istraživanje je potvrdilo da su mobilne aplikacije koje podržavaju decu sa ASD-om tokom posete stomatologu obećavajuće sredstvo. Zbog toga treba uložiti napore da se ove vrste mobilnih aplikacija razviju i testiraju na srpskom jeziku.

**Ključne reči:** autizam, studija preseka, online aplikacije za očuvanje i unapređenje oralnog zdravlja, stomatologija, deca

## Uvod

Autizam ili poremećaji iz spektra autizma (engl. *Autism Spectrum Disorder*, ASD) obuhvataju spektar stanja koja karakterišu teškoće u socijalnoj interakciji i komunikaciji, kao i prisustvo ponavljanih i stereotipnih ponašanja (1). Za osobe sa autizmom posete stomatologu mogu predstavljati izazov jer

ORIGINAL ARTICLE

UDK NUMBERS: 004.762:616.31-06.26/.36-053.2
616.896-053.2
DOI: https://www.doi.org/10.5937/zdravzast52-47345

# THE USE OF A MOBILE APPLICATION TO IMPROVE THE ORAL HEALTH OF CHILDREN WITH AUTISM

**Aleksandra Stamatović[1], Bobana Mitrašinović[2], Anđela Pavlović[3], Dejan Marković[4], Olja Jovanović[5], Jelena Vranješević[5], Julijana Jovanović[6], Dejan Ostojic[7], Jugoslav Ilic[7], Ana Vuković[4]**

[1] Health Center Požega, Republic of Serbia
[2] Health Center Vršac, Republic of Serbia
[3] School of Dental Medicine, University of Belgrade, Belgrade, Republic of Serbia
[4] Clinic for Pediatric and Preventive Dentistry, School of Dental Medicine, University of Belgrade, Belgrade, Republic of Serbia
[5] Faculty of Philosophy, University of Belgrade, Belgrade, Republic of Serbia
[6] School of Dental Medicine, University of Belgrade, Belgrade, Republic of Serbia
[7] Department of Restorative Odontology and Endodontics, School of Dental Medicine, University of Belgrade, Belgrade, Republic of Serbia

[*] Correspondence: Aleksandra Stamatović, Doctor of Dental Medicine, Požega Health Center, Republic of Serbia; DMD, student of postgraduate studies in children's dentistry, 1 Jug Bogdanova street, Požega, Republic of Serbia;
e-mail: stamatoviceva@gmail.com; phone: 0641534700

**SUMMARY**

**Introduction:** Individuals with autism spectrum disorder (ASD) often encounter significant challenges when visiting a dentist. Mobile supportive technologies have shown promise as effective assisting tools in promoting oral health-related tasks. This study aimed, in its first stage, to investigate the availability of oral health mobile applications in the Serbian language and Cyrillic script. In the second stage, our goal was to evaluate the effectiveness of an application designed specifically for dentist visits, developed in the Serbian language and using the Cyrillic alphabet.
**Method:** The cross-sectional study was conducted from November 2021 to February 2022 at the Clinic for Pediatric and Preventive Dentistry at the School of Dental Medicine in Belgrade, Republic of Serbia. The initial stage involved conducting a search of online apps, both in Serbian and English, using specific keywords: "mobile applications," "autism," "dentistry," and "oral health." In the subsequent stage, a sample of 10 families of children with ASD utilized a mobile app in Serbian and using Cyrillic script specifically developed for their dental visits. Progress in cooperation with the dentist among users of this application was assessed using a structured observation protocol based on the TEACCH method.
**Results:** The content analysis of mobile apps reveals that out of the total number of applications, 64 (70.3%) were deemed functional. More than half of these applications (59.4%) were designed to address developmental, learning, and speech difficulties. In terms of language, only one application aimed at supporting development, learning, and speech was available in Serbian, while three apps were in Croatian, utilizing the Latin script. However, among these mobile apps, only one application was identified for oral health, and it was in English. This indicates a clear need for the development of oral health apps in Serbian. A pilot test suggested that the tested mobile app effectively supports children with ASD in their visits to the dentist.
**Conclusion:** The research suggests that mobile apps supporting children with ASD during dentist visits are a promising tool. Therefore, efforts should be made to develop and test these types of mobile apps in the Serbian language.

**Key words:** autism, cross-sectional study, online applications for maintaining and improving oral health, dentistry, children

## Introduction

Autism or autism spectrum disorder (ASD) includes a spectrum of conditions that are characterized by difficulties in social interaction and communication, as well as the presence of repeated and stereotyped behaviors (1). Persons with autism might find dental visits challenging

imaju poteškoća da sarađuju tokom stomatoloških intervencija, posebno ako imaju izražene senzorne smetnje. Jednostavni zadaci oralne higijene kod kuće za njih takođe mogu biti zbunjujući. Stoga, sve navedeno može uticati na njihovo oralno zdravlje i veći rizik od oralnih bolesti i oralnih samopovreda (2).

Poteškoće u društvenim interakcijama i komunikacijskim veštinama koje karakterišu ASD izazivaju prepreke u razumevanju neverbalnih obrazaca ponašanja, uspostavljanju i održavanju kontakata, nedostatak potrebe za deljenjem osećanja sa drugima, odsustvo socijalno-emocionalnog reciprociteta, smanjenu sposobnost imitacije i razumevanja drugih ljudi i njihovih psihičkih stanja, želja i ponašanja (3). Ove karakteristike čine proces socijalizacije izazovnim, kao i proces komunikacije i ponašanja tokom poseta stomatologu. Pored toga, može se desiti da se uobičajene nefarmakološke bihejvioralne metode u stomatološkoj ordinaciji, za koje su stomatolozi obučeni na osnovnim studijama, nije moguće primeniti. S obzirom da uobičajeno stomatološko lečenje nije uvek moguće izvesti, osobama sa ASD-om je često potrebna dodatna podrška kako bi prevazišli teškoće u obavljanju svakodnevnih aktivnosti. Multidisciplinarni pristup koji podrazumeva saradnju roditelja (ili staratelja), stomatologa, psihologa ili psihijatra u održavanju, unapređenju oralnog zdravlja i kontroli ponašanja pacijenta u stomatološkoj ordinaciji, izuzetno je važan za postizanje punog potencijala oralnog zdravlja (4). Zbog toga su neophodne prilagođene i specifične strategije kako bi se prevazišle barijere i obezbedila adekvatna stomatološka nega (5). Prvi i najvažniji korak bilo bi prevazilaženje poteškoća u komunikaciji i uspostavljanje odnosa poverenja, čime se smanjuje anksioznost i unapređuje saradnja u stomatološkoj ordinaciji.

Ubrzani razvoj novih tehnologija koje se sve više koriste u savremenom svetu doneo je novu potencijalnu strategiju u stomatološkoj ordinaciji – korišćenje mobilnih aplikacija za poboljšanje komunikacije sa osobama sa ASD-om (5). Mobilne aplikacije su specijalizovani softveri koji pružaju dodatnu podršku pri uspostavljanju saradnje i komunikacije između članova porodice, terapeuta i defektologa sa osobama sa ASD-om u svakodnevnim aktivnostima. One su dizajnirane i namenjene za dnevne aktivnosti i navigaciju u okruženju da bi se pomoglo deci da budu što je moguće nezavisnija i da uspostave pozitivan odnos sa okolinom. Uglavnom se koriste za komunikaciju, učenje, praćenje dnevnih aktivnosti, zabavu i vežbanje. Korišćenje mobilne aplikacije kao savremenog edukativnog alata omogućava ne samo unapređenje saradnje sa stomatologom, već i uspostavljanje odnosa poverenja, upoznavanje sa prostorom stomatološke ordinacije pre posete stomatologu kao i sa budućim stomatološkim procedurama.

Studija je imala dva cilja. Prvi cilj je bio ispitivanje dostupnosti mobilnih aplikacija za oralno zdravlje na srpskom jeziku i ćiriličnom pismu. Drugi cilj bio je procena efikasnost aplikacije posebno dizajnirane za posete stomatologu, razvijene na srpskom jeziku i ćiriličnom pismu.

## Metode

### *Dizajn studije preseka*

Prva faza studije bila je struktuisana kao pregled onlajn prodavnica aplikacija: *Google Play* aplikacija za *Android* i *App Store* aplikacija na *Apple* platformi. To je urađeno unošenjem ključnih reči na srpskom i engleskom jeziku: „mobilne aplikacije“, „autizam“, „stomatologija“, „oralno zdravlje“ i „zubi“.

Kriterijumi za uključivanje u analizu bili su sledeći: 1) aplikacija je namenjena osobama sa ASD-om; 2) aplikacija je dostupna za besplatno preuzimanje preko *Android* i *Apple* operativnih sistema; 3) aplikacija je funkcionalna i upotrebljiva u Srbiji.

Analiza sadržaja je sprovedena radi klasifikacije aplikacija na osnovu njihove funkcionalnosti (funkcionalne/nefunkcionalne), jezika (srpski_hrvatski_bosanski_ crnogorski/ engleski), platformi za korišćenje (aplikacije dizajnirane za *Android* platformu/aplikacije dizajnirane za *Apple* platformu/aplikacije kompatibilne sa obe platforme ), i obima podrške funkcionisanju pojedinca (podrška teškoćama u razvoju, učenju i govoru/ podrška u praćenju svakodnevnih zadataka i rutina/ podrška u identifikaciji i razumevanju emocija/ podrška u korišćenju prevoza i aktivnosti na otvorenom/ podrška u roditeljstvu dece sa ASD/ podrška u aktivnostima vezanim za oralno zdravlje).

### *Dizajn pilot testiranja*

Druga faza studije je obuhvatila pilot testiranje mobilne aplikacije na srpskom jeziku i ćiriličnom pismu, koja za cilj ima podršku deci sa ASD-om tokom poseta stomatologu. Pilot testiranje je osmišljeno kao deo studentskog naučnog rada

since they have difficulties cooperating during dental interventions particularly if they have pronounced sensory disturbances. Simple oral hygiene tasks at home might be puzzling too. Therefore, these features might affect their oral health and favor higher risk for oral diseases and oral self-injuries (2).

Difficulties in social interactions and communication skills that characterizes ASD causes obstacles in understanding non-verbal patterns of behavior, establishing and maintaining contacts, lack of the need to share feelings with others, absence of social-emotional reciprocity, reduced ability to imitate and understand other people and their mental states, desires and behavior (3). These characteristics make the process of socialization challenging, as well as the process of managing behavior during dental visits. Moreover, the typical non-pharmacological behavioral methods in a dental office, for which undergraduate dentists are trained, might be impossible to apply. Since the usual dental treatment is not always possible to perform, persons with ASD often need additional support to overcome difficulties in performing daily activities. The multidisciplinary approach involving cooperation between parent (or guardian), dentist, psychologist or psychiatrist in maintaining, improving oral health, and behavioral management in dental office is extremely important in order to achieve the full potential of oral health (4). Therefore, it is necessary adapted and specific strategies in order to overcome barriers and provide adequate dental care (5). First and most important step would be overcoming difficulties in communication and establishing a relationship of trust, which reduces anxiety and improves cooperation in the dental office.

Rapid development of new technologies that are increasingly used in the modern world brought new potential strategy in dental office – using mobile applications to improve communication with ASD persons (5). Mobile applications are specialized software that provide additional support when establishing cooperation and communication between family members, therapists and special education teachers with ASD persons in everyday activities. Mobile applications are designated and intended for daily activities and navigating the environment in order to help children to be as independent as possible and to achieve a positive relationship with the environment. They were mostly used for communication, learning, monitoring daily activities, entertainment and exercise. The use of mobile application as a modern educational tool enables not only the improvement of cooperation with the dentist, but also establishing a relationship of trust, making familiar with the space of the dental office before dental visit and for future dental procedures.

The study had two aims. Firstly, to investigate the availability of oral health mobile applications in the Serbian language and Cyrillic script. Secondly, to evaluate the effectiveness of an application specifically designed for dentist visits, developed in the Serbian language and utilizing the Cyrillic alphabet.

## Method

### *Review design*

The first stage of the study was structured as a review of the online app stores: the Google Play application for Android and the App Store application on the Apple platform. This was done by inputting keywords in both Serbian and English: "mobile applications," "autism," "dentistry," "oral health," and "teeth."

The criteria for inclusion in the analysis were as follows: 1) the application is intended for individuals with ASD; 2) the application is available for free download through Android and Apple operating systems; 3) the application is functional and usable in Serbia.

The content analysis was conducted to classify applications based on their functionality (functional/non-functional), language (Serbian_Croatian_Bosnian_Montenegrin/English), platforms for usage (applications designed for the Android platform/applications designed for the Apple platform/applications compatible with both platforms), and the scope of support for an individual's functioning (support for developmental, learning, and speech difficulties/support in monitoring daily tasks and routines/support in identifying and understanding emotions/support in using transportation and outdoor activities/support in parenting children with ASD/support in activities related to oral health).

### *Pilot test design*

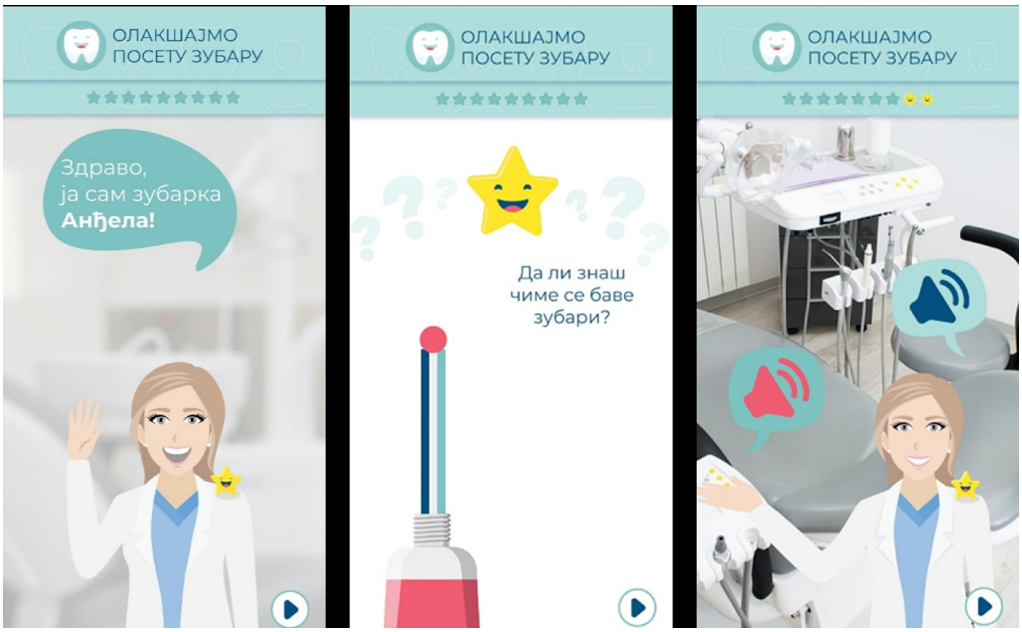
The second stage of the study included pilot testing the mobile application in the Serbian

u okviru projekta koji je podržalo Ministarstvo zdravlja Republike Srbije. Projektni tim činila je multidisciplinarna grupa, uključujući nastavnike i studente osnovnih studija Stomatološkog fakulteta Univerziteta u Beogradu, kao i Filozofskog fakulteta Univerziteta u Beogradu. Pored toga, tim je uključivao programera, veb dizajnera, fotografa, decu sa posebnim potrebama koja su se suočavala sa izazovima u saradnji u stomatološkim ustanovama i njihove roditelje ili staratelje.

Ova aplikacija (Slika 1) uključuje virtuelni obilazak stomatološke ordinacije, upoznavanje sa zvucima u ordinaciji, upoznavanje sa stomatološkim instrumentima, igre za strpljenje, koncentraciju i pažnju i upoznavanje sa postupkom pri pregledu zuba i uklanjanju plaka, kao i igre koje imaju za cilj da podrže kontrolu impulsa.

Pigodni uzorak za pilot test uključivao je desetoro dece sa ASD-om i njihove roditelje koji su dobrovoljno prihvatili učešće u istraživanju, tražeći stomatološko lečenje na Klinici za dečju i preventivnu stomatologiju Stomatološkog fakulteta u Beogradu. Posete stomatologu su bile zakazane jednom nedeljno, uvek istog dana i u isto vreme, tokom perioda praćenja od 3 meseca. Roditelji su dobili instrukcije da dozvole deci da koriste aplikaciju najmanje 15 minuta dnevno tokom perioda igre. Pogodan uzorak se sastojao od 8 dečaka i 2 devojčice, prosečne starosti od 10,3 godine. U ovoj fazi istraživanja pacijentima je, uz pomoć roditelja i/ili staratelja, data prilika da testiraju aplikaciju. Nakon korišćenja, dali su povratne informacije o svom iskustvu i predložili poboljšanje njene efikasnosti u cilju pomaganja deci sa ASD-om tokom poseta stomatološkoj ordinaciji.

Dizajn pilot testa uključivao je upotrebu metode TEACCH (eng. T*reatment and Education of Autistic and Related Communication Handicapped Children*) koja je razvijena kao pedagoška strategija namenjena osobama sa autizmom (6). Protokol je obuhvatao 10 sukcesivnih koraka, koji imaju prethodno utvrđeno trajanje, uz primenu komunikacionih strategija i bihejvioralnih tehnika (Tabela 1). Koraci su se izvodili jednom nedeljno, najmanje u 5 sesija. Svi koraci za istog pacijenta su se uvek izvodili u istoj prostoriji, istog dana u nedelji, u isto doba dana. Svaki korak je podrazumevao uspešno obavljanje određenih aktivnosti. Moguće je podeliti bilo koji od navedenih koraka na dve sesije, ako je u skladu sa individualnom procenom. Tokom prvog koraka, nakon uspešnog ulaska u ordinaciju, neophodno je da pacijent ostane u toj prostoriji i da se u njoj oseća prijatno i opušteno. Prvi susret sa pacijentom je u većini slučajeva razgovor sa roditeljima, tokom kojeg se stomatolog i pacijent upoznaju i stomatolog prikuplja sve potrebne podatke za dalji tok lečenja. Pacijenti bi uvek trebalo da imaju vremensku orijentaciju koliko će svaki korak trajati, tako da odbrojavanje uvek treba da bude najavljeno. Osoba koja izvodi intervenciju treba uvek da broji naglas, jasnim, prijatnim i opuštenim tonom.




**Slika 1.** Prezentacija aplikacije na srpskom jeziku.

language and Cyrillic script, with the aim at supporting children with ASD during their dental visits . It was designed as part of an undergraduate student's scientific work supported by the Ministry of Health of the Republic of Serbia. The project team comprised a multidisciplinary group, including teachers and undergraduate students from the School of Dental Medicine at the University of Belgrade, as well as from the Faculty of Philosophy at the University of Belgrade. Additionally, the team included a programmer, web designer, photographer, children with special needs who faced challenges cooperating in dental settings, and their parents or guardians.

Within this application (Figure 1), features included a virtual tour of the dental office, familiarization with the sounds commonly heard in the office environment, getting acquainted with dental instruments, understanding the procedure during dental examinations and plaque removal, and games aimed at supporting impulse control.

The study utilized a convenient sample consisting of 10 children with ASD and their parents who volunteered to participate, seeking dental treatment at the Clinic for Pediatric and Preventive Dentistry at the School of Dental Medicine in Belgrade. Dental visits were scheduled once a week, consistently on the same day and time, throughout a follow-up period of 3 months. Parents were instructed to allow their children to use the application daily for at least 15 minutes during their playtime.

A convenient sample comprised 8 male and 2 female participants, with an average age of 10.3 years. In this phase of the research, patients, with the aid of their parents and/or guardians, were given the chance to test the application. After using it, they provided feedback regarding their experience and offered suggestions to improve its effectiveness in assisting children with ASD during visits to the dental office.

The pilot test design included the use of TEACCH (Treatment and Education of Autistic and Related Communication Handicapped Children) method developed as a pedagogical strategy intended for people with autism (6). The protocol includes 10 subsequent steps, which have previously specified duration, with the application of communication strategies and behavioral techniques (Table 1). The steps should be carried out once a week, through at least five sessions. All steps for the same patient should always be performed in the same room, on the same day of the week, at the same time of day. Each step implies the successful performance of certain activities. It is possible to divide any of the mentioned steps into two sessions if it is in accordance with the individual assessment. During the first step after successfully entering the office, it is necessary for the patient to stay in that room and to feel comfortable and relaxed in it. The first meeting with the patient in most cases is a conversation with parents, during which the dentist and patient get to know each

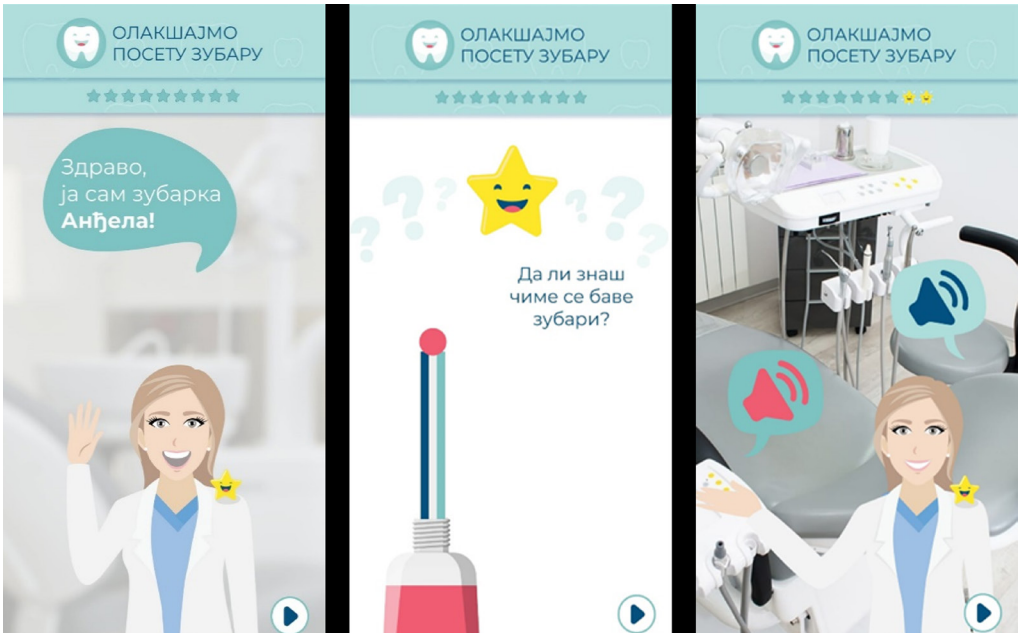



**Figure 1.** Presentation of the application in the Serbian language

**Tabela 1.** Opis korakaTEACCH metoda koji se koriste u stomatološkoj ordinaciji

| | |
|---|---|
| **Korak 1** | Ulazak u stomatološku ordinaciju (koliko god je pacijentu potrebno) |
| **Korak 2** | Sesti na stomatološku stolicu i potom sedeti na stomatološkoj stolici 10s |
| **Korak 3** | Nasloniti leđa i glavu na stomatološku stolicu i zatim ostati u toj poziciji 10s |
| **Korak 4** | Usmeriti svetlo prema licu dok pacijent sedi naslonjen na stomatološkoj stolici, zatim držati tako usmereno svetlo prema ustima pacijenta 10 s |
| **Korak 5** | Otvoriti širom usta i tako ostati 10s |
| **Korak 6** | Stomatolog stavlja ruku u usta pacijenta i drži ruku u ustima pacijenta 5s |
| **Korak 7** | Uvesti stomatološko ogledalce, zatim sprovesti stomatološki pregled korišćenjem samo ogledalca 5s |
| **Korak 8** | Uvesti stomatološku sondu, a zatim uraditi pregled korišćenjem samo sonde tokom 5s |
| **Korak 9** | Stomatološki pregled sa ogledalcem i sondom u trajanju od 5s |
| **Korak 10** | Pregled okluzije, što podrazumeva da pacijent drži zube tokom perioda centralne okluzije u trajanju od 5 do 10s |

*ako pacijent nije mogao da uđe u stomatološku ordinaciju što je računato kao rezultat 0 za potrebe ovog istraživanja.

Za statističku analizu podataka korišćene su metode deskriptivne statistike u SPSS verziji 26 (*SPSS Inc, Chicago, IL)*. Jedan stomatolog je bio angažovan u nadgledanju kliničkog stomatološkog (AV) tretmana pacijenata u pilot programu, a procena rezultata urađena je pomoću TEACCH skora. Svaki uspešan korak ima rezultat koji odgovara redosledu koraka (na primer, ako je korak 1 uspešan, skor=1; ako je korak 2 uspešan, skor=2, itd.). Na ovaj način, minimalni skor koji pacijent može postići je skor 0 (ako pacijent nije mogao da uđe u stomatološku ordinaciju), a maksimalni skor 10.

## Rezultati

Pregledom aplikacija putem onlajn prodavnica identifikovana je 91 mobilna aplikacija koja ima za cilj podršku funkcionisanju osoba sa ASD-om u različitim aspektima života, od kojih su se 64 (70,3%) smatrale funkcionalnim. Među funkcionalnim aplikacijama, više od polovine (59,4%) je dizajnirano da podrži osobe sa ASD-om sa poteškoćama u učenju i govoru. Distribucija učestalosti dostupnih aplikacija u zavisnosti od kategorije aplikacije prikazana je na slici 2.

Od ukupnog broja funkcionalnih aplikacija, samo jedna aplikacija (6,3%) je bila na srpskom jeziku i spadala je u kategoriju aplikacija za smetnje u razvoju, učenju i govoru. Tri aplikacije su bile na hrvatskom jeziku i na latiničnom pismu.

Od ukupnog broja aplikacija, samo jedna aplikacija je bila dostupna za poboljšanje oralnog zdravlja i ova aplikacija je bila na engleskom jeziku. Rezultati su pokazali odsustvo aplikacija koje se odnose na oralno zdravlje na srpskom jeziku, na ćiriličnom pismu.

Nakon pilot testiranja nove aplikacije na srpskom jeziku i ćiriličnom pismu obavljeni su intervjui sa roditeljima. Prilikom provere razumevanja sadržaja, date su sledeće sugestije: dodati glas stomatologa, dodati tajmer za odbrojavanje aktivnosti na aplikaciji, naglasiti izgled stomatološke ordinacije i stomatološke stolice, poboljšati zvukove žamora u stomatološkoj ordinaciji i zvuk stomatoloških instrumenata.

Svi roditelji su primetili smanjenu napetost kod svoje dece tokom poseta stomatologu nakon svakodnevne upotrebe aplikacije. Analiza TEACCH rezultata dece koja učestvuju u pilot studiji ukazuje na značajno poboljšanje TEACCH rezultata nakon upotrebe aplikacije (9,7±0,5) u poređenju sa TEACCH ocenama pre korišćenja aplikacije (2,1±2,3) (srednji rezultat ± standardna devijacija) (Slika 3).

## Diskusija

Rezultati ovog istraživanja pokazali su da ne postoji aplikacija na srpskom jeziku i ćiriličnom pismu namenjena pacijentima sa ASD-om u

**Table 1.** Description of TEACCH method steps applied in dental office

| | |
|---|---|
| **Step 1** | Entering the dental office (as much as the patient needs) |
| **Step 2** | Sitting in the dental chair and then sitting in the dental chair for 10s |
| **Step 3** | Leaning on the back and headrest in the dental chair, then holding the reclining position for 10s |
| **Step 4** | Directing the spotlight to the face while the patient is reclining in the dental chair, and then keeping the spotlight on the patient's mouth for 10s |
| **Step 5** | Opening the mouth wide and then holding it for 10s |
| **Step 6** | Inserting the dentist's hands into the patient's mouth and then keeping the dentist's hand in the patient's mouth for 5s |
| **Step 7** | Dental mirror introduction, followed by dental examination using only mirror during 5s |
| **Step 8** | Dental probe introduction, followed by dental examination using only probe during 5s |
| **Step 9** | Dental examination with the mirror and probe during 5s |
| **Step 10** | Occlusion examination, which implies that the patient keeps the teeth during the period of central occlusion during 5 to 10s |

*if patient could not enter the dental office that was for the purposes of this research counted as score 0.

other and the dentist gathers all the necessary data for the further treatment plan. Patients should always have time orientation how much each step will last therefore the counting should always be announced. The person performing the intervention should always count out loud, in a clear, pleasant and relaxed tone.

Descriptive statistics methods in SPSS version 26 (SPSS Inc, Chicago, IL) were used for the statistical analysis of the data. One dentist was engaged in supervising clinical dental (AV) treatment of patients in the pilot, and assessments were made using TEACCH scores. Each successful step was assigned the same score; for example, if step 1 was successful, the score was 1, and if step 2 was successful, the score was 2, and so on. In this way, the minimal score that a patient could achieve was 0 (if patient could not enter in dental office), and the maximal score was 10.

## Results

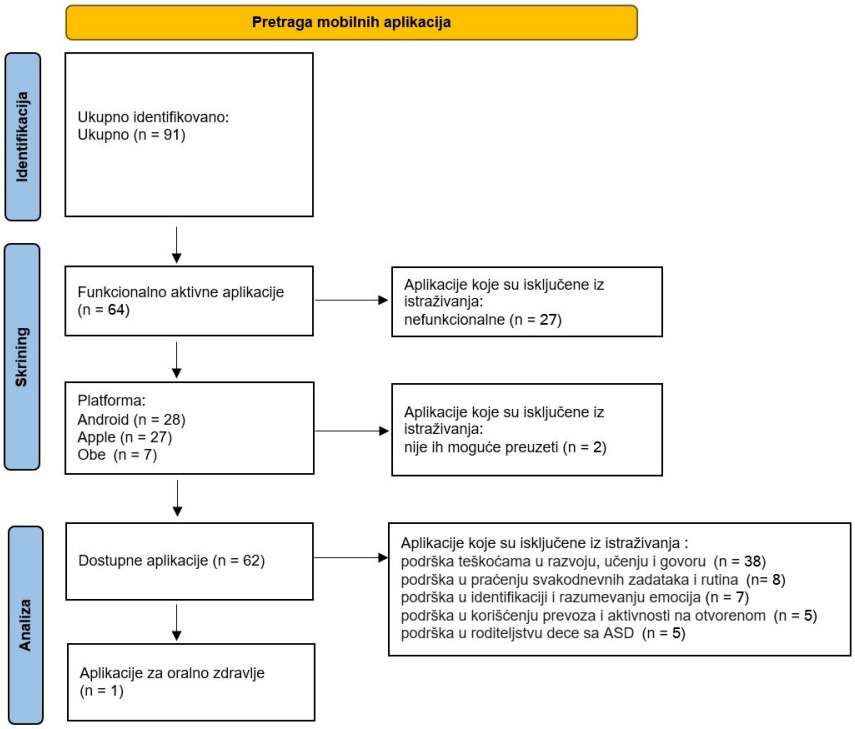
The review of the online app stores, resulted in the identification of 91 mobile applications aimed at supporting functioning of individuals with ASD in various aspects of life, with 64 (70.3%) deemed functional. Among the functional applications, more than half (59.4%) were designed to support ASD individuals with learning and speech difficulties. Frequency distribution of available applications depending on the application category is presented in the Figure 2.

Out of the total number of functional applications, only one (6.3%) was in the Serbian language, falling into the category of applications for developmental, learning, and speech difficulties. Three applications were in Croatian, all utilising the Latin script.

Among the overall number of applications, only one was available for enhancing oral health, and it was in English. These findings indicated the absence of applications related to oral health in the Serbian language using Cyrillic script.

After pilot test of the new application in the Serbian language and Cyrillic script interwiews with the parents were carried out. Regarding the comprehension of the content, several suggestions were put forward: including the voice of the dentist, integrating a timer for activity countdowns within the application, giving more prominence to images of the dental office and the dental chair, and enhancing the sounds of murmurs in the dental office along with the sound of dental instruments.

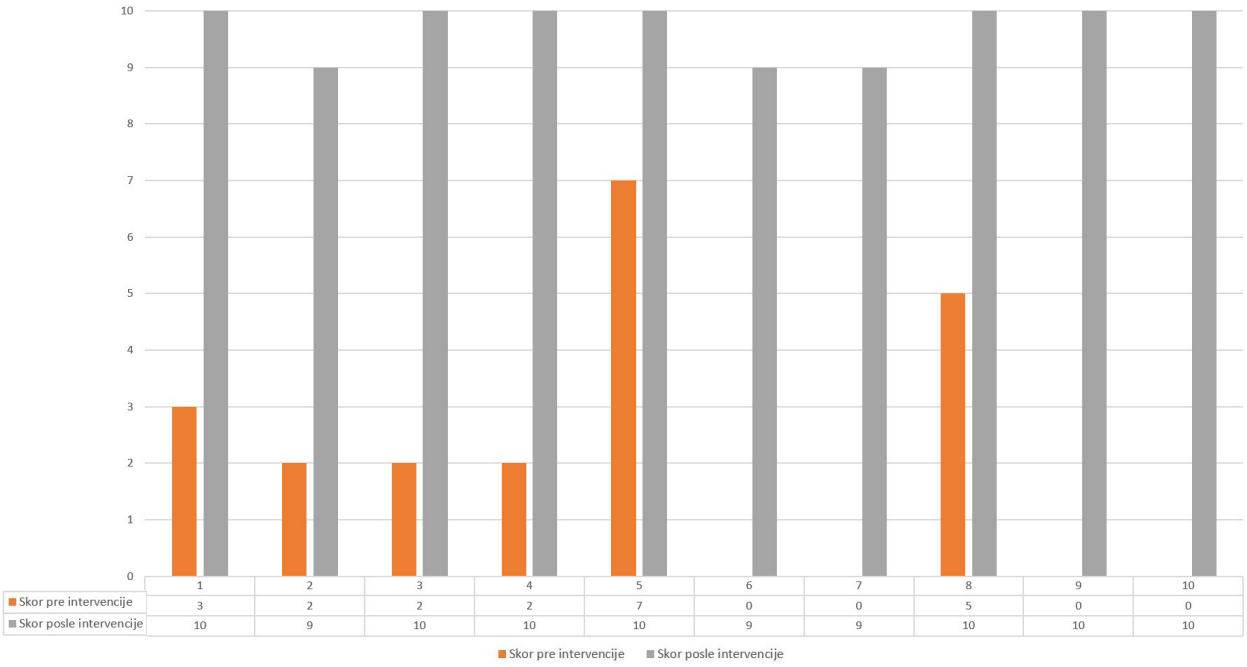
All parents observed reduced tension in their children during dental visits after the daily use of the application. An analysis of the TEACCH scores of participating children in the pilot study indicates an improvement in TEACCH scores after the application's use (9.7 ± 0.5) compared to TEACCH scores before using the application (2.1 ± 2.3) (mean score ± standard deviation) (Figure 3).




**Slika 2.** Dijagram toka koji predstavlja identifikaciju aplikacija za pomoć osobama sa ASD.

stomatološkoj ordinaciji. Pregledom literature nije pronađena nijedna studija koja procenjuje upotrebu i efikasnost mobilnih aplikacija za pripremu i prilagođavanje pacijenata prvenstveno prilikom posete stomatologu i stomatoloških intervencija.

Utvrđeno je da su anksioznost/strah od stomatologa prisutni kod 6,3% dece uzrasta od 5 do 10 godina (7). U populaciji dece sa autizmom, učestalost otežane saradnje sa stomatologom se višestruko povećava – utvrđeno je da više od polovine dece sa poremećajem autističnog spektra (50-72%) pokazuje znake anksioznosti, straha ili odbija da sarađuje sa stomatologom (3). Ovo se može pripisati strahu od nepoznatog, teškoćama u komunikaciji i pojačanoj reakciji na senzorne stimuluse. Takođe, autistični spektar ponašanja




**Slika 3.** Vizuelizacija TEACCH skorova pre i nakon pilot testiranja.

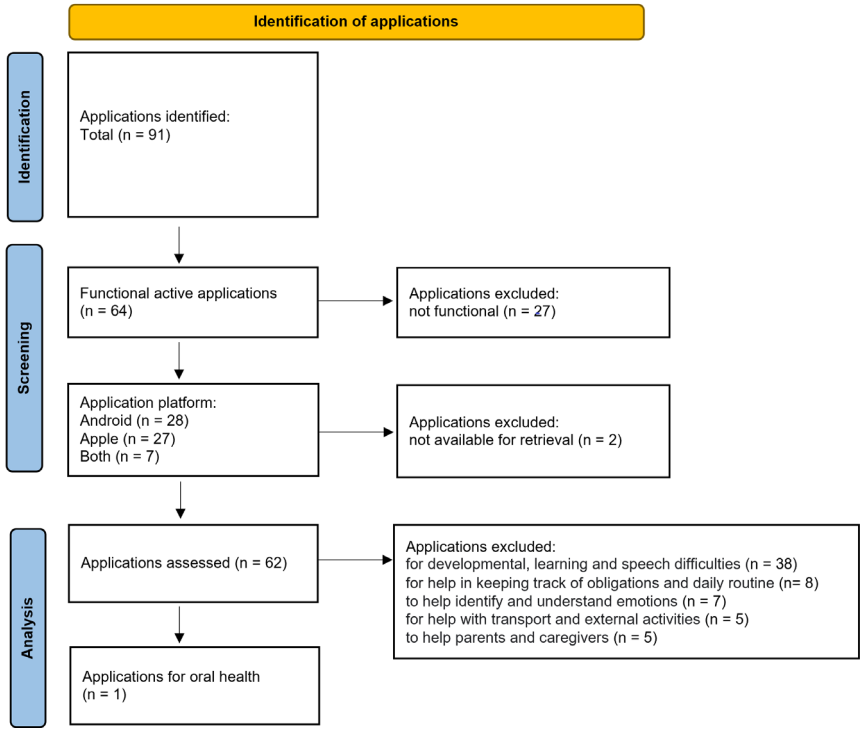



**Figure 2.** Flow diagram related to the identification of applications used to support ASD persons

However, due to the small sample size, we cannot assert statistical significance.

## Diskusija

The results of the study showed that there were no application in the Serbian language and Cyrillic script intended for ASD patients in dental office. The literature review did not find any studies evaluating the use and effectiveness of mobile applications for patient preparation and adaptation primarily for dental visits and dental interventions.

It was found that fear/anxiety related to the dentist is present in 6.3% of children of age 5 to 10 years (7). In the population of children with autism, the frequency of difficult cooperation

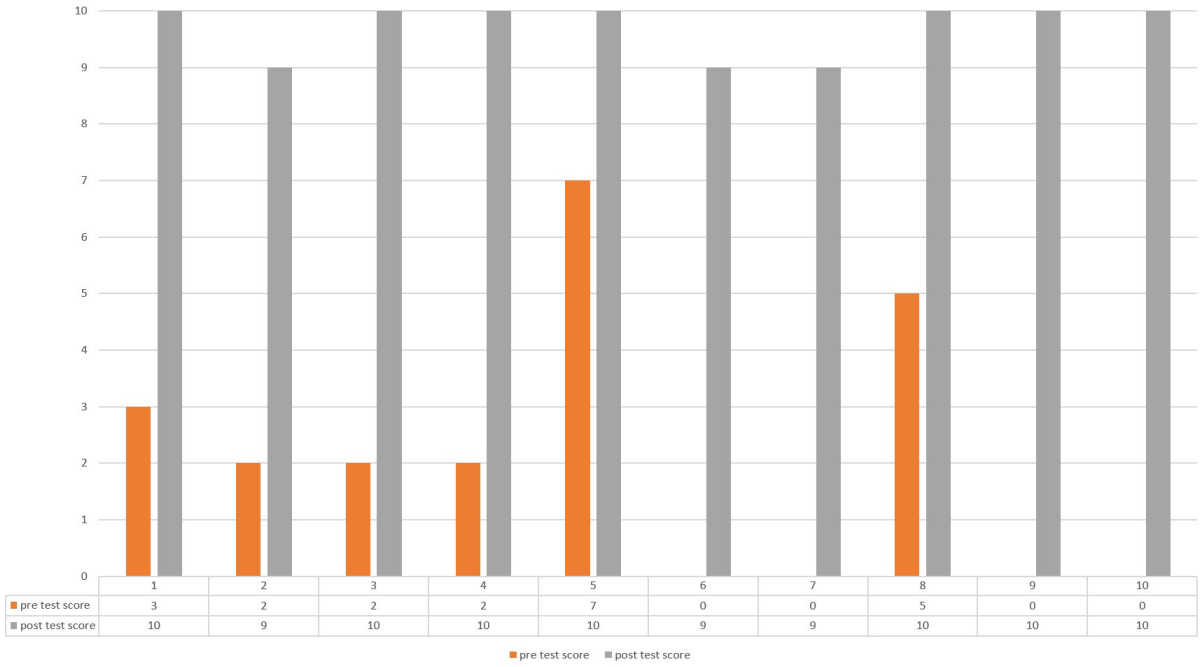



**Figure 3.** Visualization of pre and post pilot test TEACCH scores

obuhvata različite stepene poremećaja socijalne interakcije i komunikacije (1), što se često ogleda u otežanoj saradnji u stomatološkoj ordinaciji. Takođe, promene u ustaljenoj dnevnoj rutini mogu izazvati poteškoće u ponašanju i izlive besa. Napadi besa su kratkotrajne i iznenadne epizode besa i agresije u vidu neprijatnog ponašanja ili emocionalnih izliva. Često nastaju kao odgovor na nezadovoljene potrebe ili želje. Napadi besa se češće javljaju kod mlađe dece ili kod drugih osoba koje ne mogu da izraze svoje potrebe ili kontrolišu svoje emocije kada su frustrirani. Manifestuju se vikanjem, plačem, bacanjem na pod i udaranjem predmeta. Takođe, promene u ustaljenoj dnevnoj rutini mogu izazvati poteškoće u ponašanju i napade besa (8).

Osobe sa autizmom pokazuju poteškoće kada je u pitanju recipročna komunikacija/ interakcija, kao što je neočekivano reagovanje u razgovorima, pogrešno razumevanje neverbalnih poruka ili poteškoće u izgradnji prijateljstava koja su adekvatna uzrastu. Pored toga, mogu biti previše zavisni od rutine, veoma osetljivi na promene u svom okruženju ili intenzivno fokusirani na određene teme. Potrebno je da kliničari uzmu u obzir razlike u simptomima i ponašanju koji mogu varirati od osobe do osobe prilikom plana terapije. Prema kriterijumima DSM-5, osobe sa ASD moraju da ispoljavaju simptome od ranog detinjstva, čak i ako se ovi simptomi prepoznaju tek kasnije. Prema podacima iz savremene literature, dijagnoza iz spektra autizma postavlja se nakon četvrte godine života (9). Smatra se da rano započinjanje lečenja ima pozitivan uticaj na ishod autističnog spektra (10). Iz istog razloga, rana poseta stomatologu i blagovremena primena bihejvioralnih mera, preventivnih i profilaktičkih postupaka omogućila bi značajno unapređenje saradnje i unapređenje zdravlja.

Kliničko iskustvo je da je kod dece sa autizmom najteže ostvariti komunikaciju i saradnju tokom pregleda, a intervencije u ambulantnim uslovima često su teško izvodljive s obzirom na nedovoljnu obučenost stomatologa za rad sa ovom grupom pacijenata. Konvencionalne bihejvioralne tehnike za smanjenje straha od stomatološke intervencije uključuju: „reci-pokaži-uradi“, desenzitizaciju, kontrolu glasa/hipnozu, pozitivnu stimulaciju, skretanje pažnje i prisustvo ili odsustvo roditelja. Međutim, nedostatak socijalnih i komunikacijskih veština koji karakteriše ponašanje iz spektra autizma, nedostatak potrebe za deljenjem osećanja sa drugima, odsustvo socijalno-emocionalnog reciprociteta, smanjena sposobnost imitacije i razumevanja drugih ljudi i njihovih mentalnih stanja, želja i ponašanja otežavaju korišćenje i razumevanje neverbalnih obrazaca ponašanja (10). Ove karakteristike ne samo da otežavaju proces socijalizacije i prilagođavanja stomatološkom lečenju, već često znatno otežavaju i onemogućavaju primenu uobičajenih bihejvioralnih metoda za koje su stomatolozi obučeni.

Bihejvioralna teorija nalaže da što je osoba više izložena stimulansu koga se plaši, na bezbedan, nežan i postepen način, to se više gradi tolerancija na anksioznost, što će na kraju smanjiti intenzitet reakcije straha. Za decu sa poremećajem iz spektra autizma i decu sa smetnjama u učenju, ovo treba da bude praktično, vizuelno i što je moguće realnije, jer deca sa neurorazvojnim poremećajima imaju poteškoća da razumeju apstraktne pojmove (11). Farmakološke metode koje se za sada mogu primeniti u našoj zemlji su *per os* davanje sedativa, intravensko i inhalaciono davanje sedativa, ili opšta endotrahealna anestezija, pri čemu je za poslednje dve procedure potrebno prisustvo anesteziologa.

Savremeni svet, a sa njim i pandemija virusa kovid-19 doveli su do toga da se nove tehnologije koje se brzo razvijaju sve više koriste u svakodnevnom životu. Rukovodeći se ovim, a takođe i na osnovu istraživanja došlo se do zaključka da nove tehnologije mogu značajno olakšati svakodnevni život dece sa autizmom. Tehnološke metode se uglavnom zasnivaju na odvlačenju pažnje korišćenjem slušalica za slušanje muzike, igranjem igrica i gledanjem crtanih filmova na telefonu i tabletu kako bi se smanjilo senzorno opterećenje. Odvlačenje pažnje se godinama uspešno koristi u stomatologiji i zasniva se na hipotezi da percepcija bola ima jaku psihološku komponentu, što znači da ako se manje pažnje usmeri direktno na stresor ili okidač anksioznosti, percepcija bola je slabija. Stoga bi se optimalno odvraćanje pažnje moglo postići korišćenjem multisenzornog iskustva putem mobilnih aplikacija. Mobilne aplikacije i igrice angažuju ruke i prste prilikom korišćenja telefona ili tableta, a s obzirom na to da ove radnje nisu prikladne prilikom stomatološke intervencije jer je neophodna saradnja deteta, bilo bi važno razmisliti o programiranju mobilnih aplikacija tako da se zasnivaju na tehnici „razotkrivanja“ iskustava koja su nepoznata detetu i sa kojima treba da se susretne i suoči. Tera-

with the dentist increases significantly; it was determined that more than half of the children with autism spectrum disorder (50-72%) show signs of anxiety, fear, or refuse to cooperate with the dentist (3). This can be attributed to the fear of the unknown, difficulty in communication, and heightened reaction to sensory stimuli. Also, the autistic spectrum of behavior includes varying degrees of social interaction and communication disorders (1), which is often reflected in difficult cooperation in the dental office. Also, changes in the established daily routine can cause behavioral difficulties and temper tantrums. Temper tantrums are short-lived and sudden episodes of anger and aggression in the form of unpleasant behavior or emotional outbursts. They often arise in response to unsatisfied needs or desires. Tantrums are more likely to occur in younger children or others who cannot express their needs or control their emotions when frustrated. They manifest themselves by shouting, crying, throwing on the floor and hitting objects. Also, changes in the established daily routine can cause behavioral difficulties and temper tantrums (8).

Individuals with autism exhibit deficits in reciprocal communication/interaction, such as responding inappropriately in conversations, misreading nonverbal interactions, or having difficulties in building age-appropriate friendships. In addition, they may be too dependent on routine, very sensitive to changes in their environment, or intensely focused on certain subjects. Clinicians need to consider differences in symptoms and behavior that may vary from person to person when planning treatment. According to DSM-5 criteria, individuals with ASD must exhibit symptoms from early childhood, even if these symptoms are not recognized until later. According to data from contemporary literature, in the majority of cases, the diagnosis from the autism spectrum is made after the fourth year of life (9). It is believed that early initiation of treatment has a positive impact on the outcome of the autism spectrum (10). For the same reason, an early visit to the dentist and the timely application of behavioral measures, preventive and prophylactic procedures would enable a significant improvement in cooperation and improvement of health.

Clinical experience shows that in children with autism, it is most difficult to achieve communication and cooperation during the examination, and interventions in ambulatory conditions are often difficult to implement given the insufficient training of dentists to work with this group of patients. Conventional behavioral techniques for reducing dental phobia include: "Say-Show-Do", desensitization, voice control/hypnosis, positive stimulation, distraction and the presence or absence of parents. However, the deficit of social and communication skills that characterizes the autistic spectrum of behavior, the lack of need to share feelings with others, the absence of social-emotional reciprocity, the reduced ability to imitate and understand other people and their mental states, desires and behaviors make it difficult to use and understand non-verbal behavior patterns (10). These characteristics not only make the process of socialization and adaptation to dental treatment difficult, but often make it much more difficult and impossible to apply the usual behavioral methods that dentists are trained for.

Behavioral theory dictates that the more a person is exposed to the feared stimulus, in a safe, gentle and gradual way, the more tolerance to anxiety is built, which will eventually reduce the intensity of the fear reaction. For children with autism spectrum disorder and children with learning disabilities, this should be practical, visual and as realistic as possible, because children with neurodevelopmental disorders have difficulty understanding abstract concepts (11). Pharmacological methods that can be used in our country for now include per os administration of sedatives, intravenous and inhalation administration of sedatives or general endotracheal anesthesia, with the last two procedures requiring the presence of an anesthesiologist.

The modern world, and together with it the COVID-19 virus pandemic, have led to the fact that new rapidly developing technologies are increasingly used in everyday life. Guided by this, and also based on research, the conclusion was reached that new technologies can significantly facilitate the daily life of children with autism. Technological methods are mainly based on distraction using headphones to listen to music, play games and watch cartoons on the phone and tablet to reduce the sensory load. Distraction has been successfully used in dentistry for years and is based on the hypothesis that pain perception has a strong psychological component, which means that if less attention is focused directly on

pija izlaganjem se smatra prvim izborom za mnoge fobije (12). Zasniva se na ublažavanju negativnog dejstva stresora kroz ponovljeno i pojačano izlaganje pacijenta situacijama koje kod njega izazivaju anksioznost (13). Terapija izlaganjem je prilagođena za upotrebu u virtuelnom svetu (eng. *Virtual Reality Exposure Therapy*, VRET), tako što pacijentu daje osećaj prisustva u virtuelnom prostoru, što je posebno pogodno za decu sa autizmom koja obično provode veći deo dana sa tehnološkim pomagalima. Korišćenje virtuelnih aplikacija aktivira više čula (vida, sluha, dodira) i tako odvlači pažnju od spoljašnjih pokretača čula. Psihološki osećaj koji proizilazi iz ovoga je osećaj prisustva (14).

Pregledom literature potvrđeno je da preoperativna priprema pacijenata korišćenjem tehnoloških pomagala značajno smanjuje anksioznost kod dece (15). Povećana preoperativna anksioznost je povezana sa neprijatnim postoperativnim ishodom: pojačan bol, duži oporavak, postoperativna anksioznost. Takođe je povezana sa pojavom noćnog mokrenja i problemom sa spavanjem. Deca koja su bila izložena virtuelnom obilasku stomatološke ordinacije pokazala su niže nivoe preoperativne anksioznosti u poređenju sa kontrolnom grupom. Takođe, kod dece koja su za stomatološke intervencije pripremana putem interaktivnih kompjuterskih igrica ili animiranih filmova, preoperativna anksioznost je značajno smanjena u poređenju sa kontrolnom grupom koja je pripremana samo verbalno. Deca su preoperativno pripremana pre svega za opštu anesteziju uz pomoć virtuelnih slika aparata za opštu anesteziju i samog postupka opšte anestezije (16).

Mobilne aplikacije kao tehnološka pomagala su veoma primenjive u zdravstvu jer pomažu pacijentima da se informišu o zdravlju uopšte i simptomima bolesti, kao i da se kod kuće pripreme za predstojeći pregled i intervenciju. Ovo je posebno pogodno za mlađu populaciju, a pogotovo za decu sa autizmom i teškoćama u učenju i govoru, koja inače provode dosta vremena u virtuelnom svetu koristeći savremena tehnološka pomagala. Sama priprema bi započela osnovnim korišćenjem aplikacija koje se tiču oralnog zdravlja kako bi se deca sa autizmom najpre upoznala sa proizvodima za oralnu higijenu, okruženjem u stomatološkoj ordinaciji i konceptom stomatološkog pregleda. Uz korišćenje mobilnih aplikacija kod kuće, pre posete stomatologu, pacijent se „transportuje“ u virtuelni prostor koji pacijentu daje osećaj da se nalazi u imaginarnoj stomatološkoj čekaonici i ordinaciji. Na ovaj način se stimulišu auditorne i vizuelne senzacije – kod određenog broja pacijenata sa ASD-om vizuelna iskustva se doživljavaju kao prijatna, dok se, sa druge strane, zvuci poput šištanja pumpe, i zujanja kolenjaka i turbine doživljavaju kao uznemirujući. Upoznavanje sa njima putem aplikacije bilo bi značajno u pripremi za predstojeće stomatološke procedure. Takođe, aplikacija praktično prikazuje put od kuće kroz grad do čekaonice i stomatološke ordinacije. To bi pomoglo da se pažnja pacijenta skrene sa osećaja straha od nepoznatog, tako što bi se dete kroz imaginarni sadržaj upoznalo sa tim kako izgledaju stomatološka čekaonica i ordinacija, stomatološka stolica i instrumenti. Na ovaj način se detetu pomaže da se psihički pripremi za nepoznate situacije i da prevaziđe stresne faktore koji su pokretači jakih emocionalnih reakcija i napada besa u ordinaciji. Time bi se poboljšala dostupnost standardne stomatološke nege ovih pacijenata i ostvario njihov puni zdravstveni potencijal, čime se smanjuje verovatnoća da će intervencija biti obavljena u opštoj anesteziji.

Dodatne kliničke studije su potrebne da bi se procenio značaj korišćenja mobilnih aplikacija u pripremi za posete stomatologu i za uspostavljanje direktne komunikacije sa stomatologom. Praktično, to još nije potvrđeno, ali se teoretski može istaći da se mobilne aplikacije mogu koristiti kao alat za prilagođavanje i navikavanje na stomatološke intervencije, kao i za smanjenje anksioznosti i straha od nepoznatog pre i tokom posete stomatologu. Konačno, ovo bi moglo pomoći da se smanji broj poseta, da se savlada tehnika pranja zuba ili da se stomatološka intervencija završi efikasnije.

## Zaključak

Mobilne aplikacije su alati koji bi olakšali saradnju dece sa autizmom u ordinaciji, kao i upoznavanje sa intervencijom pre prve posete stomatologu, čime bi se olakšala komunikacija između deteta i roditelja sa stomatologom. Nepostojanje bilo kakve mobilne aplikacije na srpskom jeziku ide u prilog neophodnosti razvoja aplikacije za mlađu decu i decu sa smetnjama u razvoju koja ne koriste engleski jezik.

Mogućnost korišćenja mobilnih aplikacija mogla bi značajno da doprinese saradnji tokom poseta stomatologu osoba sa ASD, poboljšanju rutine oralne higijene i smanjenju straha od

the stressor or anxiety trigger, the pain perception is weaker. Therefore, the optimal distraction of attention could be achieved using a multisensory experience through mobile applications. Mobile applications and games employ hands and fingers during the use of a phone or tablet, and considering that these actions are not appropriate during a dental intervention because the cooperation of the child is necessary, it would be important to consider programming mobile applications so that they are based on the technique of "exposing" the child unknown experiences that he needs to meet and face. Exposure therapy is considered the first choice for many phobias (12). It is based on mitigating the negative effect of stressors through repeated and increased exposure of the patient to situations that cause him anxiety (13). Exposure therapy is adapted for use in the virtual world (known as VRET-Virtual Reality Exposure Therapy) by giving the patient a sense of presence in a virtual space, which is especially suitable for children with autism who normally spend most of the day with technological aids. Using virtual applications activates more senses (sight, hearing, tactile) and thus distracts attention from external sensory triggers. The psychological feeling that results from this is a sense of presence (14).

A review of the literature confirmed that preoperative preparation of patients using technological aids significantly reduces anxiety in children (15). Increased preoperative anxiety is associated with an unpleasant postoperative outcome: increased pain, longer recovery, postoperative anxiety. It is also associated with the occurrence of nocturnal urination and sleep problems. Children exposed to the virtual tour of dental study showed lower levels of preoperative anxiety than the control group. Also, in children who were prepared for dental interventions through interactive computer games or animated films, preoperative anxiety was significantly reduced compared to the control group that was only prepared verbally. Children were pre-operatively prepared primarily for general anesthesia using virtual images of the general anesthesia apparatus and the general anesthesia procedure itself (16).

Mobile applications as a technological aid are very applicable in healthcare since they help patients to be informed about health in general and symptoms of diseases as well to prepare themselves at home for the upcoming examination and intervention. This is particularly suitable for the younger population and especially children with autism and learning and speech difficulties, who normally spend a lot of time in the virtual world using modern technological aids. The preparation itself would begin with the basic use of applications related to oral health so that children with autism would first become familiar with oral hygiene products, the environment in the dental office and the concept of a dental examination. With the use of mobile applications at home, before visiting the dentist, the patient is "transported" to a virtual space that gives the patient feeling of being in an imaginary dental waiting room and office. In this way, auditory and visual sensations are stimulated - For a certain number of patients with ASD, visual experiences are perceived as pleasant while, on the other hand, sounds as the rustling of the pump, the hum of the crank and the turbine are disturbing. Getting familiar with these through the application would be of importance in preparation for oncoming dental procedures. Also, the application shows virtually the path from home through the city to the waiting room and the dental office. This would help to divert the patient's attention from the feeling of fear of the unknown, by introducing the child to the dental waiting room and office, dental chair and instruments through the imaginary content. In this way, the child is helped to be mentally prepared for unknown situations and to overcome stressful factors that are the triggers of strong emotional reactions and temper tantrums in the doctor's office. This would improve the availability of standard dental care of these patients and achieve their full health potential, thus reducing the likelihood that the intervention would be performed under general anesthesia.

Practically, it has not yet been confirmed, but theoretically it can be pointed out that mobile applications can be used as a tool to adapt and get used to dental interventions, as well as to reduce anxiety and fear of the unknown before and during the visit to the dentist. Finally, this could help to reduce the number of visits, to master the technique of teeth brushing or to complete the dental intervention more efficiently. Although confirming that use of applications in dentistry might be helpful, result of the present study should be interpreted carefully. It should be highlighted that subjects had several (at least five) visits to the

nepoznatog tokom stomatoloških tretmana – kako preventivnih, tako i terapijskih.

## Zahvalnica

Ovo istraživanje i dizajn mobilne aplikacije podržani su od strane Ministarstva zdravlja, Sektora za javno zdravlje i implementaciju projekata, Program za unapređenje oralnog zdravlja dece sa posebnim potrebama – Porodična i institucionalna podrška – faza 2; i od strane Ministarstva prosvete, nauke i tehnološkog razvoja Republike Srbije [broj granta 451-03-68/2022-14/200163].

Autori se zahvaljuju na podršci i pomoći Udruženju Autizam Srbija, Udruženju Autizam Beograd, gospođi Jeleni Šebez Inić na podršci i savetima, kao i roditeljima osoba sa autizmom. Autori se srdačno zahvaljuju na znanju i iskustvu koje su podelili sa stomatolozima.

Autori se zahvaljuju na profesionalizmu i velikom trudu gospođi Mirjani Karaklajić koja je pružila svoje znanje u oblasti veb i grafičkog dizajna i gospodinu Urošu Tomoviću koji je pružio svoje znanje u oblasti programiranja tokom kreiranja aplikacije. Autori se najsrdačnije zahvaljuju dr Milošu Ljubučiću koji je svojom ljubaznošću obezbedio fotografije korišćene za aplikaciju. Autori iskreno odaju priznanje za rad Sonje Jovanović i Aleksandre Lazarević, koje su studentkinje osnovnih studija Stomatološkog fakulteta Univerziteta u Beogradu, kao i studentima osnovnih studija Filozofskog fakulteta Univerziteta u Beogradu koji su pomogli u prikupljanju svih podataka i unosa u bazu podataka.

## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

## Reference

1. Đorđević M, Glumbić N. Primena vršnjačkih strategija u radu sa decom sa poremećajima autističkog spektra u inkluzivnom školskom kontekstu. Fakultet za specijalnu edukaciju i rehabilitaciju u Beogradu. 2015;21(1):39–52.
2. Smiljkić Z, Jeremić M, Vuković A, Perić T, Glumbić N, Marković D. Stomatološko zbrinjavanje dece sa poremećajima iz spektra autizma. Stomatolog. 2018;24(2):17–24.
3. Stein LI, Lane CJ, Williams ME, Dawson ME, Polido JC, Cermak SA. Physiological and behavioral stress and anxiety in children with autism spectrum disorders during routine oral care. Biomed Res Int. 2014;2014:694876. doi: 10.1155/2014/694876
4. Jeremić M, Ćirić P, Marković D, Vuković A. Deca sa posebnim potrebama u stomatološkoj ordinaciji. Zdravstvena zastita. 2020;49(4):53–66. doi: 10.5937/zdravzast49-27433
5. Stathopoulou A, Loukeris D, Karabatzaki Z, Politi E, Salapata Y, Drigas A. Evaluation of mobile apps effectiveness in children with autism social training via digital social stories. Int J Interact Mob Technol. 2020;14(03):4-17. doi 10.3991/ijim.v14i03.1028
6. Orellana LM, Martínez-Sanchis S, Silvestre FJ. Training adults and children with an autism spectrum disorder to be compliant with a clinical dental assessment using a TEACCH-based approach. J Autism Dev Disord. 2014;44(4):776–85. doi: 10.1007/s10803-013-1930-8.
7. Chhabra N, Chhabra A, Walia G. Prevalence of dental anxiety and fear among five to ten year old children: a behaviour based cross sectional study. Minerva Stomatol. 2012 Mar;61(3):83–9.
8. Walter H, DeMaso D. Disruptive, impulse-control, and conduct disorders . In: Kliegman R, St. Geme J, Blum N, Shah S, Tasker R, Wilson K, editors. Nelson Textbook of Pediatrics. 21st ed. Philadelphia, PA: Elsevier; 2020.
9. Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. Pediatrics. 2005;116(6):1480–6. doi: 10.1542/peds.2005-0185.
10. Fernell E, Eriksson MA, Gillberg C. Early diagnosis of autism and impact on prognosis: a narrative review. Clin Epidemiol. 2013;5:33–43. doi: 10.2147/CLEP.S41714
11. Cunningham A, McPolin O, Fallis R, Coyle C, Best P, McKenna G. A systematic review of the use of virtual reality or dental smartphone applications as interventions for management of paediatric dental anxiety. BMC Oral Health. 2021;21(1):244. doi: 10.1186/s12903-021-01602-3
12. Böhnlein J, Altegoer L, Muck NK, Roesmann K, Redlich R, Dannlowski U, et al. Factors influencing the success of exposure therapy for specific phobia: A systematic review. NeurosciBiobehav Rev. 2020;108:796–820. doi: 10.1016/j.neubiorev.2019.12.009.
13. Benito KG, Walther M. Therapeutic Process During Exposure: Habituation Model. J Obsessive CompulsRelatDisord. 2015;6:147–57. doi: 10.1016/j.jocrd.2015.01.006
14. Slater M. Immersion and the illusion of presence in virtual reality. Br J Psychol. 2018;109(3):431–3. doi: 10.1111/bjop.12305
15. Botella C, Fernández-Álvarez J, Guillén V, García-Palacios A, Baños R. Recent Progress in Virtual Reality Exposure Therapy for Phobias: A Systematic Review. Curr Psychiatry Rep. 2017;19(7):42. doi: 10.1007/s11920-017-0788-4.
16. Campbell C, Hosey MT, McHugh S. Facilitating coping behavior in children prior to dental general anesthesia: a randomized controlled trial. Paediatr Anaesth. 2005;15(10):831–8. doi: 10.1111/j.1460-9592.2004.01565.x.

dental office which might influence cooperativity since being in an already familiar setting and previous positive experience are confirmed to be supportive for patients with behavioral difficulties. More clinical studies are needed to assess the importance of using mobile apps in preparation for dental visits and for establishing direct communication with dentist.

## Conclusion

Mobile applications are the tools that would make easier cooperation of children with ASD in dental office, as well as familiarization with the intervention before their first visit to the dentist, thus facilitating mutual communication between the child and parents with the dentist. The absence of any mobile application in the Serbian language underscores the need for the development of an application tailored for younger children and those with disabilities who do not use the English language. The possibility of using mobile applications could significantly contribute the cooperation during visits to the dentist for persons with ASD, improve their oral hygiene routine, and reduce fear of the unknown during dental treatments - both preventive and therapeutic.

## Acknowledgement

This survey and design of the mobile application was supported by the Ministry of Health, Sector for Public Health and Project Implementation, Program for Oral Health Improvement in Children with Special Care Needs – Family and Institutional Support – phase 2; and the Ministry of Education, Science and Technological Development of the Republic of Serbia [grant number 451-03-68/2022-14/200163].

The authors gratefully acknowledge the support and assistance of Association Autism Serbia, Association Autism Belgrade, and Mrs. Jelena Šebez Inić for their support and advice as parents of persons with ASD. The authors warmly thank them for sharing their knowledge and experiences with dental health professionals.

The authors also express their gratitude for the professionalism and great efforts of Mrs. Mirjana Karaklajić, who provided her expertise in web and graphic design, and Mr. Uroš Tomović, who contributed his expertise in programming during the application's design process. Authors warmly thank Dr. Miloš Ljubičić who provided photos for the application.

Furthermore, the authors sincerely acknowledge the hard work of Sonja Jovanović and Aleksandra Lazarević, undergraduate students at the School of Dental Medicine, University of Belgrade, as well as Milica Dodić, Dragana Gagić, Tatjana Radaković, and Lana Radnić, undergraduate students at the Faculty of Philosophy, University of Belgrade, who participated in the development of the mobile app.

## Competing interests

The authors declared no competing interests.

## References

1. Đorđević M, Glumbić N. Application of peer strategy in working with children with autistic spectrum disorders in inclusive school context. Belgrade School of Special Education and Rehabilitation. 2015;21(1):39–52.
2. Smiljkić Z, Jeremić M, Vuković A, Perić T, Glumbić N, Marković D. Dental treatment in children with autism [article in Serbian]. Stomatolog. 2018;24(2):17–24.
3. Stein LI, Lane CJ, Williams ME, Dawson ME, Polido JC, Cermak SA. Physiological and behavioral stress and anxiety in children with autism spectrum disorders during routine oral care. Biomed Res Int. 2014;2014:694876. doi: 10.1155/2014/694876
4. Jeremić M, Ćirić P, Marković D, Vuković A. Children with special needs in the dental office. Zdravstvena zastita. 2020;49(4):53–66. doi: 10.5937/zdravzast49-27433
5. Stathopoulou A, Loukeris D, Karabatzaki Z, Politi E, Salapata Y, Drigas A. Evaluation of mobile apps effectiveness in children with autism social training via digital social stories. Int J Interact Mob Technol. 2020;14(03):4-17. doi 10.3991/ijim.v14i03.1028
6. Orellana LM, Martínez-Sanchis S, Silvestre FJ. Training adults and children with an autism spectrum disorder to be compliant with a clinical dental assessment using a TEACCH-based approach. J Autism Dev Disord. 2014;44(4):776–85. doi: 10.1007/s10803-013-1930-8.
7. Chhabra N, Chhabra A, Walia G. Prevalence of dental anxiety and fear among five to ten year old children: a behaviour based cross sectional study. Minerva Stomatol. 2012 Mar;61(3):83–9.
8. Walter H, DeMaso D. Disruptive, impulse-control, and conduct disorders . In: Kliegman R, St. Geme J, Blum N, Shah S, Tasker R, Wilson K, editors. Nelson Textbook of Pediatrics. 21st ed. Philadelphia, PA: Elsevier; 2020.
9. Mandell DS, Novak MM, Zubritsky CD. Factors associated with age of diagnosis among children with autism spectrum disorders. Pediatrics. 2005;116(6):1480–6. doi: 10.1542/peds.2005-0185.

**Primljen:** 26.10.2023. **Revizija:** 26.11.2023. **Prihvaćen:** 02.12.2023.

10. Fernell E, Eriksson MA, Gillberg C. Early diagnosis of autism and impact on prognosis: a narrative review. Clin Epidemiol. 2013;5:33–43. doi: 10.2147/CLEP.S41714
11. Cunningham A, McPolin O, Fallis R, Coyle C, Best P, McKenna G. A systematic review of the use of virtual reality or dental smartphone applications as interventions for management of paediatric dental anxiety. BMC Oral Health. 2021;21(1):244. doi: 10.1186/s12903-021-01602-3
12. Böhnlein J, Altegoer L, Muck NK, Roesmann K, Redlich R, Dannlowski U, et al. Factors influencing the success of exposure therapy for specific phobia: A systematic review. NeurosciBiobehav Rev. 2020;108:796–820. doi: 10.1016/j.neubiorev.2019.12.009.
13. Benito KG, Walther M. Therapeutic Process During Exposure: Habituation Model. J Obsessive CompulsRelatDisord. 2015;6:147–57. doi: 10.1016/j.jocrd.2015.01.006
14. Slater M. Immersion and the illusion of presence in virtual reality. Br J Psychol. 2018;109(3):431–3. doi: 10.1111/bjop.12305
15. Botella C, Fernández-Álvarez J, Guillén V, García-Palacios A, Baños R. Recent Progress in Virtual Reality Exposure Therapy for Phobias: A Systematic Review. Curr Psychiatry Rep. 2017;19(7):42. doi: 10.1007/s11920-017-0788-4.
16. Campbell C, Hosey MT, McHugh S. Facilitating coping behavior in children prior to dental general anesthesia: a randomized controlled trial. Paediatr Anaesth. 2005;15(10):831–8. doi: 10.1111/j.1460-9592.2004.01565.x.



**Received:** 10/26/2023 **Revised:** 11/26/2023 **Accepted:** 12/02/2023

## UPUTSTVO AUTORIMA

U časopisu **Zdravstvena zaštita** objavljuju se originalni naučni radovi, prethodna saopštenja, pregledi i stručni radovi, kratka saopštenja, uvodnici, pisma uredniku, meta-analize, prikazi bolesnika, aktuelne teme, prikazi stručnih knjiga i skupova, i drugo, iz svih oblasti medicine, farmacije, biohemije, stomatologije i menadžmenta u zdravstvu.

Uz rukopis za objavljivanje u časopisu **Zdravstvena zaštita** treba dostaviti propratno pismo (izjavu) potpisanu od svih autora: 1) da rad nije prethodno objavljivan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu; 2) da su rukopis pročitali i odobrili svi autori koji ispunjavaju kriterijume autorstva; 3) da su u radu kontakt podaci za sve autore tačni; 4) da autor za korespondenciju, u ime drugih autora, potpisuje Ugovor o autorskim pravima, kojim svi autori rada prenose svoja autorska prava na izdavača časopisa - Komoru zdravstvenih ustanova Srbije.

Časopis je u režimu otvorenog pristupa (engl. *Open Access*) od septembra 2019. godine i objavljuje se četiri puta godišnje. Svi autori da bi poslali rukopis za objavljivanje u časopisu elektronski treba da budu registrovani e-mail adresom na internet stranici časopisa: **https://aseestant.ceon.rs/index.php/zdravzast**. Ukoliko postoji bilo koji problem u procesu elektronskog slanja rukopisa, rukopis se može proslediti na e-mail: **urednik@komorazus.org.rs.**

### Priprema rukopisa za objavljivanje u časopisu

Rukopis dostaviti na engleskom ili spskom jeziku (latinicom), sa rezimeima na srpskom i engleskom. Tekst rada piše se sa proredom 1,5 na stranicama A4 formata. Kuca se u programu za obradu teksta Word, fontom *Times New Roman* i veličinom slova 12 i marginama od 25 mm. Izbegavati deljenje reči (hifenacije), kao i **bold** i *italic* slova. Originalni članci, opšti pregledi (uslov da autori navedu 5 autocitata) i meta-analize ne smeju prelaziti 16 strana (bez priloga), stručni rad i aktuelne teme 10 strana, članci iz istorije medicine, kazuistika (prikaz jednog ili serije slučajeva) i prethodna saopštenja – 8 strana, a komentari, pisma uredniku, izveštaji sa skupova i prikazi knjiga 3 strane. Za izradu grafičkih priloga koristiti program *Windows* iz programskog paketa *Microsoft Office* (*Excel, Word Graph*).

**Delovi rada su:** naslovna strana, sažetak na srpskom i engleskom jeziku sa ključnim rečima na srpskom i engleskom jeziku, tekst rada (Uvod, Metode, Rezultati, Diskusija, Zaključak, Literatura, Zahvalnica) i prilozi.
Tekst rada pisati kratko i jasno, a skraćenice koristiti samo za veoma dugačke nazive i za nazive koji su poznati kao skraćenice (npr. sida, HIV, itd).

### Naslovna strana

Navesti naziv rada (velikim slovima), puna imena i prezimena autora, njihove stručne titule i nazive ustanova i mesta u kojima rade. Imena autora povezati sa nazivima ustanova indeksiranim arapskim brojevima. Takođe navesti ime i prezime autora za korespondenciju, njegovu ustanovu, adresu ustanove, broj telefona i e-mail adresu.

### Sažetak i ključne reči

Druga strana treba da sadrži: naslov rada, strukturisani sažetak do 250 reči i ključne reči na srpskom jeziku. Sažetak se sastoji iz četiri dela: Uvod/Cilj, Metode, Rezultati i Zaključak. Ispod sažetka navodi se 3-8 ključnih reči. Kod prikaza jednog ili serije slučajeva sažetak ima tri dela: Uvod/cilj, Prikaz bolesnika i Zaključak, a kod preglednih radova sažetak je deskriptivan (bez podcelina). Treća strana je identična drugoj, ali je na engleskom jeziku.

**INSTRUCTIONS FOR AUTHORS**

The Journal of **Health Care** publishes original scientific papers, short communications, reviews and professional papers, short press releases, editorials, letters to the editor, meta-analyses, case reports, actual topics, reviews of expert books and conferences, in all fields of medicine, pharmacy, biochemistry, dentistry and healthcare management.

The manuscript for publication in the Journal of **Health Care** should be accompanied by a cover letter (statement) signed by all authors: 1) that the manuscript has not been previously published and that it has not been simultaneously submitted for publication in another journal; 2) that the manuscript has been read and approved by all authors who meet the authorship criteria; 3) that the contact information for all authors is correct in the manuscript; 4) that the corresponding author, on behalf of other authors, signs the Copyright Agreement, by which all authors of the work transfer their copyright to the publisher of the journal - the Chamber of Health Institutions of Serbia.

The journal has been in Open Access mode since September 2019 and it is published four times a year. All authors must be registered electronically by e-mail on the journal website: **https://aseestant.ceon.rs/index.php/zdravzast** in order to submit the manuscript for publication in the journal. If there is any problem in the process of sending the manuscript electronically, the manuscript can be forwarded to e-mail: **urednik@komorazus.org.rs.**

**Preparation of a manuscript for publication in the Journal**

The manuscript should be submitted in English or Serbian (latin alphabet), with summaries in Serbian and English. The text of the manuscript should be written with a 1.5 line spacing on A4 pages and 25 mm margins. The text should be typed in Word, Times New Roman font and font size 12. Avoid hyphenation as well as **bold** and *italic* letters. Original articles, reviews (condition for authors to cite 5 self-citations) and meta-analyses must not exceed 16 pages (without attachments), professional articles and actual topics 10 pages, articles in medical history, case reports and case series (presentation of one or a series of cases) and previous reports - 8 pages, and comments, letters to the editor, conference reports and book reviews 3 pages. To create graphical attachments, use Windows from Microsoft Office (Excel, Word Graph).

**Parts of the manuscript are:** title page, summary in Serbian and English with keywords in Serbian and English, text of the manuscript (Introduction, Methods, Results, Discussion, Conclusion, Literature, Acknowledgment) and appendices.

The manuscript should be written briefly and clearly and abbreviations used only for very long names and for names known as abbreviations (eg AIDS, HIV, etc.).

**Title page**
Give the name of the manuscript (in capital letters), full names of the authors, their affiliation. Associate author names with institution names indexed by Arabic numerals. Also provide the first and last name for the corresponding author, their institution, institution address, telephone number and e-mail address.

**Summary and keywords**
The second page should include: the title of the manuscript, a structured summary up to 250 words and keywords in Serbian. The summary consists of four parts: Introduction/Aim, Methods, Results and Conclusion. Below the summary 3-8 keywords, should be listed. When presenting one or a series of cases, the abstract should consist of three parts: Introduction/Aim, Case report and Conclusion, and in

**Uvod/Cilj**
Uvod treba da bude jasan i direktno povezan sa predmetom istraživanja. Treba da pruži najvažnije informacije o problematici kojom se bavi rad, kao i to šta je do sada o tom problemu istraživano tj. poznato, a šta je nepoznato, malo poznato, ili postoje kontroverzni podaci. Posle uvodnih napomena potrebno je navesti cilj rada.

**Metode**
U ovom delu autori opisuju kako je studija izvedena, obrazlažu izbor metoda i dizajn istraživanja.Podceline metoda rada mogu biti: dizajn studije (npr. kvantititavno ili kvalitativno istraživanje, deskriptivna ili analitička ili eksperimetalna studija, itd.), izbor ispitanika (kriterijumi za uključivanje i isključivanje iz studije), etički aspekti (broj pod kojim je studija odobrena od etičkog komiteta), instrumenti istraživanja (način prikupljanja podataka, specifičnosti korišćenih instrumenata) i statistička analiza podataka (vrste testova). Važno je navesti podatke iz literature za poznate metode, uključujući i statističke.

**Rezultati**
Tekstualno opisati rezultate istraživanja prezentovane logičkim redosledom kroz tabele, grafikone i ilustracije (prilozi se navode iza Literature).

**Diskusija**
Rezultate istraživanja uporedite sa rezultatima drugih već publikovanih relevantnih istraživanja (ako je to moguće ne starijim od pet godina).

**Literatura**
Rukopisi se pripremaju u skladu sa Vankuverskim dogovorom. Literaturni podaci označavaju se arapskim brojevima, npr. (6), redosledom kojim se pojavljuju u tekstu. Informacije o citiranju mogu se naći na internet stranici https://www.nlm.nih.gov/bsd/uniform_requirements.html. Pri citiranju literature, navode se svi autori, ali ako broj autora prelazi 6, navodi se prvih šest autora i dodaje et al. Broj radova u spisku literature ne treba da prelazi 30. Podaci sa Interneta citiraju se uz navođenje datuma pristupa tim podacima. Članke koji su prihvaćeni za publikovanje, ali nisu objavljeni, treba označiti sa u štampi (*in press*). Uz svaku referencu treba navesti DOI broj članka.

**Zahvalnica**
Potrebno je uputiti zahvalnicu svim saradnicima koji su doprineli realizaciji rada, ali koji ne ispunjavaju kriterijume za autorstvo, kao i svima koji su finansijski i materijalno pomogli realizaciji istraživanja.

**Prilozi**
Priloge čine tabele, slike (fotografije, crteži, sheme, grafikoni) i video-prilozi. Svi prilozi moraju biti na srpskom i engleskom jeziku. Za sve priloge mora postojati naslov koji se navodi iznad priloga. Svi prilozi se označavaju arapskim brojevima prema redosledu navođenja u tekstu. Korišćenje skraćenica u naslovima ili bilo kom delu priloga obavezno objasniti ispod datog priloga.

review papers, the summary is descriptive (without subsections). The third page is identical to the other, but is in English.

**Introduction/Aim**
The introduction should be clear and directly related to the subject of the research. It should provide the most important information about the problem that is being dealt with, as well as what has been investigated so far about the problem, what is known and what is unknown, or little known, or if there is controversial information. After the introductory notes, the aim of the paper should be stated.

**Methods**
In this section, the authors describe how the study was conducted, explain the choice of methods and design of the research. The sub-sections of the methods may be: study design (eg quantitative or qualitative research, descriptive or analytical or experimental study, etc.), choice of respondents (inclusion and exclusion criteria from the study), ethical aspects (the number under which the study was approved by the ethics committee), research instruments (method of data collection, specificity of instruments used), and statistical analysis of the data (types of tests). It is important to provide literature data for known methods, including statistical methods.

**The results**
Describe the results of the research presented in a logical order through tables, charts and illustrations (appendices are cited after the Literature).

**Discussion**
Compare the results of your research with the results of other relevant research already published (if possible not older than five years).

**Literature**
Manuscripts are prepared in accordance with the Vancouver Arrangement. Literature data are indicated by Arabic numerals, e.g. (6), in the order in which they appear in the text. Citation information can be found at https://www.nlm.nih.gov/bsd/uniform_requirements.html. When citing the literature, all authors should be cited, but if the number of authors exceeds 6, the first six authors are cited and added by et al. The number of references in the literature should not exceed 30. Data from the Internet are cited indicating the date of access to that data. Articles accepted for publication but not published should be marked in press. Each reference should include a DOI article number.

**Acknowledgment**
Acknowledgments should be given to all contributors who have contributed to the realization of the work but who haven't met the criteria for authorship, as well as to all those who have financially and materially assisted in the realization of the research.

**Appendices**
Appendices include tables, pictures (photos, drawings, diagrams, charts) and video attachments. All appendices must be in Serbian and English. There must be a title above all appendices for each appendix. All appendices are indicated by Arabic numerals in the order in which they appear in the text. The use of abbreviations in the headings or any part of the appendix must be explained below.

**POZIV ZA REKLAMIRANJE**

Poštovani,

U okviru časopisa **Zdravstvena zaštita** imate mogućnost oglašavanja i reklamiranja vaših proizvoda i usluga, kao i svih vidova kontinuirane edukacije i publikacija (monografija, knjiga, itd.) svim našim korisnicima.

Ovaj naučni časopis je za sve lekare, farmaceute i stomatologe. U njemu se objavljuju neobjavljeni originalni naučni radovi, pregledni i stručni članci, kratka saopštenja, uvodnici, pisma uredniku, meta-analize, prikazi bolesnika, aktuelne teme, prikazi stručnih knjiga i skupova, i drugo, iz javnog zdravlja, zdravstvenog osiguranja i ekonomike, menadžmenta u zdravstvu i svih drugih oblasti medicine, farmacije i stomatologije, čime se doprinosi promociji i razvoju nauke, struke i naučno-istraživačkog rada. Štampa se na srpskom ili engleskom jeziku sa rezimeima na srpskom i engleskom.

Cene reklama i oglasa u časopisu su:

1. Oglas u crno-beloj tehnici A4 formata za jedan broj 10.000,00 dinara, a za celu godinu (četiri broja) 30.000,00 dinara.
2. Oglas u boji A4 formata za jedan broj 20.000,00 dinara, a za celu godinu (četiri broja) 60.000,00 dinara.
3. Oglas u crno-beloj tehnici na koricama A4 formata za jedan broj 20.000,00 dinara, a za celu godinu (četiri broja) 60.000,00 dinara.
4. Oglas u boji na koricama A4 formata za jedan broj 40.000,00 dinara, a za celu godinu (četiri broja) 120.000,00 dinara.

Za sva obaveštenja, uputstva i ponude obratite se Uredniku časopisa: **urednik@komorazus.org.rs**
Sredstva se uplaćuju Komori zdravstvenih ustanova Srbije na žiro račun broj 205-4707-32 preko Komercijalne banke.

**INVITATION TO ADVERTISE**

To whom it may concern:

The Journal of **Health Care**, issued by the Chamber of Health Institutions offers the possibility of advertisement and promotion of all forms of continued education and publications (books, monographs, etc.), as well as your products and services, to all our users.

This journal is a scientific publication for all doctors, pharmacologists, biochemists, dentists and managers in health industry. Previously unpublished scientific papers are published in the journal, as well as reviews and short articles, announcements, introductions, letters to the editor, meta – analysis, case reports and case series, actual topics, depictions of expert books and conferences. In this way, the journal contributes to the promotion and development of science, as well as expertise and scientific and research work.

Pricelist for the commercials and ads in the journal are:

1. Advertisment in black - and - white technique in A4 format is 10.000,00 RSD for one issue, and 30.000,00 RSD for the entire year (four issues).
2. Advertisment in color in A4 format for one issue is 20.000,00 RSD, and 60.000,00 RSD for the entire year (four issues).
3. Advertisment in black – and - white technique on the covers of A4 format is 20.000,00 RSD for one issue, and 60.000,00 RSD for the entire year (four issues).
4. Advertisment in color on the covers of A4 format is 40.000,00 RSD, and 120.000,00 RSD for the entire year (four issues).

Feel free to contact Editorial board for all additional information, questions or inquiries:
**urednik@komorazus.org.rs**

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд
613/614
ZDRAVSTVENA zaštita = Health care : zvanični časopis Komore zdravstvenih ustanova Srbije za medicinu, farmaciju, biohemiju, stomatologiju i menadžment u zdravstvu / glavni i odgovorni urednik Sandra Grujičić. - God. 1, br. 1 (1972)- . - Beograd : Komora zdravstvenih ustanova Srbije, 1972- (Beograd : Cakum Pakum). - 26 cm
Tromesečno. - Tekst na srp i engl. jeziku. - Drugo izdanje na drugom medijumu: Здравствена заштита (Online) = ISSN 2683-4286
ISSN 0350-3208 = Zdravstvena zaštita
COBISS.SR-ID 3033858