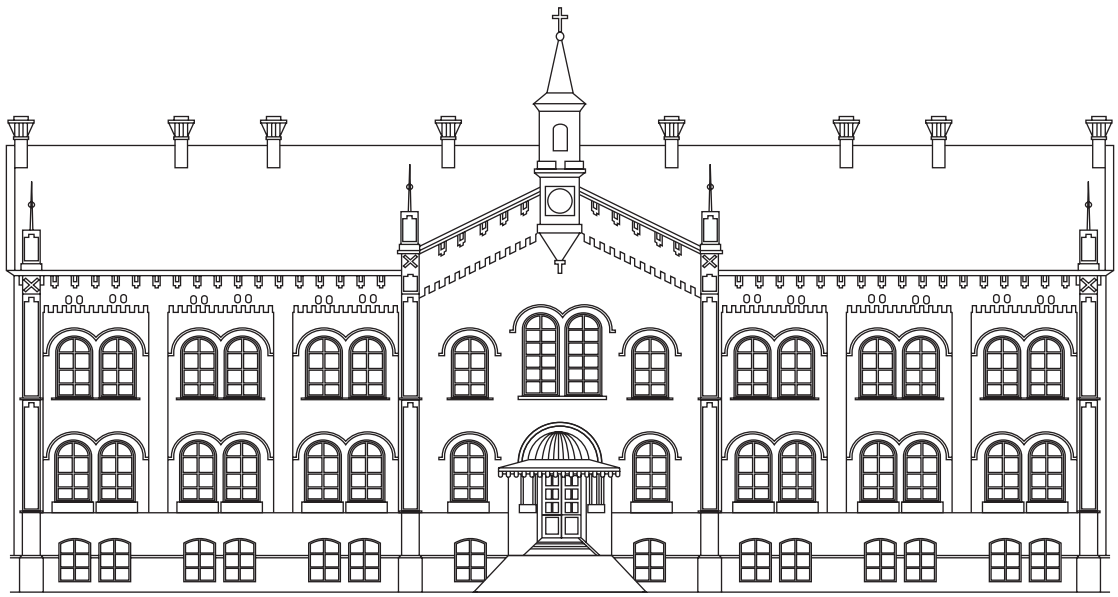
SRP ARH CELOK LEK

ISSN 0370-8179 (PRINT)
ISSN 2406-0895 (ONLINE)

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

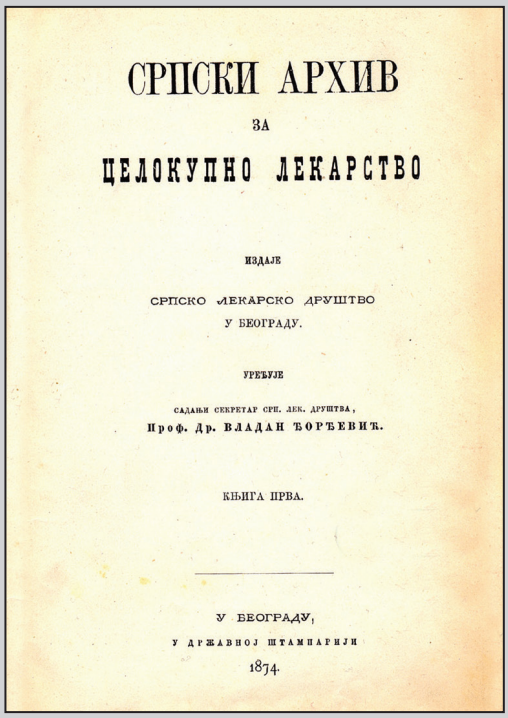


SERBIAN ARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 152 · JANUARY–FEBRUARY 2024 · ISSUE 1–2

www.srpskiarhiv.rs



СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

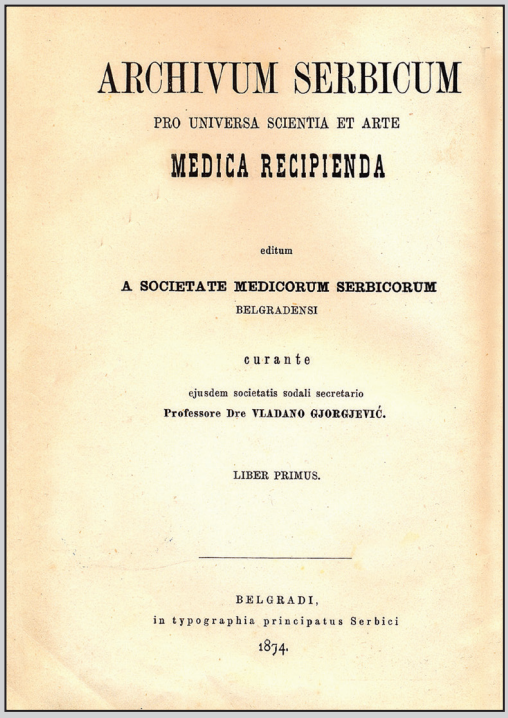
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

curante

ejusdem societatis sodali secretario

Professore Dre VLADANO GJORGJEVIĆ.

LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основаног 1872. године, први пут штампан 1874. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Објављују се: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике и регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози.

Сви рукописи који се разматрају за штампање у „Српском архиву за целокупно лекарство“ не могу да се поднесу или да буду разматрани за публиковање на другим местима. Радови не смеју да буду претходно штампани на другим местима (делимично или у потпуности).

Приспели рукопис Уређивачки одбор шаље рецензентима ради стручне процене. Уколико рецензенти предложе измене или допуне, копија рецензије се доставља аутору с молбом да унесе тражене измене у текст рада или да аргументовано образложи своје неслагање с примедбама рецензента. Коначну одлуку о прихватању рада за штампу доноси главни и одговорни уредник.

За објављене радове се не исплаћује хонорар, а ауторска права се преносе на издавача. Рукописи и прилози се не враћају. За репродукцију или поновно објављивање неког сегмента рада публикованог у „Српском архиву“ неопходна је сагласност издавача.

Радови се штампају на енглеском језику са кратким садржајем на енглеском и српском језику (ћирилица), односно на српском језику, са кратким садржајем на српском и енглеском језику.

Аутори прихватају потпуну одговорност за тачност целокупног садржаја рукописа. Материјал публикације представља мишљење аутора и није нужно одраз мишљења Српског лекарског друштва. С обзиром на брз напредак медицинске научне области, корисници треба да независно процењују информацију пре него што је користе или се на њу ослањају. Српско лекарско друштво, уредник или Уређивачки одбор „Српског архива за целокупно лекарство“ не прихватају било какву одговорност за наводе у радовима. Рекламни материјал треба да буде у складу с етичким (медицинским) и правним стандардима. Рекламни материјал укључен у овај часопис не гарантује квалитет или вредност оглашеног производа, односно тврдње произвођача.

Поднесени рукопис подразумева да је његово публиковање одобрио одговорни ауторитет установе у којој је истраживање обављено. Издавач се неће сматрати правно одговорним у случају подношења било каквог захтева за компензацију. Треба да се наведу сви извори финансирања рада.

Srpski Arhiv Za Celokupno Lekarstvo (Serbian Archives of Medicine) is the Journal of the Serbian Medical Society founded in 1872, and with first issue published in 1874. Serbian Archives of Medicine publishes articles of the Serbian Medical Society members, subscribers, as well as members of other associations of medical and related fields. The journal publishes the following article types: editorials, original papers, preliminary and short communications, case reports, video-articles, images in clinical medicine, review articles, current topics, articles for practitioners, history of medicine articles, language of medicine articles, medical ethics (clinical ethics, publication ethics) and regulatory standards in medicine, congress and scientific meeting reports, personal view articles, invited commentaries, letters to the editor, book reviews, professional news, In memoriam and other articles.

All manuscripts under consideration in the Serbian Archives of Medicine may not be offered or be under consideration for publication elsewhere. Articles must not have been published elsewhere (in part or in full).

The submitted manuscripts are forwarded by the Editorial Board to reviewers for editing and evaluation. If the reviewers find that the manuscript needs to be modified or amended, the copy of the report is sent to the author(s), requiring of them to make necessary modifications or amendments of the text or to provide argumentative explanation of their disagreement with the suggested reviewer's remarks. The final decision on acceptance of the article for publication is made by the Editor-in-Chief.

The authors shall not be remunerated for the published articles, and they are required to assign copyright of their papers to the publisher. Manuscripts and enclosures shall not be returned to the authors. Reproduction or repeated publication of any section of the manuscript already published in the "Serbian Archives" requires the publisher's approval.

The articles are printed in the English language with an abstract both in English and Serbian, or in the Serbian language, Cyrillic alphabet, with an abstract in Serbian and English.

Authors accept full responsibility for the accuracy of all content within the manuscript. Material in the publication represents the opinions of the authors and does not necessarily reflect opinions of the Serbian Medical Society. Because of rapid advances in the medical sciences, users should independently evaluate information before using or relying on it. Serbian Medical Society, the Editor or Editorial Board of the Serbian Archives of Medicine do not accept any responsibility for the statements in the articles. Advertising material is expected to conform to ethical (medical) and legal standards. Inclusion of advertising material in this publication does not guarantee the quality or value of such product or claims made by its manufacturer.

Submission of the manuscript implies that its publication has been approved by the responsible authorities at the institution where the work has been carried out. The publisher will not be held legally responsible should be any claims for compensation. Details of all funding sources for the work should be given.

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Српски архив за целокупно лекарство
Званичан часопис Српског лекарског друштва
Излази шест пута годишње

Оснивач, власник и издавач
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Председник
Проф. др Милан А. Недељковић
Интернет страна: http://www.sld.org.rs

Адреса уредништва
Српски архив
Краљице Наталије 1, 11000 Београд, Србија
Телефон: +381 (0)11 409 27 76
+381 (0)11 409 44 79
Е-пошта: office@srpskiarhiv.rs
Интернет страна: www.srpskiarhiv.rs

Претплата и експедиција
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Телефон: +381(0)11 3245-149
Текући рачуни: 205-8041-21 и
355-1009094-22

Чланци у целости доступни су на интернет страници: www.srpskiarhiv.rs

Цена претплате за календарску годину је 3.000,00 динара за појединце, 6.000,00 динара за установе и 100 евра за читаоце ван Србије. Цена појединачног примерка из текуће године је 600,00 динара, а свеске из претходних година 300,00 динара.

Штампање „Српског архива за целокупно лекарство" током 2023. године помогло је Министарство науке, технолошког развоја и иновација Републике Србије.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895

Штампано у Србији

Часопис „Српски архив за целокупно лекарство" је индексиран у базама: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

Редакција
Технички уредник: Јасмина Живковић
Лектор за српски језик: Дивна Продановић
Лектори за енглески језик: Мирко Рајић, Ана Миловановић
Корице: *MaxNova Creative*

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

Srp Arh Celok Lek
ISSN 0370-8179
UDC 61(497.11)
COBISS.SR-ID 3378434
Serbian Archives of Medicine
Official Journal of the Serbian Medical Society
Published six times per year

VOLUME 152 JANUARY–FEBRUARY 2024 ISSUE 1–2

The journal "Srpski arhiv za celokupno lekarstvo" (Serbian Archives of Medicine) is indexed in: Science Citation Index Expanded, Journal Citation Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journals, DOI Serbia.

EDITORIAL OFFICE
Technical editor: Jasmina Živković
Serbian language editor: Divna Prodanović
English language editors: Mirko Rajić, Ana Milovanović
Cover & Logo: MaxNova Creative

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

FOUNDER, OWNER & PUBLISHER
Serbian Medical Society
President
Prof. Milan A. Nedeljković, MD, PhD

PUBLISHER'S ADVISORY BOARD
Prof. Pavle Milenković, MD, PhD, president
Academician Vladimir Bumbaširević
Prof. Ljubica Đukanović, MD, PhD
Academician Nebojša Lalić
Prof. Milica Čolović, MD, PhD

EDITORIAL OFFICE
Serbian Archives of Medicine
Kraljice Natalije 1, 11000 Belgrade, Serbia
Phone: +381 (0)11 409 27 76
+381 (0)11 409 44 79
E-mail: office@srpskiarhiv.rs
Website: www.srpskiarhiv.rs

SUBSCRIPTION AND DISTRIBUTION
Serbian Medical Society
Džordža Vašingtona 19, 11000 Belgrade
Serbia
Phone: +381(0)11 3245-149
Bank accounts: 205-8041-21 and
355-1009094-22

Full-text articles are available at website: www.srpskiarhiv.rs

Calendar year subscription prices are as follows: 3,000 dinars for individuals, 6,000 dinars for institutions, and 100 euros for readers outside Serbia. The price of a current year issue is 600 dinars, and of issues from previous years 300 dinars.

The publishing of the Serbian Archives of Medicine during 2023 is supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Open Access
(CC BY-NC)

Printed in Serbia

САДРЖАЈ • CONTENTS

EDITORIAL • УВОДНИК

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

CASE REPORTS • ПРИКАЗИ БОЛЕСНИКА

CURRENT TOPIC • АКТУЕЛНА ТЕМА

REVIEW OF LITERATURE • ПРЕГЛЕД ЛИТЕРАТУРЕ

HISTORY OF MEDICINE • ИСТОРИЈА МЕДИЦИНЕ

DOI: https://doi.org/10.2298/SARH240220019T

EDITORIAL / УВОДНИК

The 30th Anniversary of the Studies in English at the Faculty of Medicine – University of Belgrade

Pursuant to the Article 10, paragraph 3 of the Law of the University, the Government of the Republic of Serbia adopted on December 20, 1995, the Decision on approval of the Medical Faculty in Belgrade, University of Belgrade, for teaching in English language. The initiative for the adoption of this solution was given by the Teaching Academic Council of the Belgrade University School of Medicine ("Medical Faculty in Belgrade, University of Belgrade" at that time official name) at the meeting of June 26th 1995, pursuant to Art. 193 of the Statute of the Medical Faculty in Belgrade (Figure 1).

As mentioned in the Council Decision, teaching in English was preceded by a long preparation of compliance plans of teaching with plans for medical schools in the European Union (EU) and the United States. The beginning of these preparations can be considered March 18th 1994, because on that day for the first time was convened a Committee composed of internationally renowned Professors of the Medical Faculty in Belgrade, appointed by the Dean, Professor Radivoje Grbic, among who were Academicians and Professors: Ljubisav Ljubiša Rakić, Past Dean, and Vladimir Kanjuh, Past Vice-Dean. The task of the Committee was to consider the proposal of organizing undergraduate and postgraduate studies in English. Tones were dissonant, because not all shared the opinion that the Medical Faculty in Belgrade should organize this type of teaching following the examples of neighboring countries, i.e. Hungary, Romania, Bulgaria, the Czech Republic and others. In such an atmosphere, it comes as no surprise it took nearly two years of work for the Coordinating Body for Studies in English (further referred to as "Board for Studies in English", or "Board") for the academic 1995/96 year, appointed by the Dean, based on the Decision of the Council of the Medical Faculty of March 15th 1996 to be reduced to only 8 members.

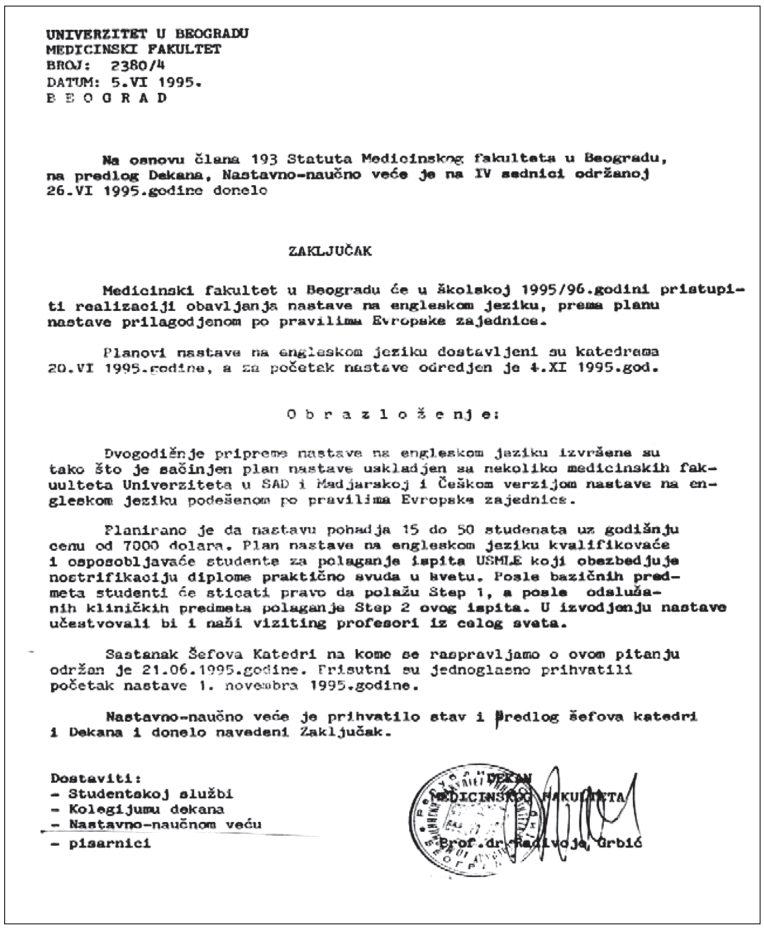
The members of the first Coordinating Body for Studies in English were the Dean, Professor Radivoje Grbić, and Vice-Deans, Professors: Slavko Simeunović, Vasilije Kalezić, Tomislav Jovanović, Rajko Dotlić, and only two additional Professors from the School: Vujadin Mujović (Department of Physiology) and Gordana Teofilovski Parapid (Department of Anatomy), and one foreign member – Professor Vasilis Thanopoulos (Athens, Greece) (Figure 2, 3).

Studies in English at the Belgrade University School of Medicine (BUSM) were created in a very challenging time under sanctions – cultural and scientific first, followed by economical – imposed on Serbia, while the rest of former Yugoslavia was falling apart. Nevertheless, it didn't stop the School's Administration in keeping the pace with the modern medical education in spite of enrolling classes of over 500 students since 1991, aiming to provide medical education in Serbian language not only for local Serbian students, but also for all refugees of all ethnic and religious backgrounds fleeing different parts of former Yugoslavia.

The idea originated from the Vice-Dean for Research, Dr Slavko Simeunović, a brilliant pediatric cardiologist and Professor of Pediatrics, who invited as his closest collaborators his classmate Professor Vujadin Mujović already

Received • Примљено: February 20, 2024
Revised • Ревизија: February 26, 2024
Accepted • Прихваћено: February 26, 2024
Online first: February 27, 2024

Correspondence to:
Gordana TEOFILOVSKI PARAPID
Honorary President, Serbian Anatomical Society Honorary President, International Committee of Symposia on Morphological Sciences
IP President, European Federation for Experimental Morphology
University of Belgrade
Faculty of Medicine
Belgrade
Serbia
gordana.teofilovski.parapid@srpskiarhiv.rs



UNIVERZITET U BEOGRADU
MEDICINSKI FAKULTET
BROJ: 2380/4
DATUM: 5.VI 1995.
B E O G R A D

Na osnovu člana 193 Statuta Medicinskog fakultata u Beogradu, na predlog Dekana, Nastavno-naučno veće je na IV sednici održanoj 26.VI 1995.godine donelo

ZAKLJUČAK

Medicinski fakultet u Beogradu će u školskoj 1995/96.godini pristupiti realizaciji obavljanja nastave na engleskom jeziku, prema planu nastave prilagodjenom po pravilima Evropske zajednice.

Planovi nastave na engleskom jeziku dostavljeni su katedrama 20.VI 1995.godine, a za početak nastave odredjen je 4.XI 1995.god.

O b r a z l o ž e n j e:

Dvogodišnje pripreme nastave na engleskom jeziku izvršene su tako što je sačinjen plan nastave usklađen sa nekoliko medicinskih fakuulteta Univerziteta u SAD i Madjarskoj i Češkom verzijom nastave na engleskom jeziku podešenom po pravilima Evropske zajednice.

Planirano je da nastavu pohadja 15 do 50 studenata uz godišnju cenu od 7000 dolara. Plan nastave na engleskom jeziku kvalifikovaće i osposobljavaće studente za polaganje ispita USMLE koji obezbedjuje nostrifikaciju diplome praktično svuda u svetu. Posle bazičnih predmeta studenti će sticati pravo da polažu Step 1, a posle odslušanih kliničkih predmeta polaganje Step 2 ovog ispita. U izvodjenju nastave učestvovali bi i naši viziting profesori iz celog sveta.

Sastanak Šefova Katedri na kome se raspravljamo o ovom pitanju održan je 21.06.1995.godine. Prisutni su jednoglasno prihvatili početak nastave 1. novembra 1995.godine.

Nastavno-naučno veće je prihvatilo stav i predlog šefova katedri i Dekana i donelo navedeni Zaključak.

Dostaviti:
- Studentskoj službi
- Kolegijumu dekana
- Nastavno-naučnom veću
- pisarnici

DEKAN
MEDICINSKOG FAKULTETA
Prof.dr Radivoje Drbić

Figure. 1. The unanimous Decision of the Teaching Academic Council of the Medical Faculty in Belgrade (Belgrade, Serbia) to adopt the English language as a language of instructions as of academic year 1995/96

collaborating with US fellow-physiologist and Professor Gordana Teofilovski-Parapid, Professor of Anatomy and once medical student of the latter and intern of the former who rotated faultlessly in Pediatrics despite advanced pregnancy and academic schedule as Assistant in Anatomy. Associate Professor in 1993 [1–16], Professor Teofilovski Parapid was promoted in Full Professor of Anatomy only 2 years later (1995) and had extensive experience in teaching medical students in the USA, basically since 1984 (see COI at the end). Developing a new, modern medical curriculum which will be easily recognized both in EU and in the USA was the goal of the three of them at the helm of the project.

In the years to come, starting from the academic year 1996/97, the Coordinating Body for Studies in English was led by Vice-Dean for Academic Affairs in English, Prof. Slavko Simeunović (1996–2000), Head of the teaching: Professor Ruben Han (2000–2004), Professor Gordana Teofilovski-Parapid (2004–2015) and following her retirement by Professor Biljana Mihaljević (2015–2023), remarkable Hematologist and Professor Dejana Jovanović who inherited a solid base to build a great future for Studies in English.

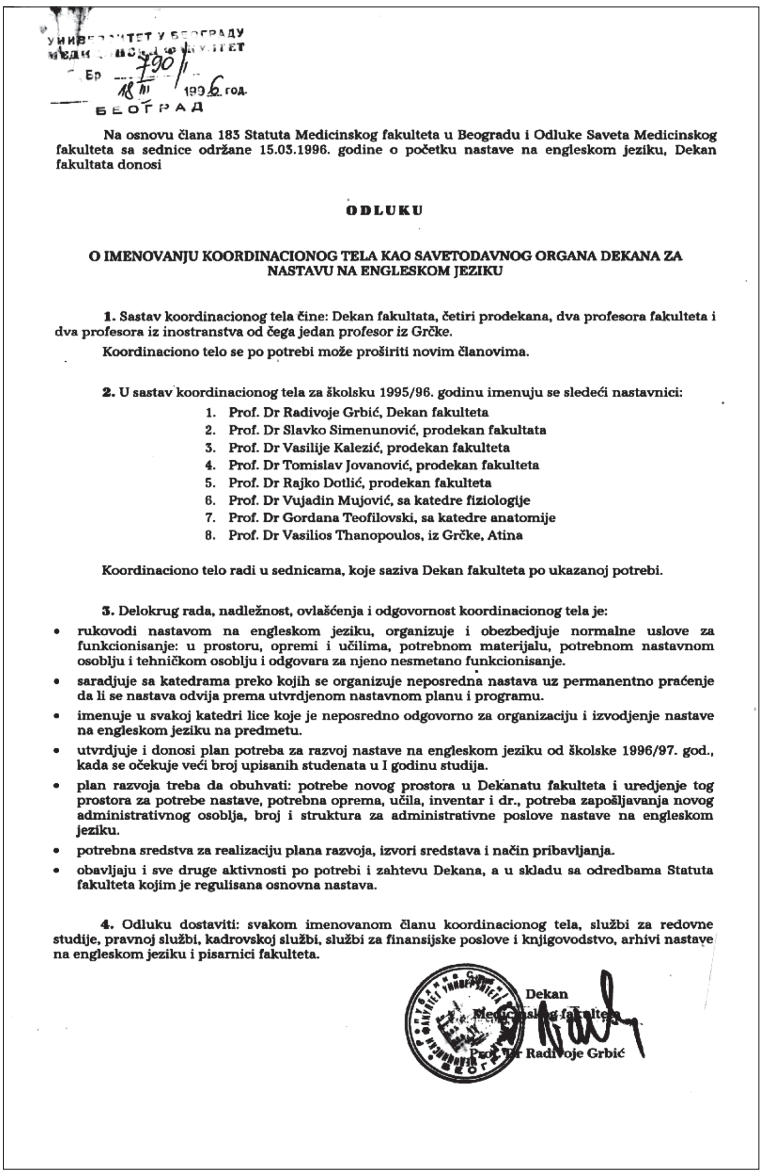
In the first period (1995–2000) of Studies in English et BUSM, a number of teaching staff was selected for teaching in English language based on the educational experience at home and abroad, scientific contribution and knowledge of English. Among those were 15 visiting professors at different Universities in the USA and other countries worldwide, many licensed to practice in the USA, over 55 members of prominent international professional association with numerous publications in leading journals and 5 members of the Serbian Academy of Sciences and Arts (SASA).

The first generation of students, 22 of them, were enrolled at BUSM Studies in English – academic year 1995/96 – with a minor delay made up through teaching on Saturdays. The next school year enrollment figures doubled and we've witnessed first groups of transfer students from medical schools in Hungary, the Czech Republic, Romania, Belgium and Iraq, and later from France, the USA and Libya.

In response to increased interest in this type of study and increasing volume and complexity of their problems, in the academic year of 1996/97, the composition of the Coordinating Body also included Academician Vladimir Kanjuh, and Professors: Miodrag Ostojić, Corresponding member of SASA, Petar Seferović, Vladimir Bumbaširević, Nenad Rosić and Branislav Vidić from Georgetown University School of Medicine (Washigton DC, USA) and Foreign Member of the SASA (Figure 4).

In 1999, the 78 days of bombing of Serbia, including the center of Belgrade and some medical facilities within it, has seriously undermined the popularity of our program. Radical changes in BUSM management that took place the very next year didn't help much either – on the contrary, despite the fact that Professor Ruben Han – the newly appointed Coordinator for Studies in English (2000–2004) – was a respected Nuclear Medicine specialist [17–22] and a good man. Whether we call it "side effects" as MDs or "collateral damage" in global politics, this was the regrettable effect on the BUSM Studies in English that – nevertheless – stood the test of time and mis-management and prevailed.

My return to the Studies in English took place on December 31, 2004, by appointment as Chair Person by the Dean of the BUSM, Academician Bogdan Đuričić, and Former Vice-Rector of the University of Belgrade. The time ahead was exciting and full of challenges: only 45 students scattered in 5 out of 6 year long medical curriculum aggravated by legislation changes and leadership changes at the BUSM during 2000–2004. Fortunately, there was Academician Professor Vladimir Bumbaširević, Vice-Dean, and almost all Divisions of the School administration were willing to help out aware of the needless decline the program suffered. Members of the Dean's Board at the time were doing their best to substitute the Coordinating Body for Studies in English, although they had sufficient



УНИВЕРЗИТЕТ У БЕОГРАДУ
МЕДИЦИНСКИ ФАКУЛТЕТ
Бр. 790/1
18 III 1996. год.
БЕОГРАД

Na osnovu člana 183 Statuta Medicinskog fakulteta u Beogradu i Odluke Saveta Medicinskog fakulteta sa sednice održane 15.03.1996. godine o početku nastave na engleskom jeziku, Dekan fakultata donosi

ODLUKU

O IMENOVANJU KOORDINACIONOG TELA KAO SAVETODAVNOG ORGANA DEKANA ZA NASTAVU NA ENGLESKOM JEZIKU

1. Sastav koordinacionog tela čine: Dekan fakultata, četiri prodekana, dva profesora fakulteta i dva profesora iz inostranstva od čega jedan profesor iz Grčke.
Koordinaciono telo se po potrebi može proširiti novim članovima.

2. U sastav koordinacionog tela za školsku 1995/96. godinu imenuju se sledeći nastavnici:
1. Prof. Dr Radivoje Grbić, Dekan fakulteta
2. Prof. Dr Slavko Simenunović, prodekan fakultata
3. Prof. Dr Vasilije Kalezić, prodekan fakulteta
4. Prof. Dr Tomislav Jovanović, prodekan fakulteta
5. Prof. Dr Rajko Dotlić, prodekan fakulteta
6. Prof. Dr Vujadin Mujović, sa katedre fiziologije
7. Prof. Dr Gordana Teofilovski, sa katedre anatomije
8. Prof. Dr Vasilios Thanopoulos, iz Grčke, Atina

Koordinaciono telo radi u sednicama, koje saziva Dekan fakulteta po ukazanoj potrebi.

3. Delokrug rada, nadležnost, ovlašćenja i odgovornost koordinacionog tela je:
- rukovodi nastavom na engleskom jeziku, organizuje i obezbeđuje normalne uslove za funkcionisanje: u prostoru, opremi i učilima, potrebnom materijalu, potrebnom nastavnom osoblju i tehničkom osoblju i odgovara za njeno nesmetano funkcionisanje.
- saradjuje sa katedrama preko kojih se organizuje neposredna nastava uz permanentno praćenje da li se nastava odvija prema utvrdjenom nastavnom planu i programu.
- imenuje u svakoj katedri lice koje je neposredno odgovorno za organizaciju i izvodjenje nastave na engleskom jeziku na predmetu.
- utvrdjuje i donosi plan potreba za razvoj nastave na engleskom jeziku od školske 1996/97. god., kada se očekuje veći broj upisanih studenata u I godinu studija.
- plan razvoja treba da obuhvati: potrebe novog prostora u Dekanatu fakulteta i uredjenje tog prostora za potrebe nastave, potrebna oprema, učila, inventar i dr., potreba zapošljavanja novog administrativnog osoblja, broj i struktura za administrativne poslove nastave na engleskom jeziku.
- potrebna sredstva za realizaciju plana razvoja, izvori sredstava i način pribavljanja.
- obavljaju i sve druge aktivnosti po potrebi i zahtevu Dekana, a u skladu sa odredbama Statuta fakulteta kojim je regulisana osnovna nastava.

4. Odluku dostaviti: svakom imenovanom članu koordinacionog tela, službi za redovne studije, pravnoj službi, kadrovskoj službi, službi za finansijske poslove i knjigovodstvo, arhivi nastave na engleskom jeziku i pisarnici fakulteta.

Dekan
Medicinskog fakulteta
Prof. Dr Radivoje Grbić

Figure 2. The first Coordinating Body for Studies in English at Belgrade University School of Medicine, BUSM, (nowadays "Faculty of Medicine University of Belgrade"), consisted of the Dean, Professor Radivoje Grbića (1), and Vice-Deans and Professors (2-5): Slavko Simeunović, Vasilije Kalezić, Tomislav Jovanović, Rajko Dotlić, with only two additional Professors from the School: Vujadin Mujović (Department of Physiology)(6), and Gordana Teofilovski Parapid (Department of Anatomy)(7), and one foreign member - Professor Vasilis Thanopoulos (Athens, Greece) (8)

workloads in their respective Councils. With them I used to share my ideas, thoughts and fears on every day bases in our Vice-Dean Office, and that was extremely useful.

Acting in that manner, we have decided to implement not only new ideas, but also some from the first period of our Studies in English (1995–2000) that have been proven good and useful irrelevant of the expense on our accounts at the time. In long run, these decisions have shown to be excellent ones for they rendered the studies not only shorter, but more efficient and popular: foreign students weren't wasting their first year of study because of insufficient knowledge of Serbian language any more, but their English skills become enriched with medical terminology, small teaching groups would allow easier and better transfer of knowledge and continual monitoring the progress of students, textbooks were carefully selected from the latest editions of textbooks recommended by the medical colleges in the USA and the United Kingdom. Keeping up with the world was enabled by many teachers of our faculty who have had experience lecturing at medical schools in USA and throughout the world, as visiting professors. In addition, a large number of guest professors from prestigious medical schools in the world would lecture with us, too. Finally, intensive re-inclusion of Belgrade and Serbia in the international flows opened up new perspectives on teaching in English language.

We succeeded bringing new students to Belgrade, although still with ruins left by bombing, and to make their stay and studies as pleasant as possible due to the support, at first site, of the Ministry of Foreign Affairs, Internal Affairs of Republic of Serbia and Ministry for Diaspora. We published modest advertising material, supported the 2nd Medical Conference of the Serbian Diaspora organized by HRH Crown Princess Katherine Karađorđević in 2011 (Figure 5), and took even personal care for finding accommodation for new students who were for the first time in Europe as we could not afford a dedicated Office at the BUSM to deal with that. Among other things the strict Academic Calendar has been posted at the beginning of each academic year, as well as, the schedules with topics and names of the lecturers, name of each of the Course Director with precise contact data, suggested readings for each curse, etc.

We have introduced the New Medical Students Convocation to welcome 1st year medical students, as an open public event with Course Directors, Faculty, Staff and alumni from Studies in English who would afterward give a traditional USA-like orientation tour through pretty big campus of the School (Figure 6).

All those efforts, and so many more not even mentioned here for the benefit of space, resulted in growing number of applicants and students, and from only 5 students enrolled in academic year 2004/05, we reached 92 in the yr. 2015/2016 (Figure 7).

Growing number of students – whether they were from Serbian expats' community worldwide who only bore Serbian last names, but were fully raised and schooled abroad or complete foreigners who have learned about an excellent and inexpensive medical school in Europe – created a healthy competition among our students who kept increasing their scores, which prompted us to award the best student for each class on the occasion of the School's Anniversary celebration, i.e. on December 9. Pictures of the awardees found the place in our flyers and that meant a lot both to them and their families, as well to us and

Figure 3. From right to left – Professor Radivoje Grbić, the Dean of Belgrade University School of Medicine, awarded students – Lamia Androniki and Biljana Naumović, née Ratković - Prof. Slavko Simeunović, the Vice-Dean, and Prof. Gordana Teofilovski-Parapid (Board Member), 2nd row – Professors: Maksimilijan Kocijančić and Radmila Matić, and awarded student Spyridon Mastoras (Belgrade, December 9, 1996 on the occasion of the celebration of the Medical Faculty Anniversary)

Figure 4. Left-right seating: Academician Vladimir Kanjuh, and Professors: Slavko Simeunović and Vujadin Mujović; Left-right standing: Prof. Gordana Teofilovski-Parapid, Nataša Ognjenović, Secretary, and Professors: Jovan Marić, Miodrag Ostojić and Vladimir Bumbaširević. All looking optimistic in spite of the circumstances (Belgrade, Serbia, March 1999)

Figure 5. HRH CP Katherine Karađorđević and Serbian Patriarch Irinej with Srdjan Srećković Minister for Diaspora Republic of Serbia, Professors: Gordana Teofilovski-Parapid, Aleksandar Vuksanović, Đorđe Bajec, Aleksandar Ljubić, and other distinguished guests

all who sought to feel the energy and enthusiasm of our program in a single page (Figure 8).

From my point of view, receiving the MD Diploma from any administrative office and not from the Dean or appointed Professor who is an MD as well, and without passing the Hippocratic Oath is not an acceptable form of graduation. Our university degree is not just like any other university degree, for we train for a calling and not a job. Irrelevant of the changes the Hippocratic Oath took over the centuries, it reminds us as MDs that our professional commitment is one of a kind, rewarding on different levels personally, but with nonetheless selfless involvement for the wellbeing of our patients even when it sacrifices our own [23]. With that in mind, in 2013, I managed to introduce Graduation ceremony for new medical doctors, no matter that the number of students who graduated would be much smaller comparing to those studying in Serbian language, and both new MDs and their families enjoyed

Figure 6. (A, B). Professor G. Teofilovski-Parapid welcomes newly enrolled class 2014-2020. First 2 rows the Course Directors and Members of Committees. From left to right: Professors K. Turza, Z. Stojšić, D. Šobić-Šaranović, M. Terzić, Dj. Macut, M. Petakov, Ž. Milićević, B. Obrenović-Kirćanski and S. Cvjetićanin. The 2nd row - Professors B. Radosavljević, E. Gvozdenović, Assistents Jeremić and Milenković, and Prof. V. Pravica

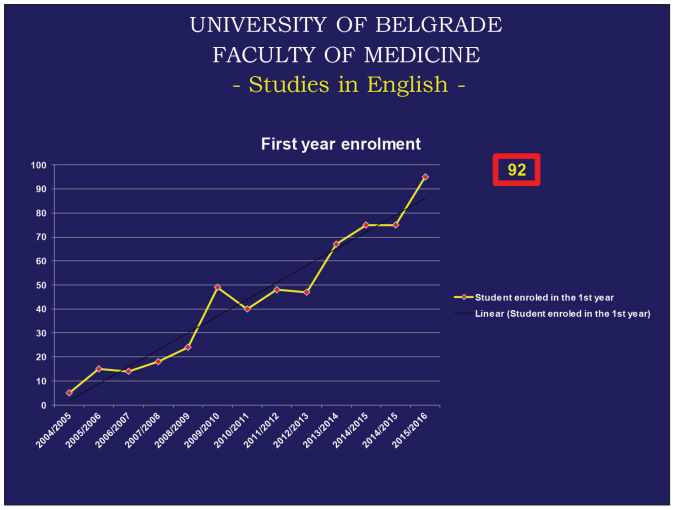


Figure 7. Increasing number of students enrolling in the 1st year of Studies in English at the Belgrade University School of Medicine from 5 in the academic yr. 2004/2005 to 92 in 2015/2016

Figure 9. Prof. Gordana Teofilovski-Parapid, on behalf of the Dean Nebojsa Lalic, Academician and Professor, with promoted medical doctors: Drs. Goran and Zoran Petrović (Sweden), A. Caleb (Nigeria), Ivan Jovanović (Serbia) and others

Figure 8. Flyer for Studies in English at BUSM, with pictures of best students awarded on December 9, 2010 Belgrade University School of Medicine Anniversary: Darko Šarović, Ljubomir Acimović, Marinela Grabovac and Igor Kapetanović

in it (Figure 9). In year 2015 our Office reported that since yr 1995, when the 1st class has been enrolled in Studies in English, 278 students from 24 countries and 4 continents got the MD Diploma from Belgrade University School of Medicine.

Studies in English made another step furtherer, and organized the first PhD Course in English – Skeletal Biology – with Course Director, Professor Marija Đurić, well established researcher (Figure 10). To this day, that is still the only one at Faculty of Medicine – University of Belgrade, as the name of the School has been changed to better suit the EU requirements.

In my personal opinion – as a seasoned researcher and experienced Professor of both my *alma mater* Belgrade University and my second one Georgetown University – the Faculty of Medicine – University of Belgrade with its

Figure 10. The first generation of PhD students in Skeletal Biology Program with some of Professors, Belgrade 2009: Left to right: Prof. Karel Turza, Petar Milovanovic (PhD student), Petar Milenkovic (PhD Student), Danijel Raspopovic (PhD Student), Prof. Gordana Teofilovski-Parapid (Chair of Studies in English), Ksenija Djukic (PhD Student), Aleksa Jovanovic (PhD Student) and Prof. Marija Djuric (Course Director of the Skeletal Biology PhD Program)

intellectual potential will manage to find its own way not only to preserve its heritage, but to further develop Studies in English bearing in mind that some smart countries, with long tradition in providing education in English, have been earning millions of bitcoins – to keep up with the latest currency gaining popularity – per year. Belgrade itself by its unique location, lovely climate, beautiful nature and people well known for its hospitality offers enough, so the rest is on us.

Each year brings memories and this one brings the special one related to the 30th Anniversary of Studies in English at Faculty of Medicine – University of Belgrade, bat the beginning of year 2024 also offers the Editorial Board of the Serbian Archives of Medicine the opportunity to express the gratitude to the reviewers for all those hours of non-paid, voluntary work invested in our journal helping us to save 152 years old tradition and to keep building the future for your work shall be remembered 30 years from today (Table 1).

Conflict of interest: Gordana Teofilovski-Parapid was the Republic of Serbia's Scientific Fund for Sciences scholar (1984), Educational Commission for Foreign Medical Graduates (Philadelphia, PA, USA) fellow (1989-1990) and faculty of Georgetown University School of Medicine (Washington DC, USA) 1993-2006/08.

Editor-in-Chief
Prof. Gordana Teofilovski-Parapid, M.D., Ph.D.
Honorary President, Serbian Anatomical Society
Honorary President, International Committee of Symposia on Morphological Sciences,
Past President, European Federation for Experimental Morphology
University of Belgrade, Faculty of Medicine,
Belgrade, Serbia
gordana.teofilovski.parapid@srpskiarhiv.rs

REFERENCES

1. Teofilovski-Parapid G, Nikolić V, Oklobdzija M, Ranković A, Mrvaljević D. Myocardial bridging of the left anterior descending coronary artery in monkey hearts. Folia Morphol (Warsz). 1994;53(1):27–32. [PMID: 8088624]
2. Teofilovski-Parapid G, Nikolić V, Ranković A, Blagotić M, Kreclović G. [Coronary arteries in the Macaca fascicularis monkey]. Srp Arh Celok Lek. 1993;121(8–12):117–9. Serbian [PMID: 7725149]
3. Teofilovski G, Filipovic B, Bogdanovic D, Trpinac D, Rankovic A, Stankovic G, DiDio LJ. Myocardial bridges over coronary arteries in Cercopithecus. Ann Anat. 1992;174(5):435–9. [DOI: 10.1016/s0940-9602(11)80268-2] [PMID: 1449220]
4. Baptista CA, Didio LJ, Teofilovski-Parapid G. Variations of the blood supply of the human conus arteriosus. Bull Assoc Anat (Nancy). 1992;76(232):9–18. [PMID: 1638063]
5. Teofilovski-Parapid G, Baptista CA, DiDio LJ, Vaughan C. The membranous portion of the interventricular septum and its relationship with the aortic valve in humans. Surg Radiol Anat. 1991;13(1):23–8. [DOI: 10.1007/BF01623136] [PMID: 2053041]
6. DiDio LJ, Baptista CA, Teofilovski-Parapid G. Anatomical variations of the abducent nerve in humans. Arch Ital Anat Embriol. 1990;95(3–4):167–72. [PMID: 2102068]
7. Baptista CA, DiDio LJ, Teofilovski-Parapid G. Variation in length and termination of the ramus circumflexus of the human left coronary artery. Anat Anz. 1990;171(4):247–53. [PMID: 2080814]
8. Baptista CA, DiDio LJ, Teofilovski-Parapid G. Variation in length and termination of the right coronary artery in man. Jpn Heart J. 1989;30(6):789–98. [DOI: 10.1536/ihj.30.789] [PMID: 2632832]
9. Baptista CA, DiDio LJ, Davis JT, Teofilovski-Parapid G. The cardiac apex and its superficial blood supply. Surg Radiol Anat. 1988;10(2):151–60. [DOI: 10.1007/BF02307825] [PMID: 3135619]
10. Malobabić S, Bogdanović D, Teofilovski G. Morphology of the human corpus callosum: the shape of its mediosagittal section. Gegenbaurs Morphol Jahrb. 1987;133(3):403–10. [PMID: 2442065]
11. Teofilovski G, Bogdanović D, Mijac M, Mrvaljević D. Some morphological characteristics of large sulci situated on the outer side of grivet monkey cerebral hemisphere. Acta Med Iugosl. 1986;40(5):331–8. [PMID: 3825586]
12. Mrvaljević D, Djordjević-Camba V, Teofilovski G, Bumbasirević V, Ranković A, Gasić M. [Morphology and function of the neglected ligament of the foot]. Srp Arh Celok Lek. 1984;112(4):481–6. Serbian [PMID: 6515479]
13. Teofilovski G. Anatomic characteristics of the grivet monkey insula. Acta Med Iugosl. 1984;38(4):241–6. [PMID: 6507140]
14. Teofilovski G, Bogdanović D, Aleksandrić B. [Anatomic characteristics of the transverse gyrus of the temporal lobe of the human brain (gyri temporales transversi)]. Srp Arh Celok Lek. 1983;111(3):319–25. Serbian [PMID: 6658596]
15. Teofilovski G. [Characteristics of the origin and morphology of the jejunal and ileal arteries]. Srp Arh Celok Lek. 1983;111(1):33–40. Serbian [PMID: 6635818]
16. Teofilovski-Parapid G. Participation of the ileocolic artery in the vascularization of the terminal ileum. Folia Morphol (Praha). 1981;29(3):216–9. [PMID: 7274847]
17. Radović B, Tatić S, Jaksić EK, Han R. [Cytological findings in scintigraphically nonfunctioning thyroid nodules]. Vojnosanit Pregl. 2010;67(10):797–801. Serbian. [DOI: 10.2298/vsp1010797r] [PMID: 21066871]
18. Jaksić E, Artiko V, Beatović S, Djokić D, Janković D, Saranović DS, et al. Clinical investigations of 99mTc-p-aminohippuric acid as a new renal agent. Nucl Med Commun. 2009;30(1):76–81. [DOI: 10.1097/mnm.0b013e328314b8bc] [PMID: 19306517]
19. Jaksić E, Beatović S, Paunković N, Stefanović A, Han R. [Variability in interpretation of static renal scintigraphy findings]. Vojnosanit Pregl. 2005;62(3):189–93. Serbian [DOI: 10.2298/vsp0503189j] [PMID: 15790046]
20. Jaksić E, Beatović S, Han R. [The role of nuclear medicine in renal transplantation]. Vojnosanit Pregl. 2004;61(3):291–7. Serbian [DOI: 10.2298/vsp0403291j] [PMID: 15330302]
21. Beatović SLj, Jaksić ED, Han RS. Measurement of renal function by calculation of fractional uptake of technetium-99m dimercaptosuccinic acid. Nucl Med Rev Cent East Eur. 2004;7(1):49–52. [PMID: 15318311]
22. Vucina J, Han R. [Production and therapeutic use of rhenium-186, 188--the future of radionuclides]. Med Pregl. 2003;56(7–8):362–5. Croatian [DOI: 10.2298/mpns0308362v] [PMID: 14587255]
23. Teofilovski-Parapid G. Physicians are humans and replaceable – the current millennium approach. Editorial. Srp Arh Celok Lek. 2023;151(1–2):6–9. [DOI: 10.2298/SARH230222020T]

Table 1. The list of the Serbian Archives of Medicine reviewers in 2023

1. Aksić Milan
2. Aleksić Predrag
3. Aničić Boban
4. Argalasova Lubica
5. Babić Rade
6. Balint Bela
7. Bančević Vladimir
8. Baščarević Zoran
9. Bašić Dragoslav
10. Beleslin Biljana
11. Belojević Goran
12. Berisavac Ivana
13. Bila Jelena
14. Bila Jovan
15. Blagojević Duška
16. Bojadžieva Sonja
17. Bokun Jelena
18. Božić Marija
19. Branković Branko
20. Bubanja Dragana
21. Budić Ivana
22. Buha Ivana
23. Bumbaširević Vladimir
24. Čanković Milenko
25. Ćeranić Miljan
26. Čolić Miodrag
27. Čolić Snježana
28. Čolović Milica
29. Čolović Radoje
30. Crnogorac Snežana
31. Čupić Maja
32. Cvetković Aleksandar
33. Dačić Krnjaja Bojana
34. Dimitrijević Milovan
35. Dimković Nada
36. Dinić Ljubomir
37. Đorđević Boban
38. Đorđević Igor
39. Đorđević Vidojko
40. Đuričić Goran
41. Đuričić Slaviša
42. Đurišić Slaviša
43. Đurković Đaković Olgica
44. Dobričić-Čevrljaković Nevenka
45. Doklestić Krstina
46. Dunjić Kostić Bojana
47. Đukanović Ljubica
48. Fang Bo
49. Glišić Branislav
50. Gojnić Miroslava
51. Hajduković Zoran
52. Ignjatović Vladimir
53. Ilijevski Nenad
54. Ille Tatjana
55. Ivanović Branislava
56. Jakšić Vesna
57. Janjić Vladimir
58. Janković Radmila
59. Janković Srđa
60. Janošević Predrag
61. Jašović-Siveska Emilija
62. Jelovac Drago
63. Jeremić Jelena
64. Jerotić Đurđa
65. Jokić Radoica
66. Joković Miloš
67. Jotić Ana
68. Jovanović Dejana
69. Jovanović Tanja
70. Jovanović Verica
71. Jovanović Simić Jelena
72. Jurišić Vladimir
73. Kadija Marko
74. Kalezić Nevena
75. Kalezić Tanja
76. Karamarković Aleksandar
77. Knežević Đorđe
78. Knežević Srbislav
79. Knežević Vladimir
80. Knežević Pogančev Marija
81. Kocić Gordana
82. Konstantinović Ljubica
83. Konstantinović Vitomir
84. Kostić Mirjana
85. Kovačević Igor
86. Kovačević Predrag
87. Krasić Dragan
88. Kravić Stevović Tamara
89. Kravljanac Ružica
90. Krunić Aleksandar
91. Kuhajda Ivan
92. Kuroyedov Alexander
93. Lalić Nensi
94. Lalošević Dušan
95. Latas Milan
96. Lavrnja Irena
97. Lazarević Dragana
98. Lazović Milica
99. Lazović Ranko
100. Lečić Toševski Dušica
101. Leković Zoran
102. Lešić Aleksandar
103. Letica Crepulja Marina
104. Ljujić Mila
105. Lovrić Robert
106. Lukač Radoslav
107. Maksimović Nataša
108. Mandić Maravić Vanja
109. Mandić Stojmenović Gorana
110. Marčinko Darko
111. Marić Gorica
112. Marić Nebojša
113. Marinković Vesna
114. Marković Aleksa
115. Marković Danica
116. Marković Miroslav
117. Martić Jelena
118. Martinović Tamara
119. Matejić Bojana
120. Matić Milan
121. Matić Anđelković Slađana
122. Mavija Milka
123. Mazicioglu Mümtaz
124. Meng Yingying
125. Mičetić Turk Dušanka
126. Micev Marjan
127. Mihalj Marija
128. Mijajlović Milija
129. Mikić Dragan
130. Milenković Pavle
131. Milenković Petar
132. Milenković Saša
133. Milenković Svetislav
134. Milić Lemić Aleksandra
135. Milinčić Nemanja
136. Milosavljević Vladimir
137. Milošević Nataša
138. Milovanović Ivan
139. Milovanović Jovica
140. Milovanović Petar
141. Milovanović Tamara
142. Milutinović Dragana
143. Mitković Marija
144. Mitković Milan
145. Mitrović Nikola
146. Nedeljković Milan
147. Nenadić Dane
148. Nešić Dejan
149. Nešić Vladimir
150. Nestorović Dragoslav
151. Nestorović Milica
152. Nikitović Marina
153. Nikolić Božana
154. Nikolić Dimitrije
155. Nikolić Igor
156. Obradović Slobodan
157. Obrenović Kirćanski Biljana
158. Palibrk Ivan
159. Parapid Biljana
160. Pavić Sladjana
161. Pavlov Maja
162. Pavlović Aleksandar
163. Pavlović Milorad
164. Pavlović Sonja
165. Pavlović Zorana
166. Pejović Milovančević Milica
167. Pekmezović Tatjana
168. Perić Momčilo
169. Petronić Ivana
170. Plešinac Karapandžić Vesna
171. Poljak Mario

172. Polovina Snežana
173. Popović Dušan
174. Popović Željko
175. Poskurica Mileta
176. Potić Milan
177. Radisavljević Miša
178. Radlović Nedeljko
179. Radojičić Aleksandra
180. Radosavljević Aleksandra
181. Radunović Goran
182. Raffay Violetta
183. Raičević Mirjana
184. Rajkovic Nataša
185. Ranin Jovan
186. Risimić Dijana
187. Ristić Arsen
188. Ristić Ljubiša
189. Salinger Sonja
190. Šantrić Milićević Milena
191. Šaponjski Jovica
192. Šarenac Tatjana
193. Savić Aleksandar
194. Šefik Bukilica Mirjana
195. Simić Dušica
196. Simić Tatjana
197. Simić Ogrizović Sanja
198. Sjeničić Marta
199. Škiljević Dušan
200. Slankamenac Petar
201. Slavković Nemanja
202. Sokić Milutinović Aleksandra
203. Sparić Radmila
204. Spasovski Goce
205. Stajević Mila
206. Stamenković Bojana
207. Stamenković Dragoslav
208. Stamenković Jelena
209. Stamenković Miroslav
210. Stanković Nebojša
211. Stavridis Sotir
212. Stefanović Igor
213. Stepić Nenad
214. Stevanović Dejan
215. Stevanović Goran
216. Stevanović Vesna
217. Stijak Lazar
218. Stjepanović Mihailo
219. Stojanović Milenković Roksanda
220. Stojanović Rundić Suzana
221. Stojičić Milan
222. Stojković Mirjana
223. Stojković Tihomir
224. Stojšić Milosavljević Anastazija
225. Stojšin Ivana
226. Stolić Radojica
227. Stošić Srboljub
228. Svetel Marina
229. Tabaković Saša
230. Tasić Velibor
231. Teofilovski Parapid Gordana
232. Tepić Snežana
233. Todorović Jovana
234. Todorović Ljubomir
235. Todorović Vera
236. Todorović Zoran
237. Tomanović Nada
238. Tomić Aleksandar
239. Toprak Hüseyin
240. Tošković Borislav
241. Trbojević Stanković Jasna
242. Trifković Branka
243. Tulić Goran
244. Vacić Zoran
245. Vasiljević Mladenko
246. Velicki Lazar
247. Vojinov Saša
248. Vojvodić Danilo
249. Vučinić Predrag
250. Vujić Dragana
251. Vuletić Biljana
252. Vuličević Zoran
253. Yang Yang
254. Yue Shiye
255. Žagar Ivana
256. Zlatković-Švenda Mirjana

DOI: https://doi.org/10.2298/SARH230915010N
UDC: 616.98:578.834]:615.371-056.34

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

COVID-19 vaccination predictors among people with mental disorders

Emilija Novaković[1,2], Mirjana Stojanović-Tasić[1,2], Tatjana Novaković[2], Aleksandra Dutina[1], Zoran Bukumirić[3], Ivana Stašević-Karličić[1,2]

[1]Dr Laza Lazarević Clinic for Mental Disorders, Belgrade, Serbia;
[2]University in Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[3]University in Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Higher rates of morbidity and mortality from the infection of COVID-19 have been recorded among people with mental disorders, especially among those suffering from severe forms, so they should be prioritized during vaccination campaigns. The aim of this study was to examine possible predictors of acceptance of vaccination against COVID-19 in patients with mental disorders.

Methods This retrospective study was conducted from January 2021 until January 2022 and included 458 patients with mental disorders treated at the Dr Laza Lazarević Clinic for Mental Disorders in Belgrade, Serbia. Patients were segregated into the vaccinated and the unvaccinated group depending on their vaccination status. A questionnaire developed specifically for the present study was administered to gather the participants' sociodemographic characteristics, while data related to their mental disorders, COVID-19 infection, and comorbidities was obtained from their medical records.

Results Eighty percent of the vaccinated group opted for the Sinopharm vaccine. Significantly higher percentage of vaccinated patients was hospitalized during the study period and had comorbidities compared to the unvaccinated group (51.4% *vs*. 32.6% and 52.8% *vs*. 37.5%, respectively). Education level, employment status, marital status, diagnostic category, and comorbidities were statistically significant predictors of COVID-19 vaccination uptake among people with mental disorders.

Conclusion Our findings show that higher level of education, greater trust in the healthcare system, and knowledge of the available vaccination points significantly contribute to the vaccination uptake in this vulnerable population group.

Keywords: COVID-19; mental disorders; vaccination

INTRODUCTION

In December 2020, a massive worldwide vaccination campaign commenced, aiming to protect the global population against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes COVID-19. Several vaccines based on different modes of action (i.e., mRNA, viral vector, whole virus, and protein subunit) are currently licensed, and their efficacy and safety profile has been demonstrated in several epidemiological studies [1, 2, 3]. Each of the available SARS-CoV-2 vaccines has been developed, evaluated, and approved according to the current scientific knowledge and the applicable regulatory guidelines and legal requirements [4].

While vaccination uptake has been satisfactory, it varies not only among countries, but also across different social categories. As higher rates of COVID-19 morbidity and mortality have been recorded among people with mental disorders, especially those suffering from severe mental illness, they should be prioritized during vaccination campaigns [5]. These persons are vulnerable, as they may have difficulty in adhering to the prescribed prevention measures due to the compromised capacity to understand the guidelines or adapt their behavior to limit the risk of contracting the infection [6, 7]. Accordingly, they were among the first population groups to be offered vaccines in several countries [8], but multidimensional strategy is still needed to enhance the healthcare access and to reduce discrimination and stigmatization of vulnerable individuals [9].

These objectives have motivated the present study, as a part of which the possible predictors of COVID-19 vaccination uptake among people with mental disorders were examined.

METHODS

This retrospective study was conducted from January 2021 until January 2022 and included 458 patients with mental disorders treated at the Clinic for Mental Disorders "Dr Laza Lazarević" Belgrade, Republic of Serbia. Each patient had a diagnosis of mental disorder according to the 10th Revision of the International Classification of Diseases (ICD-10). Prior to commencing the research, approval for all study protocols was obtained from the Ethics Committee of the Dr Laza Lazarević Clinic for Mental Disorders in Belgrade, Serbia (No. 3009, 21/02/23). The

Received • Примљено: September 15, 2023
Revised • Ревизија: December 24, 2023
Accepted • Прихваћено: January 24, 2024
Online first: January 25, 2024

Correspondence to:
Emilija NOVAKOVIĆ
Dr Laza Lazarević Clinic for Mental Disorders
Višegradska 26
11000 Belgrade, Serbia
emanovakovic95@yahoo.com

Table 1. Sociodemographic characteristics and medical data of vaccinated and unvaccinated patients with mental disorders

Variable	Vaccinated patients n (%)	Unvaccinated patients n (%)	OR (95% CI)	p-value
Gender				
male	132 (56.7)	127 (56.7)	1.02 (0.7–1.47)	0.927
female	101 (43.3)	97 (43.3)		
Age (in years):				
M ± SD	44.3 ± 11.3	43.6 ± 10.5	1.01 (0.99–1.02)	0.553
Educational level				
no education/elementary school	37 (15.9)	25 (11.2)	reference:	
secondary school	163 (70)	154 (68.8)	0.72 (0.41–1.24)	0.235
high school	19 (8.2)	34 (15.2)	0.35 (0.16–0.75)	0.007
university or higher	14 (6)	11 (4.9)	0.86 (0.34–2.20)	0.753
Employment				
employed	26 (11.2)	44 (19.6)	reference:	
unemployed	142 (60.9)	142 (63.4)	1.69 (0.99–2.90)	0.055
retired	65 (27.9)	38 (17.0)	2.78 (1.48–5.20)	0.001
Residence				
urban area	229 (98.3)	219 (97.8)	0.77 (0.21–2.91)	0.702
periurban area	4 (1.7)	5 (2.2)		
Marital status				
married	29 (12.4)	45 (20.1)	reference:	0.026
unmarried	178 (76.4)	163 (72.8)	1.79 (1.07–3.00)	0.015
divorced	21 (9.1)	12 (5.4)	2.88 (1.23–6.73)	0.312
widowed	5 (2.1)	4 (1.8)	2.05 (0.51–8.30)	
Diagnostic category				
non-psychotic disorder	21 (9)	10 (4.5)		
psychotic disorder	212 (91)	214 (95.5)	0.47 (0.22–1.02)	0.055
Comorbidities				
yes	123 (52.8)	84 (37.5)		
no	110 (47.2)	140 (62.5)	1.83 (1.26–2.66)	0.002

participation was voluntary and each patient was informed, through a special brochure, about the type and aims of the study, the data collection procedure, the nature of their involvement, and other relevant aspects. Only patients that provided written consent for using their personal data for study purposes either directly or through a legal representative were eligible for participation.

The recruited patients were segregated into the vaccinated and unvaccinated group depending on their vaccination status. The vaccinated group consisted of 233 patients with mental disorders (132 males and 101 females; mean age 44.3 ± 11.3 years). These individuals received a minimum two doses of COVID-19 vaccine at the Dr Laza Lazarević Clinic for Mental Disorders, Belgrade, Republic of Serbia. The unvaccinated group comprised age- and gender-matched 234 patients with mental disorders (127 males and 97 females; mean age 43.6 ± 10.5 years). In order to examine factors that may contribute to the decision to accept/reject vaccination, a questionnaire developed specifically for the present study was administered to gather the participants' sociodemographic characteristics, while data related to their mental disorders, COVID-19 infection, and comorbidities was obtained from their medical records.

Statistical analysis

The obtained data was subjected to statistical analyses, performed using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). Results were presented as frequency (percentage), median (range), and mean ± standard deviation. For parametric data, independent samples t-test was performed to test differences between groups, whereas numeric data with non-normal distribution and ordinal data were subjected to the Mann–Whitney U test. Chi-squared test or Fisher's exact test was performed to test differences in nominal data (frequencies), and logistic regression analysis was conducted to assess binary outcome (local and systemic adverse events) and identify potential predictors. All p-values less than 0.05 were considered statistically significant. Independent variables which were statistically significant ($p < 0.1$) in univariate logistic regression models were incorporated into the multivariate logistic regression model as the independent variables.

RESULTS

The study included a total of 458 subjects with mental disorders, who were segregated into the vaccinated and the unvaccinated group. The vaccinated group consisted of 233 patients with mental disorders (132 males and 101 females; mean age 44.3 ± 11.3 years). The unvaccinated group comprised age- and gender-matched 234 patients with mental disorders (127 males and 97 females; mean age 43.6 ± 10.5 years). Based on the socio-demographic characteristics, reported in Table 1, it is evident that unemployed and unmarried individuals predominated in both groups, and the difference was statistically significant (60.9% *vs.* 63.7% and 76.4% *vs.* 72.8%, respectively). The percentage of subjects from urban areas was significantly higher than that from periurban areas (vaccinated group 98.3% *vs.* 1.7%, unvaccinated group 97.8% *vs.* 2.2%, respectively). The two groups also differed with respect to the hospitalization rates due to the diagnosed mental disorder and comorbidities.

As shown in Figure 1, 179 (76.8%) individuals of the vaccinated group opted for the Sinopharm vaccine. The results showed that a significantly smaller number of patients were vaccinated with Pfizer (32 subjects or 13.7%) and Astra Zeneca (22 subjects or 9.4%) vaccines.

As indicated in Table 2, a significantly higher percentage of vaccinated patients was hospitalized during the study period and they had comorbidities compared to the unvaccinated group (51.4% *vs.* 32.6% and 52.8% *vs.* 37.5%,

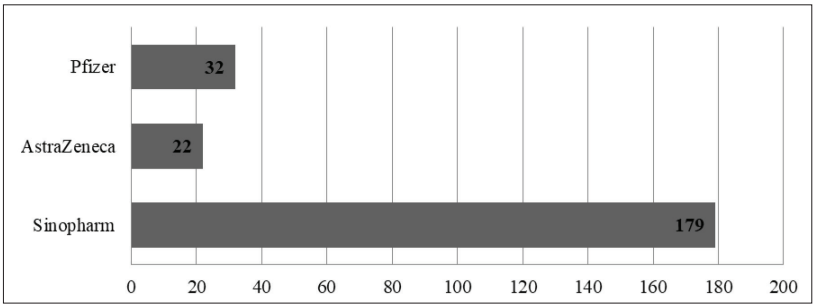


Figure 1. Distribution of COVID-19 vaccine type among vaccinated patients

Table 2. Rehospitalization due to the diagnosed mental disorder and COVID-19 data of vaccinated and unvaccinated patients with mental disorders

Variable	Vaccinated patients n (%)	Unvaccinated patients n (%)	p-value*
Hospitalization due to the mental disorder			
yes no	126 (54.1) 107 (45.9)	73 (32.6) 151 (67.4)	< 0.001
COVID-19 disease history			
yes no	20 (8.6) 213 (91.4)	6 (2.7) 218 (97.3)	0.896
COVID-19 hospitalization			
yes no	12 (5.2) 221 (94.8)	6 (2.7) 218 (97.3)	0.175

*Fisher or χ^2 test

respectively). There were no statistically significant differences in COVID-19 disease history and COVID-19 hospitalization between the vaccinated and unvaccinated patients.

According to the multivariate logistic regression model, education level, employment status, marital status, diagnostic category, and comorbidities were statistically significant predictors of COVID-19 vaccination uptake among people with mental disorders. Namely, vaccination rates were higher among patients with mental disorders who have completed higher education, who are retired, as well as those who are single or divorced compared to those who have no formal education or have only completed elementary school, are employed, and are in a relationship (Figure 2).

DISCUSSION

Within a few months of the first reported cases, COVID-19 caused a worldwide pandemic [10], prompting multiple groups of scientists across the globe to work on a vaccine. Following extensive testing, several vaccine types entered the market in December of 2020. As vaccination has historically been the most effective measure in the fight against viral disease (flu, SARS, H1N1, etc.) epidemics [11], the aim was to vaccinate as many individuals as possible. As a vulnerable group, individuals with mental health disorders were in focus of the present study, and our analyses revealed that almost 80% of those that chose to be vaccinated received the Sinopharm vaccine. This finding was expected, as the Sinopharm vaccine was the first to arrive in Serbia and was the most available vaccine type at the vaccination points. As a result, the majority of the population was vaccinated with this vaccine [12]. The vaccinated patients did not significantly differ from the unvaccinated group in terms of education, thus countering the results obtained in other studies indicating that better educated individuals generally have a more positive attitude toward vaccination [13, 14, 15]. However, as our cohort comprised solely of patients with mental health disorders (many of whom suffered from schizophrenic psychoses), they would have a lower educational level compared to the general population, rendering the results incomparable.

On the other hand, there were statistically significantly fewer employed individuals in the vaccinated relative to the unvaccinated group. Once again, this finding differs from the results obtained in most studies related to psychiatric patients as well as general population, in which unemployment is shown to be associated with greater resistance to vaccination [16, 17]. The number of retired individuals was higher in the vaccinated group. If retirement is considered a proxy for old age, this finding is supported by the results reported by other authors, indicating that elderly people with mental disorders are more likely to opt for vaccination [13, 18].

It is also worth noting that about 98% of the study participants (irrespective of their vaccination status) resided in an urban environment. Thus, as the sample was relatively small and homogenous, the obtained findings likely do not apply to other parts of Serbia, given that vaccination rates in rural areas are typically lower [14].

Analyses related to the marital status further revealed that there were statistically significantly fewer married persons in the vaccinated than in the unvaccinated group, concurring with the findings obtained by Israeli scientists who examined the factors influencing the motivation for vaccination in people with schizophrenia, and found that vaccinated respondents with schizophrenia were less likely to be married compared to healthy controls [18]. One of the possible explanations for this finding is that, if unmarried people with mental disorders have confidence in their psychiatrist, they will follow the medical advice and get vaccinated. The importance of the role of psychiatrists in the vaccination of persons with mental disorders during the COVID-19 pandemic was confirmed in several previous studies [19, 20, 21]. As noted earlier, over 90% of the patients in our entire sample have a diagnosis from the F20–F29 spectrum due to the types of psychopathology typically treated at our clinic.

We also found that, compared to the unvaccinated group, a significantly greater number of patients in the vaccinated group were hospitalized due to deterioration in their mental state during the study period. It is thus possible that, during their hospital stay, these patients were motivated by psychiatrists and other medical workers to get vaccinated, and took this opportunity to do so, given that the vaccine could be administered on the ward. These assertions are

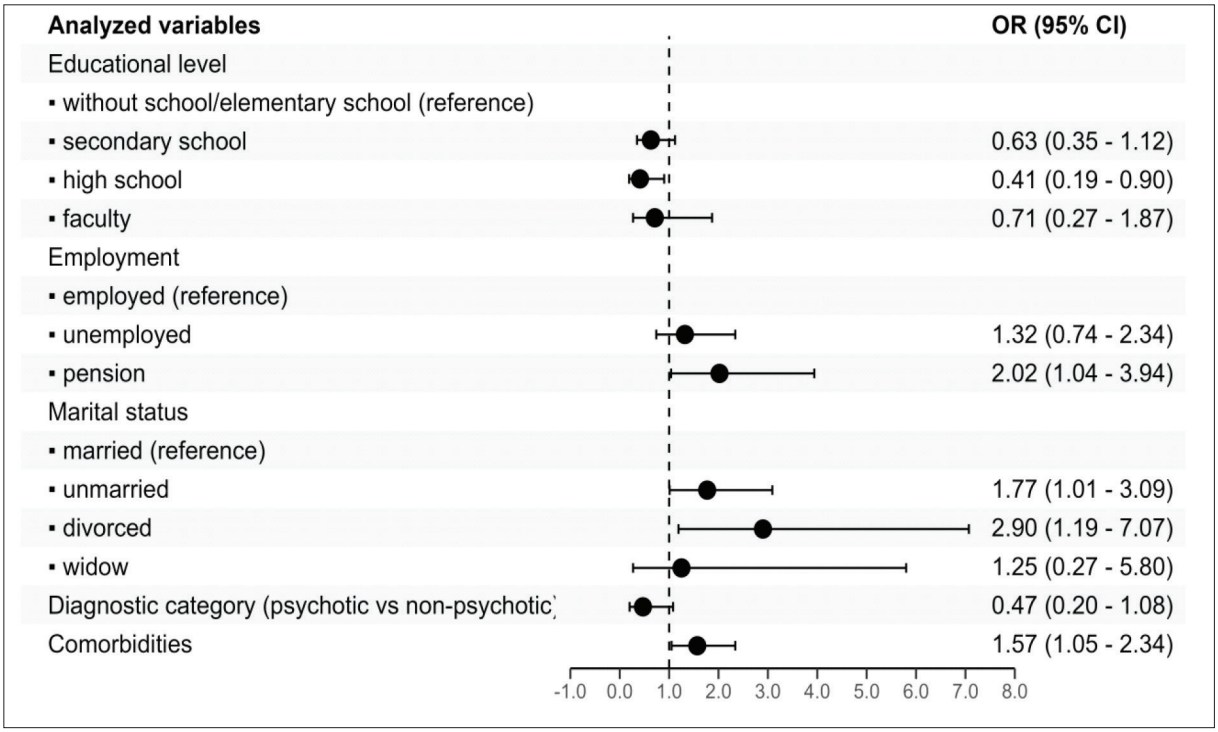


Figure 2. Multivariate logistic regression analysis results

supported by the prior findings indicating that vaccination during hospital treatment was a good strategy for increasing the vaccination coverage of this vulnerable group [22, 23].

Extant research also shows that people with mental disorders are at a more significant risk of SARS CoV-2 infection [24, 25]. Over 90% of our cohort did not contract the virus within the study period, likely due to the strong public health measures that were in force in Serbia during the peak of the epidemic. As these findings could also potentially be attributed to the personal attitudes, lifestyle, and habits of people with mental disorders during the pandemic, these factors should be examined as a part of future research.

As only 10% of the sample had COVID-19 infection, no statistically significant differences could be established in the hospitalization rates due to COVID-19 between the vaccinated and the unvaccinated group, indicating that this is another aspect that warrants additional studies based on larger samples. Still, among the 20 infected patients who were previously vaccinated, 12 (60%) required hospital treatment to combat the COVID-19 infection, while all six (100%) previously unvaccinated patients that acquired COVID-19 required hospitalization during the observed period. While these numbers are low, they are in line with the findings obtained in other studies around the world which have unequivocally demonstrated the importance of vaccination in reducing the infection rates as well as the severity of the disease [26].

Our analyses also revealed a significantly greater number of patients with comorbidities in the vaccinated relative to the unvaccinated group, which is in accordance with the data reported in pertinent literature [18]. These findings could potentially be attributed to the ample body of publicly available information indicating that comorbidities increase the risk of developing serious complications due to COVID-19 infection, which are more likely to result in a fatal outcome [27]. The fear of needing hospitalization, intensive care or a ventilator may have motivated these patients to get vaccinated [19]. Therefore, as the vaccinated group had a greater number of comorbidities on average, this factor might have contributed to the greater COVID-19-related hospitalization rates in this group.

Psychiatrists play a very important role in supporting the healthcare system in creating culturally and contextually adapted public health messages in order to overcome resistance to vaccination. Patients with more severe mental disorders – such as psychotic spectrum disorders, who comprised 90% of our sample-have additional, individual challenges that may interfere with the decision to vaccinate against COVID-19. They include lack of knowledge, neurocognitive impairment, low digital literacy, lower educational attainment, reduced ability to reason rationally, and negative mental states such as apathy and avolition [28].

Given that the patients that took part in the present study had no external barriers (such as limited vaccine availability or access to the vaccination points), it is certain that the reasons for non-vaccination and resistance were exclusively of an individual nature. Thus, we concur with the findings of a literature review conducted by Lim et al. [29] indicating that a multi-level approach is required to increase the COVID-19 vaccination uptake among patients with psychiatric diseases, which should be tailored depending on the presence and degree of resistance to vaccination, as well as the analysis of possible reasons for resistance.

In overcoming these obstacles, psychiatrists can use their medical knowledge, but also specific cognitive-behavioral and motivational interviewing techniques, which makes them

ideal vaccination ambassadors, bearing in mind their frequent contact with these patients and the unique knowledge and skillset they possess. As these experts have long-term and trust-based strong therapeutic alliances with their patients, they are also in a position to address both rational beliefs and irrational ideas about vaccination [29, 30].

CONCLUSION

Further studies are needed to determine whether people with particular mental disorders have a higher risk of SARS-CoV-2 infection and severe COVID-19. Therefore, persons with mental disorders represent a vulnerable group as they are more likely to acquire infection under epidemic conditions, and should therefore also be the target for specific motivational initiatives aimed at raising public awareness about the importance of vaccination. Our findings show that higher level of education, greater trust in the healthcare system, and knowledge of the available vaccination points significantly contribute to the vaccination uptake in this vulnerable population group.

Conflict of interest: None declared.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. C4591001 Clinical Trial Group Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15. [DOI: 10.1056/NEJMoa2034577] [PMID: 33301246]
2. Knoll MD, Wonodi C. Oxford–AstraZeneca COVID-19 vaccine efficacy. Lancet. 2021;397(10269):72–4. [DOI: 10.1016/S0140-6736(20)32623-4] [PMID: 33306990]
3. Vitiello A, Pelliccia C, Ferrara F. Drugs acting on the renin–angiotensin system and SARS-CoV-2. Drug Discov Today. 2021;26(4):870–4. [DOI: 10.1016/j.drudis.2021.01.010] [PMID: 33486116]
4. COVID-19 Vaccines: Development, Evaluation, Approval and Monitoring. Available from: https://www.ema.europa.eu/en
5. Yalçin M, Sönmez Güngör E, Ergelen M, Beşikçi Keleş D, Yerebakan Tüzer M, Öcek Baş T, et al. Characteristics and outcomes of psychiatric inpatient with severe mental illness and COVID-19: Experience from a COVID-19-Specific acute psychiatric ward in Istanbul. J Nerv Ment Dis. 2021;209(12):884–91. [DOI: 10.1097/NMD.0000000000001450] [PMID: 34710895]
6. Courtenay K. Covid-19: challenges for people with intellectual disability. BMJ. 2020;37(3):231–6. [DOI: 10.1136/bmj.m1609] [PMID: 32349992]
7. Nooraeen S, Bazargan-Hejazi S, Naserbakht M, Vahidi C, Shojaerad F, Mousavi SS, et al. Impact of COVID-19 pandemic on relapse of individuals with severe mental illness and their caregiver's burden. Front Public Health. 2023;11:1086905. [DOI: 10.3389/fpubh.2023.1086905] [PMID: 36817882]
8. Peritogiannis V, Drakatos I, Gioti P, Garbi A. Vaccination rates against COVID-19 in patients with severe mental illness attending community mental health services in rural Greece. Int J Soc Psychiatry. 2022;69(1):208–15. [DOI: 10.1177/00207640221081801] [PMID: 35253527]
9. Grune J, Savelsberg D, Kobus M, Lindner AK, Herrmann WJ, Schuster A. Determinants of COVID-19 vaccine acceptance and access among people experiencing homelessness in Germany: A qualitative interview study. Front Public Health. 2023;11:1148029. [DOI: 10.3389/fpubh.2023.1148029] Erratum in: Front Public Health. 2023 Jul 21;11:1245524. [PMID: 37033048]
10. World Health Organization. WHO EDirector-General's Opening Remarks at the Media Briefing on COVID-19-11 March 2020. Available from: https://wwwwhoint/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020 (accessed March 11, 2020).
11. Haeuser E, Serfes AL, Cork MA, Yang M, Abbastabar H, Abhilash ES, et al. Local Burden of Disease sub-Saharan Africa HIV Prevalence Collaborators. Mapping age- and sex-specific HIV prevalence in adults in sub-Saharan Africa, 2000–2018. BMC Med. 2022;20(1):488. [DOI: 10.1186/s12916-022-02639-z] [PMID: 36529768]
12. Marković M. Imunski odgovor na SARS-CoV-2 i pregled vakcina protiv COVID-19. Medicinski podmladak. 2021;72(3):20–9. [DOI: 10.5397/mp72-33315] [In Serbian]
13. Pandolfo G, Genovese G, Iannuzzo F, Bruno A, Pioggia G, Gangemi S. COVID-19 Vaccination and Mental Disorders, What Has Been Accomplished and Future Direction. Brain Sci. 2022;12(2):292. [DOI: 10.3390/brainsci12020292] [PMID: 35204055]
14. Murphy J, Vallières F, Bentall RP, Shevlin M, McBride O, Hartman TK, et al. Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. Nat Commun. 2021;12(1):29. [DOI: 10.1038/s41467-020-20226-9] [PMID: 33397962]
15. Eyllon M, Dang AP, Barnes JB, Buresh J, Peloquin GD, Hogan AC, et al. Associations between psychiatric morbidity and COVID-19 vaccine hesitancy: An analysis of electronic health records and patient survey. Psychiatry Res. 2022;307:114329. [DOI: 10.1016/j.psychres.2021.114329] [PMID: 34910966]
16. Bai W, Cai H, Jin Y, Zhang Q, Cheung T, Su Z, et al. COVID-19 vaccine hesitancy in community-dwelling and hospitalized patients with severe mental illness. Psychol Med. 2023;53(9):4288–90. [DOI: 10.1017/S0033291721004918] [PMID: 34915962]
17. Malik AA, McFadden SM, Elharake J, Omer SB. Determinants of COVID-19 vaccine acceptance in the US. EClinicalMedicine. 2020;26:100495. [DOI: 10.1016/j.eclinm.2020.100495] [PMID: 32838242]
18. Tzur Bitan D, Kridin K, Cohen AD, Weinstein O. COVID-19 hospitalisation, mortality, vaccination, and postvaccination trends among people with schizophrenia in Israel: a longitudinal cohort study. Lancet Psychiatry. 2021;8(10):901–8. [DOI: 10.1016/S2215-0366(21)00256-X] [PMID: 34364406]
19. De Picker LJ. Closing COVID-19 mortality, vaccination, and evidence gaps for those with severe mental illness. Lancet Psychiatry. 2021;8(10):854–5. [DOI: 10.1016/S2215-0366(21)00291-1] [PMID: 34364405]
20. Lim C, Van Alphen MU, Maclaurin S, Mulligan C, Macri B, Cather C, et al. Increasing COVID-19 Vaccination Rates Among Patients With Serious Mental Illness: A Pilot Intervention Study. Psychiatr Serv. 2022;73(11):1274–7. [DOI: 10.1176/appi.ps.202100702] [PMID: 35414188]
21. Stewart DE, Appelbaum PS. COVID-19 and psychiatrists' responsibilities: a WPA position paper. World Psychiatry. 2020;19(3):406–7. [DOI: 10.1002/wps.20803] [PMID: 32931089]
22. Jeon HL, Kwon JS, Park SH, Shin JY. Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: nationwide cohort study. Br J Psychiatry. 2021;218(6):344–51. [DOI: 10.1192/bjp.2020.251] [PMID: 33407954]
23. Hooper K, Hooper M, Nguyen J, Fukutomi A. Are you vaccinated? COVID-19 vaccination rates and the effect of a vaccination program in a metropolitan mental health inpatient population in Australia. Australas Psychiatry. 2023;31(1):38–42. [DOI: 10.1177/10398562221136756] [PMID: 36337038]
24. Danenberg R, Shemesh S, Tzur Bitan D, Maoz H, Saker T, Dror C, et al. Attitudes of patients with severe mental illness towards COVID-19 vaccinations: A preliminary report from a public psychiatric hospital. J Psychiatr Res. 2021;143:16–20. [DOI: 10.1016/j.jpsychires.2021.08.020] [PMID: 34438198]
25. Wang Y, Yang Y, Ren L, Shao Y, Tao W, Dai XJ. Preexisting Mental Disorders Increase the Risk of COVID-19 Infection and Associated Mortality. Front Public Health. 2021;9:684112. [DOI: 10.3389/fpubh.2021.684112] [PMID: 34434913]
26. Guo Y, Cheng C, Zeng Y, Li Y, Zhu M, Yang W, et al. Mental Health Disorders and Associated Risk Factors in Quarantined Adults During the COVID-19 Outbreak in China: Cross-Sectional Study. J Med Internet Res. 2020;22(8):e20328. [DOI: 10.2196/20328] [PMID: 32716899]

27. Machado BAS, Hodel KVS, Fonseca LMDS, Pires VC, Mascarenhas LAB, da Silva Andrade LPC, et al. The Importance of Vaccination in the Context of the COVID-19 Pandemic: A Brief Update Regarding the Use of Vaccines. Vaccines (Basel). 2022;10(4):591. [DOI: 10.3390/vaccines10040591] [PMID: 35455340]
28. Adab P, Haroon S, O'Hara ME, Jordan RE. Comorbidities and covid-19. BMJ. 2022;377:o1431. [DOI: 10.1136/bmj.o1431] [PMID: 35705219]
29. Lim C, Van Alphen MU, Freudenreich O. Becoming vaccine ambassadors: A new role for psychiatrists. Current Psychiatry. 2021;20(8):10–1,17–21,26–28,38. [DOI: 10.12788/cp.0155]
30. Mazereel V, Van Assche K, Detraux J, De Hert M. COVID-19 vaccination for people with severe mental illness: why, what, and how? Lancet Psychiatry. 2021;8(5):444–50. [DOI: 10.1016/S2215-0366(20)30564-2] [PMID: 33548184]

Предиктори за избор вакцинације против ковида 19 код особа са менталним сметњама

Емилија Новаковић[1,2], Мирјана Стојановић-Тасић[1,2], Татјана Новаковић[2], Александра Дутина[1], Зоран Букумирић[3], Ивана Сташевић-Карличић[1,2]

[1]Клиника за психијатријске болести „Др Лаза Лазаревић", Београд, Србија;
[2]Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Забележене су веће стопе оболевања и морталитета од инфекције ковидом 19 међу особама са менталним сметњама, посебно код оних који болују од тешких форми и због тога њима треба дати приоритет током вакцинације. Циљ ове студије био је да се испитају могући предиктори прихватања вакцинације против инфекције ковидом 19 код болесника са менталним сметњама.

Методе Ова ретроспективна студија спроведена је од јануара 2021. до јануара 2022. године и обухватила је 458 болесника са менталним сметњама, лечених у Клиници за психијатријске болести „Др Лаза Лазаревић" у Београду. Испитаници су подељени у две групе – вакцинисани и невакцинисани у зависности од вакциналног статуса. За потребе студије израђен је посебан упитник, како би се прикупили социодемографски подаци испитаника, док су подаци који су се односили на ментални статус, инфекцију ковидом 19 и коморбидитете добијени из њихових историја болести.

Резултати Осамдесет одсто вакцинисаних се определило за Синофармову вакцину. Значајно већи проценат вакцинисаних болесника био је хоспитализован током периода истраживања и имао је коморбидитете у односу на невакцинисану групу (51,4% према 32,6% и 52,8% према 37,5%). Ниво образовања, статус запослења, брачни статус, дијагностичка категорија и коморбидитети били су статистички значајни предиктори прихватања вакцинације против инфекције ковидом 19 код особа са менталним сметњама.

Закључак Резултати наше студије показују да виши степен образовања, веће поверење у здравствени систем и познавање доступних вакциналних места значајно доприносе прихватању вакцинације код ове осетљиве групе становништва.

Кључне речи: ковид 19; менталне сметње; вакцинација

DOI: https://doi.org/10.2298/SARH230711006G
UDC: 616.833.1-003.93-092.9; 616.833.1-001-089-092.9

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Correlation of nerve conduction velocity and the number of newly created axons in the regeneration of the facial nerve in rabbits after application of platelet-rich plasma

Milka Gardašević[1], Milan Tešić[2], Aleksandra Petković-Ćurčin[3], Boban Labović[4], Zdravko Brković[5]

[1]Military Medical Academy, Clinic for maxillofacial surgery, Belgrade, Serbia;
[2]Požarevac General Hospital, Department for Ear, Nose, and Throat and Oral and Maxillofacial Surgery, Požarevac, Serbia;
[3]Military Medical Academy, Institute for Medical Research, Belgrade, Serbia;
[4]Military Medical Academy, Clinic for Neurology, Belgrade, Serbia;
[5]University Clinical Center of Serbia, Clinic for pulmonology, Intensive Care Unit, Belgrade, Serbia

SUMMARY

Introduction/Objective Peripheral nerve lesions are frequent occurrences in both human and animal, leading to the emotional burden of disturbed facial expression and functional problems that have an impact on numerous activities of daily living.

This study aimed to investigate the nerve conduction velocity in newly created axons and the efficacy of locally applied platelet-rich plasma on the recovery of facial nerve functions after surgical transection and repair.

Methods The study was conducted in three phases, over a period of six weeks, on 24 male chinchillas, weighing 2.5–3 kg and aged between three and four months. Depending on nerve repair type, rabbits were assigned into four groups: group I (suture), group II (suture and fibrin sealant), group III (suture and platelet-rich plasma) and group IV (suture, fibrin sealant and platelet-rich plasma).

Results Most successful regeneration of the facial nerve after six weeks of nerve repair was achieved in groups III and IV in which, in addition to neurosuture, the nerve was treated with platelet-rich plasma, with or without the use of fibrin sealant (which had no role in the regeneration process), ($\alpha = 0.05$). The movements of the auricle followed the process of nerve recovery, and the number of newly created axons was directly proportional to the nerve conduction velocity ($p < 0.05$).

Conclusion Local application of platelet-rich plasma can accelerate the functional recovery of the facial nerve. Available growth factors and bioactive proteins present in platelet-rich plasma may have clinical implications for surgical treatment of patients after facial nerve injury.

Keywords: surgical repair; facial nerve; injuries; experimental animals; platelet-rich plasma

INTRODUCTION

The facial nerve innervates the facial muscles and conditions facial expression as an important part of non-verbal communication and a means of emotions recognition [1].

Facial nerve injuries accounts for 6–27% of all facial nerve palsies [2] and the most common causes of paralysis are tumor resections, basilar skull fractures, penetrating traumas and iatrogenic injures [1]. Alongside with the emotional burden of disturbed facial expression, facial nerve paralysis can cause functional problems that have an impact on numerous activities of daily life [1–4].

For surgeons, iatrogenic facial nerve injuries are of particular importance, which most often occur in different types of surgery – parotid gland tumor resection, middle ear/temporomandibular surgery, mastoidectomy, resection of neural tumors, etc. [2, 3, 4]. Iatrogenic injuries can be the result of nerve traction, thermal lesion by electrocautery and partial or complete nerve transection [1]. Determining the extent of trauma is often challenging, and the most used method for describing the severity (degree) of injury is the Sunderland scale [5].

The Sunderland scale describes the five stages of damage peripheral nerve fibers:

I. neuropraxia, as the lightest form;

II. mild axonotmesis (interruption of the axon with myelin sheaths while preserving the connective tissue sheath);

III. moderate axonotmesis (interruption of both the axon and the endoneurium);

IV. severe axonotmesis (interruption of the endo and perineurium while preserving the epineurium);

V. neurotmesis (partial or complete cutting of the nerve) [5].

Due to compression and nerve stretching during surgical procedures neuropraxia and axonotmesis are most common, but reversible in nature. In case of a partial and/or complete

Received • Примљено: July 11, 2023
Revised • Ревизија: November 16, 2023
Accepted • Прихваћено: December 21, 2023
Online first: January 12, 2024

Correspondence to:
Milan TEŠIĆ
Požarevac General Hospital
Department for Ear, Nose, and Throat and Oral and Maxillofacial Surgery
Bratstva Jedinstva 135
Požarevac
Serbia
dr.milantesic@gmail.com

nerve transection, we are referring to neurotmesis and consequent flaccid muscle paralysis, which is irreversible if the nerve is not repaired [1, 5].

In order to understand nerve damage classification scale, it is important to know the concept of Wallerian degeneration, which creates terms for nerve healing [5]. Process begins proximal to the site of injury (node of Ranvier) and continues distally to the neuromuscular junction, with the injured axon regenerating approximately 1 mm in 24 hours [6]. In cases of complete nerve transection, degeneration lasts approximately 72 hours, and days or weeks after of contusion or peripheral nerve damage [7]. By the end of the third week, Schwann cells proliferate inside the basal membrane of the distal part of the axon and if there is a defect, they bridge it. After three weeks of injury, both the neuron and the distal part of the axon are capable of regeneration [1, 8]. Reduction of epineural degeneration and perineural scar formation by application of platelet-rich plasma (PRP) could lead to faster and more complete recovery [8]. These data impose the question of biological growth factors use obtained from PRP that would promote the regeneration process of damaged nerve [8, 9].

Therefore, this study aimed to investigate the nerve conduction velocity (NCV) in newly created axons and the efficacy of locally applied PRP on the recovery of facial nerve functions after surgical transection and repair.

METHODS

Experimental design

This study was conducted at the Institute for Medical Research, Military Medical Academy in Belgrade, Serbia, from 2013 to 2015. Histological sections and analysis were done at the Institute for Pathological Anatomy, Faculty of Veterinary Medicine, University of Belgrade.

In our study a rabbit facial nerve model was used (its injury leads to asymmetry in the position and function of the auricle) for demonstrating of facial paralysis "in vivo" conditions. Each individual was in control of themselves.

The study was conducted in three phases, lasting six weeks, on 24 male chinchillas (Oryctolagus cuniculus), weighing 2.5–3 kg and aged between three and four months. Two weeks before and during the entire study, the animals were kept in the same environmental conditions (individual cages, room temperature of 23 ± 3°C, air humidity from 10% to 55% and a natural day/night cycle) with free access to food and water.

Phases of the study

The first phase – Electroneurography (ENoG) and behavioral analysis

In the first phase of the study, ENoG was performed on both auricles (left and right) in order to determine the NCV of the facial nerve. Rabbits were anesthetized with a combination of ketamine [Ketamidor® 10% injection; 35 mg/kg intramuscular (i.m.)], acepromazine (Promace®; 0.1 mg/kg i.m.) and atropine (Atropine®; 0.04 mg/kg i.m.). Two monopolar needle electrodes were placed subcutaneously in symmetrical points of the innervation field of facial nerve (*m. orbicularis oris* and *m.orbicularis oculi*). A bipolar electrode was placed above the nerve trunk, and exposed to stimulation [evoked potential determines the speed of nerve conduction (m/s)].

During the study, once a week, the left (experimental) auricula movements were observed and analyzed by behavioral method and then compared with the mobility of the right (control) ear using a five-point scale, ranging from 0 – no movement, 1 – barely detectable movements, 2 – less significant movements, 3 – larger asymmetric movements to 4 – symmetric movements [10].

The second phase

In the second phase, the following procedures were carried out:

- Preparation of PRP and fibrin sealant (FS)

The preparation of PRP was made from 5 ml of blood taken from the ear vein of each rabbit, in test tubes with 0.4 ml of citrate, by the method of double centrifugation (Figure 1A). From the 5 ml of blood taken, 0.3 ml of PRP was obtained, which with the addition of antifibrinolytics (tranexamic acid 1–5 mg per 0.5 ml cryoprecipitate) and calcium chloride (0.05 ml 10% CaCl2 per 1 ml PRP) as an activator, was applied to the site of neurorrhaphy [11].

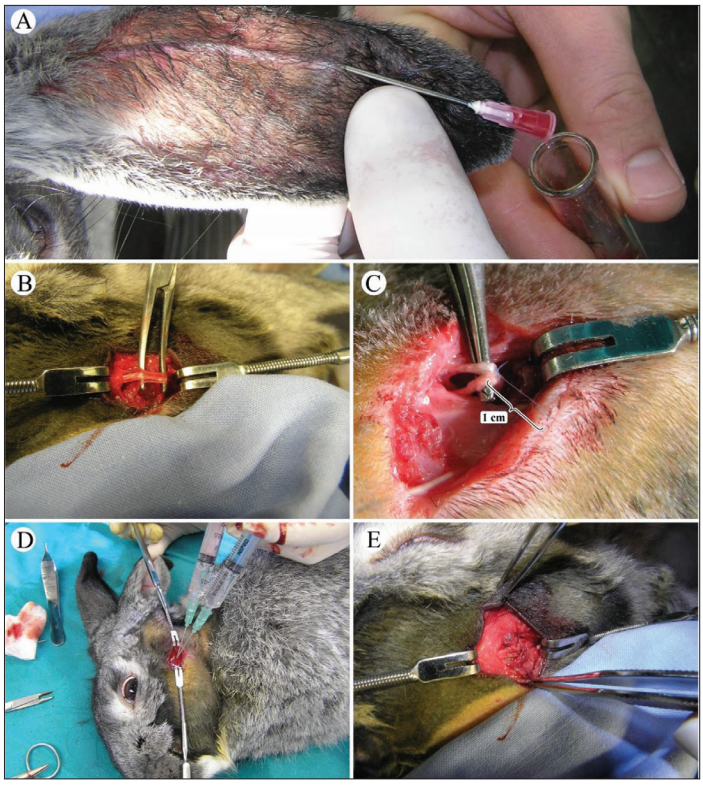


Figure 1. Preparation of platelet-rich plasma and surgical procedures: A – blood collection process: venipuncture; B – identification of facial nerve trunk; C – suture and nerve mapping; D – application of platelet-rich plasma; E – site of nerve sampling (harvesting) for histological analysis

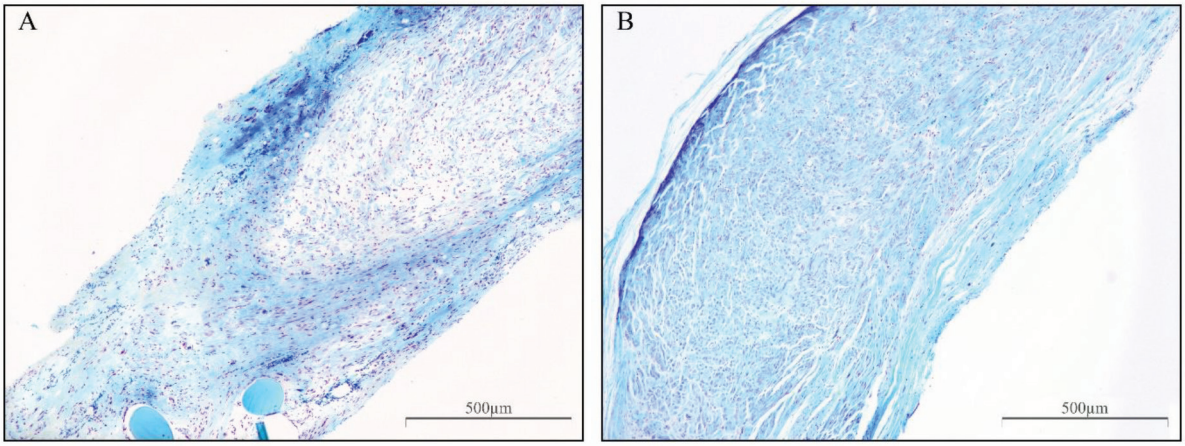


Figure 2. Histological analysis or repaired nerve: A – Group I (suture); B – Group IV (suture + fibrin sealant + platelet-rich plasma); note a greater proliferation of Schwann cells in group IV

In addition to PRP, in groups II and IV, FS was also applied, as commercial preparation Beriplast® P Combi-Set 0.5/1 ml [12].

- Surgical transection and nerve repair

Preoperatively, the same dose of anesthetic was prepared as in the first phase, with the addition of general anesthesia with the local application of mepivacaine (Mepivacaine HCl 3%) with epinephrine in a dose of 1:100.000 at the incision site. In all rabbits, an identical surgical procedure was performed; identification of the trunk of the left facial nerve, surgical transection (before bifurcation), (Figure 1B) and nerve repair. Depending on repair type, rabbits were assigned into four groups: I group (suture), II group (suture and FS), III group (suture and PRP) and IV group (suture, FS and PRP). In all groups, the nerve ends were reconstructed with an epineural suture, nylon 9-0. The mapping of the repaired part of the nerve was performed with a thread of suture, cut to a length of 1 cm (Figure 1C and 1D). Skin was sutured with nylon 5-0.

After six weeks of repair, the following was done: ENoG of the left nerve (in order to determine NCV), harvesting of nerve specimen in mapped site for histological analysis (Figure 1E), and nerve sampling from the right side for comparison.

The third phase – Histological analysis of newly created axons and ENoG

In the third phase, a histological analysis of the samples of the repaired nerves was carried out, and the proportionality between the number of newly created axons and NCV was determined.

Histological analysis

Surgical nerve specimens (5 mm in length) were fixed for 24 hours in 4% buffered formalin solution and then washed with water, dehydrated in alcohol of increasing concentration (70–100%) and lyophilized in xylene and embedded in paraffin. Paraffin blocks were cut with a microtome to a sample thickness of 3–5 µm. The sections were stained with hematoxylin and eosin, according to the manufacturer's instructions. Positive immunoreactivity for S100 was recorded as nuclear staining. The preparations were examined with a light microscope at a magnification of 400×. The average number of axons was calculated by the average number of four randomized fields of each preparation and expressed numerically (Figure 2A and 2B). After six weeks of repair, the NCV of the left auricle was determined by ENoG and results were compared with the data from the first phase.

Statistical analysis

Data were analyzed in GraphPad Prism 9.0.0 statistical package (GraphPad Software, Boston, MA, USA), with significance $p < 0.05$. Obtained values are presented as mean ± standard deviation.

After testing the normality of the distribution of variables by groups, the t-test (for features with a normal distribution) was used to determine statistical significance. For non-parametric features, the Kruskal–Wallis test was used to evaluate the significance of group differences and Wilcoxon–Mann–Whitney test for the evaluation of intergroup differences (to determine with certainty which methods of nerve repair had a statistically significant difference in the effects) [13, 14].

This study was approved by the institutional Ethics Committee (No. 5603/2, 11.03.2013., Faculty of Medicine, University of Belgrade).

RESULTS

The results were summarized on the basis of conducted ENoG examination of nerve velocity, observation scale of gross recovery of auricle movements and histological analysis of newly created axons. The most successful regeneration of the facial nerve after six weeks of repair was achieved in groups III and IV in which, in addition to the neurosuture, the nerve was treated with PRP, with or without the use

Table 1. Simultaneous comparison of groups (methods) I, II, III, and IV in third phase of the experiment

Kruskal–Wallis	Nerve conduction velocity Wilcoxon Wa; significant level (α = 0.05); n1 = n2 = 6, significant interval (28, 50)					
M1 = M2 = M3 = M4 M1 # M2 # M3 # M4 significant level (α = 0.05)	I–II H0: M2 = M1 H1: M2 > M1	I–III H0: M3 = M1 H1: M3 > M1	I–IV H0: M4 = M1 H1: M4 > M1	II–III H0: M3 = M2 H1: M3 > M2	II–IV H0: M4 = M2 H1: M4 > M2	III–IV H0: M4 = M3 H1: M4 > M3
H = 17.878	Wb = 39	Wb = 57	Wb = 57	Wb = 57	Wb = 57	Wb = 44.5
$H_{v=3,\alpha} < 7.815$	28 < Wb < 50	Wb > 50	Wb > 50	Wb > 50	Wb > 50	28 < Wb < 50
*		*	*	*	*	

M – applied method (group); H, Hv – test value; H0 – hypothesis 0; H1 – hypothesis 1; Wb – test score;
* – statistically significant difference

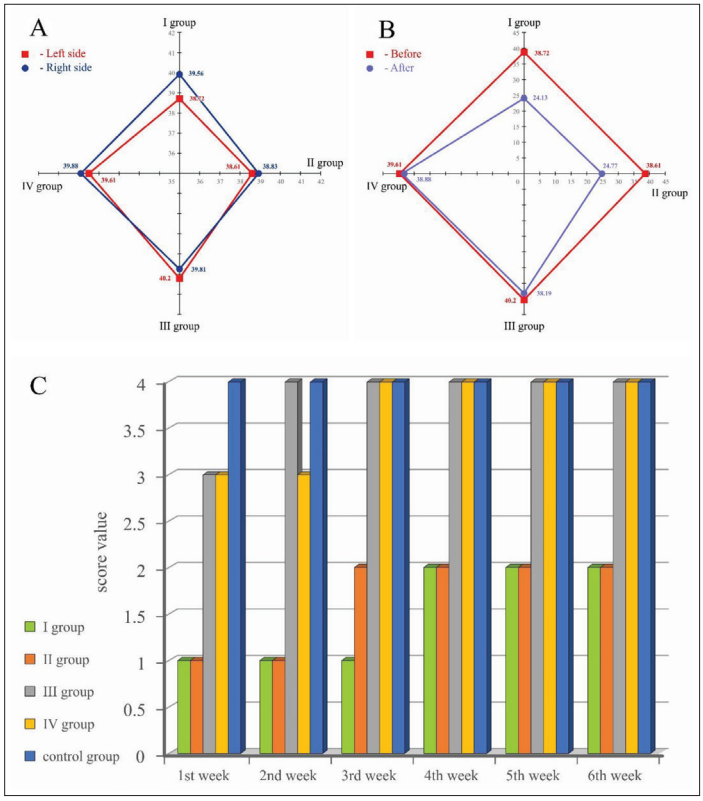


Figure 3. Comparison of nerve conduction velocity (NCV) and gross recovery of auricular movements between gropus; A – radar diagram of NCV effects of the experimental (left) and control (right) side of auricle in first phase; B – radar diagram of NCV effects before and six weeks after nerve repair (first and third phase) of the left side; C – score dependency (0–4) of the control (right) and experimental (left) side of auricula movements during six weeks period

of FS (which had no benefit in the healing process). The movements of the auricle followed the process of nerve regeneration and the number of newly created axons was directly proportional to the NCV.

In the first phase of the experiment, the NCV of the experimental (left) and control (right) side was determined in all rabbits. On the radar diagram of the NCV effects, in the space of applied methods, it can be seen that the measured values of the left and right sides are almost identical (the differences are less than one m/s in all animals), which leads to the conclusion that there is no statistically significant difference in results (Figure 3A).

In the third phase, the NCV on the left side was determined ENoG and the obtained values were compared with the results from the first phase. The analysis indicates that in groups I and II the NCV is significantly reduced compared to the same groups before the experiment, which concludes that the methods of applying the suture itself and FS are ineffective in the nerve regeneration process. In groups III and IV, where PRP was applied, the results are similar and matches the values of the same groups before nerve transection. This showed the superiority of groups III and IV compared to groups I and II (Figure 3B).

Comparison of group differences (six weeks after the nerve repair) indicates that there are no significant differences in NCV between groups I and II (calculated test value; Wb = 39). Intercomparison of group I with groups III and IV (Wb = 57), showed higher NVC values at the upper critical threshold (at significant level α = 0.05 and equal sample size; n1 = n2 = 6), so we can conclude that significantly better results are achieved with the applied reparation methods in the groups III and IV. Also, based on the test value (Wb = 57), methods applied in groups III and IV are superior prior to the method in group II, while when comparing methods III and IV, the test value (Wb = 44.5) was within the significance threshold interval, which means that there is no statistically significant difference in effects when comparing these two groups (Table 1).

During the experiment, once a week in all groups, the gross recovery of auricle movements on left side was observed, and compared with auricula movements on control side. Results were summarized based on a five-point scale. In groups III and IV the scale values from left side were almost identical to values of control side at the end of six-week period, which speaks in favor of applied PRP method (Figure 3C).

Six weeks after nerve repair and animal sacrifice, previously mapped nerve specimens were taken from left and also form right side. Samples were histologically processed. Results showed that number of newly created axons in groups III and IV are almost equal to the number in control group (Figure 4A). The FS used in groups II and IV showed inefficiency in reparation process in group II, while in the group IV (combined with PRP) effect was satisfactory and almost the same as in control group. This observation imposes that FS when used alone, has no effect in nerve healing process and priority is given to PRP. In addition to the increase in number of newly created axons, the

Table 2. Comparative overview of histological characteristics of the damaged nerve reparation six weeks after intervention

Histological characteristics	Groups			
	I	II	III	IV
Number of newly created axons	22a	26.5b	86.5	87
Number of Schwann cells	10b	12b	83.5	82

Statistical significance: [a]$p < 0.05$ *vs*. Groups II, III, and IV (Kruskal–Wallis and Mann–Whitney–Wilcoxon test); [b]$p < 0.05$ *vs*. Groups III and IV (Kruskal–Wallis and Mann–Whitney–Wilcoxon test)

histological analysis also revealed a greater proliferation of Schwann cells in groups III and IV (Table 2).

Summarizing the results of ENoG, it is shown that the growth of the number of newly created axons is directly proportional to the NCV, primarily observed in groups III and IV, which favors the application of PRP as the method of choice in nerve repair (Figure 4B).

DISCUSSION

Facial nerve injuries are complicated lesions and the treatment of consequential functional impairment and facial paralysis due to nerve injury continues to evolve, and an understanding of the various methods of injury assessment and therapy are critical to successful treatment [3]. In general, surgical procedures for the treatment of facial paralysis consist of primary neurorrhaphy, interposition nerve grafting, nerve transfers, etc. [3]. Common to all these procedures is the primary neurosuture, which should be performed whenever possible [15], with the exception of long-term facial paralysis (approximately two years after injury) in which degeneration of the end motor plates has already followed and then reinnervation procedures are futile [16]. Additional procedures such as the application of PRP, botulinum toxin and FS can be of great help in the process of nerve regeneration [3, 10, 12]. Such modalities have the potential to change the current treatment algorithm [3].

Numerous studies showing the effectiveness of PRP in tissue engineering are still at the experimental level and are consistent with the results of our study [9, 17]. Namely, analyzing the collected results with an emphasis on facial nerve regeneration, it was concluded that growth factors obtained from autologous PRP influenced the proliferation of axons in experimental animals and accelerated nerve recovery, whether PRP was used alone [18], in combination with other biological materials [19] or stem cells [20].

Growth factors obtained from PRP affect neuroregeneration processes by forming a microenvironment that leads to the proliferation of Schwann cells as the basic units in the axon synthesis process [8, 11, 14, 18–21]. It has been shown that the highest growth factor activity in the proliferation of Schwann cells is in the platelet concentrate, which is approximately ≤ 450% of the number of platelets in whole blood [22]. Therefore, in our study, there is a high percentage of Schwann cell proliferation and a high number of newly created axons, groups III and IV, (Table 2) given that the concentration of platelets in PRP (2.567.523 ± 1.126.519 × 103 /μl) was four times higher than in whole blood (593.780 ± 116.349 × 103 /μl) of rabbits.

Regarding the effectiveness of using FS in peripheral nerve regeneration [10, 12, 23], it was found that FS alone, has no or very little role in healing [10, 23]. Such data from literature are in accordance with our research, in which FS showed no benefit. As in the previously conducted meta-analysis, it can be concluded that combining FS with neurosuture only enables precise alignment of nerve fibers and their positioning, thus preventing dehiscence [12].

When it comes to functional outcomes, it was noted in our research that the movements of the auricle followed the process of nerve regeneration, and the number of newly created axons was directly proportional to the NCV. This was primarily determined in groups III and IV, which blends with the research of Li et al. [18], who confirmed the success of PRP application in the nerve regeneration after three weeks. Cho et al. [24] also support these facts with their research in which the best functional outcomes were achieved four to six weeks after surgery, while in the work of Şentürk et al. [25], the best results were achieved after five weeks. Also, in our previous research where we

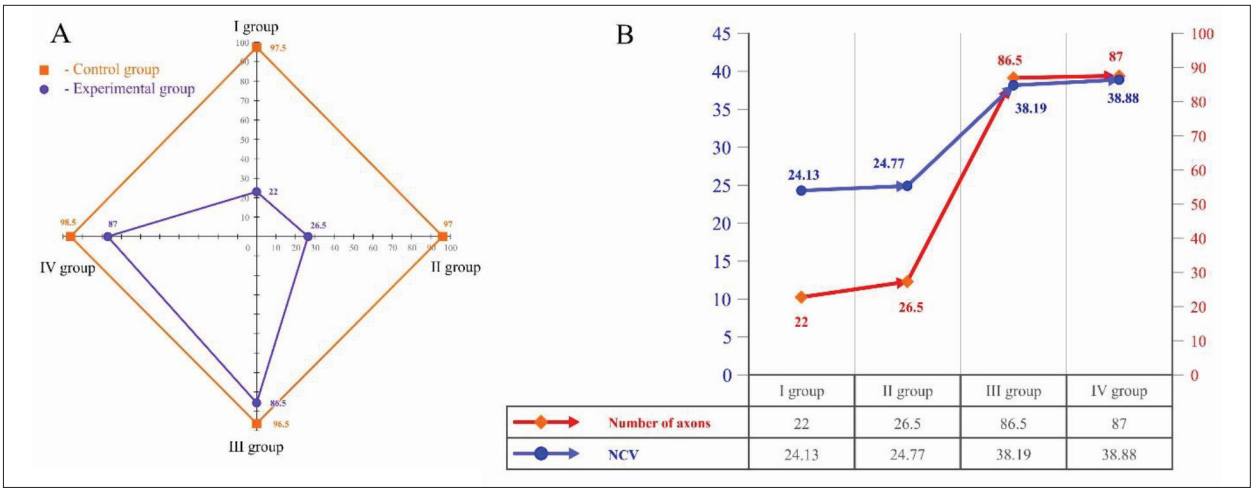


Figure 4. Number of newly created axons and their's velocity potential after nerve repair; A – radar diagram comparison of the number of newly created axons beetwen the control and experimental group; B – action potential velocity of axons between groups (I–IV)

compared the effects of PRP application on facial nerve recovery, in two time periods (six and 10 weeks), we did not find significant differences in nerve recovery in the tenth week compared to the sixth week [26].

Finally, when we "transfer" the experimental results in the clinical environment, we can say that both patients and doctors alike must be patient, because the recovery of an injured nerve (whether it is a contusion or a complete interruption of the nerve) is slow, and the optimal elapsed time for improving functional outcomes is 4–6 weeks [14, 24–27], while complete nerve recovery is achieved within 6–8 months after the onset of symptoms [3, 28, 29]. Similar to previously published research, there are limitations of our study, i.e., the knowledge obtained in "in vivo" experiments must be "moved" to clinical settings [30], in order to obtain official confirmation of the success of the PRP technique in the process of facial nerve regeneration on patients. It should also be the next phase of our study.

CONCLUSION

Electroneurographic tests performed before and six weeks after nerve repair showed a significant improvement in NCV in groups III and IV, with the results indicating almost identical values of experimental and control groups III and IV. Histological analyses revealed that the number of axons in experimental groups III and IV is significantly higher when comparing with groups I and II, and that the number of new axons in experimental groups III and IV is close to the number of the same control groups.

The FS used in group IV had no effect on nerve healing process, because, when used alone with suture it showed no benefit in group II, and as such has no significance in group IV. By objectifying the ear movements of experimental side, a higher score was confirmed in groups III and IV, which is another parameter that speaks in favor of the of PRP application.

Available growth factors and bioactive proteins present in PRP may have clinical implications for surgical treatment of patients after facial nerve injury. Clinical studies are currently based on a very small sample and further randomized studies with larger samples are necessary to better define the role of PRP in the facial nerve regeneration process.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Dragan Đurđević, veterinarian, for his immense help in working with laboratory animals and Nikola Kostić, B.Sc. physicist, on graphics and images processing.

This manuscript is a part of the research conducted for the doctoral dissertation: Gardašević M. Evaluation of the effectiveness of the application of plasma enriched with platelets in the process of facial nerve regeneration in rabbits [dissertation]. Kragujevac: University of Kragujevac; 2023.

Conflict of interest: None declared.

REFERENCES

1. Mistry RK, Hohman MH, Al-Sayed AA. Facial Nerve Trauma. 2023 Mar 1. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [PMID: 31971735];
2. Hohman MH, Bhama PK, Hadlock TA. Epidemiology of iatrogenic facial nerve injury: a decade of experience. Laryngoscope. 2014;124(1):260–5. [DOI: 10.1002/lary.24117] [PMID: 23606475]
3. Gordin E, Lee TS, Ducic Y, Arnaoutakis D. Facial nerve trauma: Evaluation and considerations in management. Craniomaxillofac Trauma Reconstr. 2015;8(1):1–13. [DOI: 10.1055/s-0034-1372522] [PMID: 25709748]
4. Zourntou SE, Makridis KG, Tsougos CI, Skoulakis C, Vlychou M, Vassion A. Facial nerve: A review of the anatomical, surgical landmarks and its iatrogenic injuries. Injury. 2021;52(8):2038–48. [DOI: 10.1016/j.injury.2021.05.029] [PMID: 34074487]
5. Sunderland S. The anatomy and physiology of nerve injury. Muscle Nerve. 1990;13(9):771–84. [DOI: 10.1002/mus.880130903] [PMID: 2233864]
6. Sulaiman W, Gordon T. Neurobiology of peripheral nerve injury, regeneration, and functional recovery: from bench top research to beside application. Ochsner J. 2013;13(1):100–8. [PMID: 23531634]
7. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal and humans. Neurotherapeutics. 2016;13(2):295–310. [DOI: 10.1007/s13311-015-0415-1] [PMID: 26754579]
8. Wang S, Liu X, Wang Y. Evaluation of platelet-rich plasma therapy for peripheral nerve regeneration: A critical review of literature. Front Bioeng Biotechnol. 2022;10:808248. [DOI: 10.3389/fbioe.2022.808248] [PMID: 35299637]
9. Alves R, Grimalt R. A review of platelet-rich plasma: History, biology, mechanism of action, and classification. Skin Appendage Disord. 2018;4(1):18–24. [DOI: 10.1159/000477353] [PMID: 29457008]
10. Farrag TY, Lehar M, Verhaegen P, Carson KA, Byrne PJ. Effect of platelet-rich plasma and fibrin sealant on facial nerve regeneration in a rat model. Laryngoscope. 2007;117(1):157–65. [DOI: 10.1097/01.mlg.0000249726.98801.77] [PMID: 17202946]
11. Sanchez M, Yoshioka T, Ortega M, Delgado D, Anitua E. Ultrasound-guided platelet-rich plasma injections for the treatment of common peroneal nerve palsy associated with multiple ligament injuries of the knee. Knee Surg Sports Traumatol Arthrosc. 2014;22(5):1084–9. [DOI: 10.1007/s00167-013-2479-y] [PMID: 23519544]
12. Koopman JE, Duraku LS, de Jong T, de Vries RBM, Michiel Zuidam J, Hundepool CA. A systematic review and meta-analysis on the use of fibrin glue in peripheral nerve repair: Can we just glue it? J Plast Reconstr Aesthet Surg. 2022;75(3):1018–33. [DOI: 10.1016/j.bjps.2022.01.007] [PMID: 35125308]
13. Fay MP, Proschan MA. Wilcoxon-Mann-Whitney or t-test? On assumptions for hypothesis tests and multiple interpretations of decision rules. Stat Surv. 2010;4:1–39. [DOI: 10.1214/09-SS051] [PMID: 20414472]
14. Bayrak AF, Olgun Y, Ozbakan A, Aktas S, Kulan CA, Kamaci G, et al. The effect of insulin like growth factor - 1 on recovery of facial nerve crush injury. Clin Exp Otorhinolaryngol. 2017;10(4):296–302. [DOI: 10.21053/ceo.2016.00997] [PMID: 28264555]
15. Terzis JK, Konofaos P. Nerve transfers in facial palsy. Facial Plast Surg. 2008;24(2):177–93. [DOI: 10.1055/s-2008-1075833] [PMID: 18470829]
16. Chu EA, Byrne PJ. Treatment considerations in facial paralysis. Facial Plast Surg. 2008;24(2):164–9. [DOI: 10.1055/s-2008-1075831] [PMID: 18470827]
17. Gardašević M, Živić M, Djurdjević D, Petković-Ćurčin A. Application of different techniques in facial nerve reconstruction on experimental models. Acta Veterinaria. 2023;73(2):155–70. [DOI: 10.2478/acve-2023-0012]

18. Li L, Cai J, Yuan Y, Mao Y, Xu L, Han Y, et al. Platelet-rich plasma can release nutrient factors to promote facial nerve crush injury recovery in rats. Saudi Med J. 2019;40(12):1209–17. [DOI: 10.15537/smj.2019.12.24747] [PMID: 31828272]
19. Şahin MM, Cayonu M, Dinc SK, Ozkocer E, Ilhan M, Uzunoğlu E, et al. Effect of chitosan and platelet-rich plasma on facial nerve regeneration in an animal model. Eur Arch Otorhinolaryngol. 2022;279(2):987–94. [DOI: 10.1007/s00405-021-06859-6] [PMID: 33956207]
20. Sun Y, Yhang R, Mao X, Zhang M. [Research of acellular xenogenic nerve combined with adipose-derived stem cells and platelet rich plasma in repair of rabbit facial nerve injury]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2018;32(6):736–44. [DOI: 10.7507/1002-1892.201711079] [PMID: 29905054]
21. Hu B, Zhang H, Xu M, Li L, Wu M, Zhang S, et al. Delivery of basic fibroblast growth factor through an in situ formatting smart hydrogel activates autophagy in Schwann cells and improves facial nerves generation via the PAK-1 signaling pathway. Front Pharmacol. 2022;13:778680. [DOI: 10.3389/fphar.2022.778680] [PMID: 35431972]
22. Zhu Y, Jin Z, Wang J, Chen S, Hu Y, Reu L, et al. Ultrasound guided platelet-rich plasma injection and multimodality ultrasound examination of peripheral nerve crush injury. NPJ Regen Med. 2020;5(1):21. [DOI: 10.1038/s41536-020-00101-3] [PMID: 33298932]
23. Benfield C, Isaacs J, Mallu S, Kurtz C, Smith M. Comparison of nylon suture versus 2 fibrin glue products for delayed nerve coaptation in an animal model. J Hand Surg Am. 2021;46(2):119–15. [DOI: 10.1016/j.jhsa.2020.09.021] [PMID: 33261957]
24. Cho HH, Jang S, Lee SC, Jeong HS, Park JS, Han JY, et al. Effect of neural-induced mesenchymal stem cells and platelet-rich plasma on facial nerve regeneration in an acute nerve injury model. Laryngoscope. 2010;120(5):907–13. [DOI: 10.1002/lary.20860] [PMID: 20422684]
25. Şentürk F, Bahadır O, Aktaş O, Bıyık AF, Ercan E. Effects of titanium prepared platelet rich fibrin on facial nerve regeneration: an experimental study. Braz J Otorhinolaryngol. 2022;88(6):867–74. [DOI: 10.1016/j.bjorl.2020.11.014] [PMID: 33441277]
26. Gardašević MF, Petković-Ćurčin A, Vojvodić DV, Marjanović U, Djurdjević D, Jović S, et al. Assessment of efficacy of platelet-rich plasma application in regeneration of the facial nerve in rabbits. Vojnosanit Pregl. 2023;80(4):349–55. [DOI: 10.2298/VSP171208048G]
27. Yadav A, Ramasamy TS, Lin SC, Chen SH, Lu J, Liu YH, et al. Autologous platelet-rich plasma grow factor reduces M1 macrophages and modulates inflammatory microenvironments to promote sciatic nerve regeneration. Biomedicines. 2022;10(8):1991. [DOI: 10.3390/biomedicines10081991] [PMID: 36009539]
28. Banks CA, Knox C, Hunter DA, Mackinnan SE, Hohman MH, Hadlock TA. Long-term functional recovery after facial nerve transection and repair in the rat. J Reconstr Microsurg. 2015;31(3):210–6. [DOI: 10.1055/s-0034-1395940] [PMID: 25629206]
29. Fliss E, Yanko R, Zaretski A, Tulchinsky R, Arad E, Kedar DJ, et al. Facial nerve repair following acute nerve injury. Arch Plast Surg. 2022;49(4):501–9. [DOI: 10.1055/s-0042-1751105] [PMID: 35919546]
30. Ricci E, Riva G, Dagna F, Cavalot AL. The use of platelet-rich plasma gel in superficial parotidectomy. Acta Otorhinolaryngol Ital. 2019;39(6):363–6. [DOI: 10.14639/0392-100X-2093] [PMID: 30933175]

Корелација брзине нервне проводљивости и броја новостворених аксона у регенерацији фацијалног нерва код кунића после примене плазме богате тромбоцитима

Милка Гардашевић[1], Милан Тешић[2], Александра Петковић-Ћурчин[3], Бобан Лабовић[4], Здравко Брковић[5]

[1]Војномедицинска академија, Клиника за максилофацијалну хирургију, Београд, Србија;
[2]Општа болница Пожаревац, Одељење за оториноларингологију и максилофацијалну хирургију, Пожаревац, Србија;
[3]Војномедицинска академија, Институт за медицинска истраживања, Београд, Србија;
[4]Војномедицинска академија, Клиника за неурологију, Београд, Србија;
[5]Универзитетски клинички центар Србије, Клиника за пулмологију, Јединица интензивне неге, Београд, Србија

САЖЕТАК

Увод/Циљ Повреде периферних нерава су честа појава и код људи и код животиња, а поред емоционалног терета поремећене експресије лица условљавају и функционалне проблеме који утичу на бројне активности свакодневног живота.

Циљ ове студије је био да испита брзину нервне проводљивости у новонасталим аксонима и ефикасност локалне примене плазме богате тромбоцитима на опоравак функција фацијалног нерва после хируршке трансекције и репарације живца.

Методе Истраживање је спроведено у три фазе, у периоду од шест недеља, на 24 чинчиле мушког пола, тежине од два и по до три килограма и старости између три и четири месеца. Према типу репарације нерва, зечеви су распоређени у четири групе: I група – сутура, II група – сутура и фибрински лепак, III група – сутура и плазма богата тромбоцитима и IV група – сутура, фибрински лепак и плазма богата тромбоцитима.

Резултати Најуспешнија регенерација фацијалног нерва шест недеља после репарације постигнута је у групама III и IV, у којима је поред неуросутуре живац био третиран плазмом богатом тромбоцитима, са употребом или без употребе фибринског лепка (који није имао улогу у процесу зарастања), ($\alpha = 0,05$). Покрети аурикуле пратили су процес нервне регенерације, а број новостворених аксона директно је био пропорционалан брзини нервне проводљивости ($p < 0,05$).

Закључак Локална примена плазме богате тромбоцитима може убрзати функционални опоравак фацијалног живца. Доступни фактори раста и биоактивни протеини садржани у плазми богатој тромбоцитима могу имати клиничке импликације за хируршким лечењем болесника после повреде фацијалног нерва.

Кључне речи: хируршка репарација; фацијални живац; повреде; лабораторијске животиње; плазма богата тромбоцитима

DOI: https://doi.org/10.2298/SARH230823113H
UDC: 613-056.24:616.716.1/.4-089

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Quality of life in correlation with presurgical psychological assessment of surgically treated patients with class III skeletal deformities

Nur Hatab[1], Zoran Jezdić[2], Filip Ivanjac[2], Vitomir S. Konstantinović[2]

[1]Ras Al-Khaimah Medical and Health Sciences University, Ras Al-Khaimah College of Dental Sciences, Ras Al-Khaimah, United Arab Emirates;
[2]University of Belgrade, School of Dental Medicine, Belgrade, Serbia

SUMMARY

Introduction/Objective Quality of life before and after mono- and bimaxillary surgery may vary from patient to patient depending on psychological assessment score. The aim of this study was to compare the quality of life before and six months after orthognathic surgery in correlation with a presurgical psychological assessment of patients with class III skeletal deformity, assuming that patients with low psychological assessment results might have a lower quality of life after surgery despite successful treatment results.

Methods For this prospective study, 30 patients (19 female,11 male) were included. Psychological assessment was obtained before, and quality of life before and after surgery in skeletal deformity class III patients. Statistical analysis was done with a statistical package for social science – SPSS.

Results The overall quality of life significantly improved in all the patients after surgery. Surgical correction of class III deformities provided a significant improvement independent of the type of surgery and the severity of the deformity, as well as gender and age. There were significant differences in post-surgical quality of life scores between patients with good and poor psychological assessment scores, related to social disability ($p < 0.05$).

Conclusion Patients with lower preoperative psychological scores experienced a lesser improvement in quality of life, particularly in the domain of social disability. This suggests that additional psychological treatment of these patients could further improve the beneficial effects of orthognathic surgery on postoperative quality of life.

Keywords: quality of life; mono–bimaxillar surgery; skeletal deformities

INTRODUCTION

The number of patients requiring correction of craniofacial disproportions, particularly class III deformities, has undoubtedly increased. Skeletal class III deformities can be a result of mandibular prognathism, maxillary deficiency, or both [1, 2, 3]. Orthognathic surgery aims to restore proper dental occlusion and facial harmony through modification of the position, shape, and size of the facial bones. Bone movement implies positional and tensional changes in the attached soft tissues. These new soft tissue relationships introduce significant changes in the facial appearance. Skeletal class III deformities can be surgically corrected by using mandibular setback surgery or bimaxillary surgery (maxillary advancement and mandibular setback) [4–7].

At the first appointment, every patient was assessed to establish the motive for the treatment. Ideally, they should initially be evaluated by a psychologist, to determine whether their expectations are realistic and possible to achieve. In clinical practice, this is seldom possible, and clinicians have to do the initial evaluation including psychological assessment. However, a patient-centered approach to examining the outcomes of the treatment is as important as the initial assessment. It complements the study of morphological and physiological responses to the treatment, as the success of the treatment must also be defined in the context of the patient's perceptions, and beyond traditional health indicators, such as mortality and morbidity [8–11].

The World Health Organization (WHO) defined quality of life (QoL) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHO study protocol, 1993); patient's perception of the treatment success becomes the most important parameter.

Present research hypothesized that the patients with low psychological assessment results and risk of body dysmorphic disorder (BDD) will have a lower QoL despite successful morphological and physiological responses to the treatment.

The aim of this study was to compare QoL before and six months after orthognathic surgery in correlation with a presurgical psychological assessment of patients with class III skeletal deformity, assuming that patients with low psychological assessment results might have lower QoL after surgery despite successful treatment results.

Received • Примљено: August 23, 2023
Accepted • Прихваћено: December 20, 2023
Online first: December 22, 2023

Correspondence to:
Filip IVANJAC
Svetogorska 18
11000 Belgrade, Serbia
filipivanjac@yahoo.com

METHODS

The study was approved by the ethics committee of the School of Dental Medicine, University of Belgrade (No. 36/24)598

All patients were provided with written informed consent to participate, and they were instructed about the aims and protocol of the study as well.

Patients with skeletal class III deformities were selected at the first visit to the Clinic for Maxillofacial Surgery, School of Dental Medicine, University of Belgrade. The exclusion criteria were the following: patients with complex craniofacial syndromes and patients with matured cleft lip and palate. The prospective study sample consisted of 30 consecutive patients (19 female and 11 male; mean age ± standard deviation: 22.27 ± 3.39 years, range 18–29 years) (Table 1).

Table 1. Distribution of patients according to sex and type of surgery

Sex	Group		Total
	Monomaxillary	Bimaxillary	
Male	7	4	11
Female	7	12	19
Total	14	16	30

Table 2. The initial assessment of patients requesting orthognathic treatment

Question	Positive finding	Negative finding
The defect		
Is there an actual deformity?	Yes	No
Is the defect minor?	No	Yes
The request		
Is the request obscure?	No	Yes
Is the requested change surgically feasible?	Yes	No
Is there a history of dissatisfaction with previous surgery?	No	Yes
Has the patient been "surgeon shopping"?	No	Yes
The decision to seek help		
Was there long-term planning?	Yes	No
Is the patient in acute crisis?	No	Yes
Is there pressure from others?	No	Yes
Is there support from friends/family?	Yes	No
Expectations		
Are the expectations reasonable?	Yes	No
Psychodynamics		
Is there evidence of the complaint reflecting deeper conflicts? E.g., poor relationship with parent who has the same feature	No	Yes
Previous history		
Is there a history of past psychiatric disturbance?	No	Yes
Is there a history of severe maladjustment in life situations?	No	Yes

The psychological assessment included a questionnaire with a number of significant questions specific to orthognathic deformities, developed by Cunningham and Feinmann [12] in 1998 at University College London, Orthodontic Department and Academic Department of Psychiatry. The questionnaire titled "The initial assessment of patients requesting orthognathic treatment" is presented in Table 2. The interview was performed during the initial appointment by a surgeon in a private consultation. Based on psychological assessment, the patients were divided into two groups: Group 1 – patients with low psychological assessment results (less than 50% positive responses) and Group 2 – patients with satisfactory psychological assessment results (more than 50% positive responses).

Afterwards, in preoperative QoL assessment, the patients were given one of the most widely used questionnaires, disease-specific measurement of the Oral Health Impact Profile (OHIP14). It measures individuals' perception of the social impact of their oral disorders and their well-being. The OHIP-14 questionnaire was developed as a shorter version of the OHIP-49, where the 49 questions might be too long or unnecessary for the purpose. Questions included in this questionnaire measure seven domains: functional limitation (OH-1, OH-2), physical pain (OH-3, OH-4), psychological discomfort (OH-5, OH-6, OH-10), physical disability (OH-7, OH-8, OH-14), psychological disability (OH-9), social disability (OH-11, OH-12), and handicap (OH-13) (Table 3).

Table 3. Questionnaire consisting of OHIP-14 items (OH-1–OH-14) for pre- and post-surgical and additional items (AD-1–AD-3) for postsurgical assessment of quality of life

Item	How often do you have problems with your teeth, mouth or dentures (during the previous month*) Please answer using the following scores: 0 (never), 1 (seldom), 2 (occasionally), 3 (often), and 4 (very often)
OH-1	Did you have trouble pronouncing words because of problems with your teeth, mouth, or dentures?
OH-2	Did you feel that your sense of taste has worsened because of problems with your teeth, mouth or dentures?
OH-3	Did you have painful aching in your mouth?
OH-4	Were you uncomfortable while eat because of problems with your teeth, mouth or dentures?
OH-5	Did you feel self-conscious because of problems with your teeth, mouth, or dentures?
OH-6	Did you feel tense because of problems with your teeth, mouth, or dentures?
OH-7	Was your diet unsatisfactory because of problems with your teeth, mouth, or dentures?
OH-8	Did you have to interrupt meals because of problems with your teeth, mouth, or dentures?
OH-9	Did you find it difficult to relax because of problems with your teeth, mouth, or dentures?
OH-10	Were you embarrassed because of problems with your teeth, mouth, or dentures?
OH-11	Were you agitated around other people because of problems with your teeth, mouth, or dentures?
OH-12	Did you have difficulty doing your usual work because of problems with your teeth, mouth, or dentures?
OH-13	Did you feel that life in general was less satisfying because of problems with your teeth, mouth, or dentures?
OH-14	Were you totally unable to function because of problems with your teeth, mouth, or dentures?
AD-1**	Did you feel discomfort while chewing?
AD-2**	Were you unsatisfied with your facial aesthetics?
AD-3**	Did you have a loss of sensitivity in your lips, tongue, or other facial area?

*Time specification was only given in a post-surgical questionnaire;
**AD – alternative-question only administered in post-surgical questionnaires

Initial cone-beam computed tomography (CBCT) scans of each patient were done for treatment planning. 3D

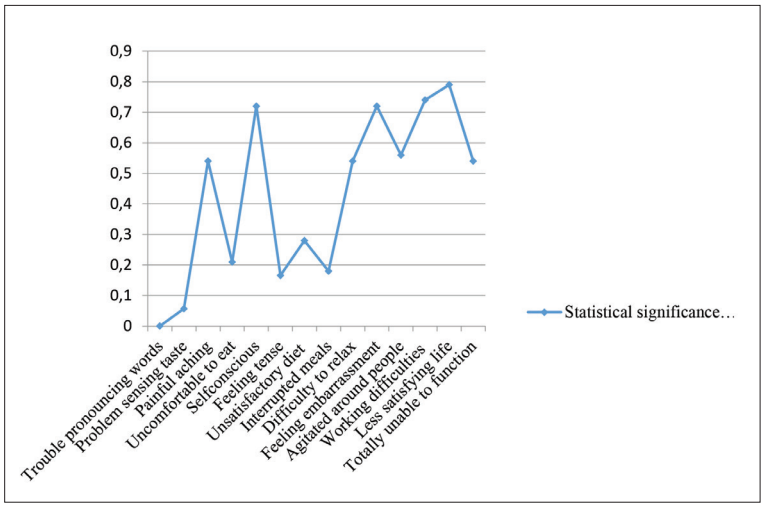


Figure 1. Pre- and postsurgical mean item scores and correlation of changes

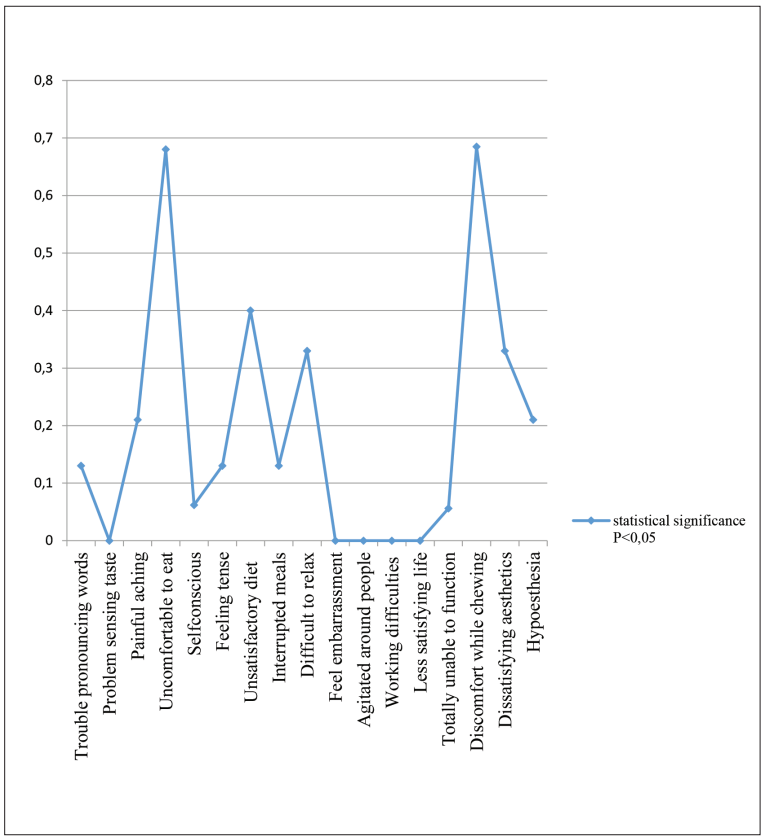


Figure 2. Differences in post-surgical scores of quality of life between patients with and without low score on the initial psychological assessment

planning was done in InVivo 5.2 software (Anatomage, San Jose, CA, USA). Study models were mounted onto a semi-adjustable articulator (Artex® ct, Amann Girrbach AG, Koblach, Austria) for manufacturing the interocclusal positioning splints.

Surgical correction of Class III deformities was performed by bilateral sagittal split osteotomy (BSSO) with mandibular setback in 14 patients and using bimaxillary surgery comprised of BSSO setback and Le Fort I osteotomy maxillary advancement in 16 patients (Table 1).

After surgical correction, the patients were hospitalized for at least five days, following the protocols: rigid fixation was applied for two weeks, and afterwards the patients wore light elastics for another two weeks. All patients underwent clinical assessment and postoperative CBCT radiological evaluation six months after the treatment to evaluate the success of the surgical procedure.

Afterwards, in the postoperative QoL assessment, patients were again given the OHIP-14 questionnaire for disease-specific measurements, now with three additional questions based on orthognathic surgery results. Rustemeyer et al. [13] added questions highly specific to orthognathic surgery to the OHIP-14 questionnaire (Table 3). Three additional questions (AD-1 to AD-3) concern chewing function, aesthetics, and post-operative loss of sensitivity.

To summarize, every patient was given the OHIP-14 questionnaire pre- and six months postoperatively, and AD-1 to AD-3 questions postoperatively only.

Statistical analysis was performed using the Statistical Package for Social Sciences, Version 18.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was performed to determine if the samples were normally distributed. Differences between pre and postoperative data and correlations between variables were calculated by the Wilcoxon signed-rank test, and differences between the groups were calculated by using the independent sample t-test. Differences were considered significant for $p < 0.05$.

RESULTS

All 30 patients involved in this study had successful surgical outcomes without complications. Surgical correction of class III deformities provided a significant improvement independent of the type of surgery and the severity of the orofacial deformity, as well as gender and age.

Psychological preoperative assessment and the QoL showed no significant differences between the scores obtained by females and males, of different ages or comparing patients treated by mono- or bimaxillary surgery.

Results of the psychological assessment showed that all patients had at least one negative response. Nevertheless, only 26.67% of patients had more than 50% of negative responses – Group 1, in the initial psychological assessment, which suggests risk of BDD. However, high percentage (73.33%) of patients had more than 50% of positive responses – Group 2.

Table 4. Pre- and post-surgical mean item scores and correlation of changes

Item	Short description	Pre-operative mean ± SD	range	Post-operative mean ± SD	range	WSR Z-value	WSR p-value
OH-1	Trouble pronouncing words	1.3 ± 1.23	0–4	0.86 ± 1.1	0–4	-1.99[a]	0.046*
OH-2	Problem sensing taste	0.16 ± 0.38	0–1	0.43 ± 0.81	0–3	-1.9[b]	0.057
OH-3	Painful aching	0.8 ± 0.92	0–3	0.7 ± 1.08	0–4	-0.61[a]	0.54
OH-4	Uncomfortable to eat	1.5 ± 1.28	0–4	1.13 ± 1.33	0–4	-1.25[a]	0.21
OH-5	Self-conscious	0.86 ± 1.1	0–4	0.76 ± 1.25	0–4	-0.35[a]	0.72
OH-6	Feeling tense	0.7 ± 0.95	0–3	0.46 ± 0.86	0–3	-1.38[a]	0.166
OH-7	Unsatisfactory diet	0.46 ± 0.73	0–3	0.33 ± 0.6	0–2	-1.07[b]	0.28
OH-8	Interrupted meals	0.9 ± 0.92	0–3	0.63 ± 1.09	0–4	-1.33[b]	0.18
OH-9	Difficulty to relax	0.66 ± 0.84	0–3	0.56 ± 0.89	0–3	-0.61[b]	0.54
OH-10	Feeling embarrassment	0.9 ± 0.92	0–3	0.80 ± 1.21	0–4	-0.36[b]	0.72
OH-11	Agitated around people	0.43 ± 0.62	0–2	0.5 ± 0.82	0–3	-0.57[b]	0.56
OH-12	Working difficulties	0.7 ± 0.98	0–3	0.6 ± 1	0–3	-0.32[a]	0.74
OH-13	Less satisfying life	0.13 ± 0.43	0–2	0.16 ± 0.46	0–2	-0.26[a]	0.79
OH-14	Totally unable to function	0.66 ± 0.92	0–3	0.56 ± s0.49	0–2	-0.61[a]	0.54

WSR – Wilcoxon signed-rank test; SD – standard deviation;
[a]based on positive rank;
[b]based on negative rank;
*statistically significant at p < 0.05

Table 5. Differences in post-surgical scores of quality of life between patients with and without low score on the initial psychological assessment

Item	Description	Group 1 Mean ± SD	Group 2 Mean ± SD	p-value
OH-1	Trouble pronouncing words	1.05 ± 1.23	0.5 ± 0.7	0.13
OH-2	Problem sensing taste	0.6 ± 0.94	0.1 ± 0.31	0.041*
OH-3	Painful aching	0.4 ± 0.69	0.85 ± 1.22	0.21
OH-4	Uncomfortable to eat	1.2 ± 1.43	1 ± 1.15	0.68
OH-5	Self-conscious	1 ± 1.45	0.3 ± 0.48	0.062
OH-6	Feeling tense	0.6 ± 0.99	0.2 ± 0.42	0.13
OH-7	Unsatisfactory diet	0.2 ± 0.42	0.4 ± 0.68	0.4
OH-8	Interrupted meals	0.2 ± 0.43	0.6 ± 0.98	0.13
OH-9	Difficulty to relax	0.9 ± 1.25	0.1 ± 0.31	0.33
OH-10	Feeling embarrassment	0.75 ± 1.01	0.2 ± 0.42	0.013*
OH-11	Agitated around people	1.1 ± 1.37	0.2 ± 0.42	0.047*
OH-12	Working difficulties	0.7 ± 0.92	0.1 ± 0.31	0.013*
OH-13	Less satisfying life	0.75 ± 1.11	0.3 ± 0.67	0.015*
OH-14	Totally unable to function	0.25 ± 0.55	0 ± 0	0.056
AD-1	Discomfort while chewing	1.2 ± 1.11	1 ± 1.22	0.685
AD-2	Dissatisfying aesthetics	0.9 + 1.01	0.1 + 0.42	0.33
AD-3	Hypoesthesia	0.4 ± 0.69	0.85 ± 0.48	0.21

Group 1 – with low score in the initial psychological assessment; Group 2 – with satisfactory score in the initial psychological assessment; SD – standard deviation;
*statistically significant at p < 0.05

Pre- and post-surgical QoL scores showed positive correlation ranks for the following items: OH-1 (trouble pronouncing words), OH-3 (painful aching), OH-4 (uncomfortable with eating), OH-5 (self-consciousness), OH-6 (feeling tense), OH-12 (working difficulties), OH-13 (less satisfying life), OH-14 (totally unable to function). While items OH-2 (problem with sense of taste), OH-7 (unsatisfactory diet), OH-8 (interrupted meals), OH-9 (difficulty to relax), OH-10 (feeling embarrassment), and OH-11 (being agitated around people) showed negative correlation ranks. Only item OH-1 (trouble pronouncing words) showed statistically significant correlation before and after surgery (Figure 1, Table 4).

Comparison of postoperative QoL between the groups 1 and 2 (psychological assessment) showed significant differences. The statistical differences were noted in items OH-2 (problem with sense of taste), OH-10 (feeling embarrassment), OH-11 (agitated around people), OH-12 (working difficulties), OH-13 (less satisfying life). We have to emphasize that items concerning social disability OH-10, OH-12, and OH-13 showed significantly higher scores in patients with poor psychological assessment with p = 0.013*, p = 0.013*, and p = 0.015*, respectively (Figure 2, Table 5). No significant differences were noticed between the two groups regarding additional questions specific to orthognathic surgery AD-1 to AD-3.

DISCUSSION

In accordance with the hypothesis, this research aimed to evaluate the impact of psychological issues on postoperative QoL in patients who had successful surgical correction of class III deformities. Orthognathic surgery intends to improve the functional and aesthetic problems of class III deformities, as well as their psychological impact, with the help of tools such as OHIP-14. In general, the findings of this prospective study indicated that surgical procedures improved the QoL in all of the patients, as was previously observed by other authors in similar researches [3, 5–11, 14, 15]. Tan et al. [15] found that psychological well-being and social function are improved after orthognathic surgery, independent of the skeletal pattern of deformity and gender. Our findings suggest that general improvement in well-being is achieved regardless of severity of deformity or gender.

Pre- and post-surgical QoL assessment showed that only item OH-1 (trouble pronouncing words) showed a statistically significant correlation before and after surgery (Table 4). This implies that resolving phonetic problems made an important difference that improved QoL significantly.

In this study, results showed that 26.67% of patients had more than 50% of negative responses – Group 1 in the initial psychological assessment, which suggests the risk of BDD. These are the patients who would be advised to undergo additional psychological support treatment. Nevertheless, a high percentage (73.33%) of patients had more than 50% of positive responses – Group 2, which suggests that these patients would not need to be referred to additional psychological support treatment. Although orthognathic surgery corrections improve the QoL in patients with negative psychological scores, the improvements

are lesser, compared to the other group, especially in the domain of social disability.

Comparison of postoperative QoL between the groups showed significant differences in items OH-2 (problem with sense of taste), OH-10 (feeling of embarrassment), OH-11 (agitated around people), OH-12 (working difficulties), OH-13 (less satisfying life). With the highlight of the social disability items OH-10, OH-12, OH-13, with p = 0.013*; 0.013*; 0.015* respectively, as the ones with the strongest statistical differences. This implies that even though the surgical results were similar, patients with good psychological scores (Group 2) felt less embarrassed, were not as agitated around others, did not have as many difficulties at work, and overall had a much more satisfying life after surgery.

Consistent with our results, other authors have also found patients with negative psychological scores less improved after surgery [10, 11, 15]. This indicates that improvements in social QoL should be considered as an independent measure of success after orthognathic surgery, in addition to improvements in oral function and facial aesthetics [15–18].

This study has practical implications as results confirm that initial psychological assessment is related to orthognathic patients QoL after surgery [13]. This multidimensional problem cannot be assessed by a single score because each dimension is associated with a specific postoperative outcome [12]. However, some patients may experience good QoL despite a severe deformity, while others experience lower QoL with mild orofacial deformity [19]. In favor of our findings, a recent review by Cremona et al. [2] implied that psychological and social domains improved after orthognathic surgery, but QoL can temporarily deteriorate during the pre-surgical phase, so they advised that a standardized assessment tool needed to be developed to assess the QoL changes. Nevertheless, sometimes the variables for the assessment of postoperative improvement in QoL do not provide an objective representation. Therefore, preoperative psychological assessment is of great importance to estimate the psychological profile of concern – patients with low psychological scores – and refer them to further psychological support, so that the overall treatment would achieve better QoL.

CONCLUSION

Patients with lower preoperative psychological scores experienced lesser improvement in QoL, particularly in the domain of social disability, suggesting that psychological treatment of these patients could further improve the beneficial effects of orthognathic surgery on postoperative QoL.

Conflict of interest: None declared.

REFERENCES

1. Araujo MTS, Squeff LR. Orthodontic camouflage as a treatment alternative for skeletal Class III. Dental Press J Orthod. 2021;26(4):e21bbo4. [DOI: 10.1590/2177-6709.26.4.e21bbo4] [PMID: 34524381]
2. Cremona M, Bister D, Sheriff M, Abela S. Quality-of-life improvement, psychosocial benefits, and patient satisfaction of patients undergoing orthognathic surgery: a summary of systematic reviews. Eur J Orthod. 2022;44(6):603–13. [DOI: 10.1093/ejo/cjac015] [PMID: 35511144]
3. Dinu C, Manea A, Tomoiagă D, Băciuț M, Almășan O, Mitre AO, et al. Recovery following Orthognathic Surgery Procedures-A Pilot Study. Int J Environ Res Public Health. 2022;19(23):16028. [DOI: 10.3390/ijerph192316028] [PMID: 36498101]
4. Seo HJ, Choi YK. Current trends in orthognathic surgery. Arch Craniofac Surg. 2021;22(6):287–95. [DOI: 10.7181/acfs.2021.00598] [PMID: 34974683]
5. De Leyva P, Eslava JM, Hernández-Alfaro F, Acero J. Orthognathic surgery and aligners. A comparative assessment of periodontal health and quality of life in postsurgical orthodontic treatment with aligners versus traditional fixed appliances: a randomized controlled trial. Med Oral Patol Oral Cir Bucal. 2023;28(3):e208–e216. [DOI: 10.4317/medoral.25555] [PMID: 37026606]
6. Chou PY, Denadai R, Chen C, Pai BC, Hsu KH, Chang CT, et al. Comparison of Orthognathic Surgery Outcomes Between Patients With and Without Underlying High-Risk Conditions: A Multidisciplinary Team-Based Approach and Practical Guidelines. J Clin Med. 2019;8(11):1760. [DOI: 10.3390/jcm8111760] [PMID: 31652792]
7. Ng JH, Chen YA, Hsieh YJ, Yao CF, Liao YF, Chen YR. One-splint versus two-splint technique in orthognathic surgery for class III asymmetry: comparison of patient-centred outcomes. Clin Oral Investig. 2021;25(12):6799–811. [DOI: 10.1007/s00784-021-03967- 9] [PMID: 33948684]
8. Sun HB, Fallah H. Efficacy and Cost of Maxillary Patient-Specific Implants in Orthognathic Surgery: A Review of Three Patient Cases. Perm J. 2022;26(1):137–42. [DOI: 10.7812/TPP/21.054] [PMID: 35609172]
9. Bhandari SK, Issar Y, Rana RP, Datana S. Evaluating the quality of life among patients undergoing orthognathic surgery using a customized questionnaire: A prospective study. APOS Trends Orthod. 2023;13(2):100–5. [DOI: 10.25259/APOS_230_2022]
10. Lin LO, Zhang RS, Mazzaferro DM, Hoppe IC, Pearl RL, Swanson JW, et al. Influence of Repaired Cleft Lip and Palate on Layperson Perception following Orthognathic Surgery. Plast Reconstr Surg. 2018;142(4):1012–22. [DOI: 10.1097/PRS.0000000000004778] [PMID: 30020234]
11. Posnick JC, Kinard BE. Orthognathic Surgery Has a Significant Positive Effect on Perceived Personality Traits and Perceived Emotional Expressions in Long Face Patients. J Oral Maxillofac Surg. 2019;77(2):408.e1–408.e10. [DOI: 10.1016/j.joms.2018.10.005] [PMID: 30414945]
12. Cunningham SJ, Feinmann C. Psychological assessment of patients requesting orthognathic surgery and the relevance of body dysmorphic disorder. Br J Orthod. 1998;25(4):293–8. [DOI: 10.1093/ortho/25.4.293] [PMID: 9884781]
13. Rustemeyer J, Gregersen J. Quality of Life in orthognathic surgery patients: Post-surgical improvements in aesthetics and self-confidence. J Craniomaxillofac Surg. 2012;40(5):400–4. [DOI: 10.1016/j.jcms.2011.07.009] [PMID: 21865051]
14. Gabardo M, Zielak J, Tórtora G, Gerber J, Meger M, Rebellato N, et al. Impact of orthognathic surgery on quality of life: Predisposing clinical and genetic factors. J Craniomaxillofac Surg. 2019;47(8):1285–91. [DOI: 10.1016/j.jcms.2019.05.001] [PMID: 31331851]
15. Tan SK, Leung WK, Tang ATH, Zwahlen RA. Patient's satisfaction with facial appearance and psycho-social wellness after orthognathic surgery among Hong Kong Chinese using the FACE-Q. J Craniomaxillofac Surg. 2020;48(12):1106–11. [DOI: 10.1016/j.jcms.2020.09.012] [PMID: 33041190]
16. Milić-Lemić A, Tanasić I, Tihaček-Šojić Lj. Stress and strain distribution in the lower jaw with shortened dental arch – a finite element method study. Srp Arh Celok Lek. 2018;146(11–12):629–33. [DOI: 10.2298/SARH171106026M]

17. Stojanović Z, Brkić Z, Vučinić P, Nikolić P, Marjanović M. Correlation between sagittal jaw position and jaw relationship in children with skeletal class III malocclusion. Srp Arh Celok Lek. 2018;146(1–2):12–9. [DOI: 10.2298/SARH170123136S]
18. Stojanović Z, Milić J, Pavlić V. Vertical facial disproportions in children with Class III malocclusion. Srp Arh Celok Lek. 2019;147(3–4):152–9. [DOI: 10.2298/SARH180319041S]
19. Hatab NA, Konstantinović VS, Mudrak JK. Pharyngeal airway changes after mono- and bimaxillary surgery in skeletal class III patients: Cone-beam computed tomography evaluation. J Craniomaxillofac Surg. 2015;43(4):491–6. [DOI: 10.1016/j.jcms.2015.02.007] [PMID: 25794643]

Квалитет живота у корелацији са преоперативном психолошком проценом код хируршки лечених пацијената са деформитетима III скелетне класе

Нур Хатаб[1], Зоран Јездић[2], Филип Ивањац[2], Витомир С. Константиновић[2]

[1]Универзитет медицинских и здравствених наука у Рас ел Хајми, Колеџ стоматолошких наука Рас ел Хајме, Рас ел Хајма, Уједињени Арапски Емирати;
[2]Универзитет у Београду, Стоматолошки факултет, Београд, Србија

САЖЕТАК

Увод/Циљ Квалитет живота пре и после мономаксиларне и бимаксиларне хирургије може да варира од пацијента до пацијента у зависности од резултата психолошке процене. Циљ овог истраживања био је да се упореди квалитет живота пре и шест месеци после хируршке интервенције, у корелацији са претхируршком психолошком проценом пацијената са деформитетима III класе, под претпоставком да пацијенти са лошијим резултатима психолошке процене могу имати нижи квалитет живота после операције, упркос успешним резултатима лечења.

Методе У ову проспективну студију укључено је 30 пацијената (19 жена и 11 мушкараца). Психолошка процена извршена је пре хируршког захвата, док је процена квалитета живота извршена пре и после хируршког захвата. Урађена је статистичка анализа података у стандардизованом програму Статистички пакет за социолошке науке – *SPSS*.

Резултати Свеукупан квалитет живота значајно се побољшао после операције код свих пацијената. Хируршка корекција деформитета III класе дала је значајно побољшање независно од врсте операције и тежине орофацијалног деформитета, као и од пола и старости. Постојале су значајне разлике у постхируршким оценама квалитета живота између пацијената који су имали позитивну и негативну психолошку процену, а тичу се социолошких потешкоћа ($p < 0,05$).

Закључак Пацијенти са негативнијом преоперативном психолошком проценом имали су мање побољшање у квалитету живота, посебно у домену социолошких потешкоћа. Може се истаћи да би психолошки третман тих пацијената додатно могао побољшати добре ефекте ортогнатске хирургије на постоперативни квалитет живота.

Кључне речи: квалитет живота; моно–бимаксиларна хирургија; деформитети скелета

DOI: https://doi.org/10.2298/SARH231003002C
UDC: 616.447-006-073

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Diagnostic potential of the infrared thermal camera in the detection of parotid region tumors

Andrija Ćosić[1], Igor Jovanović[2], Miona Andrejević-Stošović[2], Dragan Krasić[1], Goran Videnović[3], Dragan Mančić[2], Vladimir Videnović[4]

[1]University of Niš, Faculty of Medicine, Clinic for Dental Medicine, Niš, Serbia;
[2]University of Niš, Faculty of Electronic Engineering, Niš, Serbia;
[3]University of Priština, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[4]Clinical Hospital Center Zvezdara, Department of Radiology, Belgrade, Serbia

SUMMARY

Introduction/Objective Timely and accurate diagnosis is essential for successfully treating salivary gland tumors. This study aims to examine the possibility of an infrared thermal camera application in the parotid region pathology.

Methods In 36 patients with histopathologically confirmed tumors of the parotid region, the temperature of the area on the side of the tumor and the contralateral, healthy side was measured. The temperature difference was analyzed and compared with the control group. The measurement was performed using a high-resolution infrared thermographic camera. Statistical significance was tested using the T-test and Analysis of Variance (ANOVA) test.

Results The results showed that there is a highly significant difference in temperature between the tumor of the affected parotid regions and the contralateral, healthy side (all tumors: $p = 0.001$; malignant tumors: $p = 0.007$).

Conclusion We concluded that determining the temperature differences between the tumor-affected and contralateral, unaffected sides can be an important tool in diagnosing parotid region tumors.

Keywords: tumors of the parotid region; diagnosis; infrared camera

INTRODUCTION

The salivary gland tumors represent a diverse group of tumors that most often affect the parotid gland, followed by submandibular and sublingual salivary glands [1]. The classification of salivary gland tumors has been recently updated in the 5th edition of the World Health Organization Classification of Head and Neck Tumors which described several new entities of benign (sclerosing polycystic adenoma, keratocystoma, intercalated duct adenoma, striated duct adenoma) and malignant (microsecretory adenocarcinoma and sclerosing microcystic adenocarcinoma) salivary gland tumors [2].

The most common parotid salivary gland tumors are pleomorphic adenoma, Warthin's, and malignant tumors [3]. Parotid salivary gland tumors are often presented as painless masses that clinical examination cannot define. Thus, establishing a timely diagnosis is of great importance for the successful treatment of patients. Furthermore, the differentiation of benign from malignant parotid gland tumors is a big challenge for a maxillofacial surgeon since the choice of treatment method, possible complications and treatment costs depend on it.

Computed Tomography, Magnetic Resonance Imaging, Ultrasonography, Fine Needle Aspiration Biopsy and postoperative histopathological findings are key diagnostic tools used for identifying, classifying and determining the tumor's size, type and biological potential [1, 3]. All these diagnostic methods have their advantages and disadvantages. For example, ultrasound and fine-needle aspiration (FNA) are relatively inexpensive and safe procedures, but they heavily depend on the experience of the examining and intervening physician. CT and MRI are structural diagnostic procedures, like ultrasound, representing the gold standard for diagnosing and preoperative preparation of patients with tumors. However, they are not suitable for mass use due to the ionizing radiation (CT), expensive equipment, the need for highly trained personnel, and high costs.

Some authors define infrared thermography (IRT) as a functional diagnostic non-invasive, contactless, and cost-effective method that meets the basic requirements for detecting various pathological conditions [4–7]. It can assist clinicians in differential diagnosis and prognostic studies for various maxillofacial diseases [8, 9, 10].

The application of IRT is based on the fact that blood flow, influenced by the neuro-vegetative central nervous system, expands uniformly to the left and right sides of the body, resulting in a symmetrical left and right thermal pattern. Any qualitative and quantitative changes in thermal distribution may indicate an abnormality [11]. According to data retrieved

Received • Примљено: October 3, 2023
Revised • Ревизија: December 4, 2023
Accepted • Прихваћено: December 7, 2023
Online first: January 11, 2024

Correspondence to:
Andrija ĆOSIĆ
Bulevar Dr Zorana Đinđića 52
18000 Niš, Serbia
cosa72@yahoo.com

in the literature, IRT is most commonly used in oncology for diagnosis and monitoring of breast cancer and melanoma [12, 13, 14], while the application in the maxillofacial region is scarce and rarely documented [9, 10].

This study aims to examine the diagnostic potential of IRT as an easily accessible tool for mass use, which can indicate the presence of tumors in the parotid region in the early stages. This can lead to the incorporation of thermal imaging examination as a part of the standard first clinical examination in daily routine practice. The simplicity of the procedure does not require the engagement of additional staff. If thermal imaging of a patient confirms temperature asymmetry, they will be referred to more sophisticated diagnostics with a higher priority level.

METHODS

This study included 36 patients aged 40 to 90 years, who were surgically treated for tumors in the parotid region at the Department of Maxillofacial Surgery of the Clinic for Dental Medicine in Niš.

Criteria for inclusion in the study were patients in whom, based on anamnestic data and clinical examination by a maxillofacial surgery specialist, a tumor in the parotid region was diagnosed with an initial diagnosis. After thermographic imaging procedure, standard surgical treatment with histopathological verification were performed in all patients. This study was approved by the Ethics Committee on Research of the Clinic of Dentistry University of Niš, (No. 20/3-2019-2, 01-1054/2). All participants in research signed informed consent form.

For data analysis, two groups of participants were formed. The first group consisted of patients with malignant tumors and the second comprised patients with benign tumors and non-tumor lesions in the parotid region.

All subjects underwent the same thermographic protocol based on The American Academy of Thermology (AAT) [15], and the medical infrared imaging guidelines outlined by Ring and Ammer [16], and Ammoush et al. [17]. According to the mentioned guidelines, the distance between the subject and the camera was 1 m. The room temperature was 23–24°C, and all subjects rested

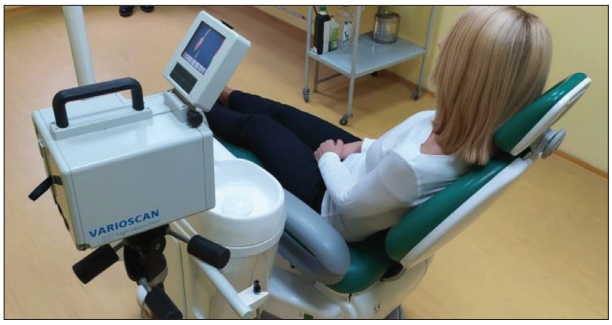


Figure 1. Experimental set-up for the thermal measurement

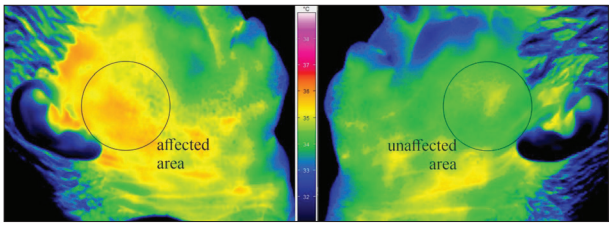


Figure 2. Thermograms of the affected area (left) and unaffected area (right) parotid regions

approximately 15 minutes before imaging, without physical activity, chewing or touching the skin of the face.

The biological behavior of tumors after histopathological verification was defined according to The International Classification of Diseases for Oncology (ICD-O-3) [18]. Malignant tumors, according to the classification above, included histomorphological codes: 8140/3 Adenocarcinoma; 8500/3 Salivary duct carcinoma (Intraductal carcinoma); 8200/3 Adenoid cystic carcinoma; 8805/3 Sarcoma; 9591/3 Non-Hodgkin's lymphoma; 8550/3 Acinic Cell Carcinoma; 9699/3 Mucosa-associated lymphoid tissue (MALT) lymphoma and histology codes 8000/6, 8010/6, 8070/6, which define various origins of metastatic carcinomas.

Benign tumors included histomorphological codes: 8561/0 Warthin's tumor; 8147/0 Basal cell adenoma; 8940/0 Pleomorphic adenoma, and 8850/0 Lipoma. The group of participants with benign tumors also included non-tumor lesions such as Lymphadenopathy and Sialadenitis. Cases where the pathologist did not clearly define the histopathological findings, were excluded from the study.

The infrared thermographic camera Varioscan high-resolution model 3021 (Jenoptik, Germany) was used.

Table 1. Distribution of the parotid region tumors according to tumor type and gender of the patient

Malignant tumors						Benign tumors/lesions			
Type	Male	Female	Total	(%)	v	Male	Female	Total	(%)
Metastatic tumor	7	3	10	(52.6)	Warthin's tumor	6	3	9	(52.9)
MALT lymphomas	1	1	2	(10.5)	Pleomorphic adenoma	1	2	3	(17.7)
Adenocarcinoma	0	1	1	(5.3)	Basal cell adenoma	0	1	1	(5.9)
Intraductal carcinoma	1	0	1	(5.3)	Sialadenitis	1	1	2	(11.8)
Adenoid cystic carcinoma	0	2	2	(10.5)	Lipomatosis	1	0	1	(5.9)
Sarcoma	1	0	1	(5.3)	Lymphadenopathy	0	1	1	(5.9)
Non-Hodgkin's lymphoma	0	1	1	(5.3)					
Acinic Cell Carcinoma	0	1	1	(5.3)					
Total	10	9	19	(100)		9	8	17	(100)

MALT – mucosa-assisted lymphoid tissue

Table 2. Measurement results of the temperature of the parotid region according to the type of tumor and the gender of the patients

Patient ID	Gender	Pathohistological finding/ diagnosis	T1 (°C)	T2 (°C)	Difference: T1-T2 (°C)
Case 1	Female	Metastatic cSCC	33.67	33.52	+0.15
Case 2	Male	Metastatic cSCC	33.97	33.14	+0.83
Case 3	Female	Metastatic cSCC	34.51	33.98	+0.53
Case 4	Male	Metastatic cSCC	34.33	34.21	+0.12
Case 5	Male	Metastatic cSCC	35.38	34.60	+0.78
Case 6	Male	Metastatic cSCC	35.19	34.66	+0.53
Case 7	Male	Metastatic cSCC	34.46	33.91	+0.55
Case 8	Male	Metastatic cSCC	34.43	34.51	-0.08
Case 9	Female	MALT lymphoma	33.72	33.37	+0.45
Case 10	Male	MALT lymphoma	34.85	35	-0.15
Case 11	Female	Adenocarcinoma	33.18	33.02	+0.16
Case 12	Male	Metastatic urothelial carcinoma	34.98	33.66	+1.32
Case 13	Male	Sarcoma	33.83	33.65	+0.18
Case 14	Male	Intraductal carcinoma	33.21	33.02	-0.19
Case 15	Female	Adenoid cystic carcinoma	34.21	34.12	+0.09
Case 16	Female	Warthin's tumor	35.07	34.3	+0.77
Case 17	Male	Warthin's tumor	33.67	33.7	-0.03
Case 18	Male	Warthin's tumor	34.86	34.72	+0.16
Case 19	Female	Warthin's tumor	32.63	32.49	0.14
Case 20	Male	Warthin's tumor	35.22	34.43	0.79
Case 21	Male	Warthin's tumor	33.64	33.61	0.03
Case 22	Male	Warthin's tumor	34.64	34.42	+0.24
Case 23	Male	Warthin's tumor	33.46	33.44	+0.02
Case 24	Female	Warthin's tumor	33.72	33.12	+0.6
Case 25	Female	Adenoma pleomorphe	33.70	33.9	-0.2
Case 26	Male	Adenoma pleomorphe	34.02	33.39	+0.63
Case 27	Female	Adenoma pleomorphe	33.88	34.29	-0.41
Case 28	Female	Basal cell adenoma	33.93	33.58	0.35
Case 29	Female	Sialadenitis	34.27	35.21	-0.94
Case 30	Male	Sialadenitis	34.84	33.94	+0.90
Case 31	Female	Lymphadenopathy	35.26	34.36	+0.90
Case 32	Male	Lipomatosis	35.33	35.38	-0.05
Case 33	Female	Adenoid cystic carcinoma	34.21	34.12	+0.09
Case 34	Female	Non-Hodgkin's lymphoma	34.88	31.61	+3.27
Case 35	Female	Aciniccell carcinoma	34.17	33.4	+0.77
Case 36	Female	Metastatic melanoma	33.16	33.05	+0.11

MALT – mucosa-assisted lymphoid tissue; cSCC – cutaneous squamous cell carcinoma; T1 – the temperature of the side affected by the tumor; T2 – temperature of the tumor-free side

The camera showed the real-time skin temperature on the display, recorded for each patient and each examined side (Figure 1).

The camera has a thermal resolution of ± 0.03°C, a temperature range from - 40 to 1200°C, and a spectral range of 8–12 μm. Absolute accuracy of the temperature measurements (factory calibrated) up to 100°C, at an ambient temperature of 22 ± 2°C, is less than ±2K; otherwise, the accuracy is less than ± 1% of the full-scale value.

On the obtained thermograms (Figure 2) regions of interest were analyzed. An affected area represents the area with tumor, and an unaffected area is a contralateral parotid region of the same patient. Digital images of the skin temperature variations were analyzed by IRBIS Professional 2.2. graphics-oriented software package (InfraTec GmbH, Dresden, Germany).

The difference in the mean temperature of the affected and unaffected side of the parotid region was tested with a Paired Samples t-Test and Analysis of Variance (ANOVA) test. Previously, data were tested with the Kolmogorov-Smirnov test to check for normality of distribution.

The temperature difference was tested through four types of statistical tests, as follows: affected and unaffected side for all patients with tumors (Test 1); affected and unaffected side for patients with malignant tumors (Test 2); affected and unaffected side for patients with benign tumors (Test 3). The level of 0.05 was taken as the statistical significance threshold for all tests. All statistical tests were performed in SPSS v20.

RESULTS

Thirty-six patients with benign and malignant tumors in the parotid region participated in our study (17 women and 19 men). The average age was 61.4 years. Men were slightly older (61.9 years) than women (60.8 years) but without statistical significance. One tumor was registered in each patient. More than half (58.8%) of benign tumors were registered in patients younger than 50, while 68.4% of malignant tumors were in patients in their seventh decade of life and later. ANOVA showed no statistically significant interaction between the effects of gender and type of tumor ($F = 0.414$, $p = 0.526$). In contrast, the interaction between the effects of age and type of tumor was statistically significant ($F = 3.655$, $p = 0.017$). The probability of developing malignant tumors was higher in older patients (Eta-square is 0.36).

The most common benign tumor in our patients was Warthin's, which accounted for 52.9% of all registered benign tumors, followed by Pleomorphic adenomas with 17.7%. The most common malignant tumors were metastatic tumors, with 52.6% of the total malignant parotid region tumors (Table 1).

Table 2. shows the temperature difference between the parotid region where the tumor is located (T1) and the contralateral, unaffected parotid region (T2) according to the gender of the patient and the pathohistological findings, that is, the diagnosis. Regardless of biological behaviour, the temperature difference in all tumors ranged from -0.03°C to 3.27°C (mean value 0.37°C). The minimum temperature difference in patients with malignant tumors was -0.08°C (Intraductal carcinoma), while the maximum was +3.27°C (Non-Hodgkin's lymphoma). The mean temperature difference in patients with malignant tumors was +0.5°C, regardless of gender. The minimum

Table 3. Paired samples t-test statistics output

Test type	Area descriptions	N	Mean value (°C)	Standard deviation	t-test	df	p-value
Test 1 (all tumors)	Affected area	36	34.27	0.70	3.577	35	0.001*
	Unaffected area	36	33.88	0.77			
Test 2 (malignant tumors)	Affected area	19	34.22	0.66	3.066	18	0.007*
	Unaffected area	19	33.69	0.78			
Test 3 (benign tumors)	Affected area	17	34.33	0.75	1.934	16	0.071
	Unaffected area	17	34.09	0.74			

*statistically significant difference; df- degrees of freedom

temperature difference in patients with benign tumors was -0.03°C (Warthin's tumor), and the maximum was 0.9°C (Sialadenitis and Lymphadenopathy). The mean temperature difference in patients with benign tumors was +0.23°C, regardless of gender.

Table 3. shows the statistical significance in the temperature difference between the tumor-affected parotid region (affected area) and the contralateral side (unaffected area) in all tumors (Test 1), malignant tumors (Test 2) and benign tumors (Test 3).

There is a highly significant difference in temperature between tumor-affected parotid regions and the contralateral, unaffected side, compared to all tumors ($t_{35} = 3.577$, $p = 0.001$) (Test 1). The mean temperature difference is 0.39°C, while the CI (95% Confidence Interval of the Difference) shows that this difference can be found from 0.17°C to 0.61°C.

Test 2 shows that there is a significant difference in temperature between malignant tumour-affected parotid regions and the contralateral, unaffected side ($t_{18} = 3.066$, $p = 0.007$) and that this difference can be found in the range of 0.17°C to 0.9°C. For Test 3 p-value is just above the cut-off value of 0.05, and the CI is narrow enough, so there is a suggestion hint of an effect of statistical significance.

DISCUSSION

The age structure of our patients with benign and malignant parotid gland tumors mostly agrees with the findings of other authors [19, 20, 21]. However, some authors reported a significantly lower average age of patients in their research [22]. This difference in the mentioned articles is probably due to the different percentages of benign and malignant tumors. In our research, the percentage of malignant tumors is higher than in the studies mentioned.

The more frequent appearance of malignant parotid region tumors after the seventh decade can also be seen in the works of other authors [23, 24], who state that the average age of patients with malignant tumors is higher by approximately one decade compared to patients with benign tumors. Mayer et al. [20] found in their study, a large number of patients (average age 78.4 years) had infiltration or metastasis of squamous skin cancer in the parotid region.

In our research, the dominant types of benign tumors were Warthin's tumor and pleomorphic adenoma, which corresponds to the works of other authors [25, 26], while the most common malignant parotid region tumor was secondary Metastatic tumor of cutaneous squamous cell carcinoma. Mucoepidermoid carcinomas, acinic cell carcinomas and adenoid cystic carcinomas are described in the literature [10, 22, 27] as the most common malignant parotid gland tumors, which contradicts our findings. Our results are in accordance with the research of Mayer et al. [20], where in surgically treated 164 patients with malignant parotid gland tumors, 71.5% were secondary (metastatic) carcinomas. Reports on using an infrared thermographic camera in diagnosing pathological conditions of the parotid region are very scarce in the literature. According to our knowledge, only one report with a limited series of 17 patients refers to the analysis of the hyperthermic reaction of the pathological process of the parotid region. It also does not specify the temperature difference between the affected and contralateral, unaffected sides [28].

Our study showed that the mean temperature on the side of malignant tumors was higher by +0.5°C compared to the contralateral unaffected side, and on the side of benign tumors by +0.23°C. The temperature difference in malignant tumors ranged from -0.08°C to +3.27°C and in benign tumors, from -0.03°C to 0.9°C (Table 2). Our results agree with the research of Durnovo et al. [10], who used thermographic analysis to include 250 patients with various pathological conditions of the maxillofacial region. In 96 patients with benign and malignant tumors (54 benign and 42 malignant) of the maxillofacial region, the authors registered higher temperature values in the region of the malignant tumor (on average +3.2 ± 0.4°C compared to the contralateral side) than in the region of the benign tumors (from +0.4-1.4°C). Macianskyte et al. [8] also registered thermal asymmetry (temperature difference between tumor-affected and unaffected sides) in histopathologically and CT-verified tumors of the maxillofacial region. In their study, when pathology was not detected upon CT evaluation, as in the case of the healthy subjects, then there was no temperature asymmetry between the sides. In contrast, when CT delineated a tumour structure, later confirmed with histopathology, then the left-right asymmetry in temperature corresponded to the location of tumour detected on CT. The temperature difference between lesion and normal zones was of 0.4 °C or higher. In our research, high statistical significance in thermal asymmetry (all tumors: T-test 3.577, P = 0.001; malignant tumors: T-test 3.066, P = 0.007) indicates the existence of a malignant parotid region tumor. Statistical significance was not found in benign tumors (Test 3), p-value is just above the cut-off value of 0.05, and the CI is narrow enough, so there is a suggestion hint of an effect of statistical significance. The lack of statistical significance does not mean there is no effect, because the true mean temperature difference could be 0.23°C, or even as large as 0.49°C (CI), and further studies with a larger sample size may help clarify the true difference.

Thermal symmetry of the face is a normal finding in healthy people and the thermogram of a healthy person shows a uniform and symmetrical change in skin temperature with a very small deviation between one side and the other, no more than 0.2–0.4°C [8]. Any asymmetric temperature distribution is an indication of dysfunction – malignant and benign tumors, inflammations, sports injuries, and myofascial pain syndrome [6, 7, 9]. Still, in our research, we considered temperature changes only as a consequence of confirmed tumor existence. Our results have shown that some histopathologically verified malignant tumors had lower thermal asymmetry than the above values. This asymmetry may be due to focusing on hypothermic necrotic zones in malignant tumors during the measurement. The change in metabolism and structural anatomical variations in the tumor region can explain the temperature asymmetry between the tumor-affected and the contralateral region. Tumors have increased metabolism, and in the tumor tissue, there are changes in the blood vessels that vascularize the tumor tissue, consequently leading to an increase in temperature in the tumor region [29]. Macianskyte et a. [8] point out that angiogenesis leading to vascularization within the tumor occurs long before any other clinical changes appear. Lahiri et al. [30] state that the reason for the hyperthermic reaction of the malignant tumor zone lies in the fact that the blood vessels formed by malignant tumors are endothelial tubes without a muscle layer and, therefore, cannot narrow upon sympathetic stimulation, which causes a hyperthermic reaction due to vasodilatation.

Timely diagnosis of a parotid region tumor is quintessential in maxillofacial surgery because an advanced malignant tumor increases the possibility of complications and may threaten the patient's life. For these reasons, every step towards the improvement of diagnostic procedures is significant and deserves special attention. Our research has shown that the presence of temperature changes may indicate the presence of tumors, more likely of malignant tumors. A limitation of this study is the relatively small number of patients, so more extensive research is needed in the future before this procedure can be routinely used.

CONCLUSION

Based on the statistical analysis of our results, we can conclude that determining the temperature difference between the tumor-affected and contralateral sides may be an appropriate a tool in diagnosing parotid region malignant tumors. In our opinion, this non-invasive and safe method with appropriate software development has diagnostic potential for detecting parotid region tumors.

ACKNOWLEDGEMENT

This work has been supported by the Ministry of science, technological development and innovation of the Republic of Serbia, contract no. 451-03-47/2023-01/200102.

Conflict of interest: None declared.

REFERENCES

1. Bell RB, Fernandes R, Andersen P. Oral, Head and Neck Oncology and Reconstructive Surgery. Elsevier. 2018;850–1.
2. Skálová A, Hyrcza MD, Leivo I. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. Head Neck Pathol. 2022;16(1):40–53. [DOI: 10.1007/s12105-022-01420-1] [PMID: 35312980]
3. Chang YJ, Huang TY, Liu YJ, Chung HW, Juan CJ. Classification of parotid gland tumors by using multimodal MRI and deep learning. NMR Biomed. 2021;34(1):e4408. [DOI: 10.1002/nbm.4408] [PMID: 32886955]
4. Tiwari D, Dixit M. Deep Multi-View Breast Cancer Detection: A Multi-View Concatenated Infrared Thermal Images Based Breast Cancer Detection System using Deep Transfer Learning. Traitement du Signal. 2021;38(6):1699–711. [DOI: 10.18280/ts.380613]
5. Verstockt J, Verspeek S, Thiessen F, Tjalma WA, Brochez L, Steenackers G. Skin Cancer Detection Using Infrared Thermography: Measurement Setup, Procedure and Equipment. Sensors (Basel). 2022;22(9):3327. [DOI: 10.3390/s22093327] [PMID: 35591018]
6. Brenner M, Braun C, Oster M, Gulko PS. Thermal signature analysis as a novel method for evaluating inflammatory arthritis activity. Ann Rheum Dis. 2006;65(3):306–11. [DOI: 10.1136/ard.2004.035246] [PMID: 16150784]
7. Moreira DG, Costello JT, Brito CJ, Adamczyk JG, Ammer K, Bach AJE, et al. Thermographic imaging in sports and exercise medicine: A Delphi study and consensus statement on the measurment of human skin temperature. J Therm Biol. 2017;69:155–62. [DOI: 10.1016/j.jtherbio.2017.07.006] [PMID: 29037377]
8. Macianskyte D, Monastyreckiene E, Basevicius A, Adaskevicius R. Comparison of segmented thermal images versus a CT scanning for detection of maxillofacial pathology. Dentomaxillofac Radiol. 2019;48(4):20180075. [DOI: 10.1259/dmfr.20180075] [PMID: 30707623]
9. Macianskyte D, Adaškevicius R. Automatic Detection of Human Maxillofacial Tumors by Using Thermal Imaging: A Preliminary Study. Sensors (Basel). 2022;22(5):1985. [DOI: 10.3390/s22051985] [PMID: 35271132]
10. Durnovo EA, Potekhina YP, Marochkina MS, Yanova NA, Sahakyan MY, Ryzhevsky DV. Diagnostic Capabilities of Infrared Thermography in the Examination of Patients With Diseases of Maxillofacial Area. Sovremennye Tehnologii v Medicine. 2014;6(2):61–5.
11. Haddad DS, Brioschi ML, Baladi MG, Arita ES. A new evaluation of heat distribution on facial skin surface by infrared thermography. Dentomaxillofac Radiol. 2016;45(4):20150264. [DOI: 10.1259/dmfr.20150264] [PMID: 26891669]
12. Jessie B, Liang J, Li Y, Fahimi B. High-Frequency Excitation and Surface Temperature Analysis of Breast Tissue for Detection of Anomaly. Biomed Res Int. 2023;2023:4406235. [DOI: 10.1155/2023/4406235] [PMID: 36817859]
13. Okabe T, Fujimura T, Okajima J, Kambayashi Y, Aiba S, Maruyama S. First-in-human clinical study of novel technique to diagnose malignant melanoma via thermalconductivity measurements. Sci Rep. 2019;9(1):3853. [DOI: 10.1038/s41598-019-40444-6] [PMID: 30846837]
14. Verstockt J, Verspeek S, Thiessen F, Tjalma WA, Brochez L, Steenackers G. Skin Cancer Detection Using Infrared Thermography: Measurement Setup, Procedure and Equipment. Sensors (Basel). 2022;22(9):3327. [DOI: 10.3390/s22093327] [PMID: 35591018]
15. The American Academy of Thermology. Guidelines For Dental-Oral And Systemic Health Infrared Thermography. Pan Am J Med Thermol. 2015;2(1):44–53. [DOI: 10.18073/2358-4696/pajmt.v2n1p44-53]
16. Ring EF, Ammer K. Infrared Thermal Imaging in Medicine. Physiol Meas. 2012;33(3):R33–46. [DOI: 10.1088/0967-3334/33/3/R33] [PMID: 22370242]

17. Ammoush M, Gzawi AM, Warawreh A, Hijazin R, Jafar H. Clinical Evaluation of Thermography as a Diagnostic Tool in Oral and Maxillofacial Lesions. Journal of the Royal Medical Services. 2018;25(3):45–9. [DOI: 10.12816/00532]
18. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin M, et al. (eds). International Classification of Diseases for Oncology (ICD – O). Third Edition, First Revision. Geneva: World Health Organisation; 2013.
19. Cunha JL, Coimbra AC, Silva JV, Nascimento IS, Andrade ME, Oliveira CR, et al. Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal. 2020;25(4):e516–e522. [DOI: 10.4317/medoral.23532] [PMID: 32388524]
20. Mayer M, Thoelken R, Jering M, Märkl B, Zenk J. Metastases of Cutaneous Squamous Cell Carcinoma Seem to be the Most Frequent Malignancies in the Parotid Gland: A Hospital-Based Study From a Salivary Gland Center. Head Neck Pathol. 2021;15(3):843–51. [DOI: 10.1007/s12105-021-01294-9] [PMID: 33544379]
21. Dell'Aversana Orabona G, Salzano G, Abbate V, Bonavolontà P, Committeri U, Seidita F, et al. Malignant tumours of the parotid gland: management of the neck (including the clinically negative neck) and a literature review. Br J Oral Maxillofac Surg. 2021;59(6):665–71. [DOI: 10.1016/j.bjoms.2020.08.026] [PMID: 33952405]
22. Zuo H. The Clinical Characteristics and CT Findings of Parotid and Submandibular Gland Tumours. J Oncol. 2021;2021:8874100. [DOI: 10.1155/2021/8874100] [PMID: 34306079]
23. Fonseca FP, Carvalho Mde V, de Almeida OP, Rangel AL, Takizawa MC, Bueno AG, et al. Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114(2):230–9. [DOI: 10.1016/j.oooo.2012.04.008] [PMID: 22769409]
24. Kara MI, Göze F, Ezirganli S, Polat S, Muderris S, Elagoz S. Neoplasms of the salivary glands in a Turkish adult population. Med Oral Patol Oral Cir Bucal. 2010;15(6):e880–5. [DOI: 10.4317/medoral.15.e880] [PMID: 20526249]
25. Barnes LB, Eveson JW, Reichart P, Sidransky D, editorss. Pathology and genetics of head and neck tumors. Lyon: IARC Press, 2005. [PMID: 16579185]
26. Franzen AM, Funzel T, Lieder A. Parotid gland metastasis of distant primary tumours: a diagnostic challenge. Auris Nasus Larynx. 2016;43(2):187–91. [DOI: 10.1016/j.anl.2015.09.010] [PMID: 26526643]
27. Dimitrijevic M, Boricic I, Tomanovic N, Dimitrijevic A, Bjelogrlić G, Krstić A, et al. Clinicopathological Analysis of 907 Major and Minor Salivary Gland Tumors. J Craniofac Surg. 2022;33(5):e507–e509. [DOI: 10.1097/SCS.0000000000008482] [PMID: 36041131]
28. Champy M, Bourjat P, Schnebelen JM. Thermograpic exploration of the parotid region. J Maxillofac Surg. 1976;4(3):163–71. [DOI: 10.1016/s0301-0503(76)80026-4] [PMID: 1066416]
29. Stark AM, Way S. The screening of well women for the early detection of breast cancer using clinical examination with thermography and mammography. Cancer. 1974;33(6):1671–9. [DOI: 10.1002/1097-0142(197406)33:6<1671::aid-cncr2820330630>3.0.co;2-4] [PMID: 4834162]
30. Lahiri BB, Bagavathiappan S, Jayakumar T, Philip J. Medical applications of infrared thermography: A review. Infrared Phys Technol. 2012;55(4):221–35. [DOI: 10.1016/j.infrared.2012.03.007] [PMID: 32288544]

Дијагностичке могућности инфрацрвене термовизијске камере у откривању тумора паротидног региона

Андрија Ћосић[1], Игор Јовановић[2], Миона Андрејевић-Стошовић[2], Драган Красић[1], Горан Виденовић[3], Драган Манчић[2], Владимир Виденовић[4]

[1]Универзитет у Нишу, Медицински факултет, Клиника за денталну медицину, Ниш, Србија;
[2]Универзитет у Нишу, Електронски факултет, Ниш, Србија;
[3]Универзитет у Приштини, Медицински факултет, Косовска Митровица, Србија;
[4]Клиничко-болнички центар „Звездара", Служба за радиологију, Београд, Србија

САЖЕТАК

Увод/Циљ Правовремена и тачна дијагноза је од великог значаја за успешно лечење тумора пљувачних жлезда. Циљ овог рада је да се испита могућност примене инфрацрвене термалне камере у патологији паротидне регије.

Методе Код 36 болесника са хистопатолошки потврђеним туморима паротидног региона мерена је температура на страни тумора и на контралатералној, здравој страни. Разлика у температури је анализирана и упоређивана са контролном групом. Мерење је обављено помоћу инфрацрвене термографске камере високе резолуције. Статистичка значајност је тестирана коришћењем т-теста и теста анализе варијансе (*ANOVA*).

Резултати Резултати су показали постојање високо значајне разлике у температури између тумором захваћене паротидне регије и контралатералне, здраве стране (сви тумори: $p = 0{,}001$; малигни тумори: $p = 0{,}007$).

Закључак Закључили смо да одређивање температурне разлике између тумором захваћене стране и контралатералне, незахваћене стране може бити важан алат у дијагностици тумора паротидног региона.

Кључне речи: тумори паротидног региона; дијагноза; инфрацрвена камера

DOI: https://doi.org/10.2298/SARH221022115M
UDC: 616.728.3-089.28

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Total knee arthroplasty in patients with a proximal tibial stress fracture associated with bilateral severe knee osteoarthritis

Slavko Manojlović[1,2], Rajko Dodik[1], Mirko Manojlović[1], Željko Jovičić[3], Dragana Dragičević-Cvjetković[4,5]

[1]Gradiška General Hospital, Department of Surgery, Gradiška, Republic of Srpska, Bosnia and Herzegovina;
[2]University of Banja Luka, Faculty of Medicine, Department of Surgery, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[3]Dr Miroslav Zotović Institute of Physical Medicine and Rehabilitation, Department of Orthopedic Surgery, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[4]Dr Miroslav Zotović Institute of Physical Medicine and Rehabilitation, Department of Rehabilitation and Balneology, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[5]University of Banja Luka, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Proximal tibial stress fractures associated with bilateral severe knee osteoarthritis are rare and, due to possible consequences, are considered a treatment challenge. This paper aims to present the applied treatment method of these patients and its results.

Methods A prospective study followed 14 patients with an average age of 74.1 years and with unilateral proximal tibial stress fracture associated with bilateral severe knee osteoarthritis. Surgical treatment involved modular total knee arthroplasty (TKA) on the fracture side, in the first act, and contralateral standard TKA, in the second act, based on the severe osteoarthritis. Rehabilitation was performed for 21 days after both operations and included the following: kinesiotherapy, electrotherapy, magnetotherapy, hydrotherapy, and thermotherapy. Monitoring parameters were as follows: X-ray, range of motion, and WOMAC index. Monitoring periods were preoperative and three, six, and nine months after the first TKA surgery.

Results The radiological findings in all patients during these follow-up periods were normal. All tibial stress fractures healed within six months after surgery. Knee function was significantly improved nine months after the first TKA surgery compared to the preoperative finding. A statistically significant improvement in the physical functioning was found in all postoperative periods, especially nine months after the first TKA surgery ($p < 0.05$).

Conclusion Modular total knee arthroplasty on the tibial stress fracture side and delayed standard total knee arthroplasty of contralateral osteoarthritic knee combined by postoperative inpatient rehabilitation give optimal final functional outcome.

Keywords: tibia; fracture; stress; knee; osteoarthritis; arthroplasty

INTRODUCTION

Stress fractures of the proximal tibia often occur as a result of the gravity loads on the osteoporotic bone. They can be related to other conditions and diseases (inflammatory rheumatism, malignancies, metabolic bone diseases), but they are most common in bilateral advanced knee osteoarthritis with marked varus deformity. In patients with such bilateral knee osteoarthritis, a stress fracture is caused by normal stresses placed on an abnormal bone [1]. This poor biomechanical condition leads to a fracture in the proximal part of tibia at the site of the new resultant force [2, 3]. Such cases are rare, but possible consequences make its treatment a challenge [4, 5]. It is most often performed by bilateral total knee arthroplasty (TKA) on both sides, in two phases. The first phase involves the TKA with a modular tibial stem on the knee with the fracture, and the second phase is performed by a standard TKA on the contralateral knee (usually three months after the first TKA and after the rehabilitation is being finished) [6]. After both surgeries, additional inpatient physical therapy is being performed. The object of this paper is to present the algorithm and the results of the treatment on a series of patients with unilateral stress proximal tibial fracture and bilateral primary knee osteoarthritis in a manner as described above.

METHODS

In the period from 2005 to 2017, 14 patients with a unilateral proximal tibial stress fracture, associated with bilateral primary knee osteoarthritis grade 4 according to the Kellgren–Lawrence classification, were surgically treated at the

Received • Примљено: October 22, 2022
Revised • Ревизија: December 10, 2023
Accepted • Прихваћено: December 18, 2023
Online first: December 26, 2023

Correspondence to:
Slavko MANOJLOVIĆ
University of Banja Luka
Faculty of Medicine
Department of Surgery
Save Mrkalja 14
Banja Luka 78 000
The Republic of Srpska
Bosnia and Herzegovina
slavko.manojlovic@gmail.com

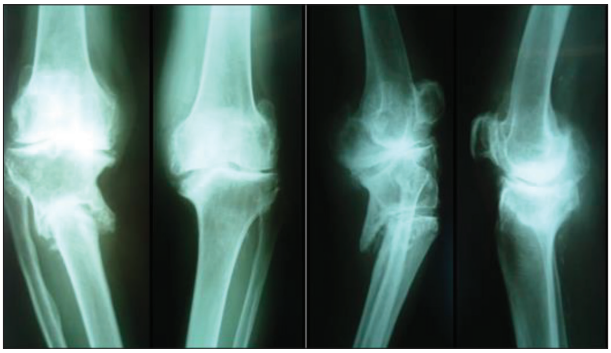


Figure 1. X-rays of both knees in a patient with a proximal metaphysis stress fracture of the right tibia, associated with severe bilateral knee osteoarthritis

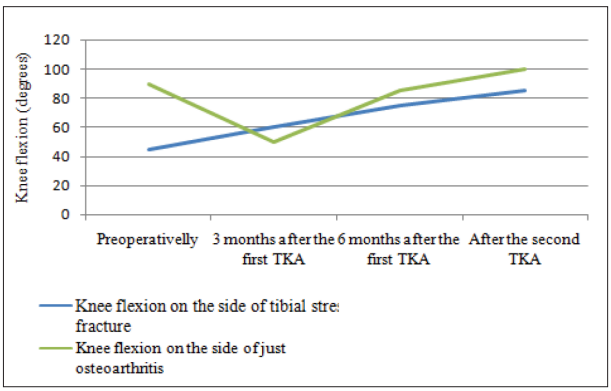


Figure 3. Improvements of average knee flexion in both knees; TKA – total knee arthroplasty

Gradiška General Hospital (Figure 1). These were also the inclusive criteria. Excluding criteria were the following: inflammatory and metabolic rheumatic disease, trauma, and previous surgery on the same leg. The treatment of choice was TKA with modular tibial stem on the fractured knee, in the first act, and standard TKA on the other knee, in the second act, for all patients. After standard preoperative preparation, the surgeries were performed under spinal anesthesia in all cases. A tourniquet was used each time. Standard mid-vastus approach was applied. Thromboprophylaxis was performed in all the patients one day preoperatively and during 21 days postoperatively. Walking with forearm crutches was allowed after the surgery, with partial support up to the pain limit. All the patients had two postoperative rehabilitation periods of 21 days each – after the first and after the second surgery. Both inpatient rehabilitation treatments were performed one month after each TKA. The rehabilitation had included kinesitherapy, occupational therapy, electrotherapy five times a week, and daily hydrotherapy. Monitoring parameters were X-rays, range of motion (knee flexion), and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) index preoperatively, and three, six, and nine months after the first surgery. Statistical analysis was performed by Student's t-test for $p < 0.05$ level of significance, using IBM SPSS Statistics, Version 19.0 (IBM Corp., Armonk, NY, USA). The study has been approved by the Ethics Committee of the Gradiška General Hospital (Reference Number 01-1758-3/20).

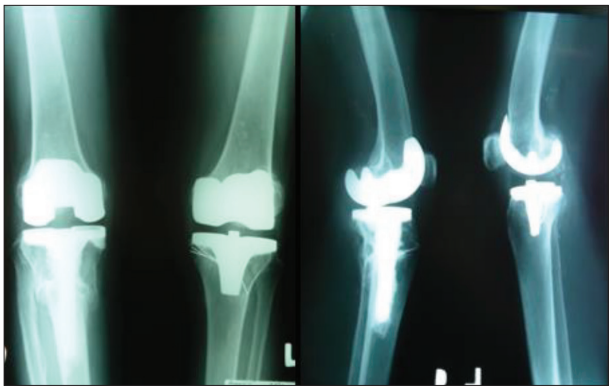


Figure 2. X-rays of both knees in a patient with a proximal metaphysis stress fracture of the right tibia, associated with severe bilateral knee osteoarthritis, treated with bilateral total knee arthroplasty in two acts, nine months after the first modular total knee arthroplasty

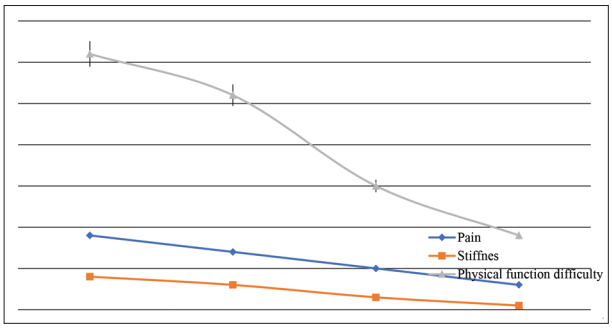


Figure 4. Subscales of the WOMAC index; X-axis: (1) three months after the first total knee arthroplasty (TKA), time of the second TKA; (2) six months after the first TKA, three months after the second TKA; (3) six months after the first TKA, three months after the second TKA; (4) nine months after the first TKA, six months after the second TKA

RESULTS

The study sample included 14 women with an average age of 74.1 ± 2.07 years on the day of the first surgery. The rate of these patients in relation to all TKA surgeries for the observed period was 0.7% (14/1970). All the patients denied any mechanism of trauma related to the pain. The limbs axis correction was confirmed after surgery and the fracture healing was clinically and radiologically confirmed in all cases six month after surgery (Figure 2), except for one case complicated by infection, being treated later through another approach.

All the patients preoperatively had a knee flexion contracture. Average extension deficit in the knee with tibial stress fracture was 15° ± 3.1°, while on the knee with osteoarthritis it was 7° ± 2.5°. At the same time, the average knee flexion in the knee with tibial stress fracture was 55° ± 2.7°, and on the knee with just osteoarthritis it was 90° ± 3.7°. Nine months after the first surgery, when the rehabilitation following the second surgery was finished, full extension was observed in both knees of all the patients. At the same time, the average flexion was 100° ± 3.2° in the arthritic knee without the fracture, and 85° ± 2.6° in the knee with proximal tibial stress fracture, which was significantly improved compared to the preoperative condition ($p < 0.05$) (Figure 3).

Pain and stiffness reduction as well as improvement of physical function (decrease of physical function difficulty) were noted by the WOMAC index at three and six months after the first TKA surgery, and were improved in relation to preoperative values. This improvement was particularly significant nine months after the first TKA surgery, when the rehabilitation following the second surgery was also finished (Figure 4).

DISCUSSION

Tibial stress fractures in patients with bilateral primary knee osteoarthritis associated with severe flexion varus deformity are rare and complex clinical condition, making its treatment a challenge [4, 6]. This type of fracture is caused by the action of repetitive gravity loads on the proximal tibial metaphysis due to the change of the axes in the knee, both in coronal and sagittal planes. The goal of the treatment in these patients is to achieve the fracture healing, satisfactory joint stability, a normal relation between the limb axes, painless joint mobility, and independent walking. Improving these factors improves the patient's quality of life. Anamnestic data about sudden worsening of the primary knee osteoarthritis symptoms can indicate the proximal tibial stress fracture. The diagnosis of these fractures is performed by radiography. The treatment of these patients is mainly surgical [7, 8]. At the time we treated the first such patient, there were very few published papers on this topic in the literature, with a very small number of cases [9, 10]. Later, we found in the literature different ways of surgical treatment: corrective osteotomies with plate fixation, intramedullary fixation, standard arthroplasty, and the modular TKA [1, 11–18]. Our choice from the beginning was the use of modular TKA in all patients with a proximal tibial stress fracture associated with bilateral primary knee osteoarthritis. Rehabilitation goals were to reduce pain and swelling, improve the range of knee motion, increase the muscular strength of thigh muscles, and achieve the independent gait. We found a radiographically correct finding in most of the patients. The average range of motion in the knees postoperatively was significantly better at six and nine months after the first TKA surgery than preoperatively. Improvement of knee extension was better and faster than knee flexion. However, knee flexion was significantly improved at six and nine months after the first TKA surgery. A small decline or stagnation in the knee flexion recovery at the third month after the first TKA surgery indicates that these limitations were caused by impaired function of the contralateral osteoarthritic knee.

Our sample consisted of elderly women. There is a study that does not confirm these results [3]. As a possible reason for the proximal tibia stress fracture occurrence in this population, associated with the physiological loss of mineral bone density, but due to difficulty in movement, we should also consider the correlation between inactivity and osteoporosis [19].

Our research indicates a significant improvement in general physical functioning as soon as three months after the first TKA. Given that modular TKA provides the primary goals to be achieved in the surgical treatment of the proximal tibial stress fracture of an osteoarthritic knee (fracture healing, osteoarthritic surfaces plasty, and local biomechanical correction), and that postoperative rehabilitation contributes to better functional results through reducing pain and swelling, it is clear why the physical functioning was significantly better as soon as three months after the first surgery. After the first TKA, the symptoms dominantly influencing the WOMAC index were related to primary osteoarthritis of the other knee.

Only after the definitive treatment is complete in these patients, i.e., after the rehabilitation following the second TKA is complete, the definitive outcome can be fully assessed. Measured by WOMAC index six months after the first TKA, i.e., after the both knees TKA surgeries, the patients experienced good physical functioning, significantly better compared to the preoperative level, but this was also the case at three months after the modular TKA surgery. Since stress fractures of the proximal tibia associated with bilateral primary knee osteoarthritis are rare, few studies, with small sample sizes, have been published [20, 21]. Soundarrajan et al. [22] performed a study on 20 patients and concluded that long-term plaster immobilization slows down the fracture healing process and even can lead to nonunion; thus, modular TKA was suggested as the treatment of choice as soon as possible. The same was confirmed by Sawant et al. [23] through the series cases of four patients. Wui et al. [24] confirmed good short-term results of the treatment with a modular prosthesis on the stress fracture side and standard TKA on the osteoarthritis side in a study of a series of cases. Shah et al. [25] published the results of a study on 62 patients and confirmed that modular stem implantation is a good solution for patients with tibial stress fracture associated with knee osteoarthritis. Studies by Indian researchers from 2019 and 2022 performed on small-samples are in correlation with our results [26, 27].

We did not find a study with the results opposed to our own.

CONCLUSION

Modular TKA followed by postponed standard knee arthroplasty at contralateral side is a suggested choice in the treatment of unilateral proximal tibial metaphysis stress fracture because its application provides a good fracture healing, osteoarthritis treatment, deformity correction, and restoring knees axes to a normal. The quality of life is expected to be significantly improved nine months after the modular TKA surgery, followed by standard contralateral TKA performed about six months after the first TKA. This treatment should include inpatient physical procedures after each surgery, because of its significant contributing to the final outcome improvement.

Conflict of interest: None declared.

REFERENCES

1. Tomlinson MP, Dingwall IM, Phillips H. Total knee arthroplasty in the management of proximal tibial stress fractures. J Arthroplasty. 1995;10(5):707–13. [DOI: 10.1016/s0883- 5403(05)80222-0] [PMID:9273389]
2. Cameron HU. Double stress fracture of the tibia in the presence of arthritis of the knee. Can J Surg. 1993;36(4):307–10. [PMID: 8370010]
3. Ivanovski A, Medjedovic D, Perisic V. Fractures of the metatarsal bones caused by fatigue. Srp Arh Celok Lek. 1998;126(3–4):107–10. [PMID: 9863365]
4. Shekhar S, Rai A, Prakash S, Khare T, Malhotra R. Single-stage long-stem total knee arthroplasty in severe arthritis with stress fracture: a systematic review. Knee Surg Relat Res. 2023;35(1):4. [DOI: 10.1186/s43019-023-00178-2] [PMID: 36658622]
5. Miller TL, Best TM. Taking a holistic approach to managing difficult stress fractures. J Orthop Surg Res. 2016;11(1):98. [DOI: 10.1186/s13018-016-0431-9] [PMID:27608681]
6. Reddy NVR, Saini MK, Reddy PJ, Thakur AS, Reddy CD. Analysis of clinical and radiological outcomes of long tibial stemmed total knee arthroplasty in knee osteoarthritis complicated by tibial stress fracture. Knee Surg Relat Res. 2022;34(1):7. [DOI: 10.1186/s43019-022-00139-1] [PMID: 35193706]
7. Gill UN, Noor SS, Haneef M, Ahmed N, Iqbal F, Najjad MKR. Management of early and late presenting tibial stress fracture with advanced osteoarthritis of the knee: A dilemma among arthroplasty surgeons in developing countries. Knee. 2021;29:95–100. [DOI: 10.1016/j.knee] [PMID: 33601273]
8. Dudko OG, Glubochenko OV, Pickula VV, Marchuk OF, Shayko-Shaykovskiy OG. Predisposing factors and treatment of osteoarthritis after surgeries performed for tibial fractures. World Science. 2019;12(52):16–9. [DOI: 10.31435/rsglobal_ws/30122019/6825]
9. Song M, Lin X, Han W, Li J, Lui W. Is proximal tibial tubercle osteotomy superior to distal tibial tubercle osteotomy for medial compartment osteoarthritis? A meta-analysis. J Orthop Surg Res. 2023;18(1):245–8. [DOI: 10.1186/s13018-023-03725-5] [PMID: 36967435]
10. Gadhe S, Bhor P, Kanade S, Kale S, Vatler A, Chaudhari P. Proximal tibial stress fracture with Grade 4 osteoarthritis of knee – experience with long stem TKR. Int J Orthop Sci. 2019;5(3):293–7. [DOI: 10.22271/ortho.2019.v5i3e.1543]
11. Haspl M, Jelić M, Pećina M. Arthroplasty in treating knee osteoarthritis and proximal tibia stress fracture. Acta Chir Orthop Traumatol Cech. 2003;70(5):303–5. [PMID: 14669593]
12. Tey IK, Chong KW, Singh I. Stress fracture of the distal tibia secondary to severe knee osteoarthritis: a case report. J Orthop Surg (Hong Kong). 2006;14(2):212–5. [DOI: 10.1177/230949900601400222] [PMID: 16914792]
13. Jeremic D, Vitosevic F, Gluscevic B, Slavkovic N, Apostolovic M, Lalosevic M, et al. Single center experience in treatment of tibial shaft fractures using the Ilizarov technique. Srp Arh Celok Lek. 2020;148(3–4):167–72. [DOI: 10.2298/SARH190901003J]
14. Milenkovic S, Mitkovic MM, Mitkovic MB. Unilateral external fixation of the tibial shaft malunion. Srp Arh Celok Lek. 2020;148(1–2):37–40. [DOI: 10.2298/SARH190908119M]
15. Khakha RS, Bin Abd Razak HR, Kley K, van Heerwaarden R, Wilson AJ. Role of high tibial osteotomy in medial compartment osteoarthritis of the knee: Indications, surgical technique and outcomes. J Clin Orthop Trauma. 2021;23:101618. [DOI: 10.1016/j.jcot.2021.101618] [PMID: 35070682]
16. Jabalameli M, Hadi H, Bagherifard A, Rahbar M, Minator, Sajjadi M. Long-stem total knee arthroplasty for proximal tibial stress fractures in the elderly patients. Arch Bone J Surg. 2018;6(5):376–80. [PMID: 30320177]
17. Kumar Saini M, Singh M, Singh D, Seervi PM, Reddy PJ, Reddy NR. Management of proximal tibial stress fracture associated with advanced knee osteoarthritis: A systematic review. Chin J Traumatol. 2023:S1008-1275(23)00068-8. Online ahead of print. [DOI: 10.1016/j.cjtee.2023.07.002] [PMID: 37543509]
18. Mittal A, Bhosale PB, Suryawanshi AV, Purohit S. One-stage long-stem total knee arthroplasty for arthritic knees with stress fractures. J Orthop Surg. 2013;21(2):199–203. [DOI: 10.1177/230949901302100217] [PMID: 24014784]
19. Wang SP, Wu PK, Lee CH, Shih CM, Chiu YC, Hsu CE. Association of osteoporosis and varus inclination of the tibial plateau in postmenopausal women with advanced osteoarthritis of the knee. BMC Musculoskelet Disord. 2021;22(1):223. [DOI: 10.1186/s12891-021-04090-2] [PMID: 33632177]
20. Osman WS, Younis AS, Thompson J, Amin AA, El-Sebai M. Knee Rheumatoid Arthritis With Lateral Tibial Plateau and Tibial Stress Fractures Managed With One-Stage Knee Joint Replacement. Arthroplast Today. 2020;6(3):487–91. [DOI: 10.1016/j.artd.2020.06.002] [PMID: 32685641]
21. Rashid RH, Zubairi AJ, Umer M, Hashmi PM, Lakdawala RH. Management of stress fractures of the proximal tibia in patients with advance knee osteoarthritis. A case series. Acta Orthop Belg. 2018;84(4):436–42. [PMID: 30879448]
22. Soundarrajan D, Rajkumar N, Dhanasekararaja P, Rajasekaran S. Proximal tibia stress fracture with osteoarthritis of knee – Radiological and functional analysis of one stage TKA with long stem. SICOT J. 2018;4:13. [DOI: 10.1051/2018006] [PMID: 29667926]
23. Sawant MR, Bendall SP, Kavanagh TG, Citron ND. Nonunion of tibial stress fractures in patients with deformed arthritic knees. Treatment using modular total knee arthroplasty. J Bone Joint Surg Br. 1999;81(4):663–6. [DOI: 10.1302/0301-620x.81b4.9091] [PMID: 10463741]
24. Wui NB, Ahmad Anuar MA, Abdul Wahid AM. Short-term outcome of early primary total knee arthroplasty for fractures around the knee in the elderly population: the experience of a secondary healthcare centre in Malaysia. Malays J Med Sci. 2020;27(4):64–71. [DOI: 10.21315/mjms2020.27.4.6] [PMID: 32863746]
25. Shah VI, Upadhyay S, Shah K, Sheth A, Kshatriya A, Patil J. Proximal fibular resection improves knee biomechanics and enhances tibial stress fracture healing in patients with osteoarthritis with varus deformity: a prospective, randomized control analysis. Arthroplasty. 2020;2(1):11. [DOI 10.1186/s42836-020-00030-y] [PMID: 35236433]
26. Gadhe SS, Bhor P, Kanade G, Kale S, Vatkar A, Chaudhari P. Proximal tibia stress fractures with grade 4 osteoarthritis of knee-experience with long stem TKR. Int J Orthop Sci. 2019;5(3):294–7. [DOI: 10.22271/ortho.2019.v5.i3e.1543]
27. Reddy NVR, Saini MK, Reddy PJ, Thakur AS, Reddy CD. Analysis of clinical and radiological outcomes of long tibial stemmed total knee arthroplasty in knee osteoarthritis complicated by tibial stress fracture. Knee Surg Relat Res. 2022;34(1):7. [DOI: 10.1186/s43019-022-00139-1] [PMID: 35193706]

Тотална артропластика колена код болесника са стресним преломом тибије удруженим са тешким обостраним остеоартритисом колена

Славко Манојловић[1,2], Рајко Додик[1], Мирко Манојловић[1], Жељко Јовичић[3], Драгана Драгичевић-Цвјетковић[4,5]

[1]Општа болница „Градишка", Одељење за хирургију, Градишка, Република Српска, Босна и Херцеговина;
[2]Универзитет у Бањој Луци, Медицински факултет, Катедра за хирургију, Република Српска, Босна и Херцеговина;
[3]Завод за физикалну медицину и рехабилитацију „Др Мирослав Зотовић", Одељење за ортопедску хирургију, Бања Лука, Република Српска, Босна и Херцеговина;
[4]Завод за физикалну медицину и рехабилитацију „Др Мирослав Зотовић", Одељење за балнеологију и рехабилитацију, Бања Лука, Република Српска, Босна и Херцеговина;
[5]Универзитет у Бањој Луци, Медицински факултет, Катедра за физикалну медицину и рехабилитацију, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Стресни преломи тибије (преломи тибије услед премора) повезани са билатералним остеоартритисом колена су ретки, али због својих последица представљају терапијски изазов. Овај рад има за циљ да прикаже примењени начин лечења ових болесника и његове резултате.

Методе Проспективна студија је пратила 14 болесника просечне старости од 74,1 године са једностраним стресним преломом тибије удруженим са билатералним тешким остеоартритисом колена. Хируршко лечење подразумева у првом чину уградњу модуларне тоталне протезе колена на страни прелома, а у другом чину имплантацију тоталне, контралатералне протезе колена на бази тешког остеоартритиса. Стационарна рехабилитација је обављена после обе операције у трајању од 21 дан и обухватала је примену кинезитерапије, радне терапије, електротерапије, магнетотерапије, хидротерапије и термотерапије. Параметри праћења били су рендгенски снимак – преоперативно и постоперативно, обим покрета преоперативно и на крају лечења и индекс *WOMAC* преоперативно и постоперативно. Периоди праћења су били: преоперативно и три, шест и девет месеци постоперативно.

Резултати Радиолошки налази код свих болесника током ових периода праћења били су нормални. Сви стресни преломи тибије су зарасли унутар шест месеци од операције. Локални налаз на коленима код свих болесника девет месеци постоперативно значајно се побољшао у поређењу са преоперативним налазом. Статистички значајно побољшање квалитета живота праћено индексом *WOMAC* утврђено је у свим постоперативним периодима праћења, посебно у деветом постоперативном месецу ($p < 0,05$).

Закључак Модуларна тотална протеза колена на страни стресног прелома тибије и одложена имплантација контралатералне протезе колена на колено захваћено остеоартритисом у комбинацији са постоперативном болничком рехабилитацијом дају оптималан функционални исход и побољшавају квалитет живота ових болесника.

Кључне речи: тибија; преломи; стрес; колено; остеоартритис; артропластика

DOI: https://doi.org/10.2298/SARH231212012S
UDC: 617.7-007

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The incidence of patients with pseudoexfoliation in two different regions of Serbia

Miroslav Stamenković[1,2], Tatjana Šarenac-Vulović[3,4], Nenad Petrović[3,4], Jovana Srejović[3,4], Katarina Ćupić[3,4], Marko Popović[1], Ivana Todorović[1], Dušan Todorović[3,4]

[1]Zvezdara University Medical Center, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia;
[3]Kragujevac University Clinical Center, Clinic of Ophthalmology, Kragujevac, Serbia;
[4]University of Kragujevac, Faculty of Medical Sciences, Department of Ophthalmology, Serbia

SUMMARY

Introduction/Objective Pseudoexfoliation (PEX) is an age-related systemic disorder, which can affect the whole body, as well as the eye. It is characterized by abnormal production and accumulation of pseudoexfoliative material. When present in the eye, it can cause different difficulties, but most common are PEX glaucoma (XFG) and intraoperative and postoperative complications of cataract surgeries. The aim of this study was to determine an incidence of patients with PEX in two different regions of Serbia.

Methods The study included 7451 patients scheduled for cataract surgery in two regions of Serbia. It was designed as a multicentric, retrospective study with evaluation of the medical records of all patients who underwent cataract surgery. The study evaluated: incidence of PEX syndrome and PEX glaucoma, age, and sex of patients, as well as preoperative antiglaucomatous therapy and intraoperative and postoperative cataract surgery complications.

Results PEX syndrome (XFS)was recorded in 676 patients (407 females and 269 males), while 243 patients had XFS. It represented 3.26% of patients included in the study. Mean age of XFG patients was 78.1 ± 2.1 years with a statistically significant difference ($p < 0.05$) among incidence of XFG in females compared to males. Intraoperative and postoperative complications during cataract surgery were significantly common in patients with PEX ($p < 0.05$)

Conclusion PEX can complicate cataract surgery, while on the other hand XFG is more difficult to treat and control than most other glaucomas. Therefore, patients with PEX require special treatment during follow-up and treatment.

Keywords: pseudoexfoliation syndrome; phacoemulsification; pseudoexfoliation glaucoma

INTRODUCTION

Pseudoexfoliation (PEX) syndrome (XFS) is an age-related systemic disorder [1, 2]. It can be presented in the whole body, as well as in the eye [3]. This disease is characterized by abnormal production and accumulation of pseudoexfoliative material [4].

The prevalence of the PEX among different nations and regions is different [5]. It is also more common after the sixth decade of the life [6]. Some studies suggested the female predomination, but the others suggested that of the male. Certainly, there is no evidence with sex-related inheritance. The highest incidence linked with geographical regions is in Scandinavian countries and Greece (the island of Crete) [7].

Pseudoexfoliative material is made of abnormal fibrotic fiber [8]. Histologically those fibers are very similar to fibrous tissue fibers. According to some earlier examinations, inflammation is the main process in the very beginning of XFS. Due to inflammation and accumulation of PEX material in trabecular meshwork it can cause intraocular pressure (IOP) rise. That condition is known as pseudoexfoliation glaucoma (XFG) [9]. It represents secondary open-angle glaucoma, usually recorded in older patients. PEX material can be deposited in all parts of the eye, with different consequences [10]. Those consequences are very important for every ophthalmologist. The most important are: XFG and cataract surgery complications (intraoperative and postoperative) [11]. Detailed ophthalmological examination is necessary for every ophthalmological patient, especially elder, to avoid many possible complications. PEXs are the most commonly present at iris pupillary margin (Figure 1) and anterior lens capsule (Figure 2). In the body PEX is accumulated in visceral organs as well as in blood vessels [8].

Cataract surgery is one of the most frequently performed operations in all medicine [12]. The results of cataract surgery are very important for the patient, for the surgeon, and for the surroundings.

The aim of this study was to determine an incidence of patients with PEX in two different regions of Serbia.

METHODS

The study was designed as a multicentric, retrospective study with evaluation of the

Received • Примљено: December 12, 2023
Accepted • Прихваћено: February 1, 2024
Online first: February 5, 2024

Correspondence to:
Dušan TODOROVIĆ
Kragujevac University Clinical Center
Clinic of Ophthalmology
Zmaj Jovina 30
34000 Kragujevac
Serbia
drdusantodorovic@yahoo.com

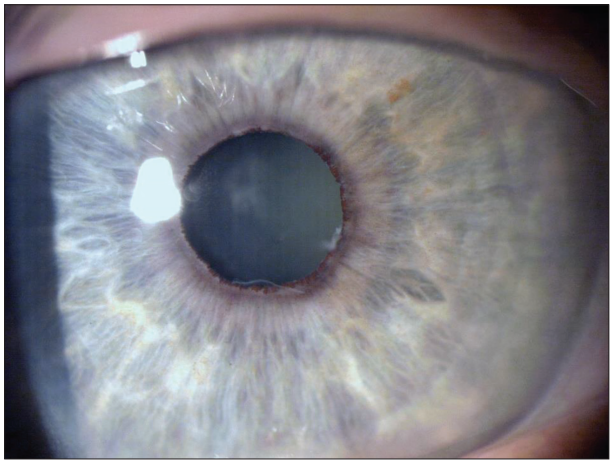


Figure 1. Pseudoexfoliations at the iris pupillary margin and anterior lens capsule

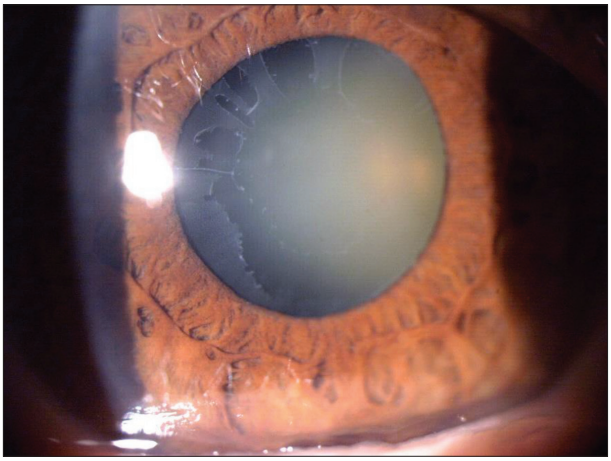


Figure 2. Pseudoexfoliations at the anterior lens capsule

medical records of all patients who underwent cataract surgery. It was conducted at the Clinic of Ophthalmology, Zvezdara University Medical Center and the Clinic of Ophthalmology, Kragujevac University Clinical Center. It included 7451 patients scheduled for cataract surgery. The study period was from November 2021 to November 2023. The written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of the Kragujevac University Clinical Center, prior to the onset of the study. The investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki and the principles of Good Clinical Practice.

The authors evaluated: incidence of PEX syndrome and PEX glaucoma, age, and sex of patients, as well as preoperative antiglaucomatous therapy and intraoperative and postoperative cataract surgery complications. The main inclusion criterion was the presence of cataract, and with no exclusion criterions.

In the preoperative preparation of patients, the presence of ocular and systemic comorbidities, antiglaucoma drugs was analyzed through the detailed review of the medical documentation. A detailed ophthalmological examination was performed for every participant before and after the cataract surgery. It included: the best corrected visual acuity, IOP measurements using Goldmann tonometry, slit lamp examination in mydriasis, indirect ophthalmoscopy. Intraocular lens (IOL) power for every patient was calculated by using SRK/T formula and by using ocular ultrasound A and B scan (Compact touch, Lumibird Medical, Cedex, Lannion, France). The same IOL companies were used in the both Clinics. The XFG was diagnosed if the IOP was above 21 mmHg, characteristic glaucoma damage of optic nerve head and visual field defects were present, as well as PEX material noticed at iris pupillary margin and/or lens anterior capsule during slit lamp examination.

The phacoemulsification was performed for all patients with the same phacoemulsification machine (Stellaris, Bausch and Lomb, Laval, Canada). The cataract surgery was done under the topical anesthesia. After performing paracentesis and central corneal incision, cohesive viscoelastic was injected in anterior chamber (AC). Then continuous capsulorhexis, hydrodissection and nucleus rotation followed. The nucleus was cracked using "stop and chop" technique and the remaining cortex was aspirated using bimanual irrigation and aspiration. After fulfilling AC and capsular bag with cohesive viscoelastic IOL was injected. The remaining viscoelastic was aspirated and intracameral solution of cefuroxime (1 mg / 0.1 ml balanced salt solution) was injected in AC. In the indicated cases, the procedure was supplemented by preventive or therapeutic implantation of the capsular tension ring. Combined eyedrops of dexamethasone and tobramycin (Tobradex®, Alcon, Vernier-Geneva, Switzerland) were prescribed to all patients, in the same way. From the first postoperative day, patients were also applied a local non-steroidal anti-inflammatory drug (Nevanac®, Alcon, Vernier-Geneva, Switzerland) in the operated eye for prophylaxis of cystoid macular oedema. The patient was then followed up by an external ophthalmologist. The presence of any intraoperative and postoperative complications was recorded.

IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA) was used for statistical analysis. According to the normality of distribution, paired t-test, χ^2, Mann–Whitney test was used in analysis of the incidence of XFS, XFG, comorbidities, number of antiglaucomatous drugs, intra and postoperative complications, as well as patients' age and sex. Values $p < 0.05$ and $p < 0.001$ were considered to be statistically significant.

RESULTS

The mean patients' age was 71.4 ± 2.3 years (median 72, range 53–91 years). According to the age of patients, most of them were in a range from 61 to 80 years old (5301 patients) (Figure 3). In total, 3558 males and 3883 females participated in the study. No statistical significance was noticed between the sexes ($p < 0.05$).

XFS was recorded in 676 patients. It represents 9.07% of all the patients who participated in the study. Among them, 407 were females and 269 were males (Figure 4).

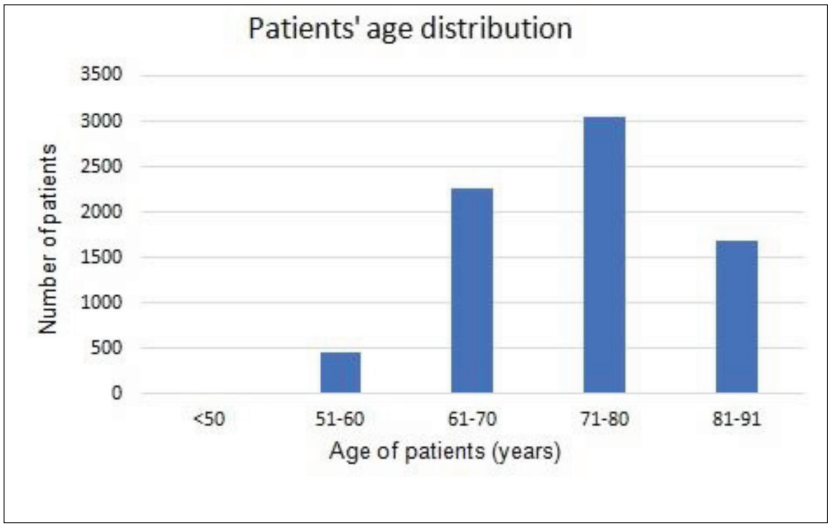


Figure 3. Patients' age distribution

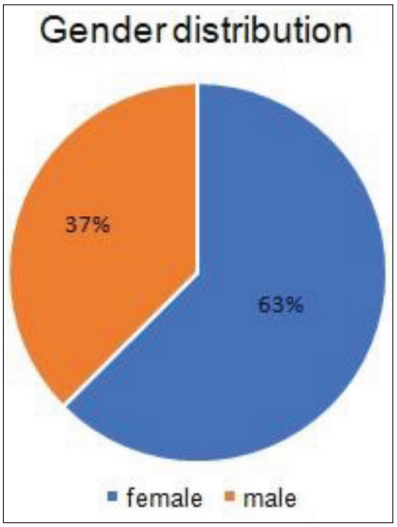


Figure 4. Patients' sex distribution

Table 1. The incidence of intraoperative complications

Intraoperative complications	PEX patients number (%)	NO PEX patients number (%)	Significance
Poor mydriasis	122 (18.04)	655 (9.66)	p = 0.023*
Posterior capsule rupture	55 (8.13)	181 (2.67)	p = 0.017*
Zonular dehiscence	71 (10.5)	273 (4.02)	p = 0.014*
Capsular tension ring implantation	23 (3.4)	171 (2.52)	p = 0.003*
Intraoperative miosis	103 (15.23)	195 (2.87)	p = 0.001*

*Statistically significant
PEX – pseudoexfoliation

Table 2. The incidence of postoperative complications

Postoperative complications	PEX patients number (%)	NO PEX patients number (%)	Significance
Corneal edema	116 (17.15)	652 (9.62)	p = 0.037*
Intraocular lense decentration	52 (7.69)	344 (5.07)	p = 0.055
Anterior chamber inflammation	118 (17.45)	477 (7.04)	p = 0.017*
Retinal detachment	21 (3.10)	269 (3.97)	p = 0.068
Cystoid macular edema	43 (6.36)	143 (2.11)	p = 0.009*

*Statistically significant
PEX – pseudoexfoliation

Statistically significant difference was measured between sexes in XFS patients ($p < 0.001$). The mean age of XFS patients was 77.5 ± 3.4 years (median 74, range 58–90 years).

We recorded 243 patients with XFG, which represents 3.26% of patients who were included in the study. Mean age of XFG patients was 78.1 ± 2.1 years (median 73, range 53–88 years). There was a statistically significant difference ($p < 0.05$) among incidence of XFG in females (n = 157) compared to males (n = 86). The mean number of the used antiglaucomatous drugs in XFG patients was 2.2 ± 0.7. No statistical significance was measured in the number of used antiglaucomatous drugs depending on patients' sex ($p > 0.05$). From these 243 XFG patients, 219 managed to successfully treat glaucoma using antiglaucomatous drugs, while argon laser trabeuloplasty (ALTP) was performed in 19 and trabeculectomy in five patients during the study.

Intraoperative complications including poor mydriasis (less than 5 mm), posterior capsule rupture, zonular dehiscence, capsular tension ring implantation were significantly more often presented in PEX patients (Table 1). Postoperative complications also occurred more commonly in patients with PEXs (Table 2).

DISCUSSION

Senile cataract is the blurring of the lens after the age of 65 [13]. Its development can be in relation to different conditions in the eye, and in the body, as well. Our results also indicate that older people are in positive correlation with cataract incidence, with no statistical significancy with sex predomination.

Cataract surgery is the only effective way of its treatment [13]. Phacoemulsification is the most performed method for cataract surgery [14]. Ultrasound energy is used to emulsify and aspirate the crystalline lens in the eye through the small corneal incision. For good results some precursors must be fulfilled: dilated pupils, stability of the iridolental diaphragm, manual dexterity, and the experience of the surgeon [15].

Our study established that PEX presentation in our group of patients was 9.07%. This result is the similar as in the other studies [16, 17], where incidence in studies ranges from 4% to 10%. We must notice that it is not same if the incidence is 4% or 10%, because for surgeon it is very important to be beware during and after surgery if PEX material is presented in the eye. According to our results, older female patients were more common. This result is in accordance with the earlier studies [10, 18]. It was also very important to notice that mean age of patients with PEX was higher in comparison to patients without PEX. According

to these findings, some suggestions to ophthalmologists are to pay attention to older female patients, recruited for cataract surgery.

Dilated pupils can be reached, using combined installation of mydriatic eye drops: tropicamide, phenylephrine, or homatropine. In some cases, it is demanded to prescribe the use of non-steroidal anti-inflammatory drug eyedrops preoperative to reach and maintain dilated pupils [19]. Patients with uveitic, diabetic, or traumatic cataract, patients with PEX deposits or patients which are using tamsulosin is very difficult to reach good dilated pupils [20]. In that case, cataract surgery becomes very complicated, and needs an experienced surgeon or the use of some intraoperative devices to get dilated pupils (ring) [21].

Stability of the iridolental diaphragm is also very important because of the zonula's weakness, which provokes very serious complications during and after the phacoemulsification surgery [22]. This condition is very often related to PEX deposits in the eye. PEX deposits in the eye predict harder nuclear form of the cataract. Dense and hard cataracts are related to a greater number of intraoperative complications [23]. An increased incidence of PEX patients in our study could be the consequence of increased referral of these patients from private to state clinics, due to higher complications rate during cataract surgery.

Based on the facts above, PEX presentation in the eye is very important for every phacoemulsification surgeon. In order to avoid difficult intra and postoperative complications, detailed clinical examination of every eye of patients must be performed [12].

Earlier investigations suggested that some PEX deposits were not recorded because of the poor dilated pupils [24]. During the surgery, PEX can be detected using the capsular stain.

In the literature, complications of cataract surgery in PEX patients are more common than in patients without PEX. The most common intraoperative complications of the phacoemulsification surgery in patients with PEX are: posterior capsule rupture, vitreous body loss, zonula dehiscence, intraoperative miosis; postoperative complications are: cystoid macular edema, nuclear fragment dislocation, posterior lens capsule opacification, corneal edema, retinal detachment, AC inflammation and hyphema, as well as IOL decentration [25].

Our study established that older patients had more frequent PEX. It seems to be in correlation with earlier epidemiological non-experimental studies. Oxidative stress which is increased in older age is the main cause of PEX production [26]. It induces inflammation and initiates the production of fibrous tissue [9, 27]. Increased production and accumulation of some abnormal fibrous fibers in the anterior segment of the eye result as PEX deposits in the all parts of the eye [4]. PEX material deposits in the iridocorneal angle, and in the retinal vessels, which make conditions to provoke XFG development [3]. According to our findings, approximately 3% of our patients had XFG. Considering that this type of glaucoma is very hard to treat and control, and that it has advanced damage of the retinal nerve fiber layer we have to pay more attention to making the decision for the cataract surgery. Some earlier studies suggested that IOP can be reduced after phacoemulsification surgery in patients with XFG [28]. Personalized, patient and detailed approach to every patient with PEX is demanded.

Every patient, which comes for cataract surgery, must be undergo a detailed ophthalmological examination, to determine PEX presence in anterior segment of the eye. That finding will help the surgeon to make good choice and strategy for future surgery.

Pseudoexfoliative material is one of the risk factors for XFG. XFG treatment demands highly intensive antiglaucomatous therapeutic approach, because of its unpredictable course of the disease. Using antiglaucomatous drugs with preservative provokes ocular surface changes, and can have impact on the IOL calculation, as well as on corneal clearness during the surgery [29]. Also, PEX material in lamina cribrosa of the optic nerve head and in the retinal vessels make good predisposition for the glaucoma disease progression. Phacoemulsification surgery must be done very carefully without fast IOP oscillations. On the other hand, it is helpful to know that IOP can be decreased and well controlled after phacoemulsification surgery, up to a year after the surgery. PEX material is associated with a deceased number of corneal endothelial cells which increase the risk for development of postoperative corneal edema [30]. So, it is very important to use as less as possible ultrasound energy during phacoemulsification as well as to inject dispersive viscoelastic in AC to protect corneal endothelial layer. Also, surgeon would have to consider the possibility to do phacoemulsification surgery in earlier stages of the cataract development, because of the lower ultrasound energy for lens emulsification.

Every surgery has complications. Phacoemulsification surgery complications are divided into: intraoperative and postoperative [25]. Our results indicated that intraoperative complications were statistically significantly increased compared to patients without PEX. Surgery plan, good technique and some devices must be well considered before the surgery.

Postoperative complications are in relation with PEX presentation, and in surgery process. Inflammation was more commonly described in patients with PEX in comparison to with patients without PEX (PEX pathophysiology) [9]. Good manipulation during surgery and preoperative preparation for it are very important in order to avoid inflammation of the eye.

Postoperative capsular opacification was statistically significant more commonly in patients with PEX in comparison to patients without PEX. Some studies also noticed that capsular opacification is more common in patients with PEX because those patients are more susceptible to inflammable postoperative and fibrous reactions [24].

CONSLUSION

Phacoemulsification has improved cataract surgery in all aspects, but still, this technique is not without risks.

Patients with PEX had more frequent occurrence of intraoperative and postoperative complications which can disrupt the final outcome of the surgery and patient's satisfaction. XFG is difficult to control and treat. All these facts indicate that PEX patients require special attention and additional caution during treatment.

Conflict of interest: None declared.

REFERENCES

1. Elhawy E, Kamthan G, Dong CQ, Danias J. Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. Hum Genomics. 2012;6(1):22. [DOI: 10.1186/1479-7364-6-22] [PMID: 23157966]
2. Wang W, He M, Zhou M, Zhang X. Ocular pseudoexfoliation syndrome and vascular disease: a systematic review and meta-analysis. PLoS One. 2014;9(3):e92767. [DOI: 10.1371/journal.pone.0092767] [PMID: 24667689]
3. Schlötzer-Schrehardt U. New pathogenetic insights into pseudoexfoliation syndrome/glaucoma. Therapeutically relevant?. Ophthalmologe. 2012;109(10):944–51. [DOI: 10.1007/s00347-012-2531-1] [PMID: 23053330]
4. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol. 2006;141(5):921–37. [DOI: 10.1016/j.ajo.2006.01.047] [PMID: 16678509]
5. Melese EK, Shibeshi MA, Sherief ST. Prevalence of Pseudoexfoliation Among Adults and Its Related Ophthalmic Variables in Southern Ethiopia: A Cross-Sectional Study. Clin Ophthalmol. 2022;16:3951–8. [DOI: 10.2147/OPTH.S391290] [PMID: 36471727]
6. Schweitzer C. Pseudoexfoliation syndrome and pseudoexfoliation glaucoma. J Fr Ophtalmol. 2018;41(1):78–90. [DOI: 10.1016/j.jfo.2017.09.003] [PMID: 29329947]
7. Kozobolis VP, Papatzanaki M, Vlachonikolis IG, Pallikaris IG, Tsambarlakis IG. Epidemiology of pseudoexfoliation in the island of Crete (Greece). Acta Ophthalmol Scand. 1997;75(6):726–9. [DOI: 10.1111/j.1600-0420.1997.tb00640.x] [PMID: 9527341]
8. Buffault J, Labbé A, Hamard P, Brignole-Baudouin F, Baudouin C. The trabecular meshwork: Structure, function and clinical implications. A review of the literature. J Fr Ophtalmol. 2020;43(7):e217–30. [DOI: 10.1016/j.jfo.2020.05.002] [PMID: 32561029]
9. Sarenac Vulovic TS, Pavlovic SM, Zdravkovic NS. Proinflammatory Cytokines Induce XFG Development. Ocul Immunol Inflamm. 2016;24(6):671–7. [DOI: 10.3109/09273948.2015.1063672] [PMID: 26651123]
10. Rumelaitiene U, Speckauskas M, Tamosiunas A, Radisauskas R, Peto T, Larsen MB, et al. Exploring association between pseudoexfoliation syndrome and ocular aging. Int Ophthalmol. 2023;43(3):847–57. [DOI: 10.1007/s10792-022-02486-0] [PMID: 36127504]
11. Faschinger C. Pseudoexfoliation glaucoma in pseudophakic eyes-still a therapeutic challenge. Graefes Arch Clin Exp Ophthalmol. 2023;261(12):3345–6. [DOI: 10.1007/s00417-023-06234-7] [PMID: 37704760]
12. Goel R, Shah S, Malik KPS, Sontakke R, Golhait P, Gaonker T. Complications of manual small-incision cataract surgery. Indian J Ophthalmol. 2022;70(11):3803–11. [DOI: 10.4103/ijo.IJO_1812_22] [PMID: 36308100]
13. Rewri P, Lohan A, Aggarwal S, Chodhary P, Singhal A. Cataract surgical reach: Falling short to catch white cataracts! Indian J Ophthalmol. 2021;69(6):1575–8. [DOI: 10.4103/ijo.IJO_2560_20] [PMID: 34011744]
14. Boulter T, Bernhisel A, Mamalis C, Zaugg B, Barlow WR, Olson RJ, et al. Phacoemulsification in review: Optimization of cataract removal in an in vitro setting. Surv Ophthalmol. 2019;64(6):868–75. [DOI: 10.1016/j.survophthal.2019.06.007] [PMID: 31276738]
15. Akpolat C, Demir M, Cevher S, Ozturk SZ, Yesiltas S. The impact of phacoemulsification surgery on vision-related quality of life in senile cataract patients. Ther Adv Ophthalmol. 2022;14:25158414211063293. [DOI: 10.1177/25158414211063293] [PMID: 35083419]
16. Ekström C, Winblad von Walter L. Incidence and baseline risk factors for pseudoexfoliation in Sweden: a long-term follow-up study. Acta Ophthalmol. 2020;98(3):310–4. [DOI: 10.1111/aos.14254] [PMID: 31573742]
17. Karger RA, Jeng SM, Johnson DH, Hodge DO, Good MS. Estimated incidence of pseudoexfoliation syndrome and pseudoexfoliation glaucoma in Olmsted County, Minnesota. J Glaucoma. 2003;12(3):193–7. [DOI: 10.1097/00061198-200306000-00002] [PMID: 12782834]
18. Aström S, Lindén C. Incidence and prevalence of pseudoexfoliation and open-angle glaucoma in northern Sweden: I. Baseline report. Acta Ophthalmol Scand. 2007;85(8):828–31. [DOI: 10.1111/j.1600-0420.2007.00992.x] [PMID: 17986290]
19. Schulz CB, Goverdhan SV, Humphry RC. An evaluation of intracameral mydriasis for routine cataract surgery. Br J Ophthalmol. 2018;102(6):784–9. [DOI: 10.1136/bjophthalmol-2017-310510] [PMID: 28903962]
20. Kwak J, Han JY, Moon SY, Nam S, Kim JY, Tchah H, et al. Relationship Between Tamsulosin Use and Surgical Complications of Cataract Surgery in Elderly Patients: Population-Based Cohort Study. Front Med (Lausanne). 2022;9:882131. [DOI: 10.3389/fmed.2022.882131] [PMID: 35665322]
21. Oudjani N, Renault D, Courrier E, Malek Y. Phacoemulsification And Zonular Weakness: Contribution Of The Capsular Tension Ring With A Thread. Clin Ophthalmol. 2019;13:2301–4. [DOI: 10.2147/OPTH.S212063] [PMID: 31849440]
22. Venkateswaran N, Henderson BA. Loose zonules in cataract surgery. Curr Opin Ophthalmol. 2022;33(1):53–7. [DOI: 10.1097/ICU.0000000000000826] [PMID: 34783703]
23. Foster GJL, Allen QB, Ayres BD, Devgan U, Hoffman RS, Khandelwal SS, et al. Phacoemulsification of the rock-hard dense nuclear cataract: Options and recommendations. J Cataract Refract Surg. 2018;44(7):905–16. [DOI: 10.1016/j.jcrs.2018.03.038] [PMID: 29960655]
24. Sternfeld A, Luski M, Sella R, Zahavi A, Geffen N, Pereg A, et al. Diagnosis of Pseudoexfoliation Syndrome in Pseudophakic Patients. Ophthalmic Res. 2021;64(1):28–33. [DOI: 10.1159/000508336] [PMID: 32353850]
25. Sarenac Vulovic T, Todorovic D, Petrovic N, Jovanovic S. The complication of cataract surgery in apetints with pseudoexfoliation. Experimental and Applied Biomedical Research. 2020. [DOI: 10.2478/sjecr-2020-0044]
26. Sarenac Vulovic TS, Pavlovic SM, Jakovljevic VLj, Janicijevic KB, Zdravkovic NS. Nitric oxide and tumour necrosis factor alpha in the process of pseudoexfoliation glaucoma. Int J Ophthalmol. 2016;9(8):1138–42. [DOI: 10.18240/ijo.2016.08.09] [PMID: 27588268]
27. Sarenac Vulovic T, Pavlovic S, Lutovac M, Zdravkovic V, Sreckovic S, Zdravkovic N. Regulatory cytokines prescribe the outcome of the inflammation in the process of pseudoexfoliation production. J Chin Med Assoc. 2019;82(12):935–40. [DOI: 10.1097/JCMA.0000000000000214] [PMID: 31800535]
28. Todorović M, Šarenac Vulović T, Petrović N, Todorović D, Srećković S. Intraocular pressure changes after uneventful phacoemulsification in early postoperative period in healthy eyes. Acta Clin Croat. 2019;58(3):467–72. [DOI: 10.20471/acc.2019.58.03.10] [PMID: 31969759]
29. Saeedi O, Chen V. BAK to the Future? Preserved and Preservative-Free Topical Glaucoma Medications. Eye Contact Lens. 2022;48(4):139–40. [DOI: 10.1097/ICL.0000000000000893] [PMID: 35296624]
30. Todorović D, Šarenac-Vulović T, Petrović N, Jovanović S, Janićijević-Petrović M, Đoković D, et al. The effect of intraocular lens material and postoperative therapy on the posterior capsule opacification development after the senile cataract surgery. Srp Arh Celok Lek. 2020;148(5–6):333–7. [DOI: 10.2298/SARH181211118T]

Инциденца пацијената са псеудоексфолијацијама у два различита региона Србије

Мирослав Стаменковић[1,2], Татјана Шаренац-Вуловић[3,4], Ненад Петровић[3,4], Јована Срејовић[3,4], Катарина Ћупић[3,4], Марко Поповић[1], Ивана Тодоровић[1], Душан Тодоровић[3,4]

[1]Универзитетски клиничко-болнички центар „Звездара", Београд, Србија;
[2]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[3]Универзитетски клинички центар „Крагујевац", Клиника за офталмологију, Крагујевац, Србија;
[4]Универзитет у Крагујевцу, Факултет медицинских наука, Катедра за офталмологију, Србија

САЖЕТАК

Увод/Циљ Псеудоексфолијације су системски поремећај повезан са годинама, који може утицати на цело тело, али и око. Карактерише га абнормална производња и акумулација псеудоексфолијативног материјала. Када је присутан у оку, може изазвати различите потешкоће, али најчешће су псеудоексфолиациони глауком и интраоперативне и постоперативне компликације операција катаракте.

Циљ овог истраживања био је да се утврди учесталост оболелих од псеудоексфолијације у два различита региона Србије.

Методе Студија је обухватила 7451 пацијента заказаног за операцију катаракте у два региона Србије. Замишљена је као мултицентрична, ретроспективна студија са евалуацијом медицинске документације свих пацијената који су били подвргнути операцији катаракте. Студија је проценила учесталост псеудоексфолијативног синдрома и псеудоексфолијативног глаукома, старост и пол пацијената, као и преоперативну антиглаукоматозну терапију и компликације интраоперативне и постоперативне операције катаракте.

Резултати Псеудоексфолијативни синдром забележен је код 676 пацијената (407 жена и 269 мушкараца), док су 243 болесника имала псеудоексфолијативни глауком. Обухватио је 3,26% пацијената укључених у студију. Просечна старост пацијената са псеудоексфолијативним глаукомом била је 78,1 ± 2,1 година са статистички значајном разликом ($p < 0,05$) између инциденције код жена у односу на мушкарце. Интраоперативне и постоперативне компликације током операције катаракте биле су значајно честе код пацијената са псеудоексфолијацијама ($p < 0,05$).

Закључак Псеудоексфолијације могу да закомпликују операцију катаракте, док је с друге стране псеудоексфолијативни глауком тежи за лечење и контролу од већине других глаукома. Због тога пацијенти са псеудоексфолијацијама захтевају посебан третман током праћења и лечења.

Кључне речи: псеудоексфолијативни синдром; факоемулзификација; псеудоексфолијативни глауком

DOI: https://doi.org/10.2298/SARH231115009M
UDC: 616.13-007.272; 617.735; 616.379-008.64-06

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Risk factors of peripheral occlusive arterial disease in patients with diabetic retinopathy due to type 2 diabetes

Miloš Maksimović
University Clinical Center of Serbia, Clinic of Eye Diseases, Belgrade, Serbia

SUMMARY
Introduction/Objective Diabetic retinopathy, peripheral vascular disease, and other diabetic complications may lead to a lowering of quality of life, significant comorbidity and mortality.
The aim of the study was to analyze the risk factors of peripheral occlusive arterial disease in patients suffering from diabetic retinopathy due to type 2 diabetes.
Methods We analyzed 63 patients having diabetic retinopathy (33 patients without and 30 patients with peripheral occlusive arterial disease). All the patients were asked for demographic data, medical history, physical findings, laboratory and vascular status.
Results Patients that have confirmed peripheral occlusive arterial disease suffered from diabetes significantly longer (32.67 *vs*. 9.71 years, $t = 12.834$, $p < 0.001$), were more often smokers (23:13, $\chi^2 = 8.92$, $p < 0.05$), had ischemic heart disease significantly more frequently (24:10, $\chi^2 = 15.643$, $p < 0.001$), used statins more frequently (21:14; $\chi^2 = 4.84$, $p < 0.05$), had claudication (25:4, $\chi^2 = 32,075$, $p < 0.001$), hair loss (30:9, $\chi^2 = 35,24$, $p < 0.001$), thinned atrophic foot skin (30:12, $\chi^2 = 28.64$, $p < 0.01$), foot ulcers (10:1, $\chi^2 = 10.013$, $p < 0.01$), significantly higher glycated hemoglobin (HbA1c) values (9.31:7.17, $t = 5.250$, $p < 0.001$), as well as glycemic control (11.60:8.20, $t = 4.913$, $p < 0.001$).
Conclusion It has been shown that the duration of type 2 diabetes, smoking, poor regulation of blood glucose levels and HbA1c significantly contributes to the development of diabetic retinopathy in patients having peripheral artery occlusion.
Keywords: type 2 diabetes; diabetic retinopathy; peripheral occlusive arterial disease; risk factors

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease due to lack of insulin activity or its inadequate activity. There is also an interaction of inheritance and the environmental and risk factor impact [1, 2]. Diabetes type 2 (T2DM), is a result of a decreased function of β-cells and/or resistance to insulin effect. T2DM makes 90–95% of diabetics. Several genetic and acquired factors are involved in etiopathogenesis of DM: gluconeogenesis and glycogenolysis followed by hyperglycemia and decreased cellular glucose disintegration manifested by characteristic signs of ischemia. Complications of DM may be acute (ketoacidosis, hyperglycemic coma) and chronic (retinopathy, nephropathy, neuropathy, peripheral vascular, coronary and cerebrovascular disease).

Retinopathia diabetica (RD) is a microvascular chronic complication of DM primarily affecting precapillary arterioles, capillaries and postcapillary venules [3, 4]. DM is one of the main causative agents of blindness in active working population. Although hyperglycemia is known to be significantly associated with RD, pathophysiological mechanisms have not been entirely clarified [4, 5]. Clinically, RD can be classified as: RD *non proliferativa* (RDNP) with mild, moderate and severe stages and RD *proliferativa* (RDP). The most frequent complications of T2DM are known and they represent the major risk factors [3] for the onset and development of RD. RD is a progressive disease with characteristic signs: microaneurysms, dot-and-blot hemorrhage, soft (cotton wool) and hard exudates as well as changes in the caliber of blood vessels and retinal reperfusion [4]. The elevation of retinal ischemia stimulates the production of vasoproliferative factors.

Peripheral arterial occlusive disease (POAD) is a condition most frequently caused by atherosclerosis, but other diseases may be of etiological importance. POAD is a major cause of lower extremity amputation, and is also related to higher probability of suffering from ischemic heart condition and cerebrovascular disease. DM, smoking, hypertension, and hyperlipidemia are the main etiological factors of POAD. Furthermore, other risk factors are also important (age, DM duration, obesity, comorbid states and complications of DM) [3, 6]. The diagnosis of POAD is established based on the history of illness, clinical findings, doppler finding and arteriography. In patients with DM, due to calcification and non-elasticity of arteries, there may be found unreal and falsely increased levels of doppler ankle-brachial index (ABI) [7, 8]. POAD is treated with revascularization (endovascular or surgical procedures) and medicamentous administration.

Received • Примљено: November 15, 2023
Revised • Ревизија: December 28, 2023
Accepted • Прихваћено: January 3, 2024
Online first: January 15, 2024

Correspondence to:
Miloš MAKSIMOVIĆ
University Clinical Center of Serbia
Clinic of Eye Diseases
Pasterova 2
11000 Belgrade
Serbia
milosmak13@gmail.com

The purpose of the study was to analyze the incidence of risk factors for the development of POAD in patients with confirmed diagnosis of RD who suffered from T2DM.

METHODS

The total number of the subjects (63) was divided into two groups: the study group (SG) of 30 patients with POAD and the control group (CG) of 33 patients without POAD. The study was conducted at the Clinic of Eye Diseases, University Clinical Center of Serbia (UCCS) and the Outpatients' Department of the Clinic of Vascular and Endovascular Surgery, UCCS.

The diagnosis of RD was established on the basis of indirect biomicroscopy by using the Volk®, Super vitreo fundus lens (Volk Optical Inc., Mentor, OH, USA). The changes in the eye fundus were evaluated. They included microaneurysms, dot-blot hemorrhage, flame hemorrhage, soft and hard exudates in RDNP as well as newly formed blood vessels (neovascularization of papillary disk and neovascularization elsewhere) in RDP.

The diagnosis of POAD was established based on the existence of at least one symptom or sign of peripheral vascular disease and reduced ABI. The ABI measurements in the patients suffering from RD were done on Siemens Acuson Antares, 2009, (Siemens, Munich, Germany), by stick probe of 8 MHz in the Clinic of Vascular and Endovascular Surgery, UCCS. The highest level of the indices obtained was the reference ABI level. The patients who had normal ABI levels (0.91–1.40) with no symptoms and signs of peripheral angiopathy belonged to the group with no signs of POAD (CG), whereas the patients with ABI levels below 0.91 were in the group with the signs of POAD (SG).

Demographic data, history of illness (T2DM duration, smoking, hypertension, ischemic heart condition, cerebrovascular disease, claudication, the use of drugs), physical exam finding [body mass index (BMI), ischemic thinned skin, hair loss, and ulceration], laboratory findings [blood cell count, total low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, triglycerides, glycemia, glycated hemoglobin (HbA1C), creatinine, urea, liver enzymes and C-reactive protein (CRP)] were evaluated followed in all the patients.

Written informed approval was acquired from all patients for the participation in the clinical study upon reading short protocol and the purpose of the study. The Ethical Committee of the UCCS (1040/28) gave approval for the conduction of this study.

The obtained data were collected in the tabular questionnaire and analyzed by the methods of descriptive and analytic statistics. The methods of descriptive statistics used were central tendency rates, relative numbers and variability rates. The methods of analytic statistics, for the estimation of statistical significance, included student t-test for numerical features, χ^2 test for attributive features and Fisher's test of accurate probability. The value $p \leq 0.05$ was used as borderline value of statistical significance whereas the value $p \leq 0.01$ as borderline value of high statistical significance. The data collected were analyzed in a tabular form by applying the program IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA).

RESULTS

Complete study results of both groups are shown in Table 1.

Demographic Data

The majority of the patients were males (60.3%). The variability in distribution of patients according to gender was not significant. The obtained results of demographic studies indicated that SG and CG groups were statistically comparable.

Medical history data

The patients with the confirmed diagnosis of POAD suffered from T2DM significantly longer. The patients in SG were more frequently smokers than in CG. Hypertension occurred within approximate values in both groups. The use of antihypertensive drugs was approximately equally present in both groups. Statins were used more by SG than CG group. SG patients were found to be suffering from ischemic heart condition more frequently than CG patients. Among the studied patients, there was none who had a positive history of cerebrovascular disease. Most SG patients complained of claudication, thus high significance was proven in the studied group.

Physical exam finding

There was no difference in BMI values. Peripheral ischemic changes (ischemic hair loss of the foot and lower extremities, atrophic, thinned skin and ischemic foot ulcerations) were significantly more frequent in the patients having the manifested POAD.

Laboratory findings

Erythrocyte, leucocyte, and platelet counts and hemoglobin concentration were similar in the studied groups. There was no difference in HDL cholesterol levels between the studied groups. However, the total and LDL cholesterol levels were significantly lower in the SG patients than in the CG ones. The difference in blood triglyceride concentration was not noticed between SGs. The average glycemia levels were significantly higher in the SG patients than in the CG ones. The HbA1c levels were higher in the SG patients than in the CG ones. There was no statistical difference in the average urea and creatinine blood levels of the studied groups. The differences of basic liver enzyme concentration were not significant in both groups. The CRP levels were within reference values in both groups, but statistically significant difference was determined between the studied groups.

Table 1. Findings of risk factors for development of peripheral arterial occlusive disease (POAD) in type 2 diabetes mellitus patients with *retinopathia diabetica*

Feature	Study group (with POAD)	Control group (without POAD)	Analytic statistic	p value
No. of subjects	30	33	-	-
Male (n)	20	18	DF = 1; χ^2 = 0.965	0.326
Female (n)	10	15		
Age ($\bar{x}$ ± SD years)	71.17 ± 5.60	71.64 ± 5.80	DF = 62; t = 0.326	0.745
DM duration ($\bar{x}$ ± SD years)	32.67 ± 2.09	9.71 ± 9.59	DF = 61; t = 12.83	< 0.001
Smoking habit (n)	23	13	DF = 1; χ^2 = 8.920	0.003
Hypertension (n)	20	20	DF = 1; χ^2 = 0.249	0.618
Antihypertensive use (n): ACE inhibitors β blockers Inhibitors of calcium channels Diuretics	 17 20 11 8	 20 19 7 5	 DF = 1; χ^2 = 0.099 DF = 1; χ^2 = 0.542 DF = 1; χ^2 = 1.841 DF = 1; χ^2 = 1.320	 0.752 0.461 0.175 0.251
Statin use (n)	21	14	DF = 1; χ^2 = 4.840	0.028
Coronary disease incidence (n)	24	10	DF = 1; χ^2 = 15.64	< 0.001
Claudication incidence (n)	25	4	DF = 1; χ^2 = 32.07	< 0.001
BMI (kg/m^2)	27.31 ± 2.87	26.09 ± 2.52	DF = 61; t = 2.03	0.08
Ischemic leg depilation (n)	30	9	DF = 1; χ^2 = 35.24	< 0.001
Ischemic skin atrophy (n)	30	12	DF = 1; χ^2 = 28.64	< 0.001
Foot ulcerations (n)	10	1	DF = 1; χ^2 = 10.01	< 0.01
Erythrocyte count (x10^{12}/l)	4.865 ± 0.53	4.736 ± 0.53	DF = 61; t = 0.345	0.731
Leucocyte count (x10^9/l)	7.3 ± 1.66	6.9 ± 2.1	DF = 61; t = 0.812	0.423
Platelet count (x10^9/l)	281.01 ± 54.4	268.55 ± 49.36	DF = 61; t = 0.945	0.348
Hemoglobin level (g/l)	133.67 ± 16.78	138.24 ± 17.85	DF = 61; t = 1.020	0.308
Total cholesterol (mmol/l)	4.32 ± 0.50	6.02 ± 1.21	DF = 61; t = 7.151	< 0.001
HDL cholesterol (mmol/l)	1.14 ± 0.23	1.15 ± 1.24	DF = 61; t = 0.210	0.835
LDL cholesterol (mmol/l)	2.86 ± 1.05	3.64 ± 0.89	DF = 61; t = 3.185	0.002
Triglycerides (mmol/l)	1.88 ± 0.84	2.25 ± 0.99	DF = 61; t = 1.573	0.006
Glycemia (mmol/l)	11.60 ± 2.10	8.2 ± 3.22	DF = 61; t = 4.913	< 0.001
HbA1c (%)	9.31 ± 1.54	7.17 ± 1.68	DF = 61; t = 5.250	< 0.001
Urea (mmol/l)	7.08 ± 2.35	7.94 ± 2.28	DF = 61; t = 1.453	0.151
Creatinine (μmol/l)	79.40 ± 17.71	84.3 ± 16.63	DF = 61; t = 1.115	0.269
ALP (U/l)	77.94 ± 21.59	75.89 ± 11.80	DF = 61; t = 0.463	0.645
GGT (U/l)	24.433 ± 7.48	27.03 ± 8.97	DF = 61; t = 1.222	0.225
ALT (U/l)	30.993 ± 8.50	29.424 ± 8.87	DF = 61; t = 0.677	0.501
AST (U/)	20.333 ± 4.50	22 ± 3.52	DF = 61; t = 1.620	0.110
CRP (mg/l)	1.533 ± 0.205	3.127 ± 1.01	DF = 61; t = 8.330	< 0.001

$\bar{x}$ - mean value; SD – standard deviation; DF – degree of freedom; DM – *diabetes mellitus*; ACE – angiotensin converting enzyme; BMI – body mass index; HDL – high density lipoprotein; LDL – low density lipoprotein; ALP – alkaline phosphatase; GGT – gamma glutamyl transferase; ALT – alanine amino transferase; AST – aspartate amino transferase; CRP – C-reactive protein

SG patients had ABI index values from 0.59 to 0.68. All CG subjects had ABI over 0.92, but below 1.40.

DISCUSSION

RD is common cause of the vision loss in patients aged 20–64 years and one of the most frequent microangiopathic complications of T2DM [9]. The prevalence of RD is around 24.5% of patients with the found of DM and around 10.7% of patients with undiagnosed DM [10]. RD may occur in every patient suffering from T2DM so RD can be prevented by the control of glycemia and elimination of other risk factors [3].

T2DM is followed by the higher risk of POAD, cardiovascular and cerebrovascular diseases. These conditions frequently require hospitalization of patients and may be accompanied by acute complication, leg amputation and lethal outcome [1, 2]. DM and POAD are approximately even between genders [3]. There were no significant differences in RD and POAD in the patients according to gender [9]. This study showed that RD occurred slightly more frequently in males than females (38:25), but there were no significance. Magri et al. [11] had similar findings with the ratio of 98:83. However, Cherchi et al. [9] studied sex distribution of RD in 20,611 patients with T2DM showed that there was higher prevalence of RD in males in spite of less present risk factors. This meant that the male sex could represent a separate risk factor for the RD onset [9].

Leley et al. [12] think that around 50% of T2DM patients develop RD later in life due to reduced retinal blood flow and microglial alterations. This makes the retina more vulnerable to oxidative and ischemic alterations leading to RD progression [12]. Our patients were of older age (over 70 years), and there was no significance between SG and CG as found by other authors [11]. However, most studies show that RD occurs in patients under 70 [13]. Such findings suggest that our patients are diagnosed and treated of RD and POAD later than patients in more developed countries.

The duration of T2DM was significantly different in our studied groups: SG (32.67 ± 2.09) *vs.* CG (9.71 ± 9.59), so this difference was highly significant. Such findings indicate that RD can be diagnosed in the period of 10 years from the onset of T2DM. That shows also that clinically manifested POAD occurs significantly later during T2DM. The duration of T2DM strongly affects the onset of POAD. Other authors found that the duration of T2DM over 10 years is a very important factor for progression of POAD and its complications [14]. Duration of diabetes and systemic risk factors affect the seriousness of RD clinical finding. Studying the severity of RD in diabetics under 25 (161) and over 25 (493), Parameswarappa et al. [15] showed that younger patients suffering from T2DM were more likely to develop threatening RD in spite of the presence of similar risk factors. We suggest that there is necessity of monitoring and treating of arterial pressure, glycemic status, and other possible diabetic complications in these patients to decrease the risk of threatening RD and POAD [2, 15].

Smoking is one of the most important risk factors for POAD in DM and atherosclerosis. However, the incidence of this risk factor is different in certain regions of the world [16]. In metanalysis of the risk of smoking in diabetics, Cai et al. [17] established that the risk for RD in diabetes type 1 was higher in smokers than non-smokers (risk ratio was 1.2; $p < 0.001$). On the other hand, the risk for retinopathy in T2DM decreased in smokers compared to non-smokers (risk ratio was 0.92; $p < 0.001$). Around three quarters of our patients suffering from POAD had the smoking habit whereas non-POAD group counted less than half smokers. The observed difference was significant. Such data shows that in our population smoking is a highly prevalent risk factor for peripheral vascular disease in DM, so that more social effort and engagement on banning smoking is required.

Hypertension is an important risk factor for the development of POAD and RD in patients with T2DM [12]. Microvascular lesions were determined in RD (thickened capillary membrane, defect of blood-retinal barrier and pericyte loss) [18]. A multicentric study including 152,844 diabetics showed that there was correlation between hypertension and RD, but it was demonstrated that the higher prevalence of RD was also present with and without hypertension [19]. In our study, hypertension was found in over 60% of similar values of the studied groups, so the differences obtained were insignificant. High incidence of hypertension in DM and RD requires the application of antihypertensive drugs [11]. Our patients took all kinds of antihypertensive drugs. The SG patients used statins more than the CG patients (21:14). The patients suffering from POAD used statins much more frequently than the patients without POAD. This is in contrast with the study of Magri et al. [11] in which it was shown that there was no significant difference between the studied groups. This suggests that our patients suffered more frequently from hyperlipoproteinemia than the patients in other populations. Nevertheless, one should be careful with prescribing statins because of their potential insulin-resistant effect [20].

It has been well known that T2DM is followed by a coronary disease [16, 17, 18]. Multiple regression analysis conducted by Kawasaki et al. [21] showed that RD was an important factor for the development of coronary complications with the following risk factors: increased triglyceride levels, smoking, age, T2DM duration, increased HbA1c level and female sex. In medical history, the incidence of ischemic heart disease in our subjects was significantly higher in SG (80%) than in CG (30.3%). Such finding may be the result of the difference in T2DM duration as well as the possibility of asymptomatic presence of coronary disease in RD patients [6, 8]. There were no history data of earlier cerebrovascular disease in our study. Carotid disease is known to be frequently asymptomatic, so the diagnosis requires duplex scan angiography [6, 11], which was not used in this study.

Obesity and BMI in our patients is similar in all subjects (BMI from 25.0 to 29.9 kg/m^2) so there was insignificant difference in the studied groups. Other researchers had similar results [11].

Intermittent claudication represents one of the major complaints in the patients with POAD. Nevertheless, the presence of decreased claudication distances and the absence of pedal pulses is not sufficient for diagnosing POAD [7, 8]. Our study showed that 25 patients in SG and only four in CG had claudication, which is highly significant in the studied groups. It was established by physical exam finding, that there was a significant difference in peripheral vascular state of our patient groups. The hair loss, thinned skin, and ulcerations were the result of low foot trophic and they may be significant signs of peripheral angiopathy. The study showed that these ischemic signs were more frequent in SG patients than in CG.

All our SG patients had decreased ABI. Decreased ABI is known to be present in patients with macroangiopathic alterations [11]. It is necessary to stress that the ABI findings in diabetics in advanced stages is of relative importance. Namely, in advanced atherosclerotic alterations due to DM, peripheral arteries become incompressible [7, 11]. Careful interpretation of these findings is required [7] since in advanced stages of occlusive disease, some diabetics may have high ABI values surpassing even 1.4 in spite of manifested critical ischemia. In advanced wall alterations, arteries may be incompressible and ABI immmeasurable [7]. Such patients were excluded from our study [2].

Changes in blood count in diabetics were described (increased leucocyte and platelet counts) [22], which was not shown in our study. This may be the result of insufficient number of subjects and study design. Our SG patients had significantly lower total and LDL cholesterol levels in comparison to CG patients. These, apparently, paradoxical data may be explained by the effect of the applied therapy of statins [21] which were more frequently used in our SG (2/3 of patients) than CG (1/2 of patients). It is undisputable that statins have significant metabolic effects reducing atherogenesis. Thus, these drugs are significantly more used in patients having POAD than in patients not having POAD [20], which was shown in our study. In the studied groups, the differences in triglyceride levels did not reach statistical significance.

In both study groups, increased HbA1c levels were found, but the values were significantly higher in patients suffering from manifested POAD. Thus, these results suggest that the impaired glycoregulation was more manifested in patients having POAD than in patients not having POAD. In SG patients, increased glycemia levels were obtained and these differences were highly significant related to CG. This indicates that the glycemia levels are not affected by insulin that is hypoglycemics only, but statin therapy, antiaggregating therapy as well as adequately prescribed diet [23]. RD treatment is conducted also using other agents such as: corticosteroids, vascular endothelial growth factor (VEGF) agents, interleukin inhibitor, Rho-kinase inhibitors, neuroprotective agents, laser therapy. All this influence the metabolic and pathogenetic vascular processes in RD [24, 25, 26].

In our patients, there were insignificant changes in urea and creatinine levels in the studied groups. This indicates that our patients did not suffer from advanced or terminal

renal insufficiency and that RD was not detected since we did not measure proteinuria. Elevated basic liver findings (alkaline phosphatase, gamma glutamyl transferase, alanine amino transferase, aspartate amino transferase) were seen in neither study groups. It is known that patients with metabolic syndrome are 2–4 times at a higher risk of cardiovascular diseases, as well as 5–9 times greater chances of T2DM development [24]. Although our study showed that disorders of the cholesterol and triglyceride metabolism had a significant atherogenic effect, according to basic liver enzyme findings it was not possible to prove hepatic insufficiency.

The increased level of CRP in T2DM patients may be a significant risk factor for DM complications. Upon summarizing the relevant clinical trials, it was shown that the increased CRP level was in correlation with RD, but not independent of other risk factors (HbA1c, BMI, albuminuria) [25]. Nevertheless, it remains unclear to what measure CRP leads to retinopathy. Correlation between CRP and RD may be explained in that CRP has proangiopoietic effect and stimulates monocytes to produce vascular VEGF-A [23]. In our study, it was shown that CRP level was significantly higher in CG than in SG, so this difference was noticed to be highly significant. A possible explanation is that the patients having POAD used statins more frequently since it is known that they lead to the CRP level decrease [24].

T2DM is a chronic metabolic disease caused by glucose metabolism disorder due to the disorder of insulin synthesis or activity. The disease is more common in adult and elderly population, in both sexes, with the tendency of progression due to congenital factors and modern way of life (decreased physical activity, increase of obesity and changes in diet) [1]. It leads to progressive microangiopathic, macroangiopathic and neuropathic diseases [1, 2, 12, 14]. RD is characterized by retinal impairment affected by several etiopathogenetic factors: synthesis of proinflammatory cytokines and chemokines, growth factor disorder, oxidative means and other factors which lead to the development of microaneurysms, retinal hemorrhage and ischemia by synthesis of vasoproliferative factors, increased permeability of retinal vessels, and serum transudation. The manifestations are thinned retina, macular edema and the loss of vision [26].

CONCLUSION

In patients suffering from RD, the following risk factors for the development of POAD were identified: T2DM duration, smoking habit, elevated glycemia level, increased HbA1c levels and more frequent occurrence of coronary disease. The patients having POAD had significantly more frequent findings of claudication, ischemic hair loss, thinned skin, and foot ulceration with significantly more frequent use of statins.

The patients suffering from RD who were not determined to have manifested POAD had significantly increased total cholesterol levels, elevated LDL cholesterol levels and increased CRP levels. They used statins less frequently in medical therapy.

The obtained results suggest that early detection and risk factor elimination is required as well as complex therapy for the patients suffering from T2DM, RD, and POAD. With these measures, complications are decreased and the quality of life of these patients is promoted.

ACKNOWLEDGEMENT

This article is part (enhanced by contemporary literature) of Specialist Academic Paper: Maksimović M. The incidence of risk factors of peripheral angiopathy in patients having diabetic retinopathy suffering from Diabetes Mellitus Type 2. Mentor: S. Milenković. Faculty of Medicine, Belgrade, 2014.

Conflict of interest: None declared.

REFERENCES

1. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185–200. [DOI: 10.7150/ijms.10001] [PMID: 25249787]
2. Maksimović M. The incidence of risk factors of peripheral angiopathy in patients having diabetic retinopathy suffering from Diabetes Mellitus Type 2. Specialist Academic Paper (Mentor: S. Milenković). Belgrade: Faculty of Medicine; 2014. (Serbian)
3. Naserrudin NA, Jeffree MS, Kaur N, Syed Abdul Rahim SS, Ibrahim MY. Diabetic retinopathy among type 2 diabetes mellitus patients in Sabah primary health clinics-Addressing the underlying factors. PLoS One. 2022;17(1):e0261249. [DOI 10.1371/journal.pone.0261249]. Erratum in: PLoS One. 2022;17(2):e0264247. [PMID: 35089931]
4. Salmon, John F. Kanski's Clinical Ophthalmology: A Systematic Approach. United Kingdom: Elsevier; 2019. p. 496–512.
5. Wang Y, Lu J, Ni J, Wang M, Shen Y, Lu W, et al. Association between glycaemia risk index (GRI) and diabetic retinopathy in type 2 diabetes: A cohort study. Diabetes Obes Metab. 2023;25(9):2457–63. [DOI: 10.1111/dom.15068] [PMID: 37353345]
6. Aday AW, Matsushita K. Epidemiology of Peripheral Artery Disease and Polyvascular Disease. Circ Res. 2021;128(12):1818–32. [DOI: 10.1161/CIRCRESAHA.121.318535] [PMID: 34110907]
7. Hur KY, Jun JE, Choi YJ, Lee YH, Kim DJ, Park SW, et al. Color Doppler Ultrasonography Is a Useful Tool for Diagnosis of Peripheral Artery Disease in Type 2 Diabetes Mellitus Patients with Ankle-Brachial Index 0.91 to 1.40. Diabetes Metab J. 2018;42(1):63–73. [DOI: 10.4093/dmj.2018.42.1.63] [PMID: 29504306]
8. Sartore G, Caprino R, Ragazzi E, Bianchi L, Lapolla A, Piarulli F. The ankle-brachial index for assessing the prevalence of peripheral artery disease and cardiovascular risk in patients with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis. 2023;33(3):560–7. [DOI: 10.1016/ j.numecd.2022.11.019] [PMID: 36646602]
9. Cherchi S, Gigante A, Spanu MA, Contini P, Mekloni G, Fois MA, et al. Sex-gender difeferences in diabetic retnopathy. Diabetology. 2020;1(1):1–10. [DOI: 10.3390/diabetology1010001]
10. Jang HN, Moon MK, Koo BK. Prevalence of Diabetic Retinopathy in Undiagnosed Diabetic Patients: A Nationwide Population-Based Study. Diabetes Metab J. 2022;46(4):620–9. [DOI: 10.4093/dmj.2021.0099] [PMID: 35193173]

11. Magri CJ, Calleja N, Buhagiar G, Fava S, Vassallo J. Ankle-brachial index in a type 2 diabetic population with proliferative retinopathy: associated risk factors and complications. Int Angiol. 2012;31(2):134–41. [PMID: 22466978]
12. Leley SP, Ciulla TA, Bhatwadekar AD. Diabetic Retinopathy in the Aging Population: A Perspective of Pathogenesis and Treatment. Clin Interv Aging. 2021;16:1367–78. [DOI: 10.2147/CIA.S297494] [PMID: 34290499]
13. Jonny, Violetta L, Kartasasmita AS, Supriyadi R, Rita C. Circulating Biomarkers to Predict Diabetic Retinopathy in Patients with Diabetic Kidney Disease. Vision (Basel). 2023;7(2):34. [DOI: 10.3390/vision7020034] [PMID: 37092467]
14. Chen YW, Wang YY, Zhao D, Yu CG, Xin Z, Cao X, et al. High prevalence of lower extremity peripheral artery disease in type 2 diabetes patients with proliferative diabetic retinopathy. PLoS One. 2015;10(3):e0122022. [DOI: 10.1371/journal.pone.0122022] [PMID: 25822410]
15. Parameswarappa DC, Rajalakshmi R, Mohamed A, Kavya S, Munirathnam H, Manayath G, et al. Severity of diabetic retinopathy and its relationship with age at onset of diabetes mellitus in India: A multicentric study. Indian J Ophthalmol. 2021;69(11):3255–61. [DOI: 10.4103/ijo.IJO_1459_21] [PMID: 34708783]
16. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1659–724. [DOI: 10.1016/S0140-6736(16)31679-8] Erratum in: Lancet. 2017;389(10064):e1. [PMID: 27733284]
17. Cai X, Chen Y, Yang W, Gao X, Han X, Ji L. The association of smoking and risk of diabetic retinopathy in patients with type 1 and type 2 diabetes: a meta-analysis. Endocrine. 2018;62(2):299–306. [DOI: 10.1007/s12020-018-1697-y] [PMID: 30128962]
18. Gillow JT, Gibson JM, Dodson PM. Hypertension and diabetic retinopathy-what is story? Br J Ophtalmol. 1999;83(9):1083–7. [DOI: 10.1136/bjo.83.9.1083] [PMID: 10460781]
19. Zhang M, Wu J, Wang Y, Wu J, Hu W, Jia H, et al. Associations between blood pressure levels and diabetic retinopathy in patients with diabetes mellitus: A population-based study. Heliyon. 2023;9(6):e16830. [DOI: 10.1016/j.heliyon.2023.e16830] [PMID: 37484372]
20. Hoogwerf BJ. Statins may increase diabetes, but benefit still outweighs risk. Cleve Clin J Med. 2023;90(1):53–62. [DOI: 10.3949/ccjm.90a.22069] [PMID: 36596598]
21. Kawasaki S, Misawa H, Tamura Y, Kondo Y, Satoh S, Hasegawa O, et al. Relationship between coronary artery disease and retinopathy in patients with type 2 diabetes mellitus. Intern Med. 2013;52(22):2483–7. [DOI: 10.2169/internalmedicine 52.9444] [PMID: 24240785]
22. Adane T, Asrie F, Getaneh Z, Getawa S. White blood cells and platelet profiles of diabetic patients at University of Gondar specialized referral hospital: A comparative cross-sectional study. J Clin Lab Anal. 2021;35(6):e23808. [DOI: 10.1002/jcla.23808] [PMID: 33938591]
23. Soyoye DO, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: A review. World J Diabetes. 2021;12(6):827–38. [DOI: 10.4239/wjd.v12.i6.827] [PMID: 34168731]
24. Wilson PWF, D'Agostino RB, Parise H, Meigs JB. The metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112(20):3066–72. [DOI: 10.1161/CIRCULATIONAHA.105.539528] [PMID: 16275870]
25. Yue T, Shi Y, Luo S, Weng J, Wu Y, Zheng X. The role of inflammation in immune system of diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Front Immunol. 2022;13:1055087. [DOI: 10.3389/fimmu.2022.1055087] [PMID: 36582230]
26. Kuroiwa DAK, Malerbi FK, Regatieri CVS. New Insights in Resistant Diabetic Macular Edema. Ophthalmologica. 2021;244(6):485–94. [DOI: 10.1159/000516614] [PMID: 34023834]

Фактори ризика периферне оклузивне артеријске болести код болесника са дијабетском ретинопатијом изазваном дијабетесом типа 2

Милош Максимовић

Универзитетски клинички центар Србије, Клиника за очне болести, Београд, Србија

САЖЕТАК

Увод/Циљ Дијабетес типа 2 је метаболичко обољење. Дијабетска ретинопатија, периферна васкуларна болест и друге компликације могу довести до лошег квалитета живота, значајног морбидитета и морталитета.

Циљ студије је анализа фактора ризика стенозантно-оклузивне болести периферних артерија код болесника са дијабетском ретинопатијом изазваном дијабетесом типа 2.

Методе Анализирали смо 63 болесника са дијабетском ретинопатијом: 33 болесника без стенозантно-оклузивне болести периферних артерија и 30 болесника са њом. Код свих болесника су испитивани демографски подаци, анамнеза, лабораторијске анализе, физикални знаци и васкуларни статус.

Резултати Болесници са оклузијом периферних артерија значајно дуже су боловали од дијабетеса (32,67 према 9,71 годину, $t = 12,834$, $p < 0,001$), чешће су били пушачи (23 : 13, $\chi^2 = 8,92$, $p < 0,05$), чешће су имали срчану исхемијску болест (24 : 10, $\chi^2 = 15,643$, $p < 0,001$), чешће су узимали статине (21 : 14; $\chi^2 = 4,84$, $p = 0,028$), имали су учесталије клаудикације (25 : 4, $\chi^2 = 32,075$, $p < 0,001$), губитак длакавости (30 : 9, $\chi^2 = 35,24$, $p < 0,001$), истањену атриофичну кожу (30 : 12, $\chi^2 = 28,64$, $p < 0,01$), улцерације прстију (10 : 1, $\chi^2 = 10,013$, $p < 0,01$). Код њих су утврђене значајно више вредности гликозираног хемоглобина (*HbA1c*) (9,31 : 7,17, $t = 5,25$, $p < 0,001$) и гликемије (11,60 : 8,20, $t = 4,913$, $p < 0,001$). Код болесника без испољених знакова оклузије периферних артерија утврђене су повишене вредности укупног (6,02 : 4,32, $t = 7,151$, $p < 0,001$) и ЛДЛ холестерола (3,64 : 2,86, $t = 3,185$, $p < 0,01$).

Закључак Код болесника са оклузијом периферних артерија испољени су фактори ризика: дужина трајања дијабетеса типа 2, пушење, повишене вредности *HbA1c*, учесталија исхемијска болест срца и нерегулисане вредности гликемије.

Кључне речи: дијабетес мелитус тип 2; дијабетска ретинопатија; периферна оклузивна артеријска болест; фактори ризика

DOI: https://doi.org/10.2298/SARH220301001L
UDC: 614.2(497.11)

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The comparison of the selected key performance indicators between the primary health care centers in Belgrade

Danica Lečić-Cvetković[1], Jovana Cvetković[1], Radmila Janičić[1], Vesna Jovanović[2], Teodora Rajković[1], Miloš Vukčević[3]

[1]University of Belgrade, Faculty of Organizational Sciences, Belgrade, Serbia;
[2]Banjica Institute for Orthopedic Surgery, Belgrade, Serbia;
[3]Mediterranean University Podgorica, Faculty of Law, Podgorica, Montenegro

SUMMARY
Introduction/Objective The purpose of the article is to analyze the efficiency of primary health care centers (PHCCs) in the city of Belgrade, using key performance indicators (KPIs).
The main objective is to present the potentiality of the application of KPIs for improving primary health care services, in order to increase efficiency.
Methods As a tool for measuring the efficiency of PHCCs in Belgrade, this article defines a set of KPIs. Based on defined KPIs, a comparative analysis of PHCCs' efficiency is conducted.
Results According to the values of the overall average efficiency rating according to all observed KPIs, the best-rated, i.e., the most efficient PHCC in Belgrade is Rakovica, and the lowest, i.e., the least efficient is the PHCC Zvezdara. It was noticed that the PHCCs Novi Beograd and Vračar are among the least efficient.
Conclusion The efficiency of primary health care can be measured by applying KPIs, and the observed results can be used as a basis for increasing the efficiency of health care services in the PHCCs in Belgrade. Based on the results, recommendations to PHCCs to improve the efficiency of health care services are: appropriate distribution of patients to selected physicians, measuring patient satisfaction, improving internal processes by engaging professional managers, increasing the ability and opportunities to apply new technologies and new knowledge, increasing the accuracy of the data used for detailed analyzes, motivate physicians to raise the level of awareness of their patients about the importance of preventive examinations.
Keywords: efficiency; health care; primary level; key performance indicators; city of Belgrade

INTRODUCTION

The health care system presents one of the most important systems in every country. This system encompasses health care infrastructure that ensures a range of programs and services and provides health protection to individuals, families, and communities [1]. They are responsible for providing patient care and health care services to societies, families, and individuals [2].

The health care system in the Republic of Serbia is one of the largest systems in the Republic of Serbia, total of 115.670 health care workers in the health care system, where 105.955 have tenure and 9.715 have non-tenure contacts [3].

According to the Euro Health Consumer Index, the health care system of the Republic of Serbia is ranked 18th out of 35 countries in Europe and has the best health care system in the region [4].

According to the Ministry of Health of the Republic of Serbia, in 2020 Belgrade had 16 primary health care centers (PHCCs) [3], with 6.750 health care workers with tenure and 621 with non-tenure contracts. The total number of employees of PHCCs is 7.371 [3]. As of June 2020, there are a total of 1.661.695 persons covered by mandatory health insurance on the territory covered by the PHCs in Belgrade [5]. Departments in PHCCs are: general medicine, preschool children pediatrics, school children pediatrics, gynecology, pediatric dentistry, dentistry [6].

Today, patients expect free choice and preferential treatment in the health care system [7]. Providing these possibilities to all patients with health care insurance in PHCCs has led to an increase in the costs of health care services. Consequently, in recent years, significant attention has been dedicated to achieving, maintaining, measuring and improving the quality of health care services in primary health care institutions [8]. The World Health Organization point out that the quality health care services should be: effective, safe, people-centered, timely, equitable, integrated and efficient [9].

In order to achieve the institution's aims and desired results, it is necessary to manage their performances [10]. Therefore, for performance measurement is essential to define a certain number of performance indicators. Also, measurement methods and referent values for the comparison of measured values of performance indicators have to be determined. Performances

Received • Примљено: March 1, 2022
Revised • Ревизија: November 1, 2023
Accepted • Прихваћено: November 28, 2023
Online first: January 9, 2024

Correspondence to:
Radmila JANIČIĆ
University of Belgrade
Faculty of Organizational Sciences
Jove Ilića 154
11000 Belgrade
Serbia
radmila.janicic@fon.bg.ac.rs

identification comprises the identification of performance indicators, measurement methods, benchmarks for comparison of results, as well as, the source and reliability of the data used [11].

According to UNI 11097, the basic characteristics of indicators are: representativeness, simplicity and ease of interpretation, capability to indicate time trends, sensitivity to changes within or outside the institution, easy data collecting and processing, ease and quick to update [12].

Key Performance Indicators (KPIs) "focus on the aspects of institution's performances that are the most critical for the current and future success of the institution" [13]. The application of KPIs in a health care institution aim to more realistically and accurately evaluate the results and determine future strategies.

Performance represents the extent to which set objectives are accomplished [14]. The concept of performance in health care services represents an instrument for bringing quality, efficiency and efficacy together [14].

Authors Smith et al. suggest that health care KPIs are a tool designed to improve health care and health system performance [15]. They can facilitate the achievement of health care policy by expressing a clear commitment to achieving specified results in a defined time period and facilitating the monitoring of progress towards achieving broader goals and objectives.

Many health care organizations have been developing KPIs for monitoring, measuring, and managing the performance of their health care systems to ensure effectiveness, efficiency, equity, and quality. Health care systems are expected to achieve and manage results in line with their established objectives and quality standards [16].

This article presents efficiency analyzes of health care services in PHCCs in Belgrade and a comparative analysis of their efficiency. The focus is on the efficiency analysis of health care services at PHCCs for three specializations: general medicine, preschool children pediatrics and gynecology. A set of defined KPIs are used to analyze the efficiency of health care services in PHCCs and their comparative analysis, according to the gathered data. The article has chosen five KPIs, based on available data, which are the most important for evaluating and measuring the efficiency of health care services in PHCCs. The criteria for choosing KPIs are [17]: feasibility (as the existence of necessary conditions and infrastructure for the KPIs measurement), relevance (as KPIs relevance for the main processes of PHCCs) and importance (importance of KPIs for the primary health care efficiency). Also, these KPIs were chosen, in order to conduct the most qualitative comparative analysis between PHCCs in Belgrade. The main objective of this article is to present the potentiality of KPIs application for improving health care services to increase the efficiency of PHCCs in Belgrade.

METHODS

The study was conducted at the end of 2021, based on official data published on the website of the Republic Fund of Health Insurance (RFHI). Data used in this study are from the first quarter of 2020, for the period from January 1st, 2020, to March 31st, 2020 [18]. In time that empirical research was done in Belgrade was 16 PHCCs. Five KPIs are defined as a tool for analyzing the efficiency are: Physician's work efficiency, Average number of first visits of registered users, Average number of issued diagnostic and therapeutic procedures, Percentage of children with three preventive examinations in the first year of life, and Percentage of obese children with status nourished. The research did not involve any human participants and the whole research was done in accordance with the ethical standards and principles of the RFHI institution.

Physician's work efficiency (PWE). The formula for the calculation of the KPI PWE is presented in (1).

$$\mathbf{PWE}=\frac{\mathbf{NVP}}{\mathbf{MAXP}}\mathbf{x\ 100\ [\%]} \qquad \mathbf{(1)}$$

Where NVP is the number of visits per physician [1], and MAXP is the maximum number of patients per physician [1].

MAXP is calculated as a quotient of the physician's total number of working minutes and the average duration of examination per patient. The aimed value of this indicator is approximately 100%.

The average number of first visits of registered patients (ANF). The formula for the calculation of the KPI ANF is presented in (2).

$$\mathbf{ANF}=\frac{\mathbf{TFV}}{\mathbf{NR}}\mathbf{\ [1]} \qquad \mathbf{(2)}$$

Where TFV is the total number of first visits to all physicians in the PHCC [1], and NR is the number of registered patients with health insurance in the PHCC [1].

The aimed value of this indicator is approximately 1 [1].

The average number of issued diagnostic and therapeutic procedures (ADTP). The physician in the PHCC can issue a diagnostic and therapeutic procedure for the primary, secondary, or tertiary level of health care. The formula for the calculation of the KPI ADTP is presented in (3).

$$\mathbf{ADTP}=\frac{\mathbf{TDTP}}{\mathbf{TNP}}\mathbf{\ [1]} \qquad \mathbf{(3)}$$

Where TDTP is the total number of issued diagnostic and therapeutic procedures in the PHCC [1], and TNP is the total number of physicians in the PHCC [1].

The aimed value of this indicator is to be as high as possible.

Percentage of children with three preventive examinations in the first year of life (PCT). This indicator applies to physicians who specialized in pediatricians. The formula for the calculation of the KPI PCT is presented in (4).

$$\mathbf{PCT}=\frac{\mathbf{NBC}}{\mathbf{CTPE}}\mathbf{x\ 100\ [\%]} \qquad \mathbf{(4)}$$

Where NBC is the number of born children in a period of one calendar year [1] and CTPE is the number of children with a minimum of three preventive examinations done in the first year of life in the observed calendar year [1].

The aimed value of this indicator is approximately 100%.

Percentage of obese children with status nourished (POC). This indicator applies to physicians who specialized in pediatricians. The formula for the calculation of the KPI POC is presented in (5).

$$\mathbf{POC} = \frac{\mathbf{NCSN}}{\mathbf{NCE66}} \mathbf{x\ 100\ [\%]} \qquad \mathbf{(5)}$$

Where NCSN is the number of children with status nourished in the PHCC [1], and NCE66 is the number of children with diagnosis code E66 (general obesity in children) in the PHCC [1].

The aimed value of this indicator is approximately 100%.

KPIs presented in this article aim to improve the quality of health care. KPI PWE - Physician's work efficiency shows the level of occupancy of the physicians and the effectiveness of their work. This KPI allows quantification and maximization of the number of patients that will be examined by physicians [19, 20, 21]. KPI ANF - the average number of first visits of registered patients shows the increase or decrease of the number of new patients examined for the first time, in the observed health care center. If the value is high or increasing, the health care center receives higher popularity among new patients, as well as higher capacity occupancy [22, 23]. KPI ADTP - the average number of issued diagnostic and therapeutic procedures shows the possible work overload or lack of work of physicians in the PHCCs. However, the more issued diagnostic and therapeutic procedures, the higher the level of competency of the health care center [24]. Measuring KPI PCT - the percentage of children with three preventive examinations in the first year of life and KPI POC - the percentage of obese children with status nourished indicates the number of children treated in the observed health care center, with an aim of preventive effect on the occurrence of children's illness and further health problems in the phases of growth and development. Also, these KPIs show the level of awareness of health care center of current children's health problems and the importance of monitoring their health, since recent studies show that the children's obesity epidemic is still in progress [25, 26].

The efficiency of health care services in PHCCs is presented in [%] and [1], depending on the KPIs (Table 1), while for the comparative analysis, values for observed KPIs have been converted in the point, using the 5-point Likert scale (Table 2).

RESULTS

Table 1 shows calculated values of KPIs defined in the previous chapter, according to the type of specialization of physicians (for general medicine, preschool children pediatrics and gynecology) in PHCCs in Belgrade. The first two defined KPIs (PWE and ANF) are applied to physicians of all three specializations. The third defined KPI (ADTP) is applied to physicians specialized in gynecology. The fourth and fifth KPIs (PCT and POC), are applied to physicians specialized in pediatrics.

Minimum and maximum values for PHCCs per observed KPIs are marked grey in Table 1. As shown in Table 1 the values of individual KPIs for some PHCCs exceed 100%. The reason is that citizens who live in Belgrade have the opportunity to choose a physician.

Based on the data shown in Table 1, i.e., obtained values for observed and defined KPIs, a comparative analysis of the efficiency of health care services in PHCCs in Belgrade is done for each KPI per each PHCC, as shown in Table 2. The values for different KPIs are not presented in the same units, and their values are in various value ranges. Therefore, values for every observed KPIs have been converted to the point using the 5-point Likert scale.

DISCUSSION

Based on data shown in Tables 1 and 2, the efficiency analysis of PHCCs was done. According to the values of KPI PWE, the analyzed efficiency of physicians in general medicine in PHCCs in Belgrade shows that PHCC Barajevo has the highest efficiency with only seven physicians in general medicine. The lowest efficiency has PHCC Zvezdara, with 52 physicians in general medicine. According to obtained data, the average efficiency of all PHCCs in Belgrade for KPI PWE for physicians in general medicine is 2.9.

According to obtained data for gynecologists, the PHCC with the highest value of KPI PWE, i.e. efficiency, is PHCC Stari Grad, while the lowest efficiency is PHCC Lazarevac. PHCC Stari Grad has three physicians, while in PHCC Lazarevac there is four physicians. PHCC Barajevo, as the most efficient in the previous analysis, by this indicator is among the PHCCs with the lowest efficiency. The average efficiency of all PHCCs in Belgrade for KPI PWE for gynecologist is 3.2.

Observing values for KPI PWE for the efficiency of pediatricians in PHCCs in Belgrade show that the least efficient is the PHCC Stari Grad, while the most efficient is PHCC Sopot. According to obtained data, the average efficiency of all PHCCs in Belgrade for KPI PWE for pediatricians is 2.8. The research done in 2022 has shown that the optimizing, professional, technological and economic environment will affect the growth of pediatric health care services efficiency [27].

The average efficiency of each PHCC is determined based on values KPI PWE according to the work efficiency of all observed physician's specializations (Table 2, column 5). Based on observed data, the conclusion is that the most efficient are PHCCs Palilula and Rakovica, while the least efficient are PHCCs Vračar and Zvezdara.

According to the observed data of KPI ANF, the lowest average number of first visits to physicians in general medicine, i.e. the lowest efficiency has PHCC Vračar, while the highest efficiency has PHCC Lazarevac. According to observed data, the average efficiency of all PHCCs for KPI ANF for the efficiency of physicians in general medicine 2.8.

Regular preventive gynecological examinations are of inestimable importance for the timely diagnosis of various diseases and sexually transmitted diseases and infections.

Table 1. The efficiency of health care services in primary health care centers (PHCCs) in Belgrade by application of key performance indicators

PHCCs	General medicine		Gynecology			Pediatrics			
	PWE [%]	ANF [1]	PWE [%]	ANF [1]	ADTP [1]	PWE [%]	ANF [1]	PCT [%]	POC [%]
PHCC- Lazarevac (with maternity ward)	82.31	1.73	69.25	0.30	255	127.28	2.31	64.16	0.00
PHCC– Barajevo	115.07	1.64	117.86	0.48	397	130.76	2.41	82.93	13.33
PHCC– Palilula	81.12	1.25	139.68	0.30	206	141.17	1.96	56.65	0.69
PHCC– Čukarica	82.18	1.16	135.93	0.37	483	114.94	1.85	72.42	0.73
PHCC– Grocka	91.72	1.25	136.51	0.50	384	109.04	1.70	64.74	6.57
PHCC– Mladenovac	101.24	1.42	121.24	0.32	529	103.87	1.56	51.21	1.37
PHCC– Novi Beograd	71.50	0.94	132.16	0.42	277	96.34	1.30	64.82	2.42
PHCC– Obrenovac	89.74	1.16	117.07	0.28	297	103.25	1.57	74.96	0.88
PHCC– Rakovica	81.24	1.08	153.13	0.48	577	121.40	1.81	70.59	43.73
PHCC- Savski Venac	95.05	1.01	161.41	0.28	426	110.94	1.28	50.68	3.70
PHCC– Sopot	88.05	1.14	91.74	0.43	448	142.52	3.02	78.91	22.22
PHCC– Stari Grad	83.39	0.90	176.31	0.37	384	89.25	1.23	65.56	1.71
PHCC- Voždovac	74.60	1.13	119.68	0.42	276	124.59	1.92	73.14	34.54
PHCC– Vračar	66.03	0.75	135.85	0.41	199	96.89	1.55	64.24	33.78
PHCC– Zemun	80.55	1.05	148.09	0.40	386	117.24	1.45	41.79	1.91
PHCC- Zvezdara	63.67	1.03	124.78	0.36	484	93.48	1.40	54.55	15.84

PWE – physician's work efficacy; ANF – average number of first visits of registered patients; ADTP – average number of issued diagnostic and therapeutic procedures; PCT – percentage of children with three preventive examinations in the first year of life; POC – percentage of obese children with status nourished

Table 2. Comparative analysis of efficiency of health care services in primary health care centers (PHCCs)in Belgrade by application of key performance indicators

PHCCs	PWE				ANF				ADTP	PCT	POC	Total average
	General medicine	Gynecology	Pediatrics	Average	General medicine	Gynecology	Pediatrics	Average	Gynecology	Pediatrics	Pediatrics	
PHCC– Lazarevac (with maternity ward)	3	1	4	**2.67**	5	1	5	**3.67**	2	2	1	**2.67**
PHCC– Barajevo	5	2	4	**3.67**	5	5	5	**5**	3	4	2	**3.89**
PHCC– Palilula	3	5	5	**4**	3	1	4	**2.67**	2	1	1	**2.78**
PHCC– Čukarica	3	3	3	**3**	3	2	4	**3**	4	3	1	**2.89**
PHCC– Grocka	4	4	2	**3.33**	3	5	3	**3.67**	3	2	1	**3**
PHCC– Mladenovac	5	3	2	**3.33**	4	2	2	**2.67**	5	1	1	**2.78**
PHCC– Novi Beograd	2	3	1	**2**	2	4	1	**2.33**	2	2	1	**2**
PHCC– Obrenovac	3	2	2	**2.33**	3	1	2	**2**	2	3	1	**2.11**
PHCC– Rakovica	3	5	4	**4**	2	5	4	**3.67**	5	3	5	**4**
PHCC- Savski Venac	4	5	2	**3.67**	2	2	1	**1.67**	4	1	1	**2.44**
PHCC– Sopot	3	1	5	**3**	3	4	5	**4**	4	3	3	**3.4**
PHCC– Stari Grad	3	5	1	**3**	1	2	1	**1.33**	3	2	1	**2.11**
PHCC– Voždovac	2	2	4	**2.67**	3	4	4	**3.67**	2	3	4	**3.11**
PHCC– Vračar	1	3	1	**1.67**	1	4	2	**2.33**	1	2	4	**2**
PHCC– Zemun	2	4	3	**3**	2	3	2	**2.33**	3	1	1	**2.33**
PHCC– Zvezdara	1	3	1	**1.67**	2	2	1	**1.67**	4	1	2	**1.89**
Mean value	**2.9**	**3.2**	**2.8**	**2.94**	**2.8**	**2.9**	**2.9**	**2.86**	**3.1**	**2.1**	**1.9**	**2.71**

PWE – physician's work efficacy; ANF – average number of first visits of registered patients; ADTP – average number of issued diagnostic and therapeutic procedures; PCT – percentage of children with three preventive examinations in the first year of life; POC – percentage of obese children with status nourished

Data from the health care survey of the population of Serbia show that preventive examinations for early detection of these diseases (Papanikolau test) are efficient 57.1%. Of all performed preventive examinations, 72.5% are done in Belgrade, while among the inhabitants of Šumadija and Western Serbia, it is 48.9% [28].

Based on the analyzes conducted in this study and based on the observed values of KPI ANF, it can be concluded that gynecology is the most visited in PHCC Grocka, i.e., this PHCC is the most efficient by this indicator. PHCCs Obrenovac and Savski Venac have the lowest efficiency. Based on observed data, the average efficiency of all PHCCs for KPI ANF for gynecologist is 2.9.

The average number of first visits to the pediatricians is higher than the average number of first visits to the physicians of other specializations. Based on observed data and performed an analysis of values of KPI ANF, it can be concluded that in the analyzed period, the highest number of

visits to pediatricians, i.e., the highest efficiency has PHCC Sopot, while the lowest efficiency has PHCC Stari Grad. According to observed data, the average efficiency of all PHCCs for KPI ANF for pediatricians is 2.9.

For every PHCC is calculated average values based on KPI ANF, based on the work efficiency of all observed specializations (Table 2, column 9). According to that indicator, the highest efficiency has PHCC Barajevo, while the lowest has PHCC Stari Grad.

Efficiency is analyzed based on the observed values of KPI ADTP for gynecologists for all PHCCs in Belgrade. PHCC Rakovica has the highest number of issued diagnostic and therapeutic procedures, i.e., it is the most efficient, while PHCC Vračar has the lowest efficiency. According to observed data, the average efficiency of all PHCCs for KPI ADTP for gynecologists is 3.1.

PHCCs' efficiency is further analyzed by the percentage of children with three preventive examinations in the first year of life – KPI PCT. Preventive examinations, during the first year of life, are of significant importance. Position of the spine and hips, vaccines, weight and others, indicate the development of the child in its first year of life. Observed data show that the values of this KPI did not exceed 83% in any PHCC. In preventive health care examinations of children up to one year of age, the most efficient is PHCC Barajevo, while the least efficient is PHCC Zemun. According to observed data, the average efficiency of all PHCCs for KPI PCT for pediatricians is 2.1.

In the last three decades, obesity in children has been on the rise, which has numerous health consequences [29]. Data from population health research of the Republic of Serbia conducted in the year 2013 show that 28.2% of children and adolescents aged from 7 to 14 years were overweight and obese, of which 14.5% of children were overweight and 13.7% were obese [30]. The same research shows that during the last 13 years, the prevalence of obesity has increased from 4.4% to 13.7%, and of overweight from 8.2% to 14.5%) [29]. Another research shows that obesity is also associated with flat feet. Children with flat feet had a significantly higher body mass index (BMI) than children without flat feet [30].

The indicator KPI POC was used in the analysis of pediatricians work efficiency. Based on the observed data, it can be concluded that the highest enrollment status of obesity, i.e., the highest efficiency has PHCC Rakovica, while the lowest efficiency has PHCC Lazarevac, with 0%. According to observed data, the average efficiency of all PHCCs for KPI POC for pediatricians is 1.9.

CONCLUSION

Previously analysis presents that it is recommend to do the overall average efficiency rating of all PHCCs in Belgrade by observing all five defined KPIs. Based on values of the total average efficiency for all observed KPIs, PHCC Rakovica is the most efficient PHCC in Belgrade, while the least efficient is PHCC Zvezdara. PHCCs Novi Beograd and Vračar are among the least efficient. Even, PHCC Rakovica has half fewer employees than other PHCCs, the percentage of selected physicians differs only by 5%. All observed KPIs present that the average efficiency of all PHCCs in Belgrade is 2.71. Since the observed scale is from one (minimum) to five (maximum), it can be concluded that the efficiency level of PHCCs in the capital of the Republic of Serbia is not at a satisfactory level.

Based on all previously shown data and analyses done in this article, the conclusion is that PHCCs in Belgrade have to improve and increase health care efficiency. The recommendations for improvement are:

– Appropriate distribution of patients to the selected physicians. Patients of health care services in PHCCs could choose their physicians. Managers of PHCCs could better organize the appropriate distribution of patients to the selected physicians;

– Improvement of internal processes by engaging professional managers, applying modern knowledge and innovative technologies to improve treatments approaches;

– Increase of data accuracy and data analysis continuation used for efficiency of health care services. By continuing analysis of the data, PHCCs could improve their efficiency;

– Physicians' motivation to raise patients' awareness of the importance of preventive examinations. Increasing the population's awareness of the importance of preventive examinations can improve the efficiency of PHCCs and the population's health.

By applying defined KPIs, presented efficiency analyses can be used for all health care institutions in the Republic of Serbia.

Conflict of interest: None declared.

REFERENCES

1. Jovanović S, Milovanović S, Mandić J, Jovović S. Sistemi zdravstvene zaštite. Engrami. 2015:37(1):75–82. [DOI: 10.5937/engrami1501075J]
2. World Health Organization. The world health report 2000: health systems: improving performance. Switzerland: World Health Organization.
3. batut.org.rs [Internet]. Serbia: Institute of Public Health of Serbia "Dr Milan Jovanovic Batut"; c2021 [cited 2021 Jan 10]. Available from: https://www.batut.org.rs/download/izvestaji/zaposleni_plan_mreze_2018_12_31.xls.
4. zdravlje.gov.rs [Internet]. Serbia: Ministry of Health of the Republic of Serbia; c2021 [cited 2021 Jan 10]. Available from: https://www.zdravlje.gov.rs/vest/335491/zdravstveni-sistem-srbije-najbolji-u-regionu-srbija-18-u-evropi-na-ehci-listi-za-2018-godinu.php.
5. rfzo.rs [Internet]. Serbia: Republic Fund of Health Insurance; c2021 [cited 2021 Nov 19]. Available from: https://www.rfzo.rs/download/ril/brreg_pofilijalama.pdf.
6. rfzo.rs [Internet]. Serbia: Republic Fund of Health Insurance; c2021 [cited 2021 Nov 19]. Available from: https://www.rfzo.rs/download/kapitacija/registracija/9.RIL%20-%20Broj%20izjava%20po%20oblastima%20rada.xls.

7. Guy M. Competition policy in Bismarck and Beveridge healthcare systems: Competition law, merger control and the relationship between competition authority and sectoral regulator in Dutch and English healthcare. Doctoral dissertation, University of East Anglia; 2016.
8. helsetilsynet.no [Internet]. Norway: Norwegian Board of Health Report Series: Report 8/2002; c2021 [cited 2021 Sep 03]. Available from: https://www.helsetilsynet.no/globalassets/opplastinger/Publikasjoner/Rapporter2002/quality_health_care_role_government_supervision_monitoring_norway_rapport_082002.pdf/.
9. who.int [Internet]. Switzerland: World Health Organization; c2021 [cited 2021 Aug 22]. Available from: https://www.who.int/news-room/fact-sheets/detail/quality-health-services.
10. Atanasov N. Model za izbor adekvatnog skupa indikatora performansi u upravljanju proizvodnjom [dissertation]. Faculty of Organizational Sciences; 2016.
11. Rajković T, Đorđević Milutinović L, Lečić-Cvetković D. Spreadsheet Model for Determining Adequate Performance Indicators of Production Management. Management: Journal of Sustainable Business and Management Solutions in Emerging Economies. 2020;25(3):13–22. [DOI: 10.7595/management.fon.2020.0011]
12. Franceschini F, Galetto M, Maisano D. Management by measurement: Designing key indicators and performance measurement systems. Berlin: Springer Science & Business Media; 2007. [DOI: 10.1007/978-3-540-73212-9]
13. Parmenter D. Key performance indicators: developing, implementing, and using winning KPIs. 4th ed. New Jersey: John Wiley & Sons; 2020.
14. Ioan B, Nestian AS, Tiță SM. Relevance of Key Performance Indicators (KPIs) in a Hospital Performance Management Model. Journal of Eastern Europe Research in Business & Economics. 2012:1–15. [DOI: 10.5171/2012.674169]
15. Smith PC, Mossialos E, Papanicolas I, Leatherman S. Health Policy and Performance Measurement. In: Performance Measurement for Health System Improvement: Experiences, Challenges and Prospects, Part V. Cambridge: Cambrige University Press; 2009. p. 509–672.
16. Arah OA, Klazinga NS, Delnoij DM, ten Asbroek AH, Custers T. Conceptual frameworks for health systems performance: a quest for effectiveness, quality, and improvement. Int J Qual Health Care. 2003;15(5):377–98. [DOI: 10.1093/intqhc/mzg049] [PMID: 14527982] Erratum in: Int J Qual Health Care. 2004;16(2):189.
17. Abdel-Razik MSM, Rizk HI, Zein MM, Abdel-Megeid SMES, Abd El Fatah SAM. Promoting the culture of key performance indicators (KPIs) among primary health care staff at health district level: An intervention study. Eval Program Plann. 2023;96:102188. [DOI: 10.1016/j.evalprogplan.2022.102188] [PMID: 36442267]
18. rfzo.rs [Internet]. Serbia: Republic Fund of Health Insurance; c2021 [cited 2021 Dec 20]. Available from: https://rfzo.rs/index.php/davaocizdrusluga/kapitacija-actual-16.
19. Poissant L, Pereira J, Tamblyn R, Kawasumi Y. The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. J Am Med Inform Assoc. 2005;12(5):505–16. [DOI: 10.1197/jamia.M1700] [PMID: 15905487]
20. Prgomet M, Georgiou A, Westbrook JI. The impact of mobile handheld technology on hospital physicians' work practices and patient care: a systematic review. J Am Med Inform Assoc. 2009;16(6):792–801. [DOI: 10.1197/jamia.M3215] [PMID: 19717793]
21. Tipping MD, Forth VE, Magill DB, Englert K, Williams MV. Systematic review of time studies evaluating physicians in the hospital setting. J Hosp Med. 2010;5(6):353–9. [DOI: 10.1002/jhm.647] [PMID: 20803675]
22. Henrique DB, Filho MG, Marodin G, Jabbour ABLDS, Chiappetta Jabbour CJ. A framework to assess sustaining continuous improvement in lean healthcare. International Journal of Production Research. 2021:59(10):2885–904. [DOI: 10.1080/00207543.2020.1743892]
23. Mundinger MO, Kane RL, Lenz ER, Totten AM, Tsai WY, Cleary PD, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. JAMA. 2000;283(1):59–68. [DOI: 10.1001/jama.283.1.59] [PMID: 10632281]. Erratum in: JAMA. 2022;327(2):185.
24. Murphy A, Wakai A, Walsh C, Cummins F, O'Sullivan R. Development of key performance indicators for prehospital emergency care. Emerg Med J. 2016;33(4):286–92. [DOI: 10.1136/emermed-2015-204793] [PMID: 26796739]
25. Grøn S, Loblay V, Conte KP, Green A, Innes-Hughes C, Milat A, et al. Key Performance Indicators for program scale-up and divergent practice styles: a study from NSW, Australia. Health Promot Int. 2020;35(6):1415–26. [DOI: 10.1093/heapro/daaa001] [PMID: 32105325]
26. MacMillan HL; Canadian Task Force on Preventive Health Care. Preventive health care, 2000 update: prevention of child maltreatment. CMAJ. 2000;163(11):1451–8. [PMID: 11192650]
27. Liu H, Wu W, Yao P. A study on the efficiency of pediatric healthcare services and its influencing factors in China – estimation of a three-stage DEA model based on provincial-level data. Socio-Economic Planning Sciences. 2022:84:101315. [DOI: 10.1016/j.seps.2022.101315]
28. batut.org.rs [Internet]. Serbia: Institute of Public Health of Serbia "Dr Milan Jovanovic Batut"; c2021 [cited 2021 Aug 21]. Available from: http://www.batut.org.rs/download/aktuelno/rgm2019/Podaci%20istrazivanje%20zdravlja%20stanovnistva%20Srbije.docx.
29. Šušnjević S, Milijašević D, Marić D, Nićiforović-Šurković O, Mijatović-Jovanović V, Ukropina S. Association between flat foot prevalence and nutritional status in schoolchildren. Srp Arh Celok Lek. 2022:150(1–2):59–63. [DOI: 10.2298/SARH210426091S]
30. Jocić Stojanović J, Veković V, Zorica Živković Z, Prijić A. Gojaznost kod dece – prevencija. Journal of the Association of Preventive Pediatrics of Serbia. 2016:2(1–2):17–20. (Serbian)

Поређење одабраних кључних индикатора перформанси примарне здравствене заштите у домовима здравља у Београду

Даница Лечић-Цветковић[1], Јована Цветковић[1], Радмила Јаничић[1], Весна Јовановић[2], Теодора Рајковић[1], Милош Вукчевић[3]

[1]Универзитет у Београду, Факултет организационих наука, Београд, Србија;
[2]Институт за ортопедију „Бањица“, Београд, Србија;
[3]Универзитет „Медитеран“, Правни факултет, Подгорица, Црна Гора

САЖЕТАК

Увод/Циљ Сврха рада је упоредна анализа ефикасности примарне здравствене заштите у домовима здравља на територији града Београда применом кључних индикатора перформанси.

Циљ рада је да се прикаже могућност унапређења здравствених услуга и повећања њихове ефикасности применом кључних индикатора перформанси.

Методе Као алат за мерење ефикасности примарне здравствене заштите у домовима здравља на територији града Београда у раду је дефинисан скуп кључних индикатора перформанси. Затим, на основу вредности дефинисаних помоћу њих, извршена је упоредна анализа ефикасности посматраних домова здравља.

Резултати На основу добијене укупне просечне оцене ефикасности по свим посматраним кључним индикаторима перформанси, најбоље оцењени, односно најефикаснији Дом здравља на територији града Београда је „Раковица“, док је најлошије оцењен, односно најмање ефикасан Дом здравља „Звездара“. Закључено је да су домови здравља „Нови Београд“ и „Врачар“ међу најмање ефикасним.

Закључак Ефикасност примарне здравствене заштите се може мерити применом кључних индикатора перформанси, а добијени резултати се могу користити као основа за повећање ефикасности пружања услуга здравствене заштите домова здравља града Београда. На основу добијених резултата, препоруке домовима здравља за унапређење ефикасности здравствених услуга су равномерна расподела пацијената према одабраним лекарима, мерење задовољства пацијената, унапређење интерних процеса ангажовањем професионалних менаџера, повећање могућности и прилика за примену нових технологија и нових знања, повећање тачности података који се користе за детаљне анализе, мотивисаност лекара да унапређују ниво свести код својих болесника о значају превентивних прегледа.

Кључне речи: ефикасност; здравство; примарни ниво; кључни индикатори перформанси; Београд

DOI: https://doi.org/10.2298/SARH230508109F
UDC: 616.1-006.03

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A very rare cutaneous epithelioid hemangioendothelioma in the right auricle in a male adult

Milan Filipović[1,2], Tatjana Filipović[1], Nebojša Videnović[1,2], Zlatan Elek[1,3], Aleksandar Božović[1,3]

[1]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Kosovska Mitrovica, Serbia;
[2]Priština Clinical Hospital Center – Gračanica, Gračanica, Serbia;
[3]Kosovska Mitrovica Clinical Hospital Center, Kosovska Mitrovica, Serbia

SUMMARY
Introduction Epithelioid hemangioendothelioma is an extremely rare tumor of vascular origin, which mainly affects soft tissues and, in rare cases, also affects the skin.
Case outline A 71-year-old man came for an examination due to a tumor localized on the antihelix of the right ear. A radical excision of the tumor and reconstruction of the defect with a preauricular transposition tunnelized Banner flap was performed.
Conclusion Epithelial hemangioendothelioma of the skin is an extremely rare, vascular tumor. It is characterized by local aggression, the appearance of local recurrences and metastatic hematogenous and lymphogenic spread. Standard dermoscopic examination of this tumor is not important. The appearance of the tumor itself has no clinical specificity, and most often resembles nodular basal cell carcinoma. An early visit to the doctor and removing the change early are the key to success in treating this tumor. So far, no case has been reported that is localized on the antihelix of the ear. Radical surgical excision is the therapy of choice.
Keywords: epithelioid hemangioendothelioma; vascular neoplasm; auricle

INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is a vascular tumor of endothelial cell origin. EHE is extremely rare, with an incidence of 1:1,000,000 [1], and the literature is limited to case reports and several retrospective studies. It most commonly occurs in the lungs, liver, and bones, but can also occur in the skin [2]. EHE was first described by Weiss and Enzinger in 1982 as a soft tissue tumor [3]. Clinically, the neoplasm usually presents as a slightly raised, erythematous, sometimes painful dermal nodule.

According to the World Health Organization classification from 2020, EHE is a tumor that is locally aggressive, with metastatic potential [4]. The rate of local recurrence of EHE is 10–15%, and the level of lymphatic and systemic metastases is 20–30% [5]. Pathohistological analysis is the gold standard for definitive diagnosis, where tumor cells are CD31-, CD34-, FLI-1-, and ERG-positive [1]. The main treatment for local changes is surgical removal. Chemotherapy and radiotherapy have not been shown to be effective due to slow tumor growth [6]. The prognosis of surgically treated local changes is good, with a five-year survival rate of 75.3% [7].

CASE REPORT

This case demonstrates a rare neoplasm which unusually presented as a cutaneous lesion. The location of the lesion on the ear is a challenging area for the surgeon to reconstruct. Local flaps, preauricular transposition tunnelized flap in this case, provide adequate reconstruction and are cosmetically acceptable. EHE requires aggressive management, given its potential to metastasize to lymph nodes, and it requires continued surveillance after treatment. It is important to consider alternative histological diagnoses in patients presenting with cutaneous lesions and how this affects management and prognosis.

A seventy-one-year-old patient was admitted to the surgery department of the Priština Clinical Hospital Center– Gračanica, due to a tumor localized on the antihelix of the right ear. On physical examination, in the area of the antihelix of the right ear, there was a nodule measuring 0.5 × 0.5 cm, above the level of the skin, with clearly defined edges, firm consistency, immobile in relation to the surface (Figure 1).

The anamnestic patient states that he noticed the change four months before and that it increased rapidly. Upon admission to our institution, the patient was in good general condition, with normal laboratory findings, conscious, oriented, normocardic, eupneic. A radical excision of the tumor was performed under local anesthesia. The reconstruction of the resulting defect was performed using a preauricular transposition flap (Banner flap) tunnelized through a cartilaginous fistula created at the helical crus. The flap was deepithelialized

Received • Примљено: May 8, 2023
Revised • Ревизија: November 13, 2023
Accepted • Прихваћено: November 17, 2023
Online first: November 21, 2023

Correspondence to:
Aleksandar BOŽOVIĆ
University of Priština – Kosovska Mitrovica
Faculty of Medicine
Department of Surgery
Anri Dinana b.b.
38220 Kosovska Mitrovica, Serbia
aleksandar.bozovic@med.pr.ac.rs

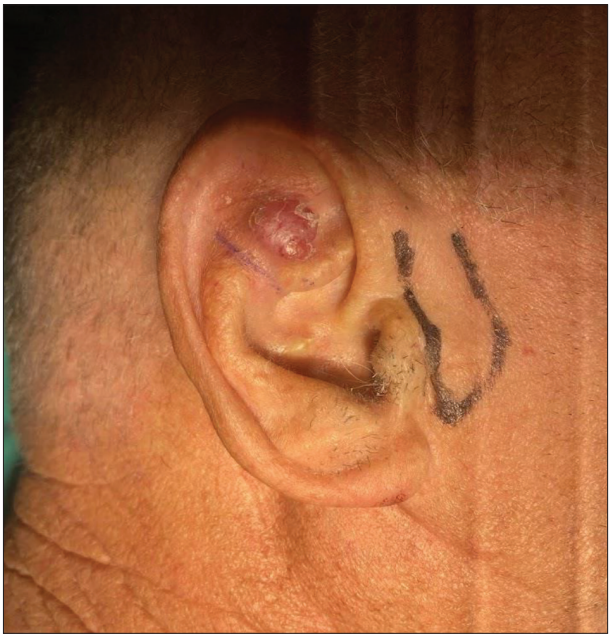


Figure 1. Appearance of the tumor preoperatively

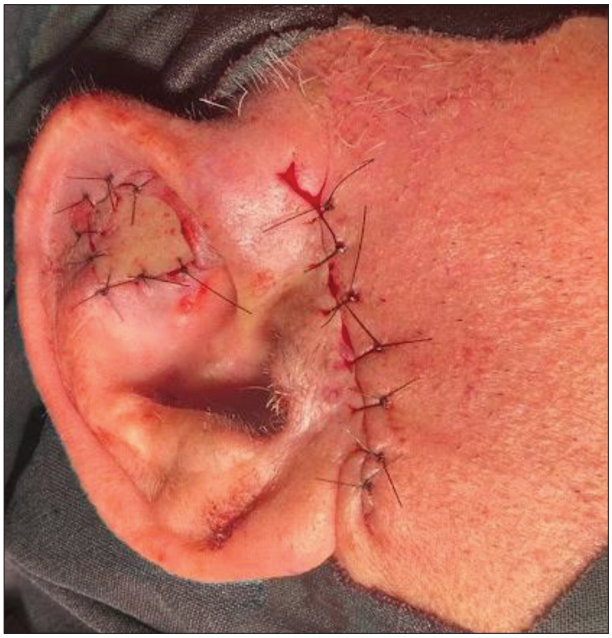


Figure 2. Appearance at the end of the operation

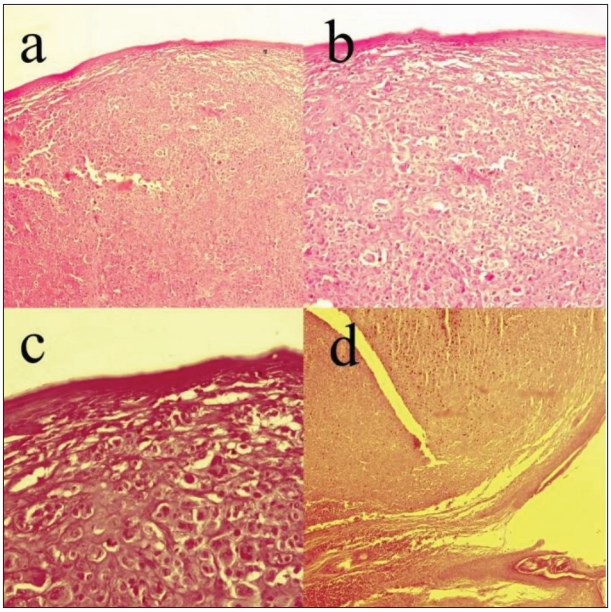


Figure 3. Histopathological findings at different magnifications show: a – 10 × 0.25; b – 10 × 0.35; c – 10 × 0.40 [non-encapsulated tumor nodule built of epithelioid cells, more abundant eosinophilic cytoplasm, round-oval nucleus with noticeable nucleolus and rare mitoses (2–3 mitoses/mm2), scattered multinuclear cells and small foci of lymphocytic infiltrates, and focal, more pronounced superficial, hyalinized stroma between tumor cells]; and d – 4 × 0.25 (the ratio of tumor tissue to healthy tissue)

at its base to allow the closure in a single step. The donor site was primarily closed (Figure 2).

In the pathohistology laboratory, pathohistological and immunohistochemical analysis of the tumor change was performed.

Histopathological findings were as follows (Figure 3):

- separated from the epidermis by a narrow free zone, limited, non-encapsulated tumor nodule built of epithelioid cells, more abundant eosinophilic cytoplasm, round-oval nucleus with noticeable nucleolus and rare mitoses (2–3 mitoses/mm^2);
- scattered multinuclear cells and small foci of lymphocytic infiltrates;
- focal, more pronounced superficial, hyalinized stroma between tumor cells.

Immunohistochemical findings were as follows:

- PRAME: + (paler coloring);
- CD34: -;
- BAP1: +;
- ERG: + (Figure 4);
- CD68: - (rare scattered single cells +);
- FLI-1: +;
- CD10: diffuse +;
- Ki-67: about 20%;
- CD31: -;
- maximum tumor thickness: 4.3 mm;
- minimum distance from the resection line in depth: 0.2 mm.

After the early postoperative period, which passed uneventfully, the patient came for regular follow-up check-ups at one, three, six, and 12 months postoperatively (Figure 5).

At each examination, clinical, laboratory, and ultrasound evaluations were performed in order to confirm the occurrence of possible metastatic changes. After a one-year follow-up, which is without clinical manifestations of disease recurrence, we will continue the follow-up in the next four-year period.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

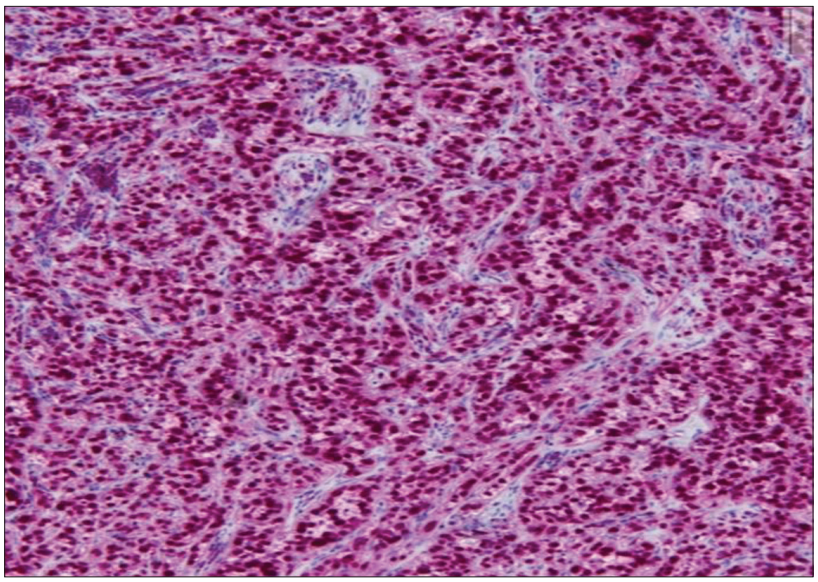


Figure 4. Positive nuclear ERG expression in tumor cells (10 × 0.25)

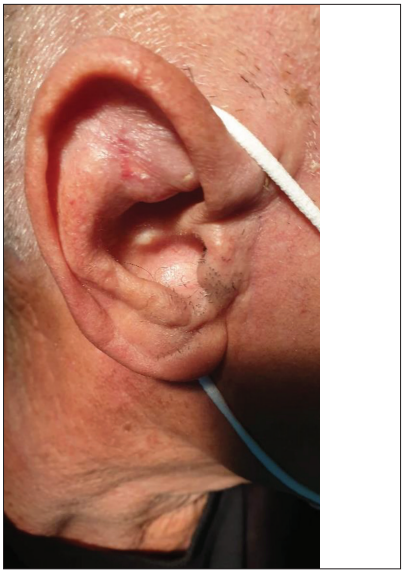


Figure 5. Postoperative appearance after six months

DISCUSSION

Cutaneous EHE is most common in adults, both men and women, but there are several cases where cutaneous EHE has been described in children [8]. According to the World Health Organization, EHE is a malignant tumor with a metastasis incidence of 20–30% and a mortality of 10–20% [4]. Deyrup et al. [9], in 2008, analyzed a series of 49 EHE subjects and concluded that large tumors (> 3 cm in diameter) with high mitotic activity (more than 3 mitoses) have a more aggressive clinical course. In our case, the mitotic activity of the tumor was low, as well as the diameter of the tumor itself, which indicates that it was a tumor with a low risk of local recurrence and systemic metastasis. According to the literature, the clinical findings of EHE vary from dermal or subcutaneous nodules, through non-healing ulcers, to small multiple red papules [10, 11].

Pathohistologically, tumor cells with eosinophilic cytoplasm, organized in hyaline or mucoid stroma, are present in EHE [12]. A large number of endothelial proteins may be useful in the diagnosis of EHE. FLI-1 protein shows greater sensitivity and specificity in the diagnosis of EHE than CD-31 and CD-34. CD-34 is positive in more than 90% of vascular tumors, so this marker has low specificity because it occurs in a large number of soft tissue tumors [13]. Based on research in 2000, Miettinen et al. [14] showed that the ERG transcription factor is a tumor marker that occurs in 42 of 43 cases of EHE (Figure 6). Based on the analysis of Flucke et al. [15], all 39 of their subjects with EHE tested for ERG were positive, as were all five tested for FLI-1.

EHE is an extremely rare tumor of vascular origin. It is characterized by local aggression, local recurrences and metastatic, hematogenous and lymphogenic spread. Standard dermoscopic examination of this tumor is unimportant. The appearance of the tumor itself has no clinical specificity, and most often resembles nodular basal cell carcinoma. Going to the doctor early and removing the change early are the key to success in treating this tumor. Radical surgical excision is the therapy of choice. There are various surgical procedures described for the reconstruction of the anterior auricle, including local flaps, skin grafts and even healing by secondary intention. The authors consider the tunnelized preauricular transposition flap a good option especially when compared to interpolated flaps, since it allows a reconstruction in a single surgical step with decreased morbidity and favorable cosmetic results.

Conflict of interest: None declared.

REFERENCES

1. Stacchiotti S, Miah AB, Frezza AM, Messiou C, Morosi C, Caraceni A, et al. Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. ESMO Open. 2021;6(3):100170. [DOI: 10.1016/j.esmoop.2021.100170] [PMID: 34090171]
2. Mc Collum JK, Al-Rohill R. Cutaneous Vascular Neoplasms of Uncertain Biological Behavior. Biology (Basel) 2021;10(11):1160. [DOI: 10.3390/biology10111160] [PMID: 34827153]
3. Chaouki A, Mkhatri A, Ballage A, Zouhair N, Mahtar M. Extensive epithelioid hemangioendothelioma of the maxillary sinus: A case report. Int J Surg Case Rep. 2019;58:70–3. [DOI: 10.1016/j.ijscr.2019.04.013] [PMID: 31015076]
4. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. Pathologica. 2021;113(2):70–84. [DOI: 10.32074/1591-951X-213] [PMID: 33179614]
5. Chen L, Han F, Yang J, Huang B, Liu H. Primary epithelioid hemangioendothelioma of the eyelid: A case report. Oncol Lett. 2022;24(5):398. [DOI: 10.3892/ol.2022.13518] [PMID: 36276489]
6. Hickman AD, Bezerra ED, Roden AC, Houdek MT, Barlow JD, Robinson SI, et al. An unusual case of aggressive malignant spread of epithelioid hemangioendothelioma. Rare Tumors. 2021;13:20363613211010858. [DOI: 10.1177/20363613211010858] [PMID: 33959241]
7. Wu X, Li B, Zheng C, Hong T, He X. Clinical characteristics of epithelioid hemangioendothelioma: a single-center retrospective study. Eur J Med Res. 2019;24(1):16. [DOI: 10.1186/s40001-019-0375-8] [PMID: 30819247]
8. Bannoura S, Putra J. Primary malignant vascular tumors of the liver in children: Angiosarcoma and epithelioid hemangioendothelioma. World J Gastrointest Oncol. 2021;13(4):223–30. [DOI: 10.4251/wjgo.v13.i4.223] [PMID: 33889274]
9. Deyrup AT, Tighiouart M, Montag AG, Weiss SW. Epithelioid hemangioendothelioma of soft tissue: a proposal for risk stratification based on 49 cases. Am J Surg Pathol. 2008;32(6):924–7. [DOI: 10.1097/pas.0b013e31815bf8e6] [PMID: 18551749]
10. Senaratne R, Casey MC, Kelly JL. Malignant epithelioid hemangioendothelioma of the ear. J Surg Case Rep. 2022;2022(3):rjac062. [DOI: 10.1093/jscr/rjac062] Erratum in: J Surg Case Rep. 2022;2022(5):rjac207. [PMID: 35280049]
11. Witte S, Weidema M, Kaal S, Versleijen-Jonkers Y, Flucke U, van der Graaf W, et al. The heterogeneity of Epithelioid Hemangioendothelioma (EHE): A case series and review of the literature with emphasis on treatment options. Semin Oncol. 2021;48(2):111–8. [DOI: 10.1053/j.seminoncol.2021.04.002] [PMID: 34176654]
12. Mansfield SA, Williams RF, Iacobas I. Vascular tumors. Semin Pediatr Surg. 2020;29(5):150975. [DOI: 10.1016/j.sempedsurg.2020.150975] [PMID: 33069294]
13. Tansir G, Rastogi S, Barwad A, Yadav R, Shamim SA, Dhamija E, et al. Management and outcomes of advanced hemangioendothelioma at a medical oncology clinic in an Indian tertiary care center. Future Sci OA. 2023;8(10):FSO827. [DOI: 10.2144/fsoa-2021-0132] [PMID: 36874373]
14. Miettinen M, Wang ZF, Paetau A, Tan SH, Dobi A, Srivastava S, et al. ERG transcription factor as an immunohistochemical marker for vascular endothelial tumors and prostatic carcinoma. Am J Surg Pathol. 2011;35(3):432–41. [DOI: 10.1097/PAS.0b013e318206b67b] [PMID: 21317715]
15. Flucke U, Vogels RJ, de Saint Aubain Somerhausen N, Creytens DH, Riedl RG, van Gorp JM, et al. Epithelioid Hemangioendothelioma: clinicopathologic, immunhistochemical, and molecular genetic analysis of 39 cases. Diagn Pathol. 2014;9:131. [DOI: 10.1186/1746-1596-9-131] [PMID: 24986479]

Веома редак кожни епителоидни хемангиоендотелиом десне ушне шкољке код одраслог човека

Милан Филиповић[1,2], Татјана Филиповић[1], Небојша Виденовић[1,2], Златан Елек[1,3], Александар Божовић[1,3]

[1]Универзитет у Приштини – Косовска Митровица, Медицински факултет, Косовска Митровица, Србија;
[2]Клиничко-болнички центар „Приштина“ – Грачаница, Грачаница, Србија;
[3]Клиничко-болнички центар „Косовска Митровица“, Косовска Митровица, Србија

САЖЕТАК

Увод Епителоидни хемангиоендотелиом је изузетно редак тумор васкуларног порекла, који углавном захвата мека ткива, а у ретким случајевима захвата и кожу.

Приказ болесника Приказан је мушкарац старости 71 годину, који долази на преглед због туморске промене локализоване на антихеликсу десне ушне шкољке. Болеснику је урађена радикална ексцизија тумора и реконструкција транспозиционим тунелизованим Банеровим флапом.

Закључак Епителоидни хемангиоендотелиом коже представља изузетно редак тумор васкуларног порекла. Карактерише се локалном агресивношћу, појавом локалних рецидива и метастатским хематогеним и лимфогеним ширењем. Стандардни дермоскопски преглед овог тумора није од значаја. Изглед саме туморске промене клинички нема специфичности и најчешће подсећа на нодуларни базоцелуларни карцином. Рани одлазак код лекара и рано уклањање промене су кључ успеха у лечењу овог тумора. До сада није објављен ниједан случај који је локализован на антихеликсу ушне шкољке. Радикална хируршка ексцизија је терапија избора.

Кључне речи: епителоидни хемангиоендотелиом; васкуларна неоплазма; ушна шкољка

DOI: https://doi.org/10.2298/SARH231018005G
UDC: 616.713-006.3

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Radical resection and reconstruction of a large sternal chondrosarcoma

Željko Garabinović[1,2], Milan Savić[1,2], Nikola Čolić[3], Milan Stojičić[2,4], Slaviša Zagorac[2,5]

[1]University Clinical Center of Serbia, Clinic for Thoracic Surgery, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Center for Radiology and Magnetic Resonance Imaging, Belgrade, Serbia;
[4]University Clinical Center of Serbia, Clinic for Burns, Plastic and Reconstructive Surgery, Belgrade, Serbia;
[5]University Clinical Center of Serbia, Orthopedic and Traumatology Clinic, Belgrade, Serbia

SUMMARY

Introduction Primary malignant tumors of the sternum are rare, with chondrosarcoma being the most common primary malignant tumor of the chest. The gold standard in treatment is surgical treatment with wide resection margins, where the rigidity of the chest wall must be ensured, with protection of internal organs with satisfactory lung function.

Case outline We present a 67-year-old patient in whom previous computed tomography and magnetic resonance imaging examinations confirmed a tumor mass involving the sternum with the associated ribs, with involvement of the soft tissues above. First, sternum resection was performed with partial resection of the associated ribs and soft tissues. Reconstruction and stabilization of the chest wall were achieved with two layers of polypropylene mesh and methyl methacrylate bone cement with antibiotics. We reconstructed the primary soft tissue defect with a combination of a large local fasciocutaneous flap raised from the abdomen and a smaller sliding flap from the chest. The secondary defect was reconstructed by wide undermining of the skin in the area of the anterior abdominal wall and a small Thiersch-type free skin graft. In the postoperative period, the flaps were vital, but there was necrosis of the free skin graft. That defect was closed secondary thanks to bandaging. Respiratory function was preserved.

Conclusion Surgical treatment is the main treatment for sternal chondrosarcoma. With an adequate preoperative and intraoperative approach, it is necessary to enable good postoperative oncological outcomes with the achievement of chest rigidity and satisfactory respiratory status.

Keywords: sternal chondrosarcoma; surgical treatment; reconstruction

INTRODUCTION

Primary malignant tumors arising from the sternum are a rare type of bone and soft tissue tumor. Chondrosarcoma is the most common primary malignant tumor of the chest, with an incidence of < 0.5 per million per year [1]. Due to the hypovascularity and slow rate of mitosis in chondrosarcomas, they are resistant to chemotherapy and radiation therapy [2]. Therefore, as the gold standard, a complete resection of the primary tumor with wide margins is the best therapeutical option for sternal chondrosarcomas [1, 3]. Excision of sternal tumors is difficult because of the anatomical proximity to neuromuscular structures and the limited surgical margins that can be achieved [2]. Reconstructive procedures must provide both, rigidity to protect the internal thoracic organs, and elasticity to maintain lung function [1].

The aim of this work is to present radical surgical resection of a rare case of sternal chondrosarcoma, as well as the method of reconstruction of the anterior chest wall defect after resection.

CASE REPORT

A 67-year-old patient was admitted to our clinic for surgical treatment of a tumor mass of the anterior chest wall. On admission, the patient states that the tumor appeared two years ago, with slow progression, no pain present, and no previous occurrence of bleeding. He denied any difficulty breathing, or weight loss. He had been treated for diabetes mellitus type 2, hypertension, has been obese and a smoker.

The physical findings were normal, except for a tumor mass fixed to the anterior chest wall, without pathological vascularization on the skin, size 17 × 10 cm, with protrusion above the level of the anterior chest wall 4 cm (Figure 1 and 2). A computed tomography (CT) and magnetic resonance imaging (MRI) examination of the chest verified a tumor mass involving the sternum and associated ribs, namely the third, fourth, fifth, sixth, and seventh rib on the right, and the third, fourth, fifth, and sixth rib on the left, with involvement of the covering muscles and subcutaneous tissue (Figure 3 and 4). A tumor biopsy was not performed before surgery because the tumor showed typical features of chondrosarcoma (slow growth, large size, localization).

Received • Примљено: October 18, 2023
Accepted • Прихваћено: December 9, 2023
Online first: January 12, 2024

Correspondence to:
Željko GARABINOVIĆ
Sundečićeva 3E
11000 Belgrade
zeljkogarabinovic@gmail.com

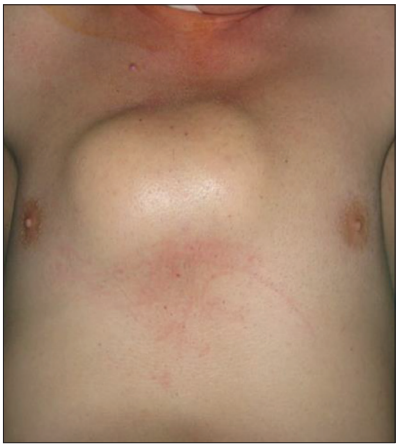


Figure 1. Preoperative view (anterior aspect)

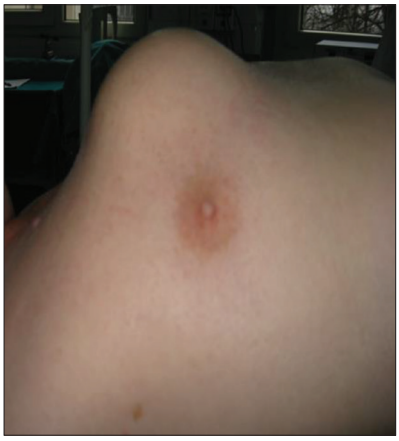


Figure 2. Preoperative view (lateral aspect)

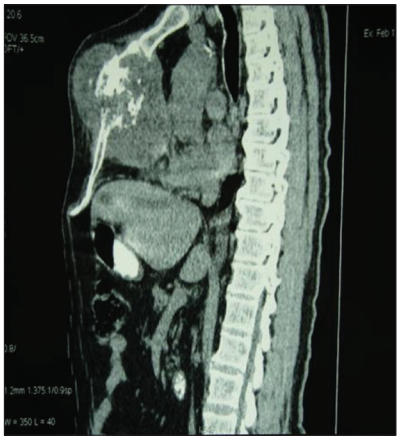


Figure 3. Preoperative chest computed tomography scan (sagittal view)

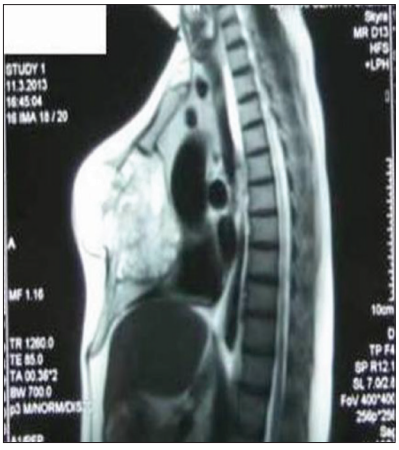


Figure 4. Preoperative chest magnetic resonance imaging scan (sagittal view)

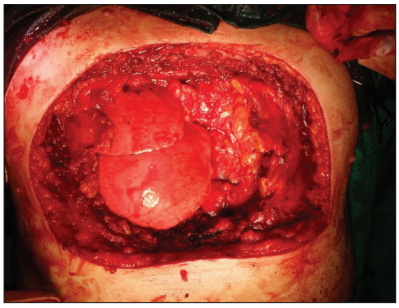


Figure 5. Intraoperative aspect (after resection)

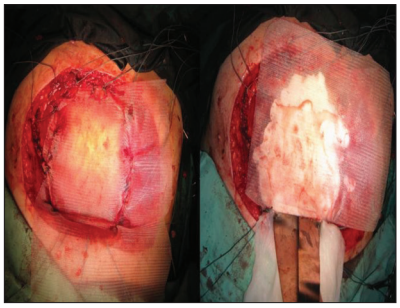


Figure 6. Intraoperative aspect after reconstruction of the anterior chest wall defect with combination of polypropylene mesh and methyl methacrylate bone cement with antibiotics

First, an en bloc resection of the sternum with partial resection of the affected ribs and soft tissues with wide margins was performed. The mediastinal structures were not affected by the tumor. After the wide excision of the tumor, a defect measuring about 24 × 18 cm remained, with the organs of the chest cavity exposed (Figure 5). The reconstruction was supposed to stabilize the chest and cover the soft tissue defect with vital tissue. Given that at the time of the operation, for technical reasons, the planned 3D model of the sternum and part of the ribs (made on the basis of CT and MRI) was not available to us beforehand, stabilization of the chest was achieved with sandwich technique, with combination of polypropylene mesh and methyl methacrylate bone cement with antibiotics (Figure 6). We reconstructed the soft tissue primary defect with a combination of a large local fasciocutaneous flap raised from the abdomen and a smaller sliding flap from the chest. The secondary defect was reconstructed by wide undermining of the skin in the region of the anterior abdominal wall and a small Thiersc-type free skin graft (Figure 7). In the postoperative period, the flaps were vital, but there was necrosis of the free skin graft, but that defect was closed secondary thanks to bandaging (Figure 8). The sutures were removed on the day 15 after the operation. There was no need for a blood transfusion. Respiratory function was preserved. The resected specimen was sent for histological examination that confirmed the diagnosis of chondrosarcoma with a free resection margin from the tumor (Figure 9).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments and comparable ethical standards.

DISCUSSION

Chondrosarcomas make up about 30% of primary bone cancers, with only 1% of primary bone cancers arising from the sternum. Chondrosarcomas occur most often in the third and fourth decade of life, and are more common in men than in women [2]. In our case, the patient is a male in the seventh decade of life.

In preoperative diagnosis and planning, CT of the chest can be considered the gold standard, providing data on dissemination, lung involvement, the presence of metastases, as well as in the assessment of mediastinal lymph node involvement [4, 5], and also important role in the postoperative follow-up of sternal chondrosarcoma, as well as sarcoma of the other localizations [6]. MRI is used to differentiate between intraosseous and extraosseous involvement, while positron emission tomography (PET) can differentiate benign from a malignant tumor, but the type of tumor cannot be distinguished [2]. Some recent studies

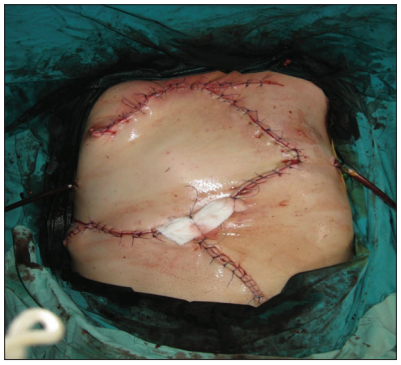


Figure 7. Postoperative aspect after reconstruction

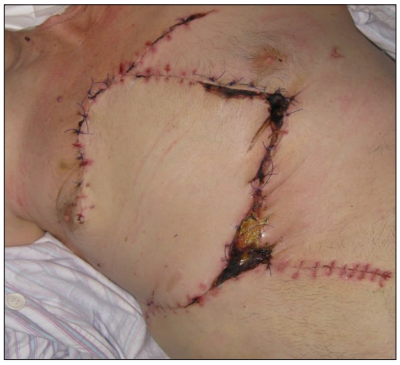


Figure 8. Presentation of necrosis of the free skin graft postoperatively

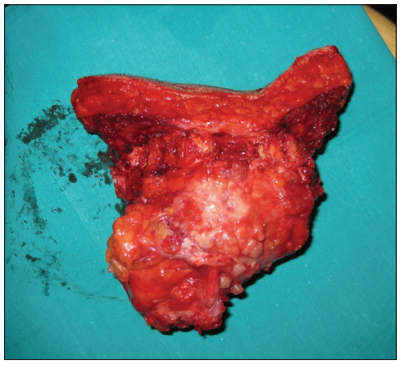


Figure 9. Resected specimen

indicate the need for larger prospective studies to evaluate the possibility of differentiating tumor subtypes based on MRI characteristics [7]. Also, PET can play an important role in the diagnosis of other types of sarcomas [8]. During the diagnostic procedure, we performed CT and MRI of the chest, while PET was not available to us at the time. In the course of preoperative diagnostics, invasive preoperative diagnostics with a surgical needle biopsy of the tumor can be performed, but it can be uncertain in cases where the sternum cortex is not affected [5]. In our case, the tumor biopsy was not performed before the operation because based on previous non-invasive preoperative diagnostic procedures and clinical presentation verified tumor that showed typical features of chondrosarcoma.

Radical resection with wide margins is the standard for treatment, given that the use of radiotherapy and chemotherapy does not provide satisfactory outcomes [9, 10, 11]. A five-year survival ranges between 64% and 92%, with negative predictors for survival being high tumor grade, incomplete (R1) resection, and tumors larger than 10 cm [9]. In the case of resection margins to be achieved, there are various recommendations, whereby margins of 4–6 cm are most often recommended [1, 5, 9], or a negative finding on frozen section, which is considered sufficient without a certain distance [5].

Although sternal chondrosarcomas are rare, if adequate treatment is not started in a timely manner, metastases can occur [12]. Metastases are mostly extrapulmonary [13].

After the resection has been performed and there is a defect in the chest wall, no reconstruction is required for defects smaller than 5 cm [1, 4]. For larger defects, it is necessary to enable the rigidity of the chest wall, obliterate the dead space, preserve lung mechanics, protect the intrathoracic organs, ensure patency with soft tissues, minimize deformities. Several prosthetic reconstruction materials are available, including synthetic, biological, metallic materials, and soft-tissue reconstruction with skin grafts, free flaps, myocutaneous flaps, fasciocutaneous flaps, each of which has its own advantages and disadvantages [14].

The sandwich technique with methyl methacrylate between two layers of polypropylene mesh is widely accepted, because it ensures the rigidity of the chest, which can be modeled according to the shape of the chest wall. It is relatively cheap, while its rigidity enables the stability of the chest wall and the covering of vital structures, while infection, dislocation and fracture of methyl methacrylate are most often cited as the disadvantages of this method of reconstruction [4]. Lardinois et al. [15] reported on 26 cases of reconstruction using the sandwich technique, in which there were no deaths within 30 days, and postoperative complications were recorded in four patients, while none of the others numerous studies have not noted an increased rate of infection [11, 15, 16, 17]. In a series of cases in 20 patients in which this reconstruction technique was applied, Foroulis et al. [18] reported only one case of a methyl methacrylate fracture that was accidentally discovered during follow-up, on a follow-up chest CT scan after a year and a half of reconstruction, and there was no dislocation or a violation of the chest wall stability.

Reconstruction of soft tissue defects of the chest wall depends on the location and size of the defect, the availability of local and regional options, information on previous surgery, radiotherapy, the general condition of the patient and the prognosis of the disease [4].

The advantage of applying local fasciocutaneous flaps is multiple. They are easy and quick to remove, they are very reliable because they have good vascularization, the fixation of the fascia achieves excellent tensile strength, so the skin closes tightly, they have identical or similar characteristics of the tissue they replace, blood loss is minimal, and after their application, numerous possibilities remain for the following reconstructions, if necessary. The thoracoabdominal flap is a fasciocutaneous rotator flap. They can be based laterally or medially, whereby laterally based flaps preserve the intercostal arteries, while medially based flaps preserve the upper epigastric perforator branches [19].

In conclusion, it is important to note that chondrosarcomas of the sternum, as very rare tumors, which are resistant to chemotherapy and radiotherapy, represent a real challenge for surgical treatment, given that surgical treatment is the main form of treatment for these tumors. Careful preoperative diagnosis, operative approach, as well as adequate reconstruction of defects and soft tissues of the chest wall, enabling good postoperative oncological outcomes with the achievement of chest wall rigidity and satisfactory respiratory status.

Conflict of interest: None declared.

REFERENCES

1. Kawana S, Yamamoto H, Maki Y, Sugimoto S, Toyooka S, Miyoshi S. Reconstruction of Anterior Chest Wall with Polypropylene Mesh: Two Primary Sternal Chondrosarcoma Cases. Acta Med Okayama. 2017;71(3):259–62. [DOI: 10.18926/AMO/55210] [PMID: 28655947]
2. Yousefi Y, Sadrizadeh A, Sadrizadeh S. Huge sternal chondrosarcoma: a case report. Asian Cardiovasc Thorac Ann. 2018;26(8):632–4. [DOI: 10.1177/0218492318803813] [PMID: 30269524]
3. Pavelescu C, Bebliuc A, Asmarandei R, Safta MS, Zaharia O, Costache VS, et al. Giant Sternal Chondrosarcoma in a 50-Year-Old Patient. Healthcare (Basel). 2022;10(1):158. [DOI: 10.3390/healthcare10010158] [PMID: 35052321]
4. Brito ÍM, Teixeira S, Paupério G, Choupina M, Ribeiro M. Giant chondrosarcoma of the chest wall: a rare surgical challenge. Autops Case Rep. 2020;10(3):e2020166. [DOI: 10.4322/acr.2020.166] [PMID: 33344295]
5. Kozak K, Łochowski MP, Białas A, Rusinek M, Kozak J. Surgical treatment of tumours of the sternum - 10 years' experience. Kardiochir Torakochirurgia Pol. 2016;13(3):213–6. [DOI: 10.5114/kitp.2016.62608] [PMID: 27785134]
6. Marić N, Nikolić A, Cvijanović V, Ristanović A, Vešović N, Stojković D, et al. Redak slučaj primarnog sinovijalnog sarkoma pleure. Vojnosanit Pregl. 2021;78(4):467–70. [DOI: 10.2298/VSP20190110068M]
7. Gülçin Bozbeyoğlu S, Toksoz Yildirim AN. Can we distinguish conventional osteosarcoma subtypes (osteoblastic and chondroblastic) based on their magnetic resonance signal intensities? Srp Arh Celok Lek. 2023;151(9–10):536–41. [DOI: 10.2298/SARH220920085G]
8. Zivgarević L, Žunić S. 18F-fluorodeoksiglukozna pozitronska emisiona tomografija - kompjuterizovana tomografija u primarnom sarkomu pluća. Srp Arh Celok Lek. 2022;150(9–10):594–7. [DOI: 10.2298/SARH220507069Z]
9. Gritsiuta AI, Bracken A, Abbas AE, Petrov RV. Complex anterior chest wall reconstruction after extensive oncologic resections: a narrative review. Shanghai Chest. 2021;5:41. [DOI: 10.21037/shc-21-8] [PMID: 35495182]
10. Abdulfatah E, Rottmann D, Morag Y, Pantanowitz L, Udager AM, Hao W, et al. Conventional chondrosarcoma of the rib cage and sternum: clinicopathological and molecular analysis of 27 patients treated at a single institution. Hum Pathol. 2023;136:63–74. [DOI: 10.1016/j.humpath.2023.03.011] [PMID: 37019410]
11. Lo Iacono G, Mazzella A, Mohamed S, Petrella F, Sedda G, Casiraghi M, et al. The Role of Surgery in Primary Chest Wall Tumors: Over 20 Years' Experience in Resection and Reconstruction. Cancers (Basel). 2023;15(7):2153. [DOI: 10.3390/cancers15072153] [PMID: 37046813]
12. Jadhav SS, Dhok AP, Mitra KR, Onkar PM, Phatak SV. Chondrosarcoma of Sternal Origin: A Rare Case. Cureus. 2023;15(6):e40393. [DOI: 10.7759/cureus.40393] [PMID: 37456492]
13. Jalil RA, Abdallah FA. Multiple local recurrences of primary sternal chondrosarcoma: tumor manipulation or self-seeding. J Cardiothorac Surg. 2023;18(1):114. [DOI: 10.1186/s13019-023-02213-5] [PMID: 37031192]
14. Sanna S, Brandolini J, Pardolesi A, Argnani D, Mengozzi M, Dell'Amore A, et al. Materials and techniques in chest wall reconstruction: a review. J Vis Surg. 2017;3:95. [DOI: 10.21037/jovs.2017.06.10] [PMID: 29078657]
15. Lardinois D, Muller M, Furrer M, Banic A, Gugger M, Krueger T, et al. Functional assessment of chest wall integrity after methylmethacrylate reconstruction. Ann Thorac Surg. 2000;69(3):919–23. [DOI:10.1016/ S0003-4975(99)01422-8] [PMID: 10750784]
16. Fouad FA. Chest wall resection and reconstruction: analysis of 11 cases after methylmethacrylate reconstruction. J Egypt Natl Canc Inst. 2006;18(3):175–82. [PMID: 17671526]
17. Weyant MJ, Bains MS, Venkatraman E, Downey RJ, Park BJ, Flores RM, et al. Results of chest wall resection and reconstruction with and without rigid prosthesis. Ann Thorac Surg. 2006;81(1):279–85. [DOI: 10.1016/j. athoracsur.2005.07.001] [PMID: 16368380]
18. Foroulis CN, Kleontas AD, Tagarakis G, Nana C, Alexiou I, Grosomanidis V, et al. Massive chest wall resection and reconstruction for malignant disease. Onco Targets Ther. 2016;9:2349–58. [DOI: 10.2147/OTT.S101615] [PMID: 27143930]
19. Sakamoto A, Noguchi T, Matsuda S. Thoracoabdominal flap reconstruction after resection of superficial soft-tissue sarcomas in the chest wall. J Surg Case Rep. 2021;2021(1):rjaa571. [DOI: 10.1093/jscr/rjaa571] [PMID: 33542811]

Радикална ресекција и реконструкција великог хондросаркома стернума

Жељко Гарабиновић[1,2], Милан Савић[1,2], Никола Чолић[3], Милан Стојичић[2,4], Славиша Загорац[2,5]

[1]Универзитетски клинички центар Србије, Клиника за грудну хирургију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија;
[4]Универзитетски клинички центар Србије, Клиника за опекотине, пластичну и реконструктивну хирургију, Београд, Србија;
[5]Универзитетски клинички центар Србије, Клиника за ортопедску хирургију и трауматологију, Београд, Србија

САЖЕТАК

Увод Примарни малигни тумори стернума су ретки, при чему је хондросарком најчешћи примарни малигни тумор грудног коша. Златни стандард у лечењу представља хируршко лечење са широким ресекционим маргинама, при чему се мора обезбедити ригидност грудног коша са заштитом унутрашњих органа уз задовољавајућу плућну функцију.

Приказ болесника Приказујемо случај 67-годишњег болесника код кога је претходним прегледима компјутеризованом томографијом и магнетном резонанцом верификована туморска маса која захвата стернум са припадајућим ребрима, са захватањем меких ткива изнад. Најпре је учињена ресекција стернума са парцијалном ресекцијом припадајућих ребара и меких ткива. Реконструкција и стабилизација зида грудног коша постигнута је са два слоја полипропиленске мрежице и метил-метакрилатног коштаног цемента са антибиотиком. Мекоткивни примарни дефект реконструисали смо комбинацијом великог локалног фасциокутаног режња одигнутог са предела абдомена и мањег клизајућег режња са грудног коша. Секундарни дефект је реконструисан широким подминирањем коже у пределу предњег трбушног зида и малим слободним кожним трансплантатом типа Тирш. У постоперативном периоду режњеви су били витални, али је дошло до некрозе слободног кожног трансплантата. Тај дефект се затворио секундарно захваљујући превијању. Респираторна функција је била очувана.

Закључак Хируршко лечење је основни вид лечења хондросаркома стернума. Адекватним преоперативним и интраоперативним приступом потребно је омогућити добре постоперативне онколошке исходе уз постизање ригидности грудног коша и задовољавајућег респираторног статуса.

Кључне речи: хондросарком стернума; хируршко лечење; реконструкција

DOI: https://doi.org/10.2298/SARH220815105P
UDC: 616.345-006

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

The presence of adenocarcinoma of the right colon and polyp in colonic graft in a female patient with colon interposition due to caustic stricture of the esophagus in childhood

Stojan Latinčić[1,2], Maja Pavlov[1,2], Jovica Vasiljević[1,2], Dragan Vasin[1,3], Milena Papović[2]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Centre of Serbia, Clinic for Digestive Surgery – First Surgical Clinic, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Emergency Department, Belgrade, Serbia

SUMMARY

Introduction Colon interposition is considered an effective option for esophageal replacement in children, particularly in cases of caustic esophageal stricture. The use of colonic tissue grafts for esophageal replacement can lead to late complications, including the development of precancerous lesions and malignant tumors. The aim of the paper is to describe a female patient who was diagnosed with adenocarcinoma of the right colon at the age of 71, 60 years after surgery for benign esophageal stricture.

Case outline A 71-year-old female presented to our clinic in January 2023 with symptoms of abdominal pain. At the age of 11, the patient had bypass esophagocoloplasty with retrosternal esophagogastrocolonic anastomosis due to esophageal stricture after accidental caustic ingestion. CT imaging revealed tumor of the ascending colon, estimated stage T4aN1M0. An upper digestive endoscopic examination revealed one polyp while a lower digestive endoscopic examination confirmed the presence of a stenotic tumor in the ascending colon. Furthermore, a polypoid alteration was identified in the descending colon. CT angiography revealed that the tumor was found to receive its vascular supply through the middle colic artery, while the colonic transplant received its vascular supply through the right colic artery.

Conclusion It is recommended to implement lifelong endoscopic surveillance for patients who have undergone colon interposition. In cases such as this, it is crucial to establish a comprehensive treatment plan and employ effective diagnostic measures to ensure the preservation of the integrity and vascularization of the colonic graft.

Keywords: esophagocoloplasty; endoscopic resection; colon cancer

INTRODUCTION

Colon interposition is considered an effective option for esophageal replacement in children, particularly in cases of caustic esophageal stricture [1, 2]. The left transverse colonic graft, based on the left colic artery, is commonly used for this purpose, although the ascending or descending colon may also be utilized [3, 4, 5]. In the past, the retrosternal esophagogastric anastomosis was the most frequently employed procedure [6]. However, recent research has shown that the posterior mediastinal route may offer better outcomes for interposing the colon [7]. The choice between the retrosternal and posterior mediastinal routes for colon interposition has been a topic of debate [8]. The posterior mediastinal route has been shown to be shorter and associated with fewer cardiopulmonary complications and anastomotic leaks, potentially contributing to lower rates of hospital mortality [9].

The use of colonic tissue grafts for esophageal replacement can lead to late complications, including the development of precancerous lesions and malignant tumors. Some studies examined the late complications of colonic interposition grafts and found that the development of malignant tumors was one of the potential complications. The study highlighted the importance of long-term follow-up and surveillance to detect and manage these complications in a timely manner [10]. So, it is crucial for healthcare professionals to be aware of these risks and to implement appropriate surveillance and management strategies to ensure the long-term health and well-being of patients who have undergone this procedure.

We present a female patient who was diagnosed with adenocarcinoma of the right colon at the age of 71, 60 years after surgery for benign esophageal strictures, where a left transversal colonic graft was used for replacement of the esophagus.

CASE REPORT

A 71-year-old female presented to our clinic in January 2023 with symptoms of abdominal pain; two months earlier, she had a fever. At the age of 11, the patient had bypass esophagocoloplasty with retrosternal esophagogastrocolonic anastomosis due to esophageal stricture after accidental caustic ingestion.

Received • Примљено: August 15, 2022
Revised • Ревизија: October 19, 2023
Accepted • Прихваћено: November 13, 2023
Online first: November 15, 2023

Correspondence to:
Milena PAPOVIĆ
University Clinical Centre of Belgrade
Clinic for Digestive Surgery – First Surgical Clinic
Koste Todorovića 6
11000 Belgrade, Serbia
mina.papovic@yahoo.com

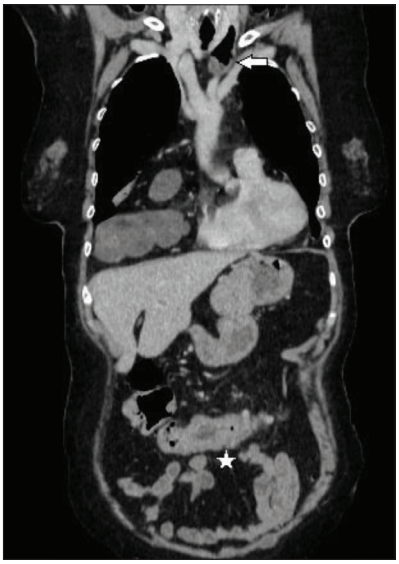


Figure 1. Coronal contrast-enhanced CT image demonstrates the colic transplant placed through the retrosternal space with eso-colic anastomosis in the thorax (white arrow) and colonic tumor in the abdomen (white star)

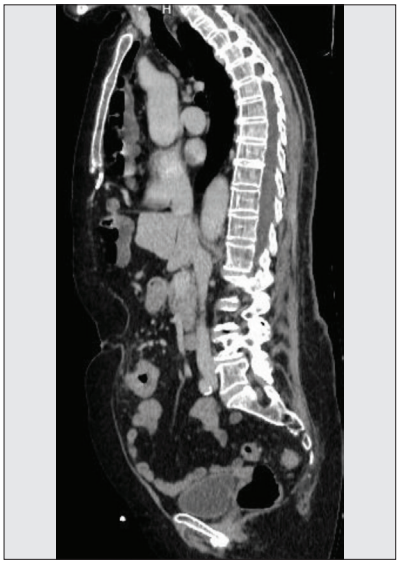


Figure 2. Sagittal contrast-enhanced CT image shows the colic transplant placed through the retrosternal space and colonic tumor in the abdomen

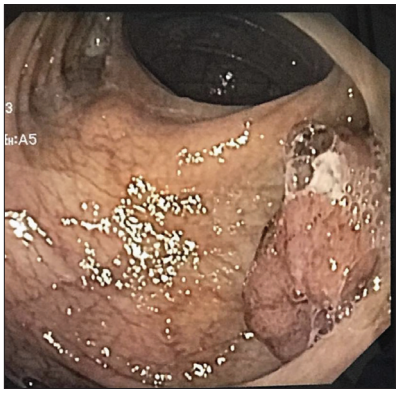


Figure 3. An upper digestive endoscopic study revealed one polyp with a narrow base suitable for electroresection at 25 cm from the dental arch

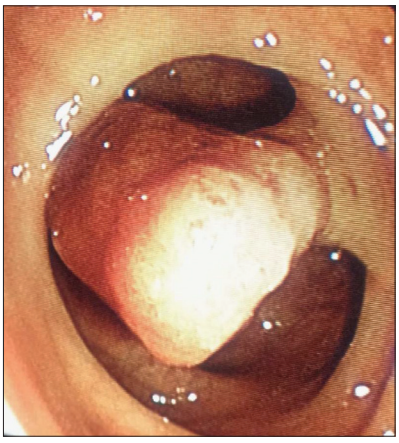


Figure 4. A polypoid change in the descending colon

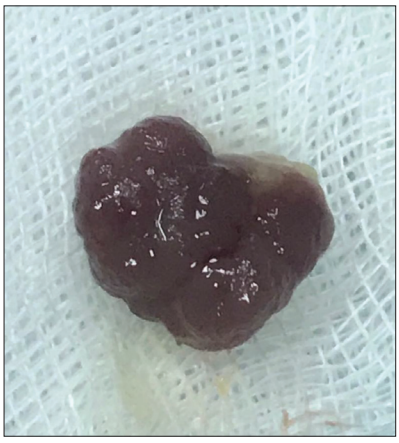


Figure 5. Electroresected polypoid change in the descending colon

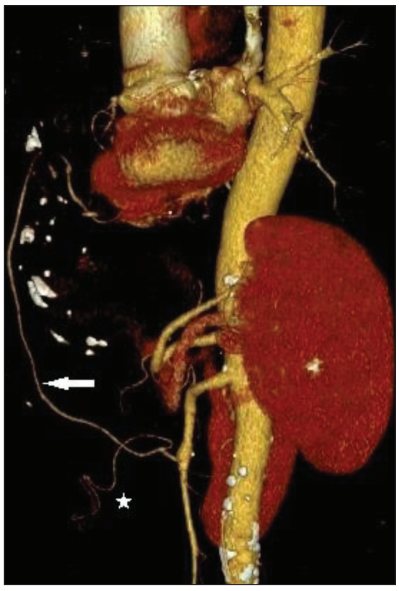


Figure 6. Three-dimensional volume rendering CT angiography clearly shows abdominal vasculature, including the superior mesenteric artery with tumor vascular supply through the middle colic artery (white star) and colonic transplant vascular supply through the right colic artery (white arrow)

Chest, abdomen, and pelvic tomography imaging revealed segmental thickening of the wall of the ascending colon, measuring approximately 50 mm in length and with a wall thickness of up to 12 mm. The imaging also indicated signs of infiltration into the surrounding mesocolon (Figures 1 and 2). Staging performed using the same imaging modality identified individual lymph nodes in the surrounding mesocolon, measuring up to 10 × 7 mm. Notably, no signs of metastatic disease were observed, leading to an estimated stage of T4aN1M0. An upper digestive endoscopic study revealed one polyp with a narrow base suitable for electroresection at 25 cm of the dental arch (Figure 3). In addition, numerous diverticula and a tortuous lumen were observed distally with neat anastomoses.

Prior to the procedure, laboratory findings revealed physiological values for a carcinoembryonic antigen, as well as for 19-9 cancer antigen.

In the subsequent diagnostic evaluation, a lower digestive endoscopic examination confirmed the presence of a stenotic tumor alteration in the ascending colon. Furthermore, a polypoid alteration was identified in the descending colon, which was deemed suitable for electroscopic resection (Figures 4 and 5). The pathohistological analysis of the electroresected polypoid alteration revealed the presence of *adenoma tubulare coli descedentis* with dysplasia *epithelialis levis (I–II)*.

Considering that the operation was 60 years ago, we performed a CT colonography with angiography in order to preserve the vascularization of the colonic graft.

CT colonography with angiography revealed a tumor located approximately 7 cm from the Bauhinia valve, measuring approximately 52 mm in length. Additionally, three-dimensional volume rendering CT angiography provided a clear visualization of the abdominal vasculature, including

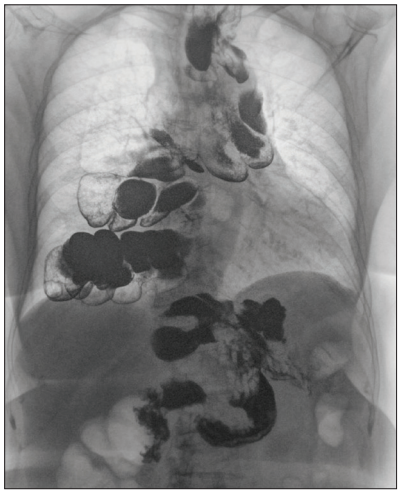


Figure 7. Barium swallow shows colon interposition with cervical esophagocolonic and abdominal gastrocolonic anastomosis

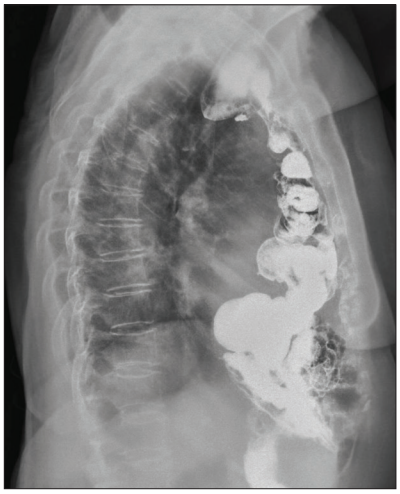


Figure 8. Barium swallow – lateral view shows retrosternal interposition of the colonic graft

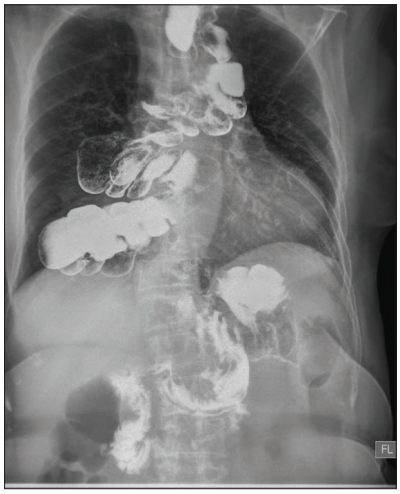


Figure 9. Passage of the contrast through the colo-gastro terminolateral anastomosis

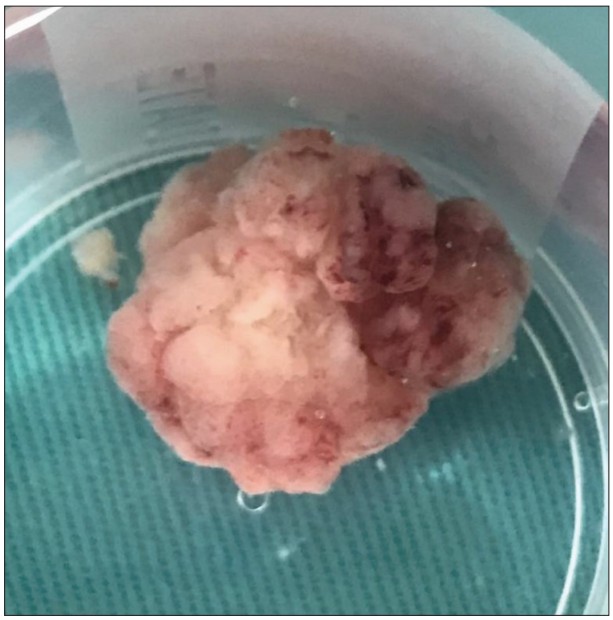


Figure 10. Electroresected polyp in the colonic graft

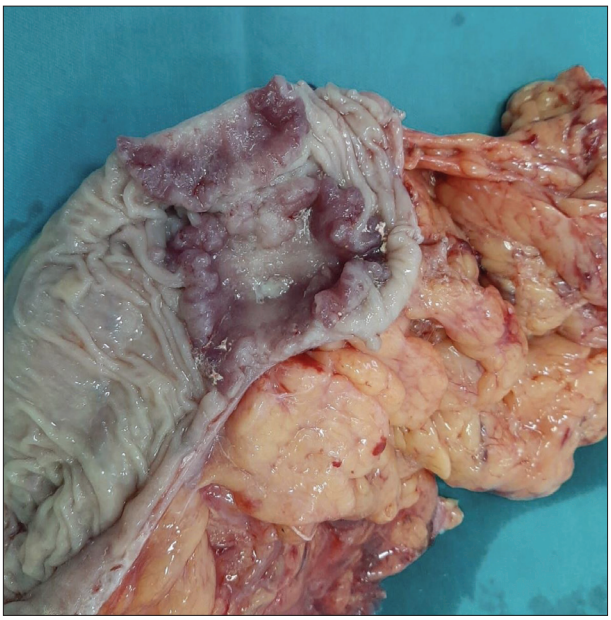


Figure 11. Specimen of the ascending colon with stenotic tumor

the superior mesenteric artery. The tumor was found to receive its vascular supply through the middle colic artery, while the colonic transplant received its vascular supply through the right colic artery (Figure 6).

Contrast radiography was performed to assess the functionality of the esophago-colo terminolateral (TL) anastomosis and colo-gastro TL anastomosis. The radiographic images revealed that the contrast passed unhindered through the esophago-colo TL anastomosis, which exhibited a normal width of the lumen (Figure 7). Similarly, the contrast smoothly passed through the colo-gastro TL anastomosis, which also displayed a normal lumen width (Figures 8 and 9).

The case was presented at a medical review board meeting and it was decided that, after induction into general anesthesia, endoscopic electroresection of the previously verified polyp in the colonic graft should be performed (Figure 10) before operation. Pathohistological finding of the electroresected polyp was *adenoma tubulovillosum coli* with low epithelial dysplasia.

The patient underwent right hemicolectomy with ileocolic anastomosis. The procedure was uneventful, as was the postoperative period. The patient was discharged on the eighth postoperative day. Macroscopically, the tumor exhibited circumferential involvement and infiltration through all layers of the wall (Figure 11). Definitive pathohistological findings showed that it was adenocarcinoma stage T3c N0(0/17) M0 Bd1. The oncology council advised the use of adjuvant therapy with 5FU/LV. At the regular follow-up the patient was without complaints. Control radiography was without signs of recurrence.

The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved. The patient's written consent was obtained for the writing of this case report.

DISCUSSION

Caustic esophageal stricture is a common indication for esophageal replacement in children. In pediatric patients, colon conduit has been found to be a suitable substitute for the esophagus, particularly when utilizing the retrosternal technique. The use of colon interposition as a conduit for esophageal replacement has been well-documented in the literature [11, 12]. Colon interposition has been shown to be the most suitable type of reconstruction for esophageal corrosive strictures, with excellent functional results and low rates of postoperative morbidity and mortality. The choice of colon graft is based on the pattern of blood supply, and the type of anastomosis is determined by the stricture level and the part of the colon used for reconstruction [13]. Current reconstruction approaches typically involve the use of an autologous conduit such as the stomach, small bowel, or colon. However, these approaches are associated with high morbidity and mortality rates. Therefore, there is a critical need for alternative approaches to esophageal reconstruction [14].

Colonic replacement of the esophagus in children leads to significant anatomical modifications. Understanding the typical post-surgical changes and recognizing the imaging characteristics of frequently encountered complications can enhance diagnostic precision for radiologists and aid surgeons in devising appropriate treatment plans for these cases. The literature emphasizes the importance of recognizing the normal postoperative changes following colonic replacement of the esophagus. The authors highlighted the need for radiologists to be familiar with the expected anatomical alterations and to differentiate them from potential complications [15].

Adenoma and adenocarcinoma are recognized as potential late complications in colonic tissue grafts utilized for esophageal substitution [16, 17]. The occurrence of malignant tumors in the transposed colon is a rare long-term complication associated with the irritation of the colonic mucosa by gastric acid content or bile. The prolonged passage time of food contents in the grafted colon, coupled with the absence of a sphincter, renders the grafted colon more susceptible to reflux from the stomach. Consequently, the grafted colon is exposed to noxious agents and carcinogens for a longer duration compared to the normal esophagus [18, 19]. Early detection and treatment are crucial in reducing morbidity and mortality rates [20].

Due to the rareness of respective cohort studies, the frequency of metachronous lesions cannot be calculated accurately. Sohn et al. [21] performed a systematic review in order to identify all reports on the development of metachronous adenoma and adenocarcinoma in colon interposition. The estimated rate of interval carcinoma is ≤ 0.22%. Considering that patients who receive the interposition procedure for benign pathologies are relevantly younger in general, their lifetime risk for the development of mucosal changes in the substitute is relatively higher [21]. Sterpetti and Sapienza [22] performed a systematic review to analyze the reports of *de-novo* adenocarcinoma arising in the transposed colon, where among 205 papers that were fully evaluated only 45 papers clearly reported patients with a transposed colon autograft in which a *de-novo* adenocarcinoma was diagnosed.

Adenocarcinoma of the interposed colon is a rare phenomenon, and the exact incidence remains unclear. However, due to the potential risk, it is recommended to implement lifelong endoscopic surveillance for patients who have undergone colon interposition [23, 24, 25]. In cases such as this, it is crucial to establish a comprehensive treatment plan and employ effective diagnostic measures to ensure the preservation of the integrity and vascularization of the colonic graft.

Conflict of interest: None declared.

REFERENCES

1. Loukogeorgakis SP, Pierro A. Replacement surgery for esophageal atresia. Eur J Pediatr Surg. 2013;23(3):182–90. [DOI: 10.1055/s-0033-1347915] [PMID: 23720209]
2. Youn JK, Park T, Kim SH, Han JW, Jang HJ, Oh C, et al. Prospective evaluation of clinical outcomes and quality of life after gastric tube interposition as esophageal reconstruction in children. Medicine (Baltimore). 2018;97(52):e13801. [DOI: 10.1097/MD.0000000000013801] [PMID: 30593168]
3. Larsson S, Lepore V, Cardillo G. Replacement of the oesophagus with a segment of colon experience of 30 cases and technical considerations. Acta Chir Scand. 1990;156(11–12):789–93. [PMID: 2075776]
4. Gündoğdu HZ, Tanyel FC, Büyükpamukçu N, Hiçsönmez A. Colonic replacement for the treatment of caustic esophageal strictures in children. J Pediatr Surg. 1992;27(6):771–4. [DOI: 10.1016/s0022-3468(05)80114-9] [PMID: 1501044]
5. Irino T, Tsekrekos A, Coppola A, Scandavini CM, Shetye A, Lundell L, et al. Long-term functional outcomes after replacement of the esophagus with gastric, colonic, or jejunal conduits: a systematic literature review. Dis Esophagus. 2017;30(12):1–11. [DOI: 10.1093/dote/dox083] [PMID: 28881882]
6. AbouZeid AA, Zaki AM, Radwan AB, Allam AM, Rawash LM, Mohammad SA. Colonic replacement of the esophagus: towards standardization of the technique. J Pediatr Surg. 2020;55(6):1145–51. [DOI: 10.1016/j.jpedsurg.2019.10.050] [PMID: 31718868]
7. Booka E, Takeuchi H, Morita Y, Hiramatsu Y, Kikuchi H. What is the best reconstruction procedure after esophagectomy? A meta-analysis comparing posterior mediastinal and retrosternal approaches. Ann Gastroenterol Surg. 2023;7(4):553–64. [DOI: 10.1002/ags3.12685] [PMID: 37416735]
8. Oida T, Mimatsu K, Kano H, Kawasaki A, Kuboi Y, Fukino N, et al. Anterior vs. posterior mediastinal routes in colon interposition after esophagectomy. Hepatogastroenterology. 2012;59(118):1832–4. [DOI: 10.5754/hge10213] [PMID: 22819902]
9. Chan ML, Hsieh CC, Wang CW, Huang MH, Hsu WH, Hsu HS. Reconstruction after esophagectomy for esophageal cancer: retrosternal or posterior mediastinal route? J Chin Med Assoc. 2011;74(11):505–10. [DOI: 10.1016/j.jcma.2011.09.006] [PMID: 22100020]
10. Neoral Č, Aujeský R, Vrba R, Stašek M. The use of retrosternally placed colon in esophageal replacement. Rozhl Chir. 2018;97(7):301–8. [PMID: 30442011]
11. Burgos L, Barrena S, Andrés AM, Martínez L, Hernández F, Olivares P, et al. Colonic interposition for esophageal replacement in children remains a good choice: 33-year median follow-up of 65 patients. J Pediatr Surg. 2010;45(2):341–5. [DOI: 10.1016/j.jpedsurg.2009.10.065] [PMID: 20152348]

12. Iascone C, Urbani L, Cavicchi F, Mascioli F, Sorrentino M, Pronio A, et al. Adenocarcinoma in the Intrathoracic Transposed Colon. Ann Thorac Surg. 2019;108(4):e223–e224. [DOI: 10.1016/j.athoracsur.2019.01.081] [PMID: 30878461]
13. Knezević JD, Radovanović NS, Simić AP, Kotarac MM, Skrobić OM, Konstantinović VD, et al. Colon interposition in the treatment of esophageal caustic strictures: 40 years of experience. Dis Esophagus. 2007;20(6):530–4. [DOI: 10.1111/j.1442-2050.2007.00694.x] [PMID: 17958730]
14. La Francesca S, Aho JM, Barron MR, Blanco EW, Soliman S, Kalenjian L, et al. Long-term regeneration and remodeling of the pig esophagus after circumferential resection using a retrievable synthetic scaffold carrying autologous cells. Sci Rep. 2018;8(1):4123. [DOI: 10.1038/s41598-018-22401-x] [PMID: 29515136]
15. AbouZeid AA, Mohammad SA, Rawash LM, Radwan AB, El-Asmar KM, El-Shafei E. The radiological assessment of colonic replacement of the esophagus in children: A review of 43 cases. Eur J Radiol. 2015;84(12):2625–32. [DOI: 10.1016/j.ejrad.2015.09.014] [PMID: 26431748]
16. Bando H, Ikematsu H, Fu KI, Oono Y, Kojima T, Minashi K, et al. A laterally-spreading tumor in a colonic interposition treated by endoscopic submucosal dissection. World J Gastroenterol. 2010;16(3):392–4. [DOI: 10.3748/wjg.v16.i3.392] [PMID: 20082488]
17. De Moura DTH, Ribeiro IB, Coronel M, De Moura ETH, Carvalho JR, Baba ER, et al. Primary adenocarcinoma arising in esophageal colon interposition for corrosive esophageal injury: a case report and review of the literature. Endosc Int Open. 2018;6(12):E1406–E1409. [DOI: 10.1055/a-0751-2812] [PMID: 30505933]
18. Grunner S, Gilshtein H, Kakiashvili E, Kluger Y. Adenocarcinoma in colonic interposition. Case Rep Oncol. 2013;6(1):186–8. [DOI: 10.1159/000350743] [PMID: 23626559]
19. Sterpetti AV, Marzo LD, Sapienza P. Risk factors for adenocarcinoma in the surgically transposed colon not exposed to the fecal stream. Etiological considerations extrapolated to sporadic colon carcinoma in the general population. Eur J Surg Oncol. 2021;47(5):931–4. [DOI: 10.1016/j.ejso.2020.10.026] [PMID: 33139129]
20. Hwang HJ, Song KH, Youn YH, Kwon JE, Kim H, Chung JB, et al. A case of more abundant and dysplastic adenomas in the interposed colon than in the native colon. Yonsei Med J. 2007;48(6):1075–8. [DOI: 10.3349/ymj.2007.48.6.1075] [PMID: 18159607]
21. Sohn M, Agha A, Trum S, Moser C, Gundling F, Hochrein A, et al. Frequency of Polyps and Adenocarcinoma in Colon Interposition After Esophagectomy in Adulthood – A Systematic Review. Anticancer Res. 2019;39(12):6419–30. [DOI: 10.21873/anticanres.13856] [PMID: 31810906]
22. Sterpetti AV, Sapienza P. Adenocarcinoma in the transposed colon: High grade active inflammation versus low grade chronic inflammation. Eur J Surg Oncol. 2019;45(9):1536–41. [DOI: 10.1016/j.ejso.2019.05.012. 15] [PMID: 31118132]
23. Ng DW, Ching Tan GH, Teo MC. Malignancy arising in a 41-year-old colonic interposition graft. Asian J Surg. 2016;39(1):45–7. [DOI: 10.1016/j.asjsur.2014.01.002] [PMID: 24637188]
24. Simões C, Moura M, Noronha Ferreira C, Rosa R, Freire JP, Carrilho Ribeiro L, et al. Lateral Spreading Tumor Arising in an Interposed Colonic Segment. ACG Case Rep J. 2019;6(10):e00245. [DOI: 10.14309/crj.0000000000000245] [PMID: 31832471]
25. Baek SH, Lee JH, Yoo DR, Kim HY, Jin M, Jang AR, et al. Colonic Intramucosal Cancer in the Interposed Colon Treated with Endoscopic Mucosal Resection: A Case Report and Review of Literature. Clin Endosc. 2019;52(4):377–81. [DOI: 10.5946/ce.2018.129] [PMID: 31370380]

Аденокарцином десног колона и присуство полипа у колоничном графту код болеснице код које је у детињству учињена колопластика због каустичне стенозе једњака

Стојан Латинчић[1,2], Маја Павлов[1,2], Јовица Васиљевић[1,2], Драган Васин[1,3], Милена Паповић[2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Универзитетски клинички центар, Клиника за дигестивну хирургију – Прва хируршка клиника, Београд, Србија;
[3]Универзитетски клинички центар, Ургентни центар, Београд, Србија

САЖЕТАК

Увод Езофагоколопластика представља адекватну процедуру код деце са езофагеалном бенигном стенозом, нарочито у случају ингестије корозивног средства. Употреба колоничног транспланата у оваквим случајевима може довести до касних компликација, укључујући и развој преканцерозних лезија и малигних тумора. Циљ рада је приказ болеснице старости 71 годину код које је дијагностикован аденокарцином десног колона шездесет година после езофагоколопластике због бенигне стенозе једњака.

Приказ болесника Болесница старости 71 годину се јавила на нашу клинику са боловима у трбуху. Код ње је 60 година раније учињена езофагоколопластика са ретростерналном езофагогастроколоничном анастомозом због стенозе једњака услед акциденталне ингестије корозивног средства. Преглед грудног коша и абдомена компјутеризованом томографијом показао је тумор асцедентног колона, процењеног стадијума *T4aN1M0*. Ендоскопијом горњих партија дигестивног тракта верификован је један полип у колоничном графту, док се колоноскопијом верификује стенозантна туморска промена асцедентног колона, као и полипоидна промена у десцедентном колону. *CT* ангиографијом се верификује да тумор васкуларизује средња колична артерија, док колонични трансплантан добија васкуларизацију преко десне количне артерије.

Закључак Неопходно је дугорочно ендоскопско праћење болесника код којих је учињена езофагоколопластика. У случајевима као што је овај, неопходно је установити план лечења и применити ефикасне дијагностичке мере како би се очували интегритет и васкуларизација колоничног графта.

Кључне речи: езофагоколопластика; ендоскопска ресекција; карцином дебелог црева

DOI: https://doi.org/10.2298/SARH230206107J
UDC: 616.71-007.1

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Primary subtalar arthrodesis with percutaneous screw fixation and bone grafting through mini-open sinus tarsi approach for Sanders type IV bilateral calcaneal fracture – three-year follow-up case report

Želimir Jovanović[1], Lazar Mičeta[1,2], Nemanja Jovanović[1], Danilo Jeremić[1,2], Nemanja Slavković[1,2]

[1]Banjica Institute for Orthopaedics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Calcaneus fractures are rare but potentially debilitating injuries. Most of them are displaced intraarticular fractures, whose management is among controversial issues. There is no consensus on whether to operate or not. The most often chosen surgical treatment is open reduction and internal fixation as the primary method. Failure of this surgery often needs secondary subtalar arthrodesis as definitive management, so primary subtalar arthrodesis in cases with severe comminution represents definitive treatment in one stage with good functional results.

Case outline We present a case of a 54-year-old male patient with a severely comminuted (Sanders type IV) bilateral calcaneus fracture. After the withdrawal of local swelling and disappearance of fracture blisters, the patient was operated on using one-stage bilateral subtalar arthrodesis with percutaneous screw fixation and bone grafting performed through a mini-open sinus tarsi approach. The early postoperative period was uneventful. The patient did not walk for the first seven postoperative weeks, after which rehabilitation was continued with partial weight bearing with a gradual increase of weight-bearing to full over the next five weeks, after which walking aids were completely phased out. Three years after surgery, the patient has no symptoms and has a close-to-normal gait.

Conclusion Although this type of injury has traditionally been treated with open reduction and internal fixation, we believe that primary subtalar arthrodesis with bone grafting through a mini-open sinus tarsi approach can benefit patients with severe comminution of calcaneus, allowing good functional results and patient satisfaction, with fewer postoperative complications and faster definitive recovery.

Keywords: intra-articular fractures; calcaneus; subtalar joint; arthrodesis

INTRODUCTION

Fractures of the calcaneus are rare, potentially debilitating injuries, which represent a therapeutic challenge even for an experienced surgeon. About 60–75% of calcaneus fractures are displaced intraarticular fractures (DIACF) [1, 2]. Operative and nonoperative treatment of DIACF have similar results, but some patient groups benefit from surgery more than others. The most widespread surgical treatment is open reduction and internal fixation (ORIF), but the results are not uniformly satisfactory. Failure to achieve an anatomical reduction of the articular surface leads to the development of painful arthrosis of the subtalar joint, requiring secondary arthrodesis in many cases [2]. This led to primary subtalar arthrodesis (PSTA) as the appropriate treatment method for DIACF [2, 3].

This paper aims to present a case of a patient with Sanders type IV calcaneus fracture treated by reduction and PSTA through a mini-open sinus-tarsi approach with osteoplasty with a graft from the bone bank and the results of a three-year follow-up.

Received • Примљено: February 6, 2023
Revised • Ревизија: October 26, 2023
Accepted • Прихваћено: October 28, 2023
Online first: November 15, 2023

Correspondence to:
Lazar D. MIČETA
Banjica Institute for Orthopaedics
Mihaila Avramovića 28
11040 Belgrade, Serbia
lmiceta@yahoo.com

CASE REPORT

The patient, a 54-year-old male, sustained a bilateral calcaneus fracture accompanied by swelling, limited range of motion (ROM), and palpatory pain after a fall from a height of three meters. There were no skin or neurovascular lesions. The patient's history revealed that he is a smoker. Radiography and CT scan showed Sanders type IV intraarticular fractures of both feet (Figure 1).

The patient was initially immobilized with compressive Robert Jones bandages. Throughout the following days, swelling of soft tissue developed in the hindfoot, and occasional fracture blisters started to appear.

The operative procedure was performed 16 days after the injury, after reducing swelling and withdrawal of fracture blisters. Surgery was performed in two acts: first on the left foot, then on the right with a patient in lateral decubitus position. Preoperatively, tourniquet cuffs were placed on both lower legs but inflated separately.

The incision, approximately 4 cm long, was made above the projection of sinus tarsi. Extraction of the articular cartilage of the

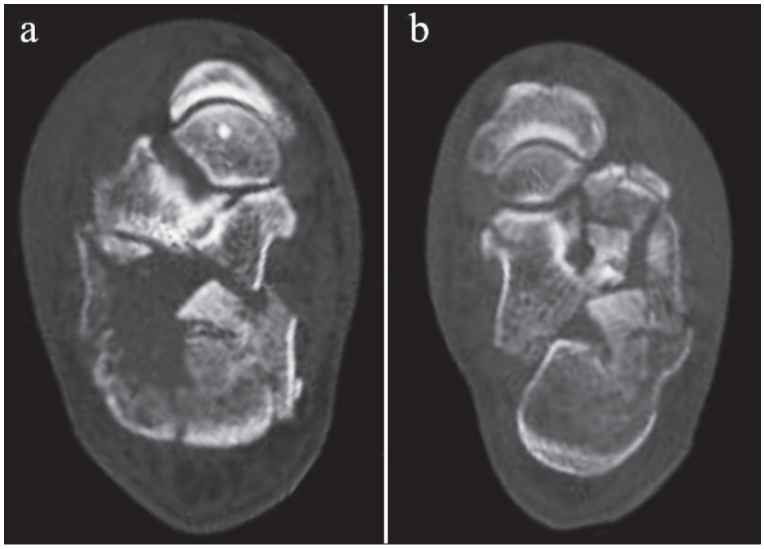


Figure 1. CT scan of both feet on admission showing severely displaced comminuted fracture of both calcaneus; a) right calcaneus fracture; b) left calcaneus fracture

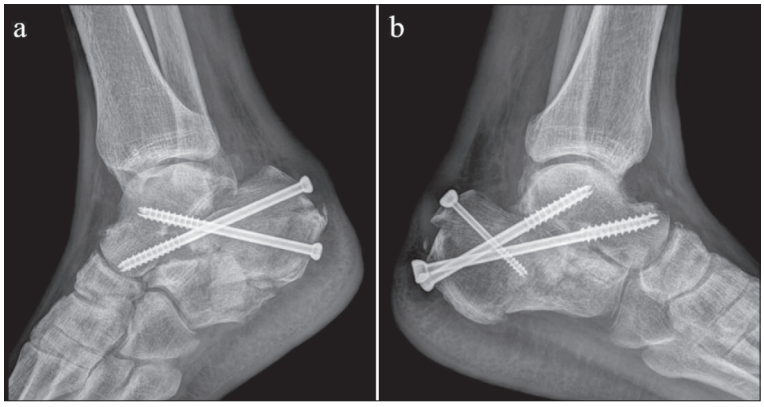


Figure 2. Immediate postoperative lateral X-rays; plain radiograph obtained immediately after surgery; a) right foot; b) left foot

talocalcaneal joint was performed. The articular space and bone defect were filled with a combination of allogenic cancellous bone grafts from our institution's bone bank and extracted bone parts of the fractured calcaneus.

The reduction of major fragments was performed by percutaneous manipulation using a Schanz screw. Fixation of fragments was obtained with two K-wires advanced from calcaneus tuberosity to the talus body. Two cannulated screws of 7 mm in diameter and 105 mm and 120 mm in length were introduced over the wires, ensuring definitive fixation of the fragments and arthrodesis of the talocalcaneal joint. The posterior-upper fragment was reduced percutaneously by another Schanz crew and then fixed with a cannulated screw 5 mm in diameter and 50 mm in length.

After fluoroscopic evaluation and wound closure, Robert Jones dressing was applied, and the patient was rolled over to the other side. Then the talocalcaneal joint of the right leg was approached in the same manner, and the same procedure was performed, with the difference of using two cannulated screws of 7 mm in diameter and 95 mm and 105 mm in length (Figure 2).

The early postoperative period was uneventful. On the sixth postoperative day, the patient was discharged, and suture removal was performed on the 14th postoperative day.

For the first seven postoperative weeks, the patient was without weight-bearing. Ankle joints' ROM was slightly limited and painless, and there was no motion in the subtalar joints. For the next five weeks, rehabilitation was continued with partial weight bearing on the forefoot and the application of silicone heel pads in footwear.

After 12 weeks, the patient was able to walk independently with crutches. In both ankles, ROM was close to physiological. Slightly lowered, painless feet arches were noted bilaterally. The patient gradually phased out walking aids and started with full-weight bearing.

Five months after surgery, the patient could walk normally, with full-weight bearing and without walking aids. The total AOFAS (American Orthopedic Foot and Ankle Society Score) was 73 of 100 (pain 30/40; function 38/50; alignment 5/10).

On three more check-ups, 11 months, 24 months, and 35 months after surgery, the patient exhibited no significant symptoms, with AOFAS scores of 72, 73, and 73, respectively, and a close-to-normal gait (Video 1), and complete return to normal life activities, including working as an electrician, as before the injury.

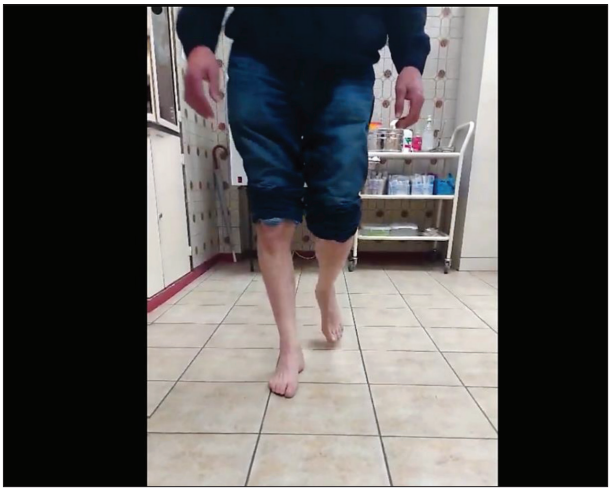
The patient has given his written consent for the publication of data in this case report. The ethics committee of the Institute for Orthopaedics Banjica decided that this paper does not require ethics committee approval (Decision number I-113/20).

DISCUSSION

The outcome of surgical treatment of DIACF is uncertain. The risk of postoperative complications is the most common reason why surgeons continue to opt for non-surgical treatment.

There are indications that less displaced DIACF treated non-operatively have similar functional results as operatively treated ones [3]. Some authors did not find a statistically significant difference in the outcome between the operative and nonoperative treatment of DIACF, emphasizing the risk of postoperative complications [4]. Nevertheless, the prevailing view is that surgical treatment of these fractures gives better functional results than non-operative treatment [3]. Buckley et al. [5] reported significantly better functional outcomes in surgically treated patients.

The most commonly used approach for the calcaneus is the extensive lateral approach, allowing good visualization and can result in difficult wound healing and is more prone to bone infections, scarring, and arthrofibrosis of the subtalar joint. One of the less invasive approaches is through sinus tarsi (STA). Shortening the operative incision only to



Video 1. Representative still – patient gait three years after the operation; available at: srpskiarhiv.rs/global/doc/42577-Other-259068-1-2-20230206.flv

the space immediately above the tarsal sinus (Mini-STA) enables satisfactory visualization with minimal trauma to the soft tissues [6].

Mini-STA and classical STA can be combined with percutaneous techniques to reduce and fix large bone fragments. Several authors presented their results with lower postoperative complications with adequate repositioning and stabilization of the subtalar joint when using STA compared to the extensive lateral approach [7, 8]. Holmes [7] reported that after 18 years of STA use, he did not encounter any complications associated with wound healing or soft tissue and bone infection. Joseph et al. [9] reported a higher percentage of complications after an extensive lateral approach compared with STA, but without statistical significance, bearing in mind that patients treated using STA were operated on earlier. Syros et al. [10] reported in their retrospective study of 36 high-risk patients with DIACF treated with STA that a short time to surgery had a negative impact on wound complication rate. Two separate meta-analyses concluded that, in the treatment of DIACF, the extensive lateral approach had significantly more complications than other, less invasive methods, with isolated percutaneous screw fixation being the one with the least complication [11, 12]. Yin et al. [13] indicated that the surgeon's volume (number of performed operations) in treating DIACF is directly correlated with the number of complications, stating that low-volume surgeons have almost 15% more complications.

In patients with Sanders type IV fractures, there have not yet been found significant differences in the outcome between ORIF and PSTA, and a low number of patients and quality studies are limiting factors for reaching a definitive conclusion. The advantages of PSTA include shorter treatment time, shorter postoperative recovery and absence from work, and lower treatment costs [14].

The results of ORIF in multisegmental DIACF can be uncertain. In Sanders type IV fracture, anatomical reposition, good joint congruence, and stable fixation are challenging to achieve, and many authors advocate using PSTA as the treatment method [3, 15]. Even when anatomical reconstruction and stable fixation are achieved, early posttraumatic arthrosis of the subtalar joint may occur. Potenza et al. [2] reported good to excellent functional results after a five-year follow-up in six patients (seven calcanei) with Sanders IV type of fracture managed using PSTA through sinus tarsi approach with cannulated screws and filling of the bone defect with heterologous grafts.

Huefner et al. [16] state that in 2–17% of patients, it is necessary to perform secondary subtalar arthrodesis due to a degenerative disease that developed after reduction and osteosynthesis. They further report good to excellent results after open reduction and PSTA in patients with Sanders IV fracture, and the patients' return to total working activities was observed within 6.4 months on average. In performed expected value decision analysis Eisenstein et al. [17] concluded that performing ORIF with PSTA is optimal for patients with DIACF, compared with isolated ORIF surgery.

It is necessary to point out that obliteration of the subtalar joint reduces ROM of the foot, affects normal gait, and can cause diminished functionality. Almeida et al. [1] reported a slightly higher average AOFAS score in PSTA than in the osteosynthesis groups, ranging 65.8–86.8 and 62–82.4, respectively. Considering that our patient had a total AOFAS score of 73 out of 100 three years after surgery, it encouraged us to give even more space to PSTA as the solution for DIACF.

A study which included 424 non-operatively and operatively treated patients stated that 10% required secondary arthrodesis of the subtalar joint [5]. For certain patients, secondary subtalar arthrodesis was more common: men who do hard physical work, workers who receive compensation for injuries at work, patients with Sanders type IV fracture, and lower Böhler angle [5]. Sanders et al. [18] stated that the results of ORIF of type IV fractures are unpredictable even with experienced surgeons performing operations because successful anatomical repositioning and stable fixation are extremely difficult to achieve and that better results can be obtained by performing PSA.

The advantages of using bone grafts are reflected in the stimulation of fracture healing and a shortening of the period to full weight-bearing, increasing mechanical support of the calcaneus, and avoiding its collapse and posttraumatic arthrosis of the subtalar joint. Singh et al. [19] reported similar results in patients undergoing calcaneus osteosynthesis with or without bone grafts but with earlier full weight-bearing and better re-establishment of calcaneus anatomy in the group where bone grafts were used.

Despite the adequate choice of treatment, DIACF can cause severe patient disability. Performing PSTA in these patients reduces the risk of reintervention and shortens the postoperative recovery. The biggest obstacle to the widespread use of PSTA is the small number of reported patients treated this way. Our opinion is that the excellent results of treating our patient's extremely severe injuries should encourage others to use PSTA more often, improving their patient's quality of life.

Conflicts of interest: None declared.

REFERENCES

1. Almeida JF, Vale C, Gonzalez T, Gomes TM, Oliva XM. Osteosynthesis or primary arthrodesis for displaced intra-articular calcaneus fractures Sanders type IV – A systematic review. Foot Ankle Surg. 2022;28(3):281–7. [DOI: 10.1016/j.fas.2021.04.006] [PMID: 33893034]
2. Potenza V, Caterini R, Farsetti P, Bisicchia S, Ippolito E. Primary subtalar arthrodesis for the treatment of comminuted intra-articular calcaneal fractures. Injury. 2010;41(7):702–6. [DOI: 10.1016/j.injury.2009.12.002] [PMID: 20074730]
3. Sharr PJ, Mangupli MM, Winson IG, Buckley RE. Current management options for displaced intra-articular calcaneal fractures: Non-operative, ORIF, minimally invasive reduction and fixation or primary ORIF and subtalar arthrodesis. A contemporary review. Foot Ankle Surg. 2016;22(1):1–8. [DOI: 10.1016/j.fas.2015.10.003] [PMID: 26869492]
4. Dickenson EJ, Parsons N, Griffin DR. Open reduction and internal fixation versus nonoperative treatment for closed, displaced, intra-articular fractures of the calcaneus: long-term follow-up from the HeFT randomized controlled trial. Bone Joint J. 2021;103–B(6):1040–6. [DOI: 10.1302/0301-620X.103B6.BJJ-2020-1962.R2] [PMID: 34058883]
5. Buckley R, Tough S, McCormack R, Pate G, Leighton R, Petrie D, et al. Operative compared with nonoperative treatment of displaced intra-articular calcaneal fractures: a prospective, randomized, controlled multicenter trial. J Bone Joint Surg Am. 2002;84(10):1733–44. [DOI: 10.2106/00004623-200210000-00001] [PMID: 12377902]
6. Liu GT, Vanpelt MD, Lalli T, Raspovic KM, Wukich DK. Surgical Management of Displaced Intra-Articular Calcaneal Fractures: What Matters Most? Clin Podiatr Med Surg. 2019;36(2):173–84. [DOI: 10.1016/j.cpm.2018.10.002] [PMID: 30784529]
7. Holmes GB. Treatment of Displaced Calcaneal Fractures Using a Small Sinus Tarsi Approach. Tech Foot Ankle Surg. 2005;4(1):35–41. [DOI: 10.1097/01.btf.0000156336.58175.e1]
8. Khazen G, Rassi CK. Sinus Tarsi Approach for Calcaneal Fractures: The New Gold Standard? Foot Ankle Clin. 2020;25(4):667–81. [DOI: 10.1016/j.fcl.2020.08.003] [PMID: 33543722]
9. Joseph NM, Sinkler MA, Magister S, Bacharach A, Pang A, Boes K, et al. Fixation of displaced intra-articular calcaneus fractures is safe using either sinus tarsi or extensile lateral approach. Injury. 2023:S0020-1383(23)00168–7. [DOI: 10.1016/j.injury.2023.02.036] Online ahead of print. [PMID: 36878733]
10. Syros A, Perez J, Hodgens BH, Boden AL, Constantinescu DS, Smith B, et al. Sinus tarsi approach in high-risk patients with displaced intra-articular calcaneus fractures: A case series. J Orthop. 2022;34:282–7. [DOI: 10.1016/j.jor.2022.09.009] [PMID: 36158039]
11. Zhang L, Su P, Li J. Complications in the Management of Displaced Intra-articular Calcaneal Fractures: A Systematic Review and Network Meta-Analysis of 2538 Patients. J Foot Ankle Surg. 2022;61(6):1348–56. [DOI: 10.1053/j.jfas.2022.07.001] [PMID: 35934608]
12. Shi F, Wu S, Cai W, Zhao Y. Comparison of 5 Treatment Approaches for Displaced Intra-articular Calcaneal Fractures: A Systematic Review and Bayesian Network Meta-Analysis. J Foot Ankle Surg. 2020;59(6):1254–64. [DOI: 10.1053/j.jfas.2020.03.021] [PMID: 32828631]
13. Yin H, An Y, Dong L. Surgeon case volume and the risk of complications following surgeries of displaced intra-articular calcaneal fracture. Foot Ankle Surg. 2022;28(7):1002–7. [DOI: 10.1016/j.fas.2022.02.003] [PMID: 35177328]
14. Buckley R, Leighton R, Sanders D, Poon J, Coles CP, Stephen D, et al. Open Reduction and Internal Fixation Compared With ORIF and Primary Subtalar Arthrodesis for Treatment of Sanders Type IV Calcaneal Fractures. J Orthop Trauma. 2014;28(10):577–83. [DOI: 10.1097/BOT.0000000000000191] [PMID: 24983433]
15. Schepers T. The primary arthrodesis for severely comminuted intra-articular fractures of the calcaneus: a systematic review. Foot Ankle Surg. 2012;18(2):84–8. [DOI: 10.1016/j.fas.2011.04.004] [PMID: 22443992]
16. Huefner T, Thermann H, Geerling J, Pape HC, Pohlemann T. Primary subtalar arthrodesis of calcaneal fractures. Foot Ankle Int. 2001;22(1):9–14. [DOI: 10.1177/107110070102200102] [PMID: 11206830]
17. Eisenstein ED, Kusnezov NA, Waterman BR, Orr JD, Blair JA. Open reduction and internal fixation (ORIF) versus ORIF and primary subtalar arthrodesis for complex displaced intraarticular calcaneus fractures: An expected value decision analysis. OTA Int. 2020;1(2):e005. [DOI: 10.1097/OI9.0000000000000005] [PMID: 33937643]
18. Sanders R, Fortin P, DiPasquale T, Walling A. Operative treatment in 120 displaced intraarticular calcaneal fractures. Results using a prognostic computed tomography scan classification. Clin Orthop Relat Res. 1993;(290):87–95. [PMID: 8472475]
19. Singh AK, Vinay K. Surgical treatment of displaced intra-articular calcaneal fractures: is bone grafting necessary? J Orthop Traumatol. 2013;14(4):299–305. [DOI: 10.1007/s10195-013-0246-y] [PMID: 23670493]

Примарна супталарна артродеза са перкутаном фиксацијом завртњима и попуњавањем дефекта коштаним графтом кроз мини-отворен *sinus tarsi* приступ у решавању билатералног прелома каланеуса IV типа по Сандерсу – приказ болесника са трогодишњим периодом праћења

Желимир Јовановић[1], Лазар Мичета[1,2], Немања Јовановић[1], Данило Јеремић[1,2], Немања Славковић[1,2]

[1]Институт за ортопедију „Бањица", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Преломи калканеуса су ретке, али потенцијално онеспособљавајуће повреде. Најчешће се ради о дислоцираним интраартикуларним преломима чије збрињавање представља једно од контроверзних питања. Не постоји консензус о томе да ли треба или не спровести оперативно лечење. Најчешће изабрани хируршки третман је отворена репозиција и унутрашња фиксација као примарни метод. Неуспех ове операције често захтева секундарну супталарну артродезу као дефинитивну меру лечења, тако да се примарна супталарна артродеза у случајевима са тешком коминуцијом показује као добар метод дефинитивног једноетапног лечења са добрим функционалним резултатима.

Приказ болесника Приказујемо случај 54-годишњег мушкарца са билатералним комунитивним (IV типом по Сандерсу) преломом калканеуса. После повлачења локалног отока и повлачења була, болесник је оперисан применом једноетапне билатералне супталарне артродезе са перкутаном фиксацијом уз попуњавање дефекта коштаним алографтом кроз мини-отворен *sinus tarsi*. Рани постоперативни период је прошао без компликација. Првих седам постоперативних недеља болесник није ходао, након чега је рехабилитација настављена са ходом са делимичним ослонцем уз постепено повећање оптерећења током наредних пет недеља, а после тога су помагала за ходање потпуно укинута. Три године после операције болесник нема симптоме и хода скоро нормално.

Закључак Иако се ова врста повреде традиционално лечи отвореном репозицијом и унутрашњом фиксацијом, верујемо да примарна супталарна артродеза уз попуњавање дефекта коштаним алографтом кроз мини-отворен *sinus tarsi* може бити од користи болесницима са тешком коминацијом калканеуса, омогућавајући добре функционалне резултате и задовољство пацијената, са мање постоперативних компликација и бржим опоравком.

Кључне речи: интраартикуларни преломи; калканеус; супталарни зглоб; артродеза

DOI: https://doi.org/10.2298/SARH221104007M
UDC: 616.61-008.6

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Genotype/phenotype relationship in mild congenital nephrotic syndrome

Bilsana Mulić[1], Amira Peco-Antić[2], Fatih Ozaltin[3]

[1]Novi Pazar General Hospital, Pediatric Department, Novi Pazar, Serbia;
[2]Acibadem Bel Medic, Belgrade, Serbia;
[3]Hacettepe University, Faculty of Medicine, Department of Pediatric Nephrology, Ankara, Türkiye

SUMMARY

Introduction Congenital nephrotic syndrome (CNS) is a severe disease complicated by hemodynamic instability, infections, thrombosis, growth disorder and progressive renal failure leading to end-stage kidney disease within a few years. The mutations of *NPHS1* encoding nephrin is the most common cause of the CNS.

The aim of this paper was to present a patient with *NPHS1* homozygous Ser350Pro missense mutation that unexpectedly caused a mild clinical course of CNS.

Case outline We present a female patient who was diagnosed with severe nephrotic syndrome at 2.5 months of age. While waiting for the result of the genetic analysis, she was treated unsuccessfully with corticosteroids and angiotensin converting inhibitor (ACEI) four weeks, and then under Cyclosporine A (CsA) and ACEI she achieved partial remission within three months. Initially, the milder clinical course was explained by the positive effect of CsA, but as partial remission persisted even after the discontinuation of this drug, it remains unclear what influenced the improvement of the clinical course of the disease. At the time of writing this paper, the patient was 10.9 years old with normal serum creatinine, normal blood pressure and non-nephrotic proteinuria.

Conclusion *NPHS1* homozygous Ser350Pro missense mutation may be presented by a mild clinical course of CNS. Further studies are needed to clarify a more predictive CNS genotype/phenotype relationship.

Keywords: *NPHS1* gene; nephrin; hereditary nephrotic syndrome; infant

INTRODUCTION

Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorder characterized by massive, nephrotic proteinuria, hypoalbuminemia, and edema, manifested in utero or during the first three months of life. CNS consequences are numerous including hemodynamic instability, infections, thrombosis, growth disorder and progressive renal failure leading to end-stage renal disease (ESRD) usually in the early childhood [1].

In most cases the CNS is caused primarily by the underlying genetic abnormality related to structural and regulatory proteins of the glomerular filtration barrier [2, 3]. However, it can rarely be secondary, caused by congenital infections (syphilis, cytomegalovirus infection, toxoplasma, rubella, pertussis, immunodeficiency virus infection, malaria, hepatitis B) or due to immune disease of the mother [3–6].

Nowadays, genetic diagnosis of hereditary CNS is possible in 85% of cases. More than 80% of genetic causes of CNS include mutations of the genes *NPHS1, NPHS2, WT1, PLCE1* and *LAMB2*, while other less commonly mutated genes account for an additional ~5% of CNS diagnoses [2]. The mutations of *NPHS1* or *NPHS2* are the most common causes of the CNS [2, 7]. An established genetic diagnosis of the CNS has a great influence on its management and prognosis. Since CNS is almost always a serious disease that is resistant to immunosuppressive therapy, management is very challenging and may require daily albumin infusions and intensive symptomatic treatments, but when optimal conservative measures are not successful to avoid complications, early unilateral or bilateral nephrectomy may be indicated [4]. Therefore, most children require renal replacement therapy in early childhood and the mortality rate is high [1, 4, 8]. However, although patients with CNS often have an inevitable rapid progression to ESRD, extremely rare milder cases of the disease indicate that genetic diagnosis is not always reliable for predicting the clinical course of CNS [9, 10].

The aim of this report was to present our patient with *NPHS1* homozygote Ser350Pro missense mutation that unexpectedly manifested a mild clinical course. This way, we wanted to point out the possible variations of the CNS genotype–phenotype relationship.

CASE REPORT

We present a female who was diagnosed with severe nephrotic syndrome at 2.5 months of age (Table 1). It had been noticed that her placenta was enlarged. Parents denied consanguinity. An infectious or immunological etiology of the

Received • Примљено: November 4, 2022
Accepted • Прихваћено: December 20, 2023
Online first: January 12, 2024

Correspondence to:
Bilsana MULIĆ
Novi Pazar General Hospital
Pediatric Department
Generala Živkovića 1
36300 Novi Pazar
Serbia
emmulic@mts.rs

Table 1. Trends of renal function, serum protein, proteinuria and therapy over time

Age (months)	sCr (μmol/l)	eGFR (ml/min./1.73 m2)	Serum albumin (g/l)	Serum protein (g/l)	Urine protein/creatinine (mg/mg)	Daily iv albumin	Captopril (mg/kg BW/day)	CsA** (mg/kgBW/day)
2.5	15	134.7	9	37	28.2	-	-	-
7.3	25	100.8	37	62	32.8	12 g / 24 h	0.4	-
9	28	95	26	55	33	12 g / 24 h	0.4	6.2*
10.5	35–40	76.6	31	60	3.6	12 g / 24 h	0.6	5.8
12	33–83	84.8	31	63	5	-	0.9	4.5
18	26	139.4	23	55	3.6	-	0.7	4.6
20.5	25–40	148	18	53	4.9	-	0.9	7.2
24	21	184.3	18	51	4.9	-	1.2	6.6
30	27	153.3	18	54	4	-	1.2	6.6
42	43–45	103.7	-	-	-	-	5.4	
57.5	16	306.2	19	56	3.2	-	0.9	4.3
Lost to follow-up								
9 years	45	136	33	65	1.5	-	0.5	?
10.5 years	39.9	180	30	63	1.5	-	0.3	-
10.9 years	31	197	32	66	1.45	-	0.3	-

sCr – serum creatinine; eGFR – estimated glomerular filtration rate; iv – intravenous; BW – body weight; CsA – cyclosporine A; **therapy started at the age of eight months

CNS was ruled out by appropriate investigations. A kidney biopsy was performed, which showed immature glomeruli with a mild degree of mesangial cell hypercellularity and microcystic dilatation of proximal tubules. A genetic analysis was requested abroad and homozygous *NPHS1* (NM_004646.4) c.1048T>C (p. Ser350Pro) missense mutation was reported. Due to hemodynamic instability caused by severe hypoalbuminemia, the patient required daily albumin infusions through a central venous catheter, which was changed several times due to infections. In addition, the patient received diuretics, vitamin D, thyroxin, and iron, as well as anticoagulants, gamma globulin replacement and antibiotics during frequent infections. Angiotensin-converting enzyme inhibitor (ACEI) was introduced into therapy in the third month of life, and corticosteroids from the seventh month for four weeks, without improvement of the disease. Cyclosporine A (CsA) treatment was then initiated with continuing ACEI, and partial remission was achieved within three months, together with resolving the need for albumin infusion. CsA and ACEI continued for the next four years. From the fourth to the ninth year of life, the girl was lost from medical follow-up because the situation in the family worsened due to the mother's illness (severe depression that required long-term hospital treatment), which most likely caused her not to receive regular medication, including CsA. During the most recent check-up, after the improvement of the mother's illness, the girl was 10.9 years old, body height was 125 cm (-2.85 z), body weight 28.5 kg (-1.36 z), body mass index was 18.2 kg/m2 (0.37 z). Her short stature may not only be the result of a chronic disease, but also the influence of genetics, as both parents are short. She was normotensive, without edema. Her serum creatinine was normal as well as serum protein, and her proteinuria was in non-nephrotic range (416.8 mg / 24 hours) (Table 1).

Ethical approval was granted by the local Ethics Committee of the Novi Pazar General Hospital. The number of the ethical approval is 3498/2023. A signed, informed parental consent was taken for this publication.

DISCUSSION

It is very well known that an established genetic diagnosis of CNS has great influence of its management and prognosis; in genetic forms of CNS the use of immunosuppressive drugs should be avoided and renal biopsy is not necessary [4, 6]. However, the genetic diagnosis is not always able to reliably indicate the severity of the disease, which has a great impact on the treatment of the disease and its acceptance by the patient and parents or caregivers. Variable disease penetrance can be a function of the specific mutation(s) involved or of allele dosage as well as the modulating influence of additional genetic variants but may also reflect the action of unlinked modifier genes, epigenetic changes or environmental factors [11].

While waiting for the genetic diagnosis, we tried treatment with corticosteroids without success, and then with CsA, during which a partial remission occurred and the need for albumin infusions ceased. The decision to introduce CsA in our patient was motivated by numerous problems in our patient related to daily intravenous albumin infusions, as well as reports on the favorable effect of CsA in hereditary nephrotic syndrome, which is explained by its ability to stabilize the actin cytoskeleton beyond its immunosuppressive effects [12, 13, 14]. In the previous report [15], the favorable course of the disease was mainly attributed to the effects of ACEI and CsA. However, since the patient was under very low and irregular doses of CsA for the next six years, its influence on the course of the disease is not entirely clear. The antiproteinuric effect of ACEI cannot be underestimated but our patient received the drug in a small dose and probably irregularly. When everything is taken into consideration, it seems most likely

Table 2. Clinical and genetic characteristics of the *NPHS1* patients with mild congenital nephrotic syndrome course

Study	Age at onset	Mutation in *NPHS1*	Clinical course	Treatment
Bérody et al. [8]	No data	c.2131C > A(p.Arg711ser) homozygous missense mutation	Renal survival of 30 years	No data
Kestilä et al. [16]	After birth	Fin-major mutation in one gene and a missense mutation (a change of arginine-743 to cysteine in the extracellular Ig-5 domain) in the other one.	Partial remission	Indomethacin and Enalapril started at three months of age
Lenkkeri et al. [18]	11 days	Compound heterozygous for two different sequence variants in exons 9 and 27 (NM_004646.4:c.1048T>C:p.Ser350Pro; M_004646.4:c.3478C>T:p.Arg1160Ter)	Remission at six months	Supportive
Espinosa et al. [19]	No data	c.3478 C > T in exon 27 homozygous missense mutation	Remission at 11 years of age	No data
Li et al. [20]	50 days	c.3312-23C > T intron 25 c.2207T > C exon 16 c.928G > A in exon 8	Remission	Glucocorticoids
Our case	2.5 months	Ex9: c.1048T > C p. (Ser350Pro)	Partial remission at 12 months	CsA + ACEI during four years

CsA – Cyclosporine A; ACEI – angiotensin converting inhibitor

that the *NPHS1* genetic disorder had the primary and decisive influence on the milder course of the disease in our patient. *NPHS1* gene is localized to chromosome 19q13.1 and encodes for nephrin protein, which is a fundamental constituent of the slit diaphragm, and plays a crucial role in cell signaling [16]. Patrakka et al. [17] found that most *NPHS1* patients have the negative nephrin expression as well as the lack of slit diaphragm in kidneys that strongly indicate the total lack of functional nephrin in these patients causing massive proteinuria. Only one out of 46 patients with CNS had some nephrin expression retained in the kidneys associated with a mild CNS clinical course (Table 2). The authors suggested nephrin expression to be predictive for the favorable course of *NPHS1* disease [17]. This way of predicting the clinical course of the disease is generally not applied in clinical practice, and the findings of genetic analysis are mainly used. Table 2 presents other patients reported in the literature with a mild CNS clinical course. The homozygous missense mutation in exon 9 of the *NPHS1* gene designated as Ex9: c.1048T>C p. (Ser350Pro) was demonstrated in our patient. This mutation was first reported by Lenkkeri et al. [18] in 1999. To our knowledge, this homozygous mutation is not known to cause benign CNS except in our patient. Espinosa et al. [19] reported a patient who had spontaneous CNS remission at six months of age with an *NPHS* mutation identical to our patient (c.1048T>C (p. Ser350Pro) in exon 9) in one gene and different one in the other gene (c.3478C>T(p. Arg1160Ter) in exon 27). Wong et al. [9] performed *NPHS1* mutation analysis in 19 patients, five Caucasian patients and 14 Maori patients with a highly variable and protracted timeline to ESRD with median renal survival of 30 years versus 0.7 years in Caucasian patients. A Chinese study described complete remission of CNS under corticosteroid therapy in a girl who had heterozygous *NPHS1*mutation [20]. In a Turkish study no association between the *NPHS1* mutation type (protein truncating or missense) and survival or age at diagnosis was found, but the patients with mutations affecting transmembrane or intracellular domains of nephrin in ≥ 1 alleles had a significantly longer survival time than patients with mutations affecting the extracellular domain in both alleles [7].

It can be concluded that *NPHS1* homozygous Ser350Pro missense mutation may be presented by a mild clinical course of CNS. More data are needed before the question of phenotype/genotype correlations in CNS can be addressed.

Conflict of interest: Not declared.

REFERENCES

1. Hölttä T, Jalanko H. Congenital nephrotic syndrome: is early aggressive treatment needed? Yes. Pediatr Nephrol. 2020;35(10):1985–90. [DOI: 10.1007/s00467-020-04578] [PMID: 32377865]
2. Lipska-Ziętkiewicz BS, Ozaltin F, Hölttä T, Bockenhauer D, Bérody S, Levtchenko E, et al. Genetic aspects of congenital nephrotic syndrome: a consensus statement from the ERKNet-ESPN inherited glomerulopathy working group. Eur J Hum Genet. 2020;28(10):1368–78. [DOI: 10.1038/s41431-020-0642-8] [PMID: 32467597]
3. Peco Antić A. Kongenitalni nefrotski sindrom. U: Peco Antić A. Glomerulske dečje bolesti. Beograd: Digital Art Company; 2021. str. 111–34.
4. Boyer O, Schaefer F, Haffner D, Bockenhauer D, Hölttä T, Bérody S, et al. Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group. Nat Rev Nephrol. 2021;17(4):277–89. [DOI: 10.1038/s41581-020-00384-1] [PMID: 33514942]
5. Kouli A, Trab SS, Alshaghel S, Mouti MB, Hamdoun H. Congenital nephrotic syndrome as a complication of whooping cough: a case report. Oxf Med Case Reports. 2020;2020(2):omaa007. [DOI: 10.1093/omcr/omaa007] [PMID: 32128219]
6. Vivarelli M, Gibson K, Sinha A, Boyer O. Childhood nephrotic syndrome. Lancet. 2023;402(10404):809–24. [DOI: 10.1016/S0140-6736(23)01051-6] [PMID: 37659779]
7. Cil O, Besbas N, Duzova A, Topaloglu R, Peco-Antić A, Korkmaz E, et al. Genetic abnormalities and prognosis in patients with congenital and infantile nephrotic syndrome. Pediatr Nephrol. 2015;30(8):1279–87. [DOI: 10.1007/s00467-015-3058-x] [PMID: 25720465]
8. Bérody S, Heidet L, Gribouval O, Harambat J, Niaudet P, Baudouin V, et al. Treatment and outcome of congenital nephrotic syndrome. Nephrol Dial Transplant. 2019;34(3):458–67. [DOI: 10.1093/ndt/gfy015] [PMID: 29474669]

9. Wong W, Morris MC, Kara T. Congenital nephrotic syndrome with prolonged renal survival without renal replacement therapy. Pediatr Nephrol. 2013;28(12):2313–21. [DOI: 10.1007/s00467-013-2584-7] [PMID: 23949594]
10. Rong L, Chen L, Rao J, Shen Q, Li G, Liu J, et al. Genetic Variations and Clinical Features of NPHS1-Related Nephrotic Syndrome in Chinese Children: A Multicenter, Retrospective Study. Front Med (Lausanne). 2021;8:771227. [DOI: 10.3389/fmed.2021.771227] [PMID: 34859019]
11. Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C, Kehrer-Sawatzki H. Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Hum Genet. 2013;132(10):1077–130. [DOI: 10.1007/s00439-013-1331-2] [PMID: 23820649]
12. Lee JM, Kronbichler A, Shin JI, Oh J. Current understandings in treating children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2021;36(4):747–61. [DOI: 10.1007/s00467-020-04476-9] [PMID: 32086590]
13. Kemper MJ, Lemke A. Treatment of Genetic Forms of Nephrotic Syndrome. Front Pediatr. 2018;6:72. [DOI: 10.3389/fped.2018.00072] [PMID: 29632851]
14. Eichinger A, Ponsel S, Bergmann C, Günthner R, Hoefele J, Amann K, et al. Cyclosporine A responsive congenital nephrotic syndrome with single heterozygous variants in NPHS1, NPHS2, and PLCE1. Pediatr Nephrol. 2018;33(7):1269–72. [DOI: 10.1007/s00467-018-3961-z] [PMID: 29663071]
15. Mulić B, Miloševski-Lomić G, Paripović D, Kruščić D, Mulić M, Peco-Antić A. Congenital nephrotic syndrome may respond to cyclosporine A – A case report and review of literature. Srp Arh Celok Lek. 2017;145(7–8):407–10. [DOI: 10.2298/SARH160907070M]
16. Kestilä M, Männikkö M, Holmberg C, Gyapay G, Weissenbach J, Savolainen ER, et al. Congenital nephrotic syndrome of the Finnish type maps to the long arm of chromosome 19. Am J Hum Genet. 1994;54(5):757–64. [PMID: 8178817]
17. Patrakka J, Kestilä M, Wartiovaara J, Ruotsalainen V, Tissari P, Lenkkeri U, et al. Congenital nephrotic syndrome (NPHS1): features resulting from different mutations in Finnish patients. Kidney Int. 2000;58(3):972–80. [DOI: 10.1046/j.1523-1755.2000.00254.x] [PMID: 10972661]
18. Lenkkeri U, Männikkö M, McCready P, Lamerdin J, Gribouval O, Niaudet PM, et al. Structure of the gene for congenital nephrotic syndrome of the finnish type (NPHS1) and characterization of mutations. Am J Hum Genet. 1999;64(1):51–61. [DOI: 10.1086/302182] [PMID: 9915943]
19. Espinosa LG, Santoveña AZ, Blanco JN, Alvariño MG, Feito JB, Hijosa MM. Spontaneous remission in a child with an NPHS1-based congenital nephrotic syndrome. Clin Kidney J. 2022;15(10):1969–70. [DOI: 10.1093/ckj/sfac086] [PMID: 36158155]
20. Li Z, Zhuang L, Han M, Li F. A case report of congenital nephrotic syndrome caused by new mutations of NPHS1. J Int Med Res. 2021;49(8):3000605211038133. [DOI: 10.1177/03000605211038133] [PMID: 34396835]

Однос између генотипа и фенотипа у благом конгениталном нефротском синдрому

Билсана Мулић[1], Амира Пецо-Антић[2], Фатих Озалтин[3]

[1]Општа болница „Нови Пазар", Педијатријско одељење, Нови Пазар, Србија;
[2]*Acibadem Bel Medic*, Београд, Србија;
[3]Универзитет „Хаџетепе", Медицински факултет, Одељење за педијатријску нефрологију, Анкара, Турска

САЖЕТАК

Увод Конгенитални нефротски синдром је тешка болест компликована хемодинамском нестабилношћу, инфекцијама, тромбозом, поремећајем раста и прогресијом бубрежне инсуфицијенције до терминалног стадијума у року од неколико година. Мутације гена *NPHS1* који кодирају нефрин су најчешћи узрок конгениталног нефротског синдрома. Циљ овог рада је да опишемо болесницу са хомозиготном *NPHS1 Ser350Pro missense* мутацијом која је неочекивано изазвала благи клинички ток конгениталног нефротског синдрома.

Приказ болесника Приказан је случај девојчице којој је са два и по месеца дијагностикован тешки нефротски синдром. Док је чекала резултат генетичке анализе, девојчица је четири недеље безуспешно лечена кортикостероидима и инхибитором ензима који конвертује ангиотензин, а затим је под циклоспорином А и инхибитором ензима који конвертује ангиотензин постигла делимичну ремисију у року од три месеца. У почетку се блажи клинички ток објашњавао позитивним дејством циклоспорина А, али како је делимична ремисија трајала и после укидања овог лека, остаје нејасно шта је утицало на побољшање клиничког тока болести. У време писања овог рада болесница је имала 10,9 година, нормалан креатинин серума, нормалан крвни притисак и ненефротску протеинурију.

Закључак *NPHS1* хомозиготна *Ser350Pro missense* мутација се може испољити благим клиничким током конгениталног нефротског синдрома. Потребне су даље студије да би се разјаснио предиктивни однос између генотипа и фенотипа у конгениталном нефротском синдрому.

Кључне речи: ген *NPHS1*; нефрин; хередитарни нефротски синдром; одојче

DOI: https://doi.org/10.2298/SARH231107004L
UDC: 616.36-002-055.26; 615.225.065

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A rare case of alpha-methyldopa-induced hepatitis in pregnancy

Ivana Likić-Lađević[1,2], Miloš Petronijević[1,2], Svetlana Vrzić-Petronijević[1,2], Aleksandra Beleslin[1], Stefan Dugalić[1,2]

[1]University Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction There are three groups of disorders during pregnancy: disorders specific for pregnancy that resolve spontaneously or soon after delivery, acute hepatic disorders coinciding with pregnancy, and chronic disorders. Drug-induced liver disease prevails among women and it is estimated to be a leading cause of acute liver injury. Drug-induced hepatitis is rare in pregnancy with only a few cases reported in literature. Alpha-methyldopa is one of the commonly used drugs in pregnancy that could cause hepatotoxicity with different clinical presentations and possible adverse effects on normal course of pregnancy.

Case outline We reported a rare case of hepatotoxicity caused by alpha-methyldopa in 26 gestational weeks pregnancy in a 35-year-old patient admitted because of jaundice and elevated liver function tests. She had been using antihypertensive drug, alpha-methyldopa, from 12th gestational week, and no other medication or supplementation was recorded. Ultrasound of the abdomen excluded obstruction or any other abnormalities. Autoimmune panel was done. Biochemical analyses were indicative of toxic acute liver injury caused by alpha-methyldopa according to values of transaminase. After 13 days, patient was discharged recovered from the hospital.

Conclusion Diagnosis of alpha-methyldopa hepatotoxicity is challenging since the low incidence, unpredictability, diverse symptomatology and absence of specific biomarkers. That is why timely diagnosis is crucial for the well-being of both future mother and child.

Keywords: drug-induced hepatitis; alpha-methyldopa; hypertension in pregnancy; hepatotoxicity

INTRODUCTION

Hepatic disorders during pregnancy are divided into three groups: disorders specific for pregnancy that resolve spontaneously or soon after delivery, acute hepatic disorders coinciding with pregnancy such as acute viral hepatitis, and chronic disorders – chronic viral hepatitis or cirrhosis [1]. Drug-induced hepatotoxicity is an acute or chronic liver injury caused by medications, herbs or dietary supplements with incidence under 15 per 100,000 in general population [2]. Although drug-induced liver disease prevails among women and is estimated to be a leading cause of acute liver injury, drug-induced hepatitis is rare in pregnancy with only a few cases reported in the literature [2, 3]. Alpha-methyldopa is one of the commonly used drugs in pregnancy that could cause hepatotoxicity with different clinical presentations [4]. Diagnosis is difficult due to its rarity and diverse symptomatology. Physiological changes in pregnancy and pregnancy-induced hepatic disorders make the diagnosis even more challenging.

Hence, the aim of this paper is to report a rare case of hepatotoxicity caused by alpha-methyldopa in pregnancy, pointing out possible adverse effects of antihypertensive treatment affecting normal course of pregnancy.

CASE REPORT

A 35-year-old patient was admitted to the Clinic for Gynecology and Obstetrics at 26 weeks of gestation because of jaundice and elevated liver function tests. The patient complained of jaundice, dark urine, and pale stools starting the day before admission. No fever, pruritus, or any other symptom were reported. She had been using antihypertensive drug, alpha-methyldopa in the dose of 3 × 250 mg from 12th gestational week, no other medication or supplementation was recorded. Besides that, a normal course of pregnancy has been established. Her personal medical history was positive for chronic hypertension and she had one vaginal delivery three years previously. Upon admission, clinical examination and laboratory tests were done. Physical examination showed only skin and scleral icterus. Palpation of abdomen was without tenderness, rigidity, or guarding. No organomegaly was palpated. No leg oedema or varicosities. Vital signs were within normal range for pregnancy. Obstetrical ultrasound indicated vital singleton pregnancy with adequate amniotic fluid and normal placental insertion. Fetal biometry corresponded for 24 weeks of gestation. Laboratory findings were: leukocytes 12.8 × 10^9/L (normal range 4.0–10.0), lymphocytes 6.40% (20.00–45.00), monocytes 1.60% (4.00–8.00), hemoglobin 121

Received • Примљено: November 7, 2023
Accepted • Прихваћено: December 9, 2023
Online first: January 11, 2024

Correspondence to:
Aleksandra BELESLIN
University Clinical Centre of Serbia
Clinic for Gynecology and Obstetrics
Koste Todorovića 26
11000 Belgrade
Serbia
aleksandrabeleslin@gmail.com

g/L, platelet count 273 × 10ˆ9/L, C-reactive protein 22.4 mg/L (0.0–5.0). Prothrombin time was 15.8s, INR 1.48 (0.80–1.20), D-dimer 3.17 mg/L in fibrinogen-equivalent units (<0.50). Liver tests were as following: aspartate transaminase (AST) 1123 U/L (0–37), alanine aminotransferase (ALT) 833 U/L (40–120), total bilirubin 217,4 umol/L (0.0–20.5), direct bilirubin 111.0 umol/L (0.0–3.4), albumin 32 g/L (34–55), alkaline phosphatase 198 U/L (40–120), gamma-glutamyl transferase 40 U/L (0–38), lactate dehydrogenase 757 U/L (220–460). Serological tests for HIV, hepatitis A, B, and C, Epstein–Barr virus (EBV) and cytomegalovirus were negative. Ultrasound of the abdomen excluded obstruction or any other abnormality as cause of present state. During hospitalization, the patient was closely monitored and followed by expert perinatologist, cardiologist, and gastroenterologist. Alpha-methyldopa was suspended and nifedipine was introduced for blood pressure control. Due to further deterioration of liver function tests after two days in hospital the emergency Caesarean section was preformed when female premature neonate weighing 640 grams was born with Apgar score 2 in the first minute and 3 in the fifth minute.

Further evaluation of patient included autoimmune panel to exclude autoimmune liver disease (antinuclear antibody, antineutrophil cytoplasmic antibody, antimitochondrial antibody, anti-liver kidney microsomal antibody, anti-smooth muscle antibody). All tests were negative. Values of ceruloplasmin, blood and urine copper, urinary porphobilinogen, alpha-1 antitrypsin were within normal range. An abdominal magnetic resonance was performed, as well as magnetic resonance cholangiopancreatography, indicating liver steatosis and a 9 mm cyst in the tail of pancreas without any communication with duct of Wirsung. Liver function tests were serially monitored and the decrease was observed. Ten days after alpha methyldopa cessation values of AST was 137 U/L (0–37), ALT 221 U/L (40–120), total bilirubin 61.4 umol/L (0.0–20.5), direct bilirubin 30.6 umol/L (0.0–3.4).

The diagnosis of drug-induced hepatotoxicity was made by exclusion. Biochemical analysis were indicative of toxic acute liver injury caused by alpha-methyldopa according to values of transaminase (AST > ALT) and lactate dehydrogenase (LDH) and ALT ratio (LDH : ALT < 1.5). Since the values of transaminases and bilirubin continued to fall, the patient was discharged after 13 days.

We confirm that we have read the journal's position on issues involving ethical publication and affirm that this work is consistent with those guidelines. The written consent for publication of this article has been obtained from the patient.

DISCUSSION

A rare case of hepatotoxicity as an adverse effect of oral antihypertensive therapy in pregnancy is presented. Alpha-methyldopa is widely used drug for hypertension disorder in pregnancy that lowers blood pressure acting as central inhibitory alpha-adrenergic receptor [5]. Hepatotoxicity with alpha-methyldopa is idiosyncratic, unpredictable and according to literature starts 1–20 weeks after introduction of the drug [4, 5]. It is estimated that liver disease complicates 3% of pregnancies [6]. It is important to distinguish whether liver disease is pregnancy related or not [1]. Thorough evaluation is important to distinguish physiological changes in pregnancy, acute liver injury and wide spectrum of pregnancy-induced hepatic disorders such as hyperemesis gravidarum, acute fatty liver, intrahepatic cholestasis of pregnancy and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Pregnancy related disorders such as preeclampsia, eclampsia, and HELLP syndrome should not be misdiagnosed. Wide panel of hematological and biochemical analysis is obtained to help diagnostics. Blood tests including ALT, ALP, bilirubin, and albumin detect acute liver injury [4]. Transaminase values above 1000 U/L are indicate of hepatocellular injury which occurs in viral hepatitis, ischemic or drug-induced liver injury [5]. Our patient's liver function tests were indicative of hepatocellular injury.

Differential diagnosis includes infections such as viral hepatitis, cytomegalovirus and Epstein–Barr virus, but also autoimmune hepatitis, hypoxic hepatopathy, biliary tract obstruction, Wilson disease, hemochromatosis and Alpha-1-antitrypsin deficiency [4]. Diagnosis is mostly made by exclusion so thorough work-up is mandatory. In this case, serology and autoimmune panel were done accordingly, excluding viral and autoimmune disease. Multidisciplinary team was consulted to exclude various differential diagnosis. Imaging methods proved to be very useful. If drug induced liver injury is suspected, an abdominal ultrasound should be performed [4]. Additional imaging depends on clinical presentation. We performed ultrasound of abdomen and magnetic resonance cholangiopancreatography to exclude biliary tract obstruction.

Timely diagnosis with close monitoring is crucial because liver injury is potentially fatal both for mother and for child. Luckily, most patients recover after drug cessation, as was here the case. Our patient recovered liver function and was discharged after 13 days. Fatal outcome is also possible with only one case described in literature [7]. Because of the diversity of clinical presentation, consultations of multidisciplinary team could contribute to faster diagnosis and enable adequate therapy and follow-up.

Diagnosis of alpha-methyldopa hepatotoxicity is challenging since the low incidence, unpredictability, diverse symptomatology and absence of specific biomarkers. Clinical presentation varies from asymptomatic to foudroyant and possible fatal outcome and could lead to adverse perinatal outcome. Thus, timely diagnosis is important for patient's recovery in order to avoid neonatal morbidity and mortality.

Conflict of interest: None declared.

REFERENCES

1. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol. 2016;64(4):933–45. [DOI: 10.1016/j.jhep.2015.11.030] [PMID: 26658682]
2. Francis P, Navarro VJ. Drug-Induced Hepatotoxicity. [Updated 2022 Nov 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557535/
3. Kashkooli S, Baraty B, Kalantar J. α-Methyldopa-induced hepatitis during the postpartum period. BMJ Case Rep. 2014;2014:bcr2014203712. [DOI: 10.1136/bcr-2014-203712] [PMID: 24577181]
4. European Association for the Study of the Liver. Clinical Practice Guideline Panel: Chair; Panel members; EASL Governing Board representative. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222–61. [DOI: 10.1016/j.jhep.2019.02.014] [PMID: 30926241]
5. Lao TT. Drug-induced liver injury in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2020;68:32–43. [DOI: 10.1016/j.bpobgyn.2020.03.005] [PMID: 32312690]
6. Mikolasevic I, Filipec-Kanizaj T, Jakopcic I, Majurec I, Brncic-Fischer A, Sobocan N, et al. Liver Disease During Pregnancy: A Challenging Clinical Issue. Med Sci Monit. 2018;24:4080–90. [DOI: 10.12659/MSM.907723] [PMID: 29905165]
7. Opinc M, Kalinka J. Drug-induced liver injury in early pregnancy associated with methyldopa administration during antihypertensive therapy. J Obstet Gynecol Investig. 2021;4:e1–e4. [DOI: 10.5114/jogi.2021.106111]

Редак случај хепатитиса у трудноћи изазваног алфа-метилдопом

Ивана Ликић-Лађевић[1,2], Милош Петронијевић[1,2], Светлана Врзић-Петронијевић[1,2], Александра Белеслин[1], Стефан Дугалић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за гинекологију и акушерство, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Поремећаји функције јетре током трудноће су подељени у три групе: поремећаји специфични за трудноћу који спонтано пролазе током трудноће или одмах после порођаја, акутна оштећења јетре која коегзистирају са трудноћом и хронична оштећења. Оштећења јетре узрокована лековима се чешће јављају код жена и водећи су узрок акутног оштећења јетре. Оштећења јетре која су узрокована лековима се ретко јављају у току трудноће; свега је неколико случајева забележених у литератури. Алфа-метилдопа је један од најчешће коришћених лекова током трудноће који би могао да изазове хепатотоксичност са различитим клиничким сликама и могућим негативним утицајем на ток трудноће.

Приказ болесника Представљен је редак случај хепатотоксичности, који је узрокован алфа-метилдопом у трудноћи старој 26 гестацијских недеља код болеснице старости 35 година, која је примљена због жутице и повећаних лабораторијских вредности параметара функције јетре. Болесница је била на антихипертензивној терапији алфа-метилдопом од 12. недеље гестације, без документованог коришћења других лекова или суплементације. Ултразвук абдомена је искључио постојање оклузије или друге патологије у абдомену. Аутоимуна обољења су такође искључена. Биохемијске анализе су указале на акутно токсично оштећење јетре. Тринаест дана по обустављању терапије болесница је отпуштена опорављена из болнице.

Закључак Дијагноза хепатотоксичности проузроковане алфа-метилдопом је изазовна имајући у виду ниску инциденцију, непредвидљивост, различиту симптоматологију и одсуство специфичних биомаркера. Управо због тога је правовремена дијагноза круцијална за добробит и будуће мајке и плода.

Кључне речи: хепатитис узрокован лековима; алфа-метилдопа; хипертензија у трудноћи; хепатотоксичност

DOI: https://doi.org/10.2298/SARH230111003S
UDC: 616.61-006-033.2

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Uncommon muscle metastatic sites of renal cell carcinoma

Maja Šapić[1], Danica Ninković[1], Aleksandra Bota[1], Zorica Milošević[1,2], Aleksandra Erić-Nikolić[1]

[1]Institute of Oncology and Radiology of Serbia, Department of Radiology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY

Introduction Renal cell carcinoma (RCC) is the most common malignant renal tumor. It has a tendency for spreading to unusual and distant sites, such as the orbit, paranasal sinuses, thyroid gland, heart, skin, and muscles. Skeletal muscle metastases are accounting for only 0.4% of all metastatic localizations. Following CT, they may be presented in five different radiology types of lesions.

The aim of our case was CT evaluation of rare skeletal muscle metastatic localizations of RCC, following the time interval of their occurrence in relation to the appearance of the primary tumor, with emphasis on metastases in the levator ani muscle, since this metastatic localization of RCC has not been recorded in the previous literature.

Case outline We present a 66-year-old man after partial nephrectomy, due to a primary diagnosis of RCC. Three years after the initial diagnosis, multiple distant metastases were verified at typical localizations, as well as rare localizations such as muscles, including levator ani.

Conclusion Advanced metastases in uncommon locations are most often accompanied by a poor prognosis, therefore the further algorithm includes monitoring the whole clinical and radiological status. Metastases in the levator ani muscle have been recorded for the first time in this report. Taking into account that this muscle has very important functions, such as supporting and raising the pelvic visceral structures, as well as having control of the flow of urine and defecation, it is of great importance to include this localization in the CT evaluation.

Keywords: muscle neoplasms; kidney neoplasms; computed tomography; levator ani muscle

INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignant renal tumor with common metastatic spreading to lymph nodes, lungs, liver, opposite kidney, adrenal glands, brain, and bones. Nevertheless, it was noticed that RCC may expose unusual and distant sites of metastases, such as the orbit, paranasal sinuses, thyroid gland, heart, skin, and muscles [1]. However, skeletal muscle metastases (SMM) occur extremely seldom, accounting for 0.4% of all metastatic sites [2]. According to literature data, the average interval between the primary diagnosis of RCC and the first SMM is 32 months [3].

For the first time, according to former literature data, we noticed metastases in the levator ani muscle (Figure 1). The levator ani muscle consists of the confluence of three muscles: pubococcygeus, puborectalis, and iliococcygeus muscles. The function of the levator ani is to support and raise the pelvic visceral structures. Furthermore, it helps to manage mechanical pressures during movement and assists during respiration. In addition, the levator ani muscle through the pubococcygeal muscle, as its inferior medial part, controls the flow of urine, as well as defecation and proper sexual functioning [4, 5, 6].

Following computed tomography (CT), SMM may be presented in five different radiological types of lesions [1, 7]. In our case, type II is the most common, presented as central low attenuation with rim enhancement as it occurs in the levator ani (Figure 1).

The aim of this report was CT evaluation of unusual localizations of metastatic lesions of RCC, such as those in skeletal muscles, due to the interval of their appearance with regard to the occurrence of the primary tumor, with an accent on metastases located in the levator ani muscle, since this metastatic site of RCC was not noticed in the literature data.

CASE REPORT

We present a 66-year-old male with a primary diagnosis of clear cell renal cell carcinoma (ccRCC, Fuhrman grade II–III), initially verified four years previously. The patient underwent partial nephrectomy of the right kidney. Three years after the initial diagnosis, the patient manifested clinical exacerbations: dizziness, headaches, vomiting, and postural instability, as a consequence of brain metastases. Consequently, body and head CT exams verified distant metastases for the first time, in the left adrenal gland, left kidney, lung, brain, and in muscles (Table 1): left levator ani muscle, right thyrohyoid muscle, erector spine muscle [at the level of sixth and seventh

Received • Примљено: January 11, 2023
Revised • Ревизија: November 28, 2023
Accepted • Прихваћено: January 3, 2024
Online first: January 11, 2024

Correspondence to:
Aleksandra ERIĆ NIKOLIĆ
Institute of Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade, Serbia
eric.aleksandra@gmail.com

Table 1. Localization of skeletal muscle metastases of renal cell carcinoma with the sizes of the lesions during a one-year period between CT when muscle metastases were discovered for the first time (October 2021) and at the newest CT exam (October 2022)

Site	Size of the lesion (October 2021)*	Size of the lesion (October 2022)*	Increasing volume of the lesion (Oct. 2021 – Oct. 2022)
Levator ani$^{\Psi}$	17 × 11 × 13 mm	26 × 18 × 22 mm	4.23 its size
Thyrohyoid	10 × 8 × 10 mm 7 × 6 × 5 mm /$^{\lambda}$	11 × 13 × 19 mm 16 × 13 × 16 mm 12 × 8 × 10 mm	3.39 its size 15.85 its size /$^{\lambda}$
Erector spine C6–C7 Th8–Th9 Th9 L1 L4 L5 Sacroiliac joint	 25 × 14 × 30 mm 10 × 10 × 38 mm /$^{\lambda}$ 9 × 13 × 14 mm 5 × 7 × 4 mm /$^{\lambda}$ 8 × 17 × 26 mm	 35 × 32 × 41 mm 23 × 14 × 55 mm 8 × 6 × 15 mm 15 × 18 × 31 mm 10 × 13 × 19 mm 12 × 19 × 20 mm 24 × 37 × 53 mm	 4.37 its size 4.66 its size /$^{\lambda}$ 5.11 its size 17.64 its size /$^{\lambda}$ 13.3 its size
Diaphragm	/$^{\lambda}$	14 × 15 × 14 mm	/$^{\lambda}$
Iliacus	16 × 10 × 15 mm	20 × 10 × 16 mm	1.33 its size
Adductor magnus	17 × 15 × 23 mm	29 × 24 × 37 mm	4.39 its size
Gluteus maximus	11 × 5 × 12 mm	12 × 25 × 13 mm	5.91 its size

$^{\Psi}$Lesion in this muscle reported for the first time according to the literature;
*(AP × LL × CC, anteroposterior × laterolateral × craniocaudal);
$^{\lambda}$lesion was not detectable on the first CT exam (October 2021)

The multidisciplinary tumor board determined targeted therapy treatment with pazopanib due to metastatic disease of RCC.

Thereon, CT exams were performed every three months. After nine months, next to the ninth targeted therapy treatment, additional CT was done and new sites of muscle metastases were detected: in the erector spine muscle, at the level of the fifth lumbar vertebra, and in the costal part of the right diaphragm. In addition, all earlier metastases persisted, with the sign of progression in size (Figure 1a).

The last CT exam was done after 12 targeted therapy treatments, when the new sites of metastases were reported: one more lesion in the right thyrohyoid muscle and one lesion in the right erector spine muscle at the level of the ninth thoracic vertebrae. Most importantly, all earlier verified lesions exhibited progression in size (Table 1, Figures 1b, 1c, 2b).

Magnetic resonance imaging was not performed, due to the presence of a metallic foreign body in the patient. The multidisciplinary tumor board did not recomend the biopsy of muscle metastases, taking into account the synchronic appearance of other distant metastases, as well as small sizes of muscle lesions,

cervical vertebrae; at the level of eight thoracic vertebrae; at the level of the first lumbar vertebrae, as well as fourth lumbar vertebrae and near the right sacroiliac joint (Figure 2a)]; left iliac muscle, right adductor magnus muscle and in the right gluteus maximus muscle.

Due to the brain metastases, the patient underwent osteoplastic decompressive craniotomy occipitally left, toward tumor extirpation. Therapy continued with radiosurgery procedures (gamma knife).

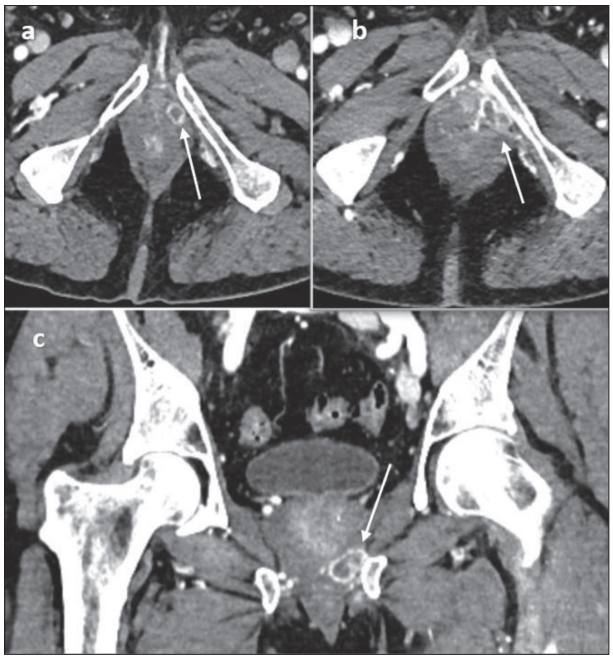


Figure 1. (a) Type II lesion, presented as central low attenuation with rim enhancement, (arrow) in the levator ani muscle, next to the ninth targeted therapy – 20 × 13 × 20 mm [anterior-posterior (AP) × latero-lateral (LL) × cranial-caudal (CC)] and progression of the same lesion three months later – 26 × 18 × 22 mm (AP × LL × CC) in **(b)** axial (arrow), and **(c)** coronal plane (arrow)

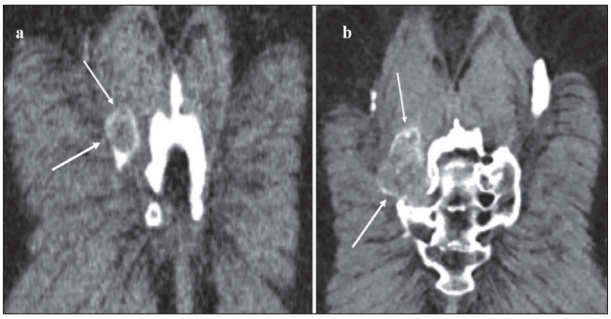


Figure 2. Coronal contrast-enhanced CT metastatic lesion in erector spine muscle near the right sacroiliac joint **(a)** initial finding (arrows) – 8 × 17 × 26 mm [anterior-posterior (AP) × latero-lateral (LL) × cranial-caudal (CC)], and **(b)** the same lesion in progression on the last CT – 24 × 37 × 53 mm (AP × LL × CC) (arrows), which is 13.3 times greater than the initial CT, making it one of the largest progressions among the recorded lesions

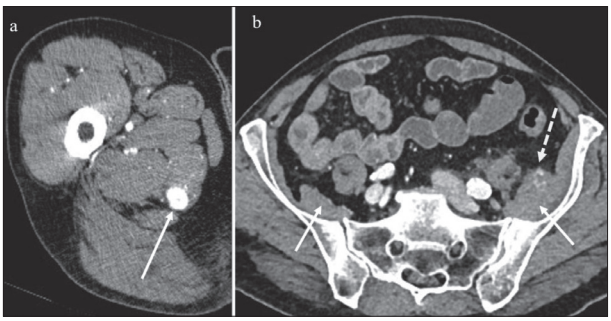


Figure 3. Axial contrast-enhanced CT metastatic type I lesion, presented as oval-shaped lesions, with homogenous enhancement **(a)** in the right adductor magnus muscle (arrow), **(b)** type II lesion (dotted arrow), and type III (arrow) in the left iliac muscle; the right iliac muscle without any type of metastases (arrow)

which manifested neither compressive effects nor clinical manifestations.

The authors declare that the article has been written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved. No personal data of the patient have been presented in the manuscript. Written consent to publish all shown material was obtained from the patient.

DISCUSSION

This case report presents rare distant skeletal metastases of RCC, including those in the levator ani muscle, which are shown for the first time.

At the time of discovery, about 16% of patients with RCC had distant metastases; around 25% of patients with localized RCC ended up having distant metastases after the nephrectomy, while skeletal muscles are extremely rare, accounting for 0.4% in all metastatic sites [1, 2]. In our case, distant metastases, including those in skeletal muscles, occurred 43 months after primary diagnosis and partial nephrectomy, which is more than the previously described average time of appearance of the first SMM, which was 32 months [3].

SMM from carcinomas are commonly located in the axial region of the body. This is of particular importance to distinguish these lesions in muscles from primary soft-tissue neoplasms [8]. We reported spinal erectors, iliac muscle, adductor magnus muscle, gluteus maximus muscle, and levator ani muscle, as the most frequent localizations of muscle metastases, which is in accordance with previous data [3].

Although skeletal muscles represent 50% of the total body mass, metastasis to these sites is very rare due to some homeostatic conditions, such as high concentration of lactate, which prevents neovascularization of metastatic deposits [8, 9].

The most common way of SMM dissemination is hematogenous. Nevertheless, spreading has also been described to occur through venous vessels, e.g., the paravertebral venous plexus, intramuscular aberrant lymph nodes, as well as through perineural spread [10]. Accordingly, the occurrence of metastases in paravertebral muscles could be explained by dissemination through the paravertebral venous plexus.

Contrary to the previous explanation, alteration of the normal protective environment, such as trauma, can make these sites suitable for developing metastatic deposits. Trauma is thought to cause focal hyperemia, with an increase in blood flow and releasing growth-promoting factors, that can trap circulating tumor cells and induce metastatic seeding [11].

By literature data, there are presented five types of muscle metastases: focal intramuscular masses (type I), abscess-like intramuscular lesions (type II), diffuse metastatic muscle infiltrations (type III), multifocal intramuscular calcifications (type IV), and intramuscular bleedings (type V) [7]. In up to 83% of cases, the most common CT presentation occurs as a discrete rim-enhancing lesion with a central hypodense area, which matches with type II [12]. In our case, this is the most common type of CT presentation as well, with the exception of oval-shaped lesions, with homogenous enhancement in the right adductor magnus muscle and in the right gluteus maximus muscle, which correspond to type I (Figure 3a). In the left iliac muscle, the lesion exhibits characteristics of both type II and III – abscess-like intramuscular lesion combined with muscle swelling (Figure 3b).

The pubococcygeal muscles form the inferior medial part of the levator ani muscle and control the flow of urine, as well as defecation and proper sexual functioning [4, 5, 6]. In our case, in the left pubococcygeal muscle is a rim-enhanced lesion, which looks like other lesions with radiology type II (Figure 1). Taking into account all previous stated functions of the levator ani muscle, we regard that it is of great importance to include this localization in consideration during the CT monitoring of metastases of RCC.

Due to the rarity of muscle metastases, it is important to notice the value of MRI, in order to distinguish primary soft tissue tumors from metastatic tumors, as it has been reported previously [7]. Nevertheless, biopsy still remains the gold standard to diagnose and differentiate RCC metastasis from other soft tissue tumors [2].

Taking into account that the metastases in the skeletal muscles are usually painless and have a small size, they can remain asymptomatic for a long time and often be detected when they reach a large size [13]. Nonetheless, in our case, all muscle metastases were reported as accidental and asymptomatic, probably due to their small size and absence of compressive effects on the nearest structures, except recurrent rectal pain and hemorrhoids likely resulted from the compressive effect of the mass on the levator ani muscle.

Patients with RCC with metastasis to rare sites most often have advanced cancers with poor prognoses [1]. At the moment when the muscle metastases were verified initially in our case, other distant metastases, including those in the brain, already existed. We would especially like to underline the significance of the appearance of the levator ani muscle metastases, reported for the first time according to the literature, due to its important physiological functions and to include this localization in consideration during the CT evaluation.

Further algorithm includes monitoring of the entire clinical and radiological status, due to administered targeted therapy, along with the size and possible occurrence of new muscle metastases.

Conflict of interest: None declared.

REFERENCES

1. Singla A, Sharma U, Makkar A, Masood PF, Goel HK, Sood R, et al. Rare metastatic sites of renal cell carcinoma: a case series. Pan Afr Med J. 2022;42:26. [DOI: 10.11604/pamj.2022.42.26.33578] [PMID: 35910051]
2. Safadi A, Abu Ahmad MS, Sror S, Schwalb S, Katz R. Simultaneous metachronous renal cell carcinoma and skeletal muscle metastasis after radical nephrectomy. Urol Case Rep. 2017;16:17–9. [DOI: 10.1016/j.eucr.2017.09.013] [PMID: 29021965]
3. Haygood TM, Sayyouh M, Wong J, Lin JC, Matamoros A, Sandler C, et. al. Skeletal Muscle Metastasis from Renal Cell Carcinoma: 21 cases and review of the literature. Sultan Qaboos Univ Med J. 2015;15(3):e327–37. [DOI: 10.18295/squmj.2015.15.03.005] [PMID: 26357552]
4. Gowda SN, Bordoni B. Anatomy, Abdomen and Pelvis: Levator Ani Muscle. 2022 Oct 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. [PMID: 32310538]
5. Nyangoh Timoh K, Moszkowicz D, Zaitouna M, Lebacle C, Martinovic J, Diallo D, et al. Detailed muscular structure and neural control anatomy of the levator ani muscle: a study based on female human fetuses. Am J Obstet Gynecol. 2018;218(1):121.e1–121.e12. [DOI: 10.1016/j.ajog.2017.09.021] [PMID: 28988909]
6. Emerich Gordon K, Reed O. The Role of the Pelvic Floor in Respiration: A Multidisciplinary Literature Review. J Voice. 2020;34(2):243–9. [DOI: 10.1016/j.jvoice.2018.09.024] [PMID: 30447797]
7. Surov A, Hainz M, Holzhausen HJ, Arnold D, Katzer M, Schmidt J, et. al. Skeletal muscle metastases: primary tumours, prevalence, and radiological features. Eur Radiol. 2010;20(3):649–58. [DOI: 10.1007/s00330-009-1577-1] [PMID: 19707767]
8. Pretell-Mazzini J, Younis MH, Subhawong T. Skeletal Muscle Metastases from Carcinomas: A Review of the Literature. JBJS Reviews. 2020;8(7):e1900114–8. [DOI: 10.2106/JBJS.RVW.19.00114] [PMID: 32618741]
9. Stergioula A, Pantelis E, Kormas T, Agrogiannis G. Case report: skeletal muscle metastasis from follicular thyroid carcinoma presenting as synovial sarcoma. Front Oncol. 2023;13:994729. [DOI: 10.3389/fonc.2023.994729] [PMID: 36845746]
10. Perisano C, Spinelli MS, Graci C, Scaramuzzo L, Marzetti E, Barone C, et al. Soft tissue metastases in lung cancer: a review of the literature. Eur Rev Med Pharmacol Sci. 2012;16(14):1908–14. [PMID: 23242715]
11. Song Q, Sun XF, Wu XL, Dong Y, Wang L. Skeletal muscle metastases of hepatocellular carcinoma: A case report and literature review. World J Clin Cases. 2021;9(14):3334–41. [DOI: 10.12998/wjcc.v9.i14.3334] [PMID: 34002142]
12. Daneti D, Senthamizhselvan K, Verma SK, Mohan P. Gastric adenocarcinoma presenting with multiple skeletal muscle metastases. BMJ Case Rep. 2021;14(1):e239518. [DOI: 10.1136/bcr-2020-239518] [PMID: 33462054]
13. Sun J, Zhang Z, Xiao Y, Li H, Ji Z, Lian P, et al. Skeletal Muscle Metastasis From Renal Cell Carcinoma: A Case Series and Literature Review. Front Surg. 2022;9:762540. [DOI: 10.3389/fsurg.2022.762540] [PMID: 35310441]

Мишићне метастазе карцинома бубрежних ћелија

Маја Шапић[1], Даница Нинковић[1], Александра Бота[1], Зорица Милошевић[1,2], Александра Ерић-Николић[1]

[1]Институт за онкологију и радиологију Србије, Служба радиолошке дијагностике, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Карцином бубрежних ћелија је најзаступљенији малигни тумор бубрега. Осим ширења на уобичајене локализације – супротан бубрег, надбубрежне жлезде, плућа, јетру, мозак, коштани систем, показује тенденцију ка појави удаљених метастаза на ретким местима, као што су орбита, параназални синуси, штитаста жлезда, срце, кожа и мишићи. Појава метастаза у скелетним мишићима је изузетно ретка, чинећи свега 0,4% свих метастатских локализација. Метастазе у скелетним мишићима, праћене компјутеризованом томографијом (*CT*), могу се презентовати у пет радиолошких типова лезија, а у нашем раду најзаступљенија лезија је по другом типу – „интрамускуларна лезија налик апсцесу".

Циљ нашег рада је била *CT* евалуација ретких локализација метастатских лезија карцинома бубрежних ћелија у скелетним мишићима, пратећи временски интервал њиховог настанка у односу на појаву примарног тумора, са акцентом на метастазе лоциране у *musculus levator ani*, будући да ова метастатска локализација карцинома бубрежних ћелија није евидентирана у досадашњој литератури.

Приказ болесника У овом раду представили смо 66-годишњег мушкарца са карциномом бубрежних ћелија десног бубрега. Три године после поставке иницијалне дијагнозе евидентиране су удаљене метастазе на типичним, али и на ретким локализацијама – скелетним мишићима, укључујући и *m. levator ani*.

Закључак Узнапредовале метастазе на нетипичним локализацијама најчешће су праћене лошом прогнозом, па је у наставку лечења битно вршити како дијагностичку, тако и клиничку евалуацију. У овом приказу је први пут евидентиран *m. levator ani* као ретка метастатска локализација. С обзиром на важне физиолошке функције овог мишића, као што су контрола мокрења и дефекације и подржавање пелвичних висцералних структура, ова локализација би требало увек да буде обухваћена *CT* евалуацијом.

Кључне речи: мишићне метастазе; неоплазма бубрега; компјутеризована томографија; *musculus levator ani*

DOI: https://doi.org/10.2298/SARH230727104A
UDC: 616.25-006-085.849

CURRENT TOPIC / АКТУЕЛНА ТЕМА

The role of radiotherapy in the treatment of malignant pleural mesothelioma – possibilities and controversy

Tatjana Arsenijević, Aleksandar Stepanović, Marina Nikitović

University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

SUMMARY

Malignant pleural mesothelioma (MPM) is a rare malignancy with poor prognosis. In recent years, significant progress has been made in the treatment of this disease, including surgical and radiotherapy techniques, systemic therapy, and immunotherapy. Due to the wide range of clinical presentations, a lack of phase-III randomized trials, and heterogeneity in treatment approach, the treatment of MPM remains challenging regardless of available diagnostic and therapeutic guidelines.

The limited possibility to avoid critical healthy organs (particularly lungs), overexposure of which can lead to severe, and even fatal, radiation-induced toxicity, makes high-dose radical radiotherapy very demanding. Thus, the majority of patients in the era of conventional radiotherapy were mostly referred to no more than palliative radiotherapy.

Technological development in radiotherapy such as respiratory gating, 4D computed tomography, intensity-modulated radiotherapy, volumetric modulated arc therapy, stereotactic techniques, and proton therapy, made a step forward in treating MPM with this modality. Today, MPM radiotherapy can be considered in various indications, alone or in combination with surgery and systemic treatment.

However, many questions remain open, and further investigation is needed especially in dose escalation possibility and lung sparing.

Keywords: malignant pleural mesothelioma; radiotherapy; treatment

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare malignancy, but the outcome remains poor with less than 5% of the five-year overall survival for all stages [1, 2, 3]. To date, it is of great oncological concern since it is correlated with significant morbidity and severe symptoms such as pleural effusion, dyspnea, pain, and fatigue [4, 5].

Due to various clinical presentations of MPM and challenging clinical scenarios, the treatment of MPM must be decided by a multidisciplinary approach, with an individually tailored strategy concerning the stage of the disease, histology, performance status, comorbidities, and patient preferences [6].

In the absence of clear data on the radiosensitivity of mesothelioma, clinical evidence points out that it is a rather radioresistant disease, needing a high dose of radiotherapy to the near proximity of critical healthy structures in order to obtain local control. With conventional radiotherapy (2D and 3D conformal radiotherapy), the treatment of MPM was mainly directed to surgery and systemic therapy, while radiotherapy was usually palliative or adjuvant in selected cases [4].

Technological developments in radiotherapy including respiratory gating, 4D computed tomography (4DCT), intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiotherapy (SBRT), and proton therapy, brought back the interest to radiotherapy alone or in combination with systemic therapy and/or surgery. The choice of the radiotherapy technique depends on the clinical context, treatment intent (curative or palliative), localization and bulk of the target, organs at risk, and planned dose [7].

In the treatment of MPM today, radiotherapy has five major indications: 1) hemithorax irradiation prior to extrapleural pneumonectomy (EPP); hemithorax irradiation after extrapleural pneumonectomy; 3) hemithorax irradiation after lung spearing therapy (pleurectomy/decortication and/or systemic therapy); 4) prophylactic (procedural path) irradiation, and 5) palliation.

In 2019, Gomez et al. [8] published detailed guidelines for radiotherapy target delineation and treatment delivery for all the above-mentioned indications.

All five indications will be discussed focusing on novel radiotherapy technique possibilities, current practice, and open questions.

MPM RADIOTHERAPY PLANNING

Every radiotherapy treatment planning starts with the patient immobilization. For MPM patients it is usually a wing board, with arms

Received • Примљено: July 27, 2023
Revised • Ревизија: October 17, 2023
Accepted • Прихваћено: October 31, 2023
Online first: November 15, 2023

Correspondence to:
Tatjana ARSENIJEVIĆ
University of Belgrade
Faculty of Medicine
Institute for Oncology and Radiology of Serbia
Pasterova 14
11000 Belgrade, Serbia
tatjanaarsenijevic96@gmail.com

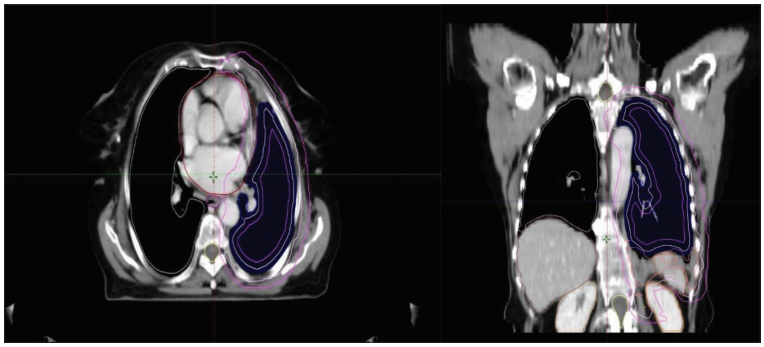


Figure 1. 4D computed tomography of the thorax; target volume delineation and organs at risk; gross tumor volume – orange contour at coronal slice; clinical target volume – light pink contour; planning target volume – purple contour; organs at risk: spinal column – yellow contour; esophagus – brown contour; heart – red contour; both lungs delineated, both kidneys and liver (Institute for Oncology and Radiology of Serbia)

overhead, the procedural scar marked with led markers. Standard 3D or 4DCT is performed in free breathing, from the lung apex to the third lumbar vertebrae due to low diaphragm insertions, with 2.5–3 mm thick slices. Prior diagnostic positron emission tomography – computed tomography is advisory for better gross tumor volume (GTV) delineation. The clinical target volume encompasses the entire thoracic cavity, as well as mediastinal lymph nodes. Planning target volume (PTV) is an additional margin of 5–10 mm in all directions for respiratory and set-up uncertainties. Organs at risk include both lungs, heart, kidneys, spinal cord, liver, and esophagus (Figure 1).

HEMITHORAX RADIOTHERAPY PRIOR TO EPP

Surgery for mesothelioma after IMRT radiation therapy was introduced by de Perrot et al. [9] in 2016 as a trial resembling standard hypofractionated preoperative radiotherapy approach in other malignant tumor localization, predominantly rectal cancer. A high radiotherapy dose of 25 Gy in five fractions was delivered to the whole hemothorax, with a simultaneous integrated boost of 5 Gy to GTV, aiming to inhibit reimplantation of malignant cells after surgery. Significant risk of high-grade cardiopulmonary toxicity was avoided by immediate surgery, six days after completion of radiotherapy. Overall survival in the whole group of patients was 36 months, but almost 30% of the patients had grade 3 or higher complications, including three treatment-related deaths. SMART trial in 2020 provided promising outcomes with this technique, but due to significant treatment-related morbidity it was not widely adopted [4, 5, 8, 9, 10].

To date, no randomized prospective trial results have supported this approach, suggesting that it can only be considered in highly experienced centers and clinical trials for obtaining more data [8, 11].

HEMITHORAX RADIOTHERAPY AFTER EPP

Malignant pleural mesothelioma spreads over the pleural surface, making it very difficult to achieve R0 resection at surgery [4]. The rationale for hemithorax radiotherapy after EPP is the reduction of local recurrence after the surgery which is higher than 30%. Still, there is very little randomized trial data to support this approach [2].

One of the first trials in 2011 (MARS) testing EPP followed by classic 3D conformal 54 Gy postoperative radiotherapy versus standard oncological care (no pneumonectomy) failed to reach feasibility. The trial showed that surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients [12]. The latter IMRT technique Swiss trial (SAKK 17/04) in 2015 randomized patients who achieved complete remission due to induction chemotherapy (cisplatin/pemetrexed) and EPP to the group receiving up to 55.9 Gy IMRT hemothorax radiotherapy and the group set to only follow-up. The trial was closed prematurely showing no significant differences between the groups regarding local relapse-free survival and overall survival, on cost of grade 5 pneumonitis in the radiotherapy group. It was concluded that the addition of hemithorax radiotherapy brings an additional treatment burden, with no patient benefits [4, 13]. Although this was the largest international multicenter phase 2 randomized trial, multiple institutional studies pushed forward with modern radiotherapy techniques after EPP and reported significant improvement in locoregional control rates as well as overall survival rates [7, 14, 15]. On the other hand, lung toxicity was still of major concern leading to significant treatment-related morbidity and mortality due to grade 5 radiation pneumonitis, which in some series was up to 46% [7, 15]. In the years that came, greater experience with novel radiotherapy techniques (IMRT, VMAT, helical tomotherapy, etc.) and treatment planning, developed strict dose constraints to organs at risk (mainly lungs) lead to the reduction of toxicity of grade 3 or higher to less than 10% [7, 8].

The postoperative radiation field includes the entire pleural bed and the treatment dose is 45–54 Gy with a boost to R1 or R2 residual disease up to 54–60 Gy.

In the absence of definitive data that support the evidence, EPP postoperative hemithorax radiotherapy can be considered for operable MPM patients' stage I–III but only in centers of excellence with experience in this modality for mesothelioma according to current recommendations [6, 11, 16].

HEMITHORAX RADIOTHERAPY AFTER LUNG-SPARING PROCEDURES

Given the high risk of perioperative mortality after EPP, the trend in surgical approach is switched to less aggressive (lung-sparing) procedures such as pleurectomy/decortication. It is believed that this management has no negative impact on overall survival with lower treatment-related risks [17]. However, the cytoreductive approach imposed a question of adjuvant therapy for reducing the risk of local recurrence. Delivering a high dose of radiotherapy to both

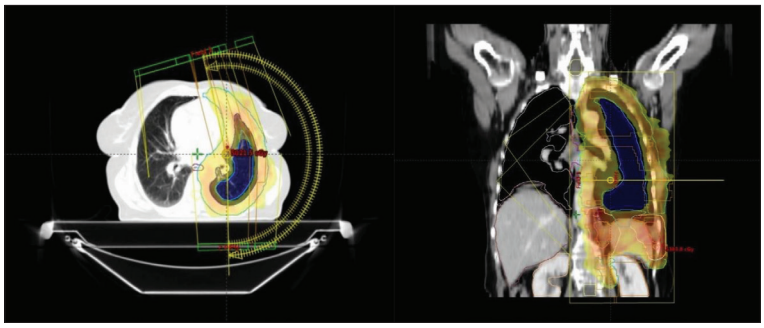


Figure 2. Radical hemithorax irradiation with 50.4 Gy to the whole hemithorax (orange color wash) and boost to gross tumor volume up to 60 Gy (red color wash); lung sparing procedure; RapidArc technique (two hemi arcs – yellow calibrated arcs) (Institute for Oncology and Radiology of Serbia)

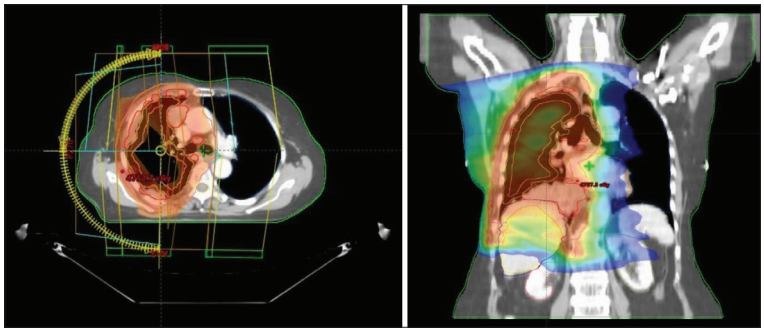


Figure 3. Palliative radiotherapy; multiple infiltrations of the right chest wall and mediastinum (red contour – gross tumor volume); RapidArc technique (Institute for Oncology and Radiology of Serbia)

intact lungs is one of the most challenging scenarios in radiation oncology due to the high risk of severe and even life-threatening treatment-related toxicity (pneumonitis).

In 2016, the results of a multicenter phase 2 trial that used 50.4 Gy with the IMRT technique in the lung-sparing multimodality treatment of MPM (IMPRTIN trial) have shown that it can be administered safely with no grade 4 or 5 pneumonitis and improved disease-free and overall survival [18]. Comparable following studies of radical radiotherapy in the lung-sparing approach brought emerging evidence that > 45 Gy of modern technique radiotherapy can be delivered with acceptable toxicity levels [7].

In the target volume delineation GTV is delineated. The clinical target volume includes all GTV sites and the entire virtual space around the pleura. An additional 10 mm margin is added for PTV. The treatment dose is 50.4 Gy in 28 fractions with a boost to GTV up to 60 Gy (Figure 2).

To date, several ongoing studies are testing the safety and outcomes of this multimodality lung-sparing approach (NGR-LU006, NCT00715611, etc.). Until we obtain more detailed data, it is recommended that this demanding technique is to be considered and performed in highly experienced centers, preferably within clinical trials.

PROPHYLACTIC (PROCEDURAL PATH) RADIOTHERAPY

The rationale for radiotherapy of intervention sites is seen in the risk reduction of chest wall infiltration and subcutaneous spread following biopsy, thoracoscopy, or thoracotomy in patients with MPM. However, despite several single-center encouraging results, no large, prospective trial or meta-analysis so far has demonstrated a statistically significant reduction of the risk for procedural path dissemination [19, 20]. Thus, this procedure is not recommended upfront according to current protocols but can be considered on case-to-case bases.

PALLIATIVE RADIOTHERAPY

Radiotherapy is the symptom-relieving treatment of choice in MPM patients. The choice of radiotherapy technique and the treatment dose depends on the clinical presentation, performance status of the patient, and stage of the disease. In the current protocols, palliative radiotherapy doses range from 8 Gy in a single fraction, through 20 Gy in five fractions, to 30–39 Gy in 10–13 fractions or higher (Figure 3). Novel trials suggest that a higher dose per fraction (≥ 4 Gy per fraction) is associated with better outcome introducing 36 Gy in six fractions (SYSTEMS-2 trial) and SBRT [5, 7].

FUTURE OF MPM RADIOTHERAPY

The high local recurrence rate and high risk of radiation-induced toxicity focused the interest on other high-precision radiotherapy modalities such as SBRT, proton therapy, and adaptive radiotherapy. Also, the combination of radiotherapy and advanced surgical techniques, immuno-, and/or target therapy is evolving [2].

SBRT aims to deliver high, ablative radiotherapy dose to a limited target, making it suitable for low-tumor-burden patients or oligoprogressive disease.

Although there is a very limited amount of data regarding proton beam therapy for MPM, results of recent studies suggest that it can bring improvements in normal tissue sparing and PTV covering, with no greater than grade 3 toxicity due to its physical phenomenon of rapid dose fall-off (Bragg peak) [21].

The concept of adaptive radiotherapy is the creation of new radiotherapy treatment plans during the course of treatment to adapt to changes in target volumes detected by image-guided radiation therapy. This concept may be favorable for MPM, where dose constraints are difficult to meet due to large target volumes. Definitive conclusions are lacking, though [7].

CONCLUSION

The treatment of MPM remains challenging, especially in the field of radiation oncology. Though there are many concerns and open questions, it seems that novel radiotherapy techniques have promising possibilities for the local treatment of this disease. That being said, a more radical radiotherapy approach can be considered for the treatment of MPM patients in highly experienced radiotherapy centers, preferably within clinical trials.

Ethics: This article was written in accordance with the ethical standard of the institutions and the journal.

Conflicts of interest: None declared.

REFERENCES

1. Alpert N, van Gerwen M, Taioli E. Epidemiology of mesothelioma in the 21st century in Europe and United States, 40 years after restricted/banned asbestos use. Trans Lung Cancer Res. 2020;9(1):S28–S38. [DOI: 10.21037/tlcr.2019.11.11] [PMID: 32206568]
2. Davis A, Ke H, Kao S, Pavlakis N. An update on emerging therapeutic options for malignant pleural mesothelioma. Lung Cancer (Auckl). 2022;13:1–12. [DOI: 10.2147/LCTT.S288535] [PMID: 35264891]
3. Cimen F, Agackiran Y, Düzgün S, Aloglu M, Senturk A, Atikcan S. Factors affecting the life expectancy in malignant pleural mesothelioma: Our 10 years of studies and experience. Medicine (Baltimore). 2022;101(39):e30711. [DOI: 10.1097/MD.0000000000030711] [PMID: 36181042]
4. Hanna GG, John T, Ball DL. Controversies in the role of radiotherapy in pleural mesothelioma. Transl Lung Cancer Res. 2021;10(4):2079–87. [DOI: 10.21037/tlcr-20-583] [PMID: 34012816]
5. Cramer G, Simone CB 2nd, Busch TM, Cengel KA. Adjuvant, neoadjuvant, and definitive radiation therapy for malignant pleural mesothelioma. J Thorac Dis. 2018;10(Suppl 21):S2565–S2573. [DOI: 10.21037/jtd.2018.07.65] [PMID: 30206500]
6. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, et al. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(2):129–42. [DOI: 10.1016/j.annonc.2021.11.005] [PMID: 34861373]
7. Luna J, Bobo A, Cabrera-Rodriguez JJ, Pagola M, Martin-Martin M, Gonzalez Ruiz MA, et al. GOECP/SEOR clinical guidelines on radiotherapy for malignant pleural mesothelioma. World J Clin Oncol. 2021;12(8):581–608. [DOI: 10.5306/wjco.v12.i8.581] [PMID: 34513595]
8. Gomez DR, Rimner A, Simone CB 2nd, John Cho BC, de Perrot M, Adjei AA, et al. The Use of Radiation Therapy for the Treatment of Malignant Pleural Mesothelioma: Expert Opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thoracic Oncol. 2019;14(7):1172–83. [DOI: 10.1016/j.jtho.2019.03.030] [PMID: 31125736]
9. de Perrot M, Feld R, Leigh NB, Hope A, Waddell TK, Keshavjee S, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2016;151(2):468–73. [DOI: 10.1016/j.jtcvs.2015.09.129] [PMID: 26614413]
10. Breen WG, Garces YI, Olivier KR, Park SS, Merrell KW, Nichols FC, et al. Surgery for Mesothelioma After Radiation Therapy (SMART); A Single Institution Experience. Front Oncol. 2020;10:392. [DOI: 10.3389/fonc.2020.00392] [PMID: 32266156]
11. Kindler HL, Ismaila N, Armato SG 3rd, Bueno R, Hesdorffer M, Jahan T, et al. Treatment of malignant pleural mesothelioma: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(13):1343–73. [DOI: 10.1200/JCO.2017.76.6394] [PMID: 29346042]
12. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomized feasibility study. Lancet Oncol. 2011;12(8):763–72. [DOI: 10.1016/S1470-2045(11)70149-8] [PMID: 21723781]
13. Stahel RA, Reisterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomized, international, multicenter phase 2 trial. Lancet Oncol. 2015;16(16):1651–8. [DOI: 10.1016/S1470-2045(15)00208-9] [PMID: 26538423]
14. Simon M, Shochat T, Peled N, Zer A, Kramer MR, Eldanet O, et al. Intensity-modulated radiotherapy is a safe and effective treatment for localized malignant pleural mesothelioma. Thorac Cancer. 2018;9(11):1470–5. [DOI: 10.1111/1759-7714.12860] [PMID: 30240138]
15. Arrieta O, Lozano-Ruiz F, Blake-Cerda M, Catalan R, Lara-Mejia L, Salinas MA, et al. Locoregional control and toxicity after pleurectomy/decortication and intensity-modulated pleural radiation therapy in patients with malignant pleural mesothelioma. Thoracic Canc. 2020;11(12):3448–55. [DOI: 10.1111/1759-7714.1366] [PMID: 33030313]
16. Scherpereel A, Opitz I, Berghmans T, Psallidas I, Glatzer M, Rigau D, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J. 2020;55(6):1900953. [DOI: 10.1183/13993003.00953-2019] [PMID: 32451346]
17. Danuzzo F, Maiorca S, Bonitta G, Nosotti M. Systematic Review and Meta-Analysis of Pleurectomy/Decortication versus Extrapleural Pneumonectomy in the Treatment of Malignant Pleural Mesothelioma. J Clin Med. 2022;11(19):5544. [DOI: 10.3390/jcm11195544] [PMID: 36233416]
18. Rimner A, Zauderer MG, Gomez DR, Adusumilli PS, Parhar PK, Wu AJ, et al. Phase II study of hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality therapy in patients with malignant pleural mesothelioma. J Clin Oncol. 2016;34(23):2761–8. [DOI: 10.1200/JCO.2016.67.2675] [PMID: 27325859]
19. Bayman N, Appel W, Ashcroft L, Baldwin DR, Bates A, Darlison L, et al. Prophylactic Irradiation of Tracts in Patients with Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial. J Clin Oncol. 2019;37(14):1200–8. [DOI: 10.1200/JCO.18.01678] [PMID: 30920878]
20. Bergamin S, Tio M, Stevens MJ. Prophylactic procedure tract radiotherapy for malignant pleural mesothelioma: A systematic review and meta-analysis. Clin Transl Radiat Oncol. 2018;13:38–43. [DOI: 10.1016/j.ctro.2018.09.004] [PMID: 30302406]
21. Cramer GM, Simone CB 2nd, Busch TM, Cengel A. Advances in Radiation Therapy for Malignant Pleural Mesothelioma. In: Jeremić B. (eds). Advances in Radiation Oncology in Lung Cancer. Medical Radiology. Berlin, Heidelberg: Springer; 2023. p. 849–61. [DOI: 10.1007/174_2022_333]

Улога радиотерапије у лечењу малигног мезотелиома плеуре – могућности и контроверзе

Татјана Арсенијевић[1,2], Александар Степановић[1,2], Марина Никитовић[1,2]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Институт за онкологију и радиологију Србије, Београд, Србија

САЖЕТАК

Малигни мезотелиом плеуре је редак малигнитет са лошом прогнозом. Последњих година постигнут је значајан напредак у лечењу ове болести, укључујући хируршке и радиотерапијске технике, као и системску терапију и имунотерапију. Због широког спектра клиничке презентације, недостатка рандомизованих студија III фазе, хетерогености у терапијском приступу, лечење малигног мезотелиома плеуре остаје изазовно и поред доступних водича за дијагностику и терапију.

Ограничена могућност избегавања критичних здравих органа (посебно плућа), чије прекомерно излагање зрачењу може довести до озбиљне, па чак и фаталне токсичности, чини радикалну радиотерапију високим дозама веома захтевном. Стога је већина болесника са мезотелиомом у ери конвенционалне радиотерапије упућивана само на палијативну радиотерапију.

Технолошки развој у радиотерапији, укључујући респираторни гејтинг, 4*D* компјутеризовану томографију, интензитетом модулисану радиотерапију, волуметријски модулисану лучну радиотерапију, технике стереотаксе и протонску терапију, направио је значајан искорак у лечењу малигног мезотелиома плеуре зрачењем. Данас се радиотерапија мезотелиома може разматрати у различитим индикацијама, сама или у комбинацији са хируршким и системским лечењем. Ипак, многа питања остају отворена, и неопходна су даља истраживања, посебно у смислу ескалације радиотерапијских доза и боље поштеде плућног паренхима.

Кључне речи: лечење; малигни мезотелиом плеуре; радиотерапија

DOI: https://doi.org/10.2298/SARH231001008Z
UDC: 616-002.52

REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Systemic lupus erythematosus – diagnosis and classification of the disease in the past and in present times

Valentina Živković, Bojana Stamenković, Sonja Stojanović

University of Niš, Faculty of Medicine, Niš, Serbia;
Institute for Treatment and Rehabilitation, Niška Banja, Niš, Serbia

SUMMARY

The main feature of systemic lupus erythematosus (SLE) is its heterogeneity, which mainly refers to clinical presentation, the course of disease and prognosis, which can impact any organ and various immunoserological tests. As a result, prompt illness recognition and right diagnosis are extremely complicated processes based on the most recent classification standards and the doctor's clinical expertise with specific patients.

In contrast, not all SLE patients are included when using classification criteria, which are based on a definition of a homogenous group by the specified, restricted number of clinical and immunoserological domains and for the purpose of conducting clinical or epidemiological investigations. Classification criteria have evolved over the last 50 years in response to new understandings and advances. This process began with the American College of Rheumatology (ACR) criteria in 1971 and continued through their updates in 1982 and 1997, followed by Systemic Lupus International Collaborating Clinics 2012 and the European League Against Rheumatism (EULAR)/ACR 2019. EULAR/ACR 2019 criteria have proven their high validity (sensitivity and specificity) in numerous studies, as well as adequate diagnostic usefulness, defined by 24 items in 10 domains, with the fulfillment of the essential precondition of antinuclear antibody positivity.

Keywords: systemic lupus erythematosus; diagnosis; classification criteria

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterized with wide heterogeneity of clinical manifestations and immunoserological findings and is considered a multisystemic autoimmune disease with insufficiently elucidated etiopathogenesis, thought to be caused by a combination of genetic, epigenetic, immune, hormonal and environmental factors [1]. Presumably, it signifies a decline in immune tolerance to one's own antigens added with excessive B and T cell activation, complement binding and cytokine activation; these processes result in the formation of immune complexes that precipitate in the blood vessels, and typically cause persistent, chronic inflammation of different tissues and organs [2].

There is a wide spectrum of clinical presentations of the disease, from moderate types affecting only the skin and the joints to "malignant" versions affecting the kidneys, heart, lungs, and brain. Owing to the variability of SLE, there is no single "gold standard" or set of precise, validated diagnostic criteria for the diagnosis of SLE; rather, classification criteria are used to assist clinical experience in this process [3, 4]. Considering the high morbidity and death rates associated with SLE, prompt identification and early treatment initiation are critical for preventing illness relapse and subsequent organ damage and achieving stable remission [5]. A good strategy to reach these goals would be to improve the classification criterion's sensitivity and specificity and bring them closer to the diagnostic criteria.

DEFINITION OF DIAGNOSTIC AND CLASSIFICATION CRITERIA

A set of symptoms, indicators, and tests that are employed in routine clinical practice in order to properly select patients are known as diagnostic criteria. The right diagnosis results in the right therapy induction. The classification criteria represent standardized set of a limited number of items agreed upon by a group of experts, primarily intended to create well-defined, homogeneous sets of patients for the purposes of clinical or epidemiological research [3]. They are not created to be used neither for disease diagnosis, nor for making decisions about treatment. Classification criteria do not involve all SLE patients; they involve most of the patients with the key shared standardized disease characteristics [6, 7].

In rheumatology, the diagnostic criteria are equivalent or closely resemble the classification criteria for diseases that have a known etiology, including gout and Lyme disease, for which the classification criterion's sensitivity and specificity reaches 100% [3]. Diagnostic criteria for the majority of other rheumatic disorders,

Received • Примљено: October 1, 2023
Revised • Ревизија: December 21, 2023
Accepted • Прихваћено: December 29, 2023
Online first: January 15, 2024

Correspondence to:
Valentina ŽIVKOVIĆ
Bulevar dr Zorana Đinđića 127/23
Medijana
18106 Niš
Serbia
ljubisa.nina@gmail.com

including SLE, are based on a combination of the most recent classification criteria and the clinician's expertise and intuition (the gold standard). Classification criteria may lead to an incorrect or too early diagnosis of SLE if they are applied for diagnostic purposes [8]. On the other hand, some SLE patients do not meet the requirements for SLE classification. The classification criteria are updated on a regular basis to reflect new discoveries and developments in the field of disease pathogenesis. The purpose of this document is to provide the review of the SLE classification criteria from 1971 to 2019.

THE AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA

The American College of Rheumatology (ACR), previously known as the American Rheumatism Association, established the initial SLE classification criteria in 1971. The criteria comprised 14 items [9]. Later, in 1982 and 1997, these criteria were changed. The 1982 revision included the confirmation of positive results for antinuclear antibodies (ANA) by immunofluorescent or equivalent assay, as well as positive results for anti-double stranded DNA (anti-dsDNA) antibody and positive results for anti-Smith antibodies. Additionally, the unification of the involvement of specific organ systems into a single criterion and the exclusion of alopecia and Raynaud's phenomenon due to low sensitivity and specificity were utilized [10, 11].

Afterwards, several groups of researchers have employed new statistical methods in order to improve the ACR classification criteria, namely researchers from a Cleveland clinic, whose criteria demonstrated high sensitivity and specificity when compared to 1971 and 1982 criteria [12]. Moreover, the Boston criteria developed by Costenbader et al. [13] that were based on the Cleveland clinical criteria and included renal pathology and antiphospholipid antibodies, have shown a noticeably poorer specificity when compared to the updated ACR criteria. The aforementioned classification criteria are mostly historical in nature and were not frequently employed in clinical and epidemiological investigations since they were not used as a basis for SLE diagnosis in everyday clinical practice.

In the 1997 ACR modification of the SLE classification criteria, the findings of antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant) or false-positive serological tests for syphilis were added, whereas the findings of lupus cells were eliminated (Table 1) [14, 15]. The ACR 1997 criteria were not adopted only as the standard for patient eligibility for clinical and epidemiological research, but also were used additionally as diagnostic standards for the next 20 years. In total, 11 items make up the ACR 1997: nine clinical and two laboratory indicators, with a minimum of four criteria required for the SLE diagnosis. These criteria can be presented concurrently or serially, regardless of their duration.

Laboratory criteria include the following two: ANA positivity (not drug-induced) confirmed by immunofluorescence testing or an equivalent assay as an independent criterion, and positive immunology tests (antibodies against phospholipids, anti-Smith, or anti-dsDNA antibodies). The following are the clinical criteria: involvement of the kidneys, hematopoietic system, central nervous system, skin, mucosa (in the form of painless oral or nasopharyngeal ulcerations), joints, and serosa [14–17].

Table 1. 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (Tan 1982; Hochberg 1997)

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion Pericarditis – documented by echocardiography or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation is not peformed Cellular casts may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures Psychosis (in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia-with reticulocytosis Leukopenia < 4000 / mm on ≥ 2 occasions Lymphopenia < 1500 / mm on ≥ 2 occasions Thrombocytopenia < 100,000 / mm in the absence of offending drugs
Immunologic disorder	Anti-double-stranded DNA Anti-Smith antibodies Antiphospholipid antibodies based on abnormal serum level of IgG or IgM anticardiolipin antibodies, positive test result for lupus anticoagulant using a standard method, or false-positive serologic test result for syphilis
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Nevertheless, the primary flaw of the ACR 1997 criteria was that SLE could theoretically be classified without meeting any of the immunological requirements. Due to that fact, for clinical studies, in addition to the fulfillment of ACR criteria, the presence of autoantibodies was also the prerequisite in order for a study participant to be enrolled [18, 19].

SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS CLASSIFICATION CRITERIA

A major shortcoming in the ACR 1997 criteria was addressed by Systemic Lupus International Collaborating Clinics (SLICC), an international group that developed new criteria in 2012 [18, 20]. A total of 17 criteria,

comprising six immunological and 11 clinical, were used to define SLICC 2012. The SLE classification required the following:

1. meeting a minimum of four requirements, with at least one clinical and one immunological criterion, or
2. lupus nephritis as the sole criterion in the presence of ANA or anti-dsDNA antibodies [18].

In comparison to ACR 1997, definition of SLICC 2012 indicated a substantial advancement for several reasons. Skin changes were broadly covered under two distinct criteria, one for acute and subacute alterations and the other for chronic ones. Alopecia, a highly common (though nonspecific) symptom, was also taken into consideration under a different criterion. Furthermore, the definition of arthritis has undergone substantial modifications. It is now based on the presence of palpable pain in two or more joints combined with morning stiffness that lasts longer than thirty minutes and is not based on radiography. Based on measuring proteinuria by using the urine protein/creatinin ratio without setting a time limit for urine collection, lupus nephritis can be confirmed [21, 22]. Due to a lack of SLE specificity, the neurological criterion encompasses a wide range of neuropsychiatric indications but does not cover not all of the potential signs [23, 24]. Hemolytic anemia, leucocytopenia/lymphocytopenia and thrombocytopenia were singled out and placed into three separate hematological criteria, with a focus on ruling out other potential causes (such as drug use, infections, and other associated disorders).

SLICC 2012 brought some significant changes to immunological criteria compared to ACR 1997. Since these criteria were split into six distinct categories (ANA, anti-dsDNA antibodies, anti-Smith antibodies, anti-phospholipid antibodies, low complement, positive direct Coombs test in the absence of hemolytic anemia), giving them the attention they deserve, as each of them now may impact the classification of SLE. If ANA are absent, positivity of anti-dsDNA is rare and may result from a laboratory error.

SLICC 2012's most significant finding was the fact that biopsy-confirmed lupus nephritis added with one immunological parameter (positive ANA or anti-dsDNA) was sufficient to classify a patient as having SLE [18]. This finding was shown by nearly 1% of patients diagnosed with SLE, which was solely based on biopsy-confirmed nephritis and positive serology.

When using clinical diagnosis as the gold standard, the results of a meta-analysis published by Dutch authors in 2018 showed that SLICC 2012 criteria classified more patients as having SLE, previously identified as having incomplete erythematous lupus,"probable SLE, or non-differentiated connective tissue disease", adding to higher sensitivity of SLICC 2012 when compared to ACR 1997 [25]. Nevertheless, the research indicates that between 50% and 90% of people with incomplete SLE never develop SLE, and their labeling as SLE may result in hazardous or needless therapy [26, 27, 28]. Based on the results from numerous studies, it was not possible to draw any conclusion about the diagnostic significance of SLICC and ACR criteria due to incomplete data on the duration of the disease, or due to the long duration of the disease [25, 29, 30, 31].

Finally, it can be concluded from a plethora of research regarding the validity of the ACR 1997 and SLICC 2012 criteria that the latter one was superior due to its higher sensitivity and capacity to identify SLE patients at earlier stages of the illness [25, 32, 33].

THE EUROPEAN LEAGUE AGAINST RHEUMATISM / THE AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA

The European League Against Rheumatism (EULAR) and ACR assembled a panel of specialists aiming to develop new classification criteria with enhanced sensitivity, specificity and validity for SLE and with maximized diagnostic value. Using the multiphase technique, the panel worked for five years until defining the SLE EULAR/ACR 2019 classification criteria [34]. This study began with the 21 "candidate" criteria, arranged into clinical and immunological domains, two of which were labeled as the entry criteria. Based on the literature research and data about sensitivity and specificity, it was determined that just one criterion should be employed as the "entry" criterion – positive ANA in the titer of ≥ 1:80 on HEp-2 cells or an equivalent test (positive, at any time), with the definition of seven clinical and three immunological domains.

The 2019 EULAR/ACR classification criteria (EULAR/ACR 2019) were the first to adopt a scoring system which has significantly improved their usage. Scores were allocated to distinct manifestations (i.e., clinical and immunological categories), that varied in their contribution to the overall score.

The clinical domains included general symptoms, hematological, neuropsychiatric, mucocutaneous, serous, musculoskeletal, and renal symptoms; the immunological domains included complement and antibodies specific to SLE (anti-dsDNA antibodies or anti-Smith antibodies), anti-phospholipid antibodies (anti-cardiolipin antibodies or anti-beta(2)GP1 antibodies or lupus anticoagulant), and scores on a scale from 2 to 10. In order to be classified as having SLE, an individual must have a total score of at least ten points and meet at least one clinical criterion (Table 2).

The 2019. EULAR/ACR classification criteria (EULAR/ACR 2019) were the first to employ a scoring system, which greatly increased the usefulness of the classification criteria. In particular, individual manifestations, i.e., clinical and immunological domains, were assigned different scores, contributing differently to the total score.

While positive ANA is the fundamental need for an SLE classification (EULAR/ACR 2019), it is important to consider the uncommon occurrence of ANA negative SLE patients. The term seronegative SLE refers to 1–5% of SLE patients who have negative ANA and anti-dsDNA antibodies but other supportive criteria positive and frequently present along with anti-Ro and/or anti-La positivity [35].

According to the EULAR/ACR 2019 definition, a non-infectious fever, defined as a body temperature more than 38.3°C, carries two points, and is practically the only new criterion. Various acute, subacute, and chronic alterations

Table 2. EULAR/ACR classification criteria for SLE (Aringer 2019)

Entry criterion: Positive ANA test result ANA at a titer of ≥ 1:80 on HEp-2 cells, or an equivalent positive test result (ever)	
If absent, do not classify as SLE; if present, apply additive criteria	
Additional criteria Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on ≥ 1 occasion is sufficient. SLE classification requires ≥ 1 clinical criterion and ≥ 10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score	
Criteria	Weight
Clinical domains	
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria > 0.5 g per 24 hours	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10
Immunologic domains	
Antiphospholipid antibodies	
Anticardiolipin antibodies or anti-β2GP1 antibodies or lupus anticoagulant	2
Complement proteins	
Low C3 or low C4	3
Low C3 and low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody or anti-Smith antibody	6
Classify as SLE with a score of ≥ 10 if entry criterion is fulfilled	

EULAR/ACR – European League Against Rheumatism / American College of Rheumatology; SLE – systemic lupus erythematosus; ANA – antinuclear antibody; C – complement; dsDNA – double-stranded DNA; HEp-2 – human epithelial type 2; β2GP1 – β2 glycoprotein 1

of the skin are worth 2–6 points. Lupus nephritis class II or V has the value of eight points, while nephritis class III or IV on renal biopsy brings 10 points and those are sufficient for the SLE classification if added with positive ANA as the entry criterion. Urinary sediment is no longer included in the renal domain due to method subjectivity and the quick shifting of results following initial glucocorticoid medication. Proteinuria > 500 mg / 24 hours is worth four points. Most of the time, lupus arthritis is non-erosive and is not linked to anti-cyclic citrullinated peptide antibodies, which carry a considerable number of points – more than half of those needed for an SLE classification (six points).

Compared to the ACR 2019, the SLICC 2012 criteria covered significantly more neuropsychiatric manifestations. These manifestations include multiple mononeuritis, myelitis, peripheral or cranial neuropathy; however, because of their uncommon and rare occurrence, these entities are excluded from the EULAR/ACR 2019 criteria. Only the acute confusion states (in the absence of toxic-metabolic causes, uremia, and the usage of drugs), epilepsy and psychosis were kept, as they were the only conditions marked as typical and rather specific.

In conclusion, the EULAR/ACR 2019 contains fewer domains than SLICC 2012, which makes their application easier. Also, the ability to classify SLE early and more accurately is a significant benefit of EULAR/ACR 2019 [4]. These criteria kept their excellent specificity at the ACR 1997 level of 93%, while their sensitivity increased nearly to the SLICC 2012 level (96% *vs.* 97%) [5, 36]. Additionally, they are shown to be valid in more than 20 investigations, thus constituting the "gold standard" for inclusion criteria in clinical trials [7, 37–40].

Despite defining the EULAR/ACR 2019 classification criteria, a broad spectrum of clinical and serological findings in patients with SLE may sometimes produce confusion and delay the correct diagnosis, increasing the risk of organ damage and increased morbidity and mortality [41–47].

CONCLUSION

Since there were no opportunities to define diagnostic criteria over the last 50 years, specific requirements for SLE classification criteria have been established. These criteria are not intended to diagnose or involve every case of a disease, but rather to define homogenous sets of patients for the purpose of conducting various multicentric clinical or epidemiological studies.

The EULAR/ACR 2019 classification criteria resulted from the progression of ACR 1971 and their updates in 1982, and 1997, to the SLICC 2012 standards. The EULAR/ACR 2019 satisfied the stringent methodology requirements and incorporated additional information, greatly increasing their clinical and diagnostic usefulness.

When comparing two sets of criteria, we can say that SLICC 2012 added a lot of new items in comparison to ACR 1997, whereas EULAR/ACR 2019 made application easier by lowering the number of domains compared to SLICC 2012 by compressing the hematological, mucocutaneous, and neurological domains. While EULAR/ACR 2019 underwent a major structural transformation by specifying the entrance criteria and scoring system for distinct domains and items within the same domain, ACR 1997 and SLICC 2012 maintained their structural similarity. When compared to ACR 1997, it is possible to draw the conclusion that SLICC 2012 dramatically increased sensitivity but lowered specificity, whereas EULAR/ACR

2019 have again raised specificity, with the maintenance of a high sensitivity.

Diagnosing SLE remains difficult despite the most recent EULAR/ACR 2019 classification criteria definition, and it is primarily based on clinical assessments and current classification criteria as a starting point.

Even though there have been significant advancements and discoveries in the fields of genetics and etiopathogenesis of SLE, the 21st century SLICC 2012 and EULAR/ACR 2019 classification criteria remain grounded in clinical manifestations and autoimmune serology, just like the ACR criteria that were established half a century ago.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

REFERENCES

1. Zucchi D, Silvagni E, Elefante E, Signorini V, Cardelli C, Trentin F, et al. Systemic lupus erythematosus: one year in review 2023. Clin Exp Rheumatol. 2023;41(5):997–1008. [DOI: 10.55563/clinexprheumatol/4uc7e8] [PMID: 37133502]
2. Kiriakidou M, Lee Ching C. Systemic Lupus Erythematosus. Ann Intern Med. 2020;172(11):ITC81–ITC96. [DOI: 10.7326/AITC202006020] [PMID: 32479157]
3. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson RS, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken). 2015;67(7):891–7. [DOI: 10.1002/acr.22671] [PMID: 26199203]
4. Fanouriakis A, Tziolos N, Bertsias G, Boumpas TD. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021;80(1):14–25. [DOI: 10.1136/annrheumdis-2020-218272] [PMID: 33051219]
5. Aringer M, Johnson RS. Classifying and diagnosing systemic lupus erythematosus in the 21st century. Rheumatology (Oxford). 2020;59(5):v4–v11. [DOI: 10.1093/rheumatology/keaa379] [PMID: 33280013]
6. Fries JF, Hochberg MC, Medsger TA Jr, Hunder GG, Bombardier C. Criteria for rheumatic disease. Different types and different functions. The American College of Rheumatology Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1994;37(4):454–62. [DOI: 10.1002/art.1780370403] [PMID: 7605403]
7. Aringer M, Costenbader K, Dörner T, Johnson RS. Advances in SLE classification criteria. J Autoimmun. 2022;132:102845. [DOI: 10.1016/j.jaut.2022.102845] [PMID: 35725680]
8. Larosa M, Iaccarino L, Gatto M, Punzi L, Doria A. Advances in the diagnosis and classification of systemic lupus erythematosus. Expert Rev Clin Immunol. 2016;12(12):1309–20. [DOI: 10.1080/1744666X.2016.1206470] [PMID: 27362864]
9. Fries FJ, Siegel CR. Testing the 'preliminary criteria for classification of SLE'. Ann Rheum Dis. 1973;32(2):171–7. [DOI: 10.1136/ard.32.2.171] [PMID: 4571393]
10. Tan EM, Cohen AS, Fries JF, Masi TA, McShane JD, Rothfield FN, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271–7. [DOI: 10.1002/art.1780251101] [PMID: 7138600]
11. Levin RE, Weinstein A, Peterson M, Testa AM, Rothfield FN. A comparison of the sensitivity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1984;27(5):530–8. [DOI: 10.1002/art.1780270508] [PMID: 6721885]
12. Clough JD, Elrazak M, Calabrese LH, Valenzuela R, Braun WB, Williams GW. Weighted criteria for the diagnosis of systemic lupus erythematosus. Arch Intern Med. 1984;144(2):281–5. [PMID: 6421256]
13. Costenbader KH, Karlson EW, Mandl LA. Defining lupus cases for clinical studies: the Boston weighted criteria for the classification of systemic lupus erythematosus. J Rheumatol. 2002;29(12):2545–50. [PMID: 12465149]
14. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. [DOI: 10.1002/art.1780400928] [PMID: 9324032]
15. Feletar M, Ibañez D, Urowitz BM, Gladman DD. The impact of the 1997 update of the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus: what has been changed? Arthritis Rheum. 2003;48(7):2067–9. [DOI: 10.1002/art.11167] [PMID: 12847702]
16. Bruce IN, Buie J, Bloch L, Bae SC, Costenbader K, Levy RA, et al. Lupus spectrum ambiguity has long-term negative implications for patients. Lupus Sci Med. 2023;10(1):e000856. [DOI: 10.1136/lupus-2022-000856] [PMID: 37534513]
17. Morand EF, Fernandez-Ruiz R, Blazer A, Niewold TB. Advances in the management of systemic lupus erythematosus. BMJ. 2023;383:e073980. [DOI: 10.1136/bmj-2022-073980] [PMID: 37884289]
18. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677–86. [DOI: 10.1002/art.34473] [PMID: 22553077]
19. Furie AR, van Vollenhoven FR, Kalunian K, Navarra S, Romero-Diaz J, Werth PV, et al. Trial of Anti-BDCA2 Antibody Litifilimab for Systemic Lupus Erythematosus. N Engl J Med. 2022;387(10):894–904. [DOI: 10.1056/NEJMoa2118025] [PMID: 36069871]
20. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. J Autoimmun. 2014;48–49:10–3. [DOI: 10.1016/j.jaut.2014.01.004] [PMID: 24461385]
21. Weening JJ, D'Agati VD, Schwartz MV, Seshan VS, Alpers EC, Appel BG, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney International. 2004;65(2):521–30. [DOI: 10.1111/j.1523-1755.2004.00443] [PMID: 14717922]
22. Fanouriakis A, Bertsias G, Liapis G, Marinaki S, Papagianni A, Stangou M, et al. Multidisciplinary approach to lupus nephritis: Clinical pearls, pitfalls, and positioning of newly-approved agents. Lupus. 2023;32(10):1155–63. [DOI: 10.1177/09612033231191944] [PMID: 37499240]
23. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsänoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum. 2001;45(5):419–23. [DOI: 10.1002/1529-0131(200110)45:5<419::aid-art360>3.0.co;2-x] [PMID: 11642640]
24. Carrión-Barberà I, Salman-Monte TC, Vílchez-Oya F, Monfort J. Neuropsychiatric involvement in systemic lupus erythematosus: A review. Autoimmun Rev. 2021;20(4):102780. [DOI: 10.1016/j.autrev.2021.102780] [PMID: 33609799]
25. Hartman EAR, van Royen-Kerkhof A, Jacobs JWG, Welsing PMJ, Fritsch-Stork RDE. Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis. Autoimmun Rev. 2018;17(3):316–22. [DOI: 10.1016/j.autrev.2018.01.007] [PMID: 29366725]
26. Bourn R, James JA. Preclinical lupus. Curr Opin Rheumatol. 2015;27(5):433–9. [DOI: 10.1097/BOR.0000000000000199] [PMID: 26125103]
27. Lambers WM, Westra J, Bootsma H, de Leeuw K. From incomplete to complete systemic lupus erythematosus; A review of the predictive serological immune markers. Semin Arthritis Rheum. 2021;51(1):43–8. [DOI: 10.1016/j.semarthrit.2020.11.006] [PMID: 33360229]
28. Sternhagen E, Bettendorf B, Lenert A, Lenert PS. The Role of Clinical Features and Serum Biomarkers in Identifying Patients with Incomplete Lupus Erythematosus at Higher Risk of Transitioning to Systemic Lupus Erythematosus: Current Perspectives. J Inflamm Res. 2022:15:1133–45. [DOI: 10.2147/JIR.S275043] [PMID: 35210816]

29. Amezcua-Guerra LM, Higuera-Ortiz V, Arteaga-García U, Gallegos-Nava S, Hübbe-Tena C. Performance of the 2012 Systemic Lupus International Collaborating Clinics and the 1997 American College of Rheumatology classification criteria for systemic lupus erythematosus in a real-life scenario. Arthritis Care Res (Hoboken). 2015;67(3):437–41. [DOI: 10.1002/acr.22422] [PMID: 25073545]
30. Sag E, Tartaglione A, Batu ED, Ravelli A, Khalil MAS, Marks DS, et al. Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicentre study. Clin Exp Rheumatol. 2014;32(3):440–4. [PMID: 24642380]
31. Aberle T, Bourn RL, Chen H, Roberts CV, Guthridge MJ, Bean K, et al. Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. Lupus Sci Med. 2017(4):1–7. [DOI: 10.1136/lupus-2016-000176] [PMID: 28409015]
32. Chang LS, Huang PY, Kuo HC, Tu YK, Tseng PT, Liang CS, et al. Diagnostic accuracy of the American College of Rheumatology-1997, the Systemic Lupus International Collaborating Clinics-2012, and the European League Against Rheumatism-2019 criteria for juvenile systemic lupus erythematosus: A systematic review and network meta-analysis. Autoimmun Rev. 2022;21(9):103144. [DOI: 10.1016/j.autrev.2022.103144] [PMID: 35842200]
33. Pons-Estel GJ, Wojdyla D, McGwin G Jr, Magder LS, Petri MA, Pons-Estel BA; Grupo Latino Americano De Estudio del Lupus (GLADEL), Alarcón GS; LUMINA cohort. The American College of Rheumatology and the Systemic Lupus International CollaboratingClinics classification criteria for systemic lupus erythematosus in two multiethnic cohorts: a commentary. Lupus. 2014;23(1):3–9. [DOI: 10.1177/0961203313512883] [PMID: 24285098]
34. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9):1151–9. [DOI: 10.1136/annrheumdis-2018-214819] [PMID: 31383717]
35. Aringer M, Johnson SR. Systemic Lupus Erythematosus Classification and Diagnosis. Rheum Dis Clin North Am. 2021;47(3):501–11. [DOI: 10.1016/j.rdc.2021.04.011] [PMID: 34215376]
36. Aringer M, Petri M. New classification criteria for systemic lupus erythematosus. Curr Opin Rheumatol. 2020;32(6):590–6. [DOI: 10.1097/BOR.0000000000000740] [PMID: 32925250]
37. Lazar S, Kahlenberg JM. Systemic Lupus Erythematosus: New Diagnostic and Therapeutic Approaches. Annu Rev Med. 2023;74:339–52. [DOI: 10.1146/annurev-med-043021-032611] [PMID: 35804480]
38. Cheng S, Ding H, Xue H, Cao L. Evaluation of the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus in children and adults. Clin Rheumatol. 2022;41(10):2995–3003. [DOI: 10.1007/s10067-022-06293-x] [PMID: 35852777]
39. Schmidtmann I, Kraus D, Weinmann A, Pütz K, Claßen P, Schleicher EM, et al. Validation of the 2019 EULAR/ACR classification criteria for systemic lupus erythematosus in an academic tertiary care centre. RMD Open. 2023;9(3):e003037. [DOI: 10.1136/rmdopen-2023-003037] [PMID: 37419524]
40. Lu W, Tian F, Ma J, Zhong Y, Liu Z, Xue L. Diagnostic accuracy of the European League against rheumatism/American College of Rheumatology-2019 versus the Systemic Lupus International Collaborating Clinics-2012 versus the ACR-1997 classification criteria in adult systemic lupus erythematosus: A systematic review and meta-analysis. Front Immunol. 2022;13:1023451. [DOI: 10.3389/fimmu.2022.1023451] [PMID: 36311745]
41. Živković V, Stanković A, Cvetković T, Mitić B, Kostić S, Nedović J, et al. Anti-dsDNA, anti-nucleosome and anti-C1q antibodies as disease activity markers in patients with systemic lupus erythematosus. Srp Arh Celok Lek. 2014;142(7–8):431–6. [DOI: 10.2298/SARH1408431Z] [PMID: 25233687]
42. Živković V, Cvetković T, Mitić B, Stamenković B, Stojanović S, Radovanović-Dinić B, et al. Monocyte chemoattractant protein-1 as a marker of systemic lupus erythematosus: an observational study. Rheumatol Int. 2018;38(6):1003–8. [DOI: 10.1007/s00296-017-3888-x] [PMID: 29181621]
43. Živković V, Mitić B, Stamenković B, Stojanović S, Dinić BR, Stojanović M, et al. Analysis on the risk factors for organ damage in patients with systemic lupus erythematosus: a cross-sectional single-center experience. Sao Paulo Med J. 2019;137(2):155–61. [DOI: 10.1590/1516-3180.2018.0258060219] [PMID: 31314876]
44. Živković V, Stamenković B, Stojanović S, Cvetković T, Radovanović-Dinić B. Quality of life and severity of fatigue in patients with systemic lupus erythematosus. Acta Medica Medianae. 2018;57(3):100–6. [DOI: 10.5633/amm.2018.0314]
45. Lam NV, Brown JA, Sharma R. Systemic Lupus Erythematosus: Diagnosis and Treatment. Am Fam Physician. 2023;107(4):383–95. [PMID: 37054414]
46. Ceccarelli F, Perricone C, Natalucci F, Picciariello L, Olivieri G, Cafaro G, et al. Organ damage in Systemic Lupus Erythematosus patients: A multifactorial phenomenon. Autoimmun Rev. 2023;22(8):103374. [DOI: 10.1016/j.autrev.2023.103374] [PMID: 37301273]
47. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae S, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2023;83(1):15–29. [DOI: 10.1136/ard-2023-224762] [PMID: 37827694]

Системски еритемски лупус – дијагноза и класификација болести некад и сад

Валентина Живковић, Бојана Стаменковић, Соња Стојановић

Универзитет у Нишу, Медицински факултет, Ниш, Србија;
Институт за лечење и рехабилитацију „Нишка Бања", Ниш, Србија

САЖЕТАК

Главна особина системског еритемског лупуса је хетерогеност, која се односи, између осталог, на имуносеролошке налазе, клиничку презентацију, ток и прогнозу болести, при чему сваки орган може бити погођен. Стога је правовремено препознавање болести и постављање дијагнозе веома сложен когнитивни процес, који се заснива на актуелним класификационим критеријумима и клиничком искуству лекара који је усмерен према појединцу. Супротно томе, класификациони критеријуми се заснивају на дефинисању хомогене групе према претходно задатом ограниченом броју клиничких и имуносеролошких домена у циљу извођења клиничких и епидемиолошких студија и не обухватају све оболеле од системског еритемског лупуса. Последњих пола века класификациони критеријуми су се у складу са сазнањима и напредовањем у овој области мењали, почев од критеријума Америчког колеџа за реуматологију (*ACR*) постављених 1971. и њихових ревизија 1982. и 1997. год., преко Међународне сарадничке клинике за системски лупус (*SLICC*) 2012, све до Европске лиге против реуматизма (*EULAR*)/*ACR* 2019. год. *EULAR*/*ACR* 2019 су у многобројним студијама доказали своју високу валидност (сензитивност и специфичност), као и добру дијагностичку вредност, а дефинишу их 24 ставке у 10 домена уз испуњење основног предуслова да су антинуклеусна антитела позитивна.

Кључне речи: системски еритемски лупус; дијагноза; класификациони критеријуми

DOI: https://doi.org/10.2298/SARH231113114V
UDC: 61:929 Коперникус Н.; 61(091)

HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Nicolaus Copernicus and medicine – 550th anniversary of the birth and 480th anniversary of the death of a scientist who turned the view of the world upside down

Danijela Vučević[1], Milica Radosavljević[2], Janko Samardžić[2], Miroslav Radenković[2], Tatjana Radosavljević[1]

[1]University of Belgrade, Faculty of Medicine, Ljubodrag Buba Mihailović Institute of Pathophysiology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Institute of Pharmacology, Clinical Pharmacology and Toxicology, Belgrade, Serbia

SUMMARY
This year sees the 550th anniversary of the birth and 480th anniversary of the death of Nicolaus Copernicus, internationally recognized as the father of modern astronomy, who "stopped the Sun, moved the Earth" and turned the view of the world upside down. However, the fame of Nicolaus Copernicus is not referred only to the fields of astronomy, mathematics, canon and civil law, as well as theology, economy and diplomacy. This Renaissance polymath was also one of the most respected practicing physicians at the time. Noteworthy, Nicolaus Copernicus paid special attention to the poor, supplying them with free medical advice, assistance and medicines. Therefore, our paper deals with this less known aspect of the famous scientist's life.
Keywords: Nicolaus Copernicus; medical education; medical practice; history of medicine

INTRODUCTION

The scientist's job is to search for truth within the framework approved by God and morality.
Nicolaus Copernicus

The father of modern astronomy, Mikolaj Kopernik (Mikolaj Koppernigk), better recognized by his Latin name Nicolaus Copernicus (1473–1543) was a 16th century Polish priest who devoted his entire life to a heliocentric (sun-centered) model of the universe [1–8] (Figure 1).

Although Copernicus's name refers to the theory of heliocentrism, the ancient Greek astronomer Aristarchus of Samos was the first man who introduced the idea of solar centrality in the third century B.C. [1, 6, 9]. Unfortunately, his idea was not accepted [9]. Moreover, according to the contrary explanation of the universe, also known as the geocentric theory of an Egyptian astronomer from Alexandria named Claudius Ptolemaeus (Ptolemy, 87–150 A.D.), the Sun, as well as the planets and stars moved around the motionless Earth [5, 6, 7, 10]. This doctrine (Ptolemy's cosmic model) had been the only undoubtedly accepted way of understanding the universe for centuries [10].

Ptolemy's cosmic model was strongly supported by two millennia of philosophical earth-centered view of the universe, geocentric doctrine described in the Bible, religious authorities, and many people across the Christian world [1, 3, 6, 10, 11]. However, Copernicus realized that geocentric vision of the solar system was unworkable [7]. In his groundbreaking book called *De Revolutionibus orbium coelestium libri sex* ("Six books on the revolutions of the heavenly spheres") published

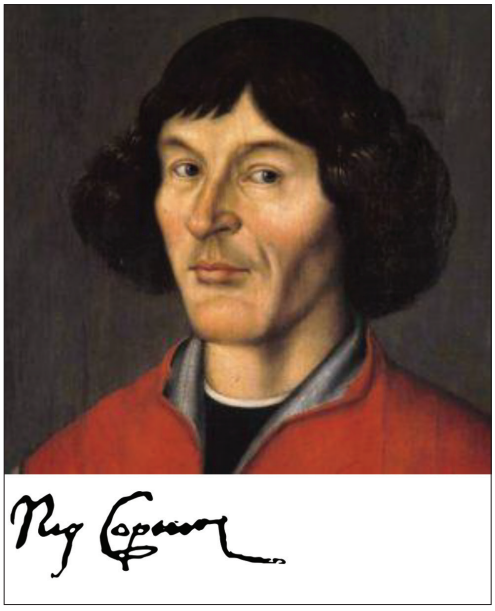


Figure 1. Nicolaus Copernicus (1473–1543); the portrait of Nicolaus Copernicus with his signature below; (Town Hall in Toruń, anonymous painter,1580); source: https://en.wikipedia.org/wiki/Nicolaus_Copernicus

Received • Примљено: November 13, 2023
Revised • Ревизија: December 19, 2023
Accepted • Прихваћено: December 22, 2023
Online first: December 26, 2023

Correspondence to:
Tatjana RADOSAVLJEVIĆ
Institute of Pathophysiology
Faculty of Medicine
University of Belgrade
Dr Subotića 9
Belgrade 11000, Serbia
tatjana.radosavljevic@med.bg.ac.rs

Figure 2. One of the first copies of Copernicus's famous treatise titled *De revolutionibus orbium coelestium* ("On the Revolutions of the Heavenly Spheres"), with a schematic diagram of his heliocentric theory; source: https://goaravetisyan.ru/bs/chto-sluchilos-s-kopernikom-kto-takoi-kopernik-nikolai-kopernik/

in the last hours of his life, in 1543, he "stopped the Sun, moved the Earth" and "turned the whole science of astronomy upside down" [3, 6, 10] (Figure 2).

In such context, in *De Revolutionibus orbium coelestium* (into English it is also translated as "On the Revolutions of Haevenly Bodies") Copernicus said: "At the middle of all things lies the Sun. As the location of this luminary in the cosmos, that most beautiful temple, would there be any other place or any better place than the centre, from which it can light up everything at the same time? Hence the Sun is not inappropriately called by some the lamp of the universe, by others its mind, and by others its ruler" [12]. In the intended Preface of the same book, Copernicus also noted: "Perhaps there will be babblers who, although completely ignorant of mathematics, nevertheless take it upon themselves to pass judgement on mathematical questions and, badly distorting some passages of Scripture to their purpose, will dare find fault with my undertaking and censure it. I disregard them even to the extent as despising their criticism as unfounded" [11, 12]. It was the very beginning of the Scientific Revolution (the so-called Copernican Revolution), which has been fundamental for understanding the real nature of matter and space and further development of the modern concept of science, philosophy, and religion [3, 4, 7, 8, 10].

Although most people did not believe Copernicus, and despite the fact that his book was on The Catholic Church Index of Forbidden Books (in Latin, *Index Librorum Prohibitorum*) from 1616 until 1835, Copernicus inspired scientists, such as Tycho Brahe (1546–1601), Johannes Kepler (1571–1630), Galileo Galilei (1564–1642), and Isaac Newton (1642–1727) [2, 3, 7, 11]. From that moment, thanks to the revolutionary work of Copernicus, his successors continued to strengthen evidence-based science by means of observations, mathematical measurements, and logical arguments [2, 4, 7]. Among a plenty of published data regarding Copernicus's outstanding contributions to the development of human civilization, it seems that German writer Johann Wolfgang von Goethe has been the most concise when he wrote the following: "Of all discoveries and opinions, none may have exerted a greater effect on the human spirit than the doctrine of Copernicus … In its converts it authorized and demanded a freedom of view and greatness of thought so far unknown, indeed not even dreamed of" [1]. Noteworthy, Copernicus's fame is not referred only to the field of astronomy [8]. This Renaissance polymath was also a canon, mathematician, jurist, and a practicing physician, as well as an economist, classical scholar, polyglot, writer, translator, cartographer, governor, administrator, military leader, and a diplomat [3, 10, 13].

A BRIEF BIOGRAPHY

Copernicus was born on February 19, 1473 in Torun (in Polish, *Torún*), a major port on the Vistula River [1, 3]. Before Copernicus's birth, this northern trading city belonged to the Prussian Confederation [5]. However, after the Thirteen Years' War against the Teutonic Order, according to the Second Treaty of Torun in 1466, the so-called Royal Prussia, consisting of Torun and the western region of Prussia, became a part of the Kingdom of Poland [3, 5, 10].

Copernicus's father, also named Mikolaj Kopernik, grew up into a family of prosperous copper traders in Cracow (in Polish, *Kraków*), the capital of Poland at the time [1, 5]. It is speculated that there is a link between the word 'copper' and the family name Kopernik [3]. In 1460, Copernicus's father left Cracow and went to Torun, where he was a copper trader, as well as a civic leader and a magistrate [12]. Three years later, Mikolaj Kopernik married Barbara Watzenrode, who came from a rich family of merchants and municipal officials from Torun [3, 5, 12]. They had two sons (Andreas and Nicolaus) and two daughters (Barbara and Katharina), of whom Nicolaus Copernicus was the youngest child [3, 12].

When Nicolaus was only 10 years old, his father passed away [12]. In such circumstances, his uncle, Lukas Watzenrode, a thoroughly educated man and the future Bishop of Warmia (in German, *Ermland*), took care of his nephews and cousins [1, 3, 5, 10]. Nicolaus and Andreas completed their elementary education in Torun [3, 12]. In 1488, at the age of 15, Copernicus continued his education at the cathedral school of Wloclawek [12]. The teacher of Copernicus was Mikolaj Wodka (1442–1494) of Kwidzyn, called Abstenius, a famous Polish physician and astronomer [14]. After three years of study there, Copernicus enrolled at the Cracow Academy (today the Jagiellonian University), where he obtained a good standard academic training (*facultas artium*) [1, 10, 14]. Shortly thereafter, in the autumn of 1496, thanks to the support of his eminent uncle, Copernicus went to Italy to improve his academic learning at the most prestigious universities at the time [1, 10]. In such context, he studied canon and civil law in Bologna (1496–1501) and medicine in Padua (1501–1503), which he combined with receiving the degree of Doctor of Canon Law in Ferrara (1503) [10].

Figure 3. Tower of Nicolaus Copernicus at Frombork, reconstructed since World War II; source: https://en.wikipedia.org/wiki/Copernicus_Tower_in_Frombork.jpg

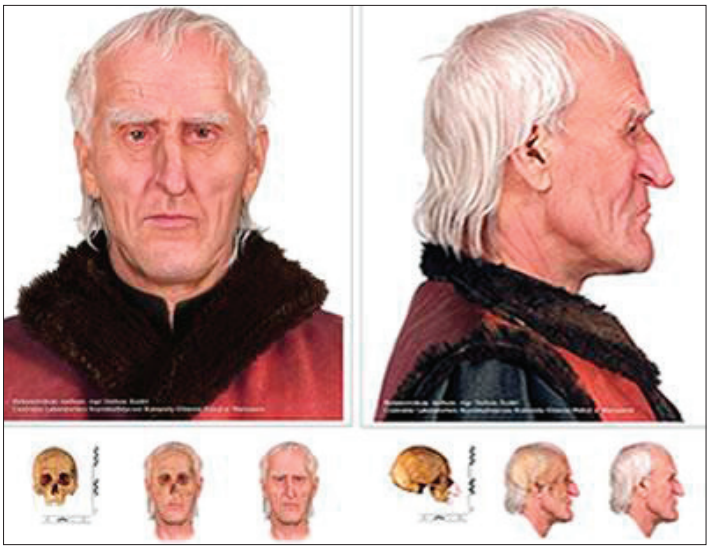


Figure 5. Reconstruction of Copernicus's appearance (2005); source: https://www.vreme.com/mozaik/lobanja-iz-groba-broj-trinaest/

In 1503, Copernicus returned to the northern Warmia region and rejoined his uncle in the Bishopric Palace in Heilsberg (in Polish, *Lidzbark Warminski*) [1]. He spent several years there, predominantly working as secretary and personal physician of his uncle [10]. After his uncle's death in 1512, Copernicus left Lidzbark Warminski residence and moved to Frauenburg (in Polish, *Frombork*), where he spent the rest of his life as the canon of the cathedral [1]. Simultaneously, he took care of administrative and diplomacy matters of the diocese [5]. In March of 1513, Copernicus built an observation tower near the cathedral [1] (Figure 3). There, next almost 30 years, he observed celestial bodies with neverending passion [1, 3].

By 1543, Copernicus was suffering from the consequences of a severe stroke [11]. He was paralyzed on his right side and in addition to his body, his mind was also deeply affected [1]. As it is previously noted, Copernicus received a copy of his printed masterpiece *De revolutionibus* on his deathbed [11] (Figure 4). "Before closing his eyes for the last time, Copernicus was able to gaze for a moment at the book which was to ensure his immortality" [15]. He died at the age of 70, on May 24, 1543. Bishop Tiedeman Giese describes last moments of his best friend: "He suddenly became ill, with blood flowing profusely from his mouth, followed by a paralysis of his right arm and the right side of his body. Death came quickly, as Copernicus himself had predicted" [15].

Figure 4. Death of Nicolaus Copernicus painted by Aleksander Lesser (1814–1884); source: https://en.wikipedia.org/wiki/File:Death_of_Nicolaus_Copernicus.PNG

Copernicus was buried in an unmarked tomb beneath the floor of the Frombork Cathedral, as was common practice at the time [11]. Since the majority of over 100 graves in this cathedral are unmarked, every search for the exact place of Copernicus's grave failed for over two hundred years [16]. Finally, in 2004, Copernicus's biographer Jerzy Sikorski and archeologist Jerzy Gassowski thought that place around the St. Cross Altar could be important for the beginning of a new search of Copernicus's grave, as Copernicus was in charge of this altar

during his priestly service [16, 17]. Indeed, in 2005, in tomb number 13 near the St. Cross Altar, an incomplete skeleton was found [17]. After facial reconstruction, it was postulated that the remains of Copernicus's body have been discovered [16, 17] (Figure 5).

In order to prove it, mitochondrial (mt) and nuclear DNA analyses of the skeletal remains were performed. The mtDNA profiles obtained from three upper molars and the femurs were identical, indicating that the remains belong to the same person. Identical mtDNA profiles were also found in two hairs that were tucked in the pages of a book called *Calendarium Romanium Magnum*, written by a German mathematician and astronomer Johannes Stöffler. This book, that Nicolaus Copernicus had used for many years, currently may be seen in the Museum Gustavianum in Uppsala in Sweden [16].

On May 22, 2010, human remains of Nicolaus Copernicus were reburied ceremonially in the Archcathedral Basilica in Frombork [11].

COPERNICUS'S MEDICAL EDUCATION

The University of Padua was founded in 1222 [18]. Although it was a catholic university, it attracted students from all over the known world due to its tolerant approach and respect for religious and political liberties (*Universa Universis Patavina Liberta* – Paduan freedom is universal for everyone) [14, 19]. Students participated in elections of the deans [14]. They also chose their professors and approved the statutes [14, 19]. The Medical School of this university, opened in 1250, was considered as the best center for medical education in Europe [19].

In October 1501, Copernicus enrolled at the Paduan School of Medicine [15]. At that time, the study of medicine lasted three years [14]. Theoretical Medicine, based on Book I of the *Canon of Medicine* by Avicenna, *Aphorisms* by Hippocrates, and *Tegni* by Galen, was the most important subject in the curriculum [14, 19]. In order to obtain practical knowledge, it was obligatory to read the text about fever (*De febribus*) from Book IV of Avicenna's *Canon of Medicine*, as well as two texts regarding specific diseases ("Specific diseases between the head and the heart" – *De morbis particularibus a capite usque ad cor* and "Specific diseases below the heart" – *De morbis particularibus a corde infra*) from Book III of the Avicenna's *Canon of Medicine* [15, 19]. Book IX of *Almansor* by Rhazes was also a part of the practical medical training [19]. After two years of study, students were qualified for a bachelor's degree, while three years of study was obligatory for a doctorate [15]. Additionally, a training period under a colleague with experience, which lasted one year, was necessary for a degree of licentiate [14, 15].

It is known that Copernicus's professors of Theoretical Medicine were Girolamo de Urbino, Philippo Pomodora, and Girolamo Pindemonte, while Giovanni d'Aquila gave him instructions in practical medicine [15]. Copernicus attended lectures by eminent anatomists, Marco Antonio della Torre (1481–1511) and Gabriele Zerbi (1486–1505) [15], as well as famous anatomist and surgeon, Alessandro Benedetti (1450–1512), who built the first wooden anatomical theatre [18]. Professor Benedetti performed dissections personally there [20]. His medical textbook *Historia corporis humani sive anatomice* ("The history of the human body") published in 1493 was very popular among the students [18, 20]. According to the curriculum of the Paduan School of Medicine, at Copernicus's time, each senior student had to participate in public dissections once a year [21].

Copernicus also attended lectures by Girolamo Fracastoro (1478–1553), who taught logic [22]. This illustrious physician, philosopher, astronomer, mathematician and poet is recognized as one of the founders of modern pathology and epidemiology since he believed that infections were induced by disease-carrying germs [15, 22]. Professor Fracastoro also believed that these germs could be transmitted by air or contact [22]. Unfortunately, his ideas were not accepted [15, 22]. Noteworthy, he wrote an epic poem about syphilis, in which he for the first time used the word 'syphilis' to designate the so-called "French disease," a common incurable disease in Europe at that time [14, 22].

It seems that Copernicus's masters were prominent mathematician and physician Pietro Trapolini, and famous hygienist and anatomist Bartolomeo da Montagna Junior [14].

Copernicus studied medicine in Padua very seriously [15, 21]. Therefore, he purchased the following medical textbooks: *Super quarta Fen primi Canonis Avicennae* by Hugo Senensis (1485), *Practica medicinae* by Joannes Michael Savonarola (1486), *Practica siue Philonium* by Valescus Tarenta (1490), *Liber pandectarum medicinae* by Matthaeus Silvaticus (1498), and *Chirurgia magistri* by Pietro de Argelatta (1499) [21]. On the margin of one of his medical treatises, Copernicus wrote this note: "Remember this, Doctor! Avicennas saying that ignorance leads to manslaughter is true…" [13, 21].

Since archives of the Paduan School of Medicine for the period 1503–1507 have been destroyed, there is no possibility to check if Copernicus obtained the degree of doctor of medicine [15]. However, it is hard to believe that Copernicus practiced medicine without possessing his doctorate, having in mind the strict conditions governing the practice of medicine in Warmia [14, 15]. In such context, in a letter from Duke Albrecht of Prussia, Copernicus is designated as a doctor of medicine [14]. Similarly, in 1581, Marcin Kromer, the famous Polish historian and Bishop of Warmia, placed a commemorative plaque in honor of Nicolaus Copernicus, *artium et medicinae doctor*, opposite the cathedral in Frombork [14, 15]. In addition, the portrait of Nicolaus Copernicus painted by Tobias Stimmer shows him holding a sprig of lily-of-the-valley – a symbol of the medical profession [14, 15, 21] (Figure 6).

During his therapeutic practice, Copernicus continuously kept expanded his medical knowledge [15, 21]. Thus, 14 books that dealt with medical issues were found in his personal library [23], including *De praeparatione hominis* by Hippocrates, *De affectorium locorum notitia* by Galen, *Breviarum practicae medicinae* by Bartholomeus de Montagne (Venice, 1499), and *Practica in arte chirurgica* by Joannis de Vigo (1516) [14].

Figure 6. The portrait of Nicolaus Copernicus with lilly-of-the-valley painted by Tobias Stimmer, 1587; it is the oldest graphic image of the illustrious scientist; source: https://en.wikipedia.org/wiki/Nicolaus_Copernicus

COPERNICUS'S MEDICAL PRACTICE

Copernicus was an experienced physician, full of self-sacrifice and honesty in dealing with his patients [14]. However, he paid special attention to the poor, supplying them with free medical advice, assistance and medicines [14, 15]. Polish historian Szymon Starowolski in his book *Scriptorum Polonorum Hecatontas* wrote that "Nicolaus Copernicus was respected as the second Aesculapius, because he knew various medicines, tried them, prepared them himself and used them with success. The poor people worshiped him as some kind of God" [14]. In the historical-documentary drama titled *Copernicus*, written by Miodrag Ilić, Copernicus is described as a man "whose calm and serious face, long black hair and steely patience in his look, voice and movement reveal spiritual maturity and inner strength" (Figure 1) [24]. In this drama, he remained faithful to the Hippocratic Oath even during the attack of the Prussian army, when he gave birth to the wife of a peasant Tadeusz [25].

In addition to his uncle, bishop Lucas Watzenrode, Copernicus treated four consecutive Warmian bishops (Fabianus Lusianus, who suffered from severe chronic diseases, Mauritius Ferber, troubled by digestive disorders, gout, and nephrolithiasis, Joannes Dantiscus, and Tiedemann Giese, who suffered from malaria and infections of the upper respiratory tract) [14, 21, 26]. He was also a physician of the Frombork's canons, such as his leprous brother Andreas, who was forced to leave Frombork and died in Italy in 1518 [21, 26], as well as Felix Reich, troubled by severe hemorrhages in 1538 [21]. Copernicus provided medical assistance to the relatives of his fellow canons as well [21, 26]. Thus, on February 24, 1532, Copernicus made a prescription with drugs for the stomach for the seriously ill sister of a canon Archacy Freundt [26]. Besides, he was always at the disposal of the patients of the Holy Spirit in Frombork [21].

Copernicus's medical fame crossed the borders of Frombork, so he frequently traveled to Gdańsk and Allenstein (in Polish, *Olsztyn*), providing consultations to the Dukes of Prussia [15]. Copernicus also collaborated with his colleagues from Gdańsk, Olsztyn, Königsberg (in Polish, *Królewiec*), Lubawa, and Elblag [13]. In the most difficult cases, Copernicus asked for medical advice from other distinguished physicians, including Laurentius Wilde and Jan Benedict Solfa, the official physicians to the Polish King Sigismund the Old I (in Polish, *Zygmunt Stary*) [21].

In 1541, when Copernicus received the urgent request of Prince Albrecht Hohenzollern, ruler of Ducal Prussia, regarding treatment of his sick friend, the Prince Counselor Georg von Kunheim, it was undoubtedly the peak moment of Copernicus's medical practice [15, 26]. Interestingly, Prince Albrecht was the same person who, as the great master of the Teutonic Order of Prussia, tried to conquer Olsztyn during Teutonic wars 1519–1521 [26]. At the time, in 1516, Copernicus, as the administrator of the chapter's estates, had a residence in the castle of Olsztyn [27]. In 1520, Copernicus, as a commissioner of Warmia, was nominated by the chapter to negotiate with Albrecht Hohenzollern [12, 27]. Regarding this matter, Copernicus wrote to king Sigismund I the Old that he "would act as befitted noble and honourable citizens faithful to the king, and was even prepared to die for the cause" [27]. He decided to built additional fortifications at the castle of Olsztyn [12, 27]. In that way, Copernicus stopped the invasion of the Teutonic troops [27]. However, times had changed. After a short period of time, the Teutonic order in Prussia ceased to exist, and in 1525, the great master become a secular prince in Prussia [26]. As aforementioned, in 1541, Prince Albrecht wanted to save the life of his seriously ill friend [15], and Copernicus was the sixth physician whom the Prince Albrecht asked for help. It was not surprising, because Georg von Kunheim had a malignant tumor on his neck and all efforts of other physicians to improve his condition failed. Therefore, Copernicus at the age of 68 decided to go to Königsberg. Prince Albrecht expressed his gratitude that the chapter allowed "especially pleasant to him master Nicolaus Copernicus, the doctor of medicine" to travel so far and that "in such an old age" [26]. Copernicus spent over three weeks at the bedside of the patient [15, 26]. When he come back to Frombork, he asked for an opinion from royal physician Jan Benedict Solfa [28]. Later, Copernicus sent opinion of his colleague to Prince Albrecht. In such context, on June 21, 1541, Copernicus wrote to prince Albrecht: "To the serene and honorable Prince Albrecht, by the grace of God margrave of Brandenburg, Duke of Prussia and Wendland, burgrave of Neuenburg, and Prince of Rügen, my gracious Lord: Just yesterday I received from Jan Benedict Solfa, the physician

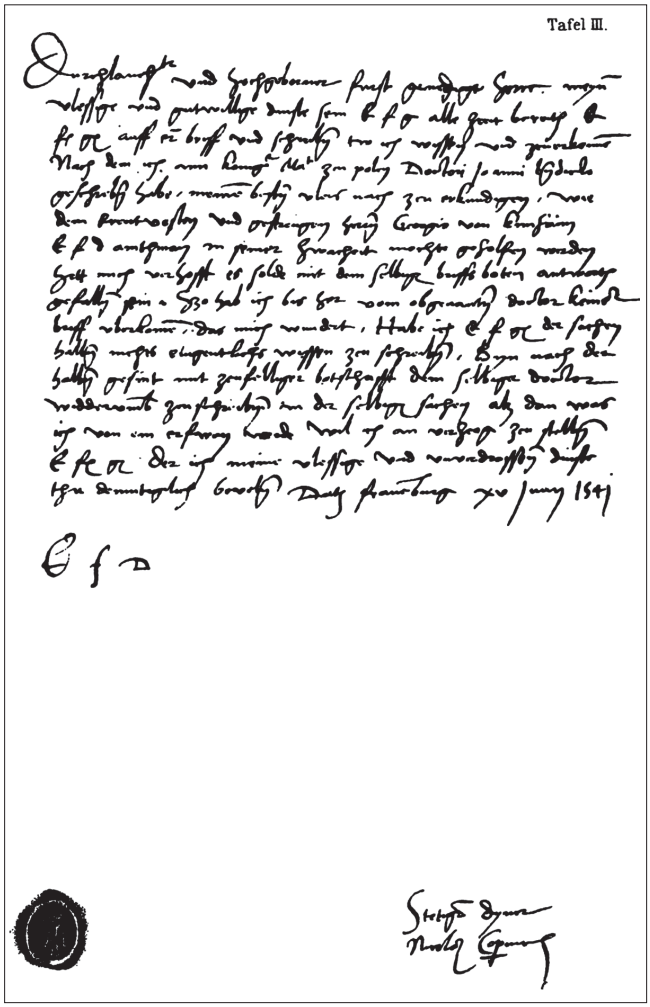


Figure 7. German-language letter from Copernicus to Duke Albrecht of Prussia with medical advice for Georg von Kunheim (1541); source: https://en.wikipedia.org/wiki/File:Copernicus-an-Herzog-Albrecht.png

of his Majesty the King of Poland, a letter and an answer to my message about honorable Georg von Kunheim. But since no mention is made therein of any other special or extraneous matters, I have forwarded the original letter to your Princely Grace. From it your Princely Grace will learn this doctor's opinion and advice. If I knew anything better to contribute there to that would be helpful in restoring that good man, Princely Grace's officer, to health, no labor, exertion, and trouble would be vexatious to me that would be beneficial to your Princely Grace, to whose service I am devoted. Your Princely Grace's obedient servant, Nicolaus Copernicus" (Figure 7) [28]. Georg von Kunheim died in September 1543, at the age of 53 [26].

Books from Copernicus's private collection are of particular interest for investigating his medical practice, since he used to leave hand-written prescriptions on their margins and blank pages [15]. Thus far, 14 prescriptions in accordance with mediaeval knowledge and practice written by Copernicus have been found [26]. Most of them were used for the treatment of renal disorders [23, 26]. For that purpose, Copernicus often prescribed drugs used by Avicenna [23], and also wrote out herbal remedies described in the widely accepted book *De materia medica* by Dioscorides [14]. In order to treat renal colic and hematuria, Copernicus used herbal ingredients, such as nettle (*Urtica dioica*), goosegrass (*Galium aparine*), rosemary (*Rosmarinus officinalis*), cubeb (*Piper cubeba*), common pumpkin (*Cucurbita pepo*), almond seeds, etc. [23].

In the library of the University of Uppsala in Sweden, one can see on a margin of a Euclides's book typical example of an expensive prescription by Copernicus [14, 15]. This prescription consisted of 21 components of animal, vegetable, and mineral origin, in combination with precious stones and metals (powdered gold, silver, emerald, sapphire, and coral) [15].

Copernicus also believed in simple traditional remedies, as well as medicines based on his own experience [14, 15, 21]. For example, he prescribed cloves with honey against cough, and cloves with warm red wine against diarrhea [14]. On the other hand, Copernicus never prescribed drugs whose components were obtained from urine, frogs, snakes, bats, animal claws, etc. [21].

In 1519, Copernicus successfully struggled against epidemics [13, 14, 15]. Namely, he constructed an innovative drinking-water supply system for Warmian population [14, 15]. With profound gratitude, Copernicus's fellow citizens engraved on the watermain in Frombork a poem with the following verse: "His wisdom has given to men what nature had denied them" [15].

Published data indicates that Jan Brożek, the most prominent Polish mathematician of the 17th century, was in a position to read Copernicus's correspondence and notes [15]. According to his reports, Copernicus investigated an analogy between human body and the mechanics of Archimedes, in order to apply mathematics in medical practice [14, 15]. Unfortunately, the reports quoted by Brożek have been lost, so there is no way to know more details regarding this Copernicus's idea [15].

CONCLUSION

The main interest of Nicolaus Copernicus was reflected in the heliocentric planetary system. His autography "On the Revolutions of Haevenly Bodies" has changed the way people saw the universe and was inscribed on the UNESCO Memory of the World Register in 1999. In addition, Nicolaus Copernicus permanently developed a growing interest in medicine and was a prominent and beloved physician. This aspect of his life also deserves to be remembered.

ACKNOWLEDGEMENT

The Ministry of Science, Technological Development and Innovation of the Republic of Serbia supported this article through grant N° 200110.

Ethics: This article was written in accordance with the ethical standards of the institutions and the journal.

Conflict of interest: None declared.

REFERENCES

1. Hawking S. On the shoulders of giants. 1st ed. London: Penguin books; 2003.
2. Balchin J. Quanum leaps: 100 scientists who changed the world. 1st ed. Beograd: Laguna; 2009. (Serbian)
3. Gledić V. Nikola Kopernik – život i delo. 1st ed. Beograd: Admiral books; 2009. (Serbian)
4. Perry M. An intelectual history of modern Europe. 2nd ed. Beograd: Clio; 2020. (Serbian)
5. Zielinska T. Nicolaus Copernicus. In: Ceccarelli M, editor. Distinguished figures in mechanism and machine science. Dordrecht: Springer Science & Bussines Media; 2007. p. 117–34.
6. Marinković B. Nikola Kopernik i njegovo delo. U: Ilić-Dajović M, Marinković B, urednici. Matematički list Društva matematičara, fizičara i astronoma SR Srbije, godina VII, br. 3. Beograd: BIGZ; 1973. p. 73–85. (Serbian)
7. Jonathan Huston Riverdale High School. Copernicus' Role in the Scientific Revolution: Philosophical Merits and Influence on Later Scientists; 2014, Young Historians Conference, 11 [accessed 27.10.2023]. Available from: https://pdxscholar.library.pdx.edu/younghistorians/2014/oralpres/11
8. Willy H. Copernicus, the man, the work, and its history. Proc Am Philos Soc. 1973;117(6):413–22.
9. Tim L. A Brief Biography of Nicolaus Copernicus [accessed 27.10.2023]. Available from: https://localhistories.org/a-brief-biography-of-nicolaus-copernicus/
10. Bejrowski P. Nicolaus Copernicus: a Renaissance man and his contribution to the development of modern science [accessed 27.10.2023]. Available from: https://polishhistory.pl/nicolaus-copernicus-a-renaissance-man-and-his-contribution-to-the-development-of-modern-science/
11. Nicolaus Copernicus. Famous scientists. Famous scientists. org [accessed 27.10.2023]. Available from: https://www.famousscientists.org/nicolaus-copernicus/
12. O'Connor JJ, Robertson EF. Nicolaus Copernicus. Biography [accessed 27.10.2023]. Available from: https://mathshistory.st-andrews.ac.uk/biographies/copernicus/
13. Rutkowski B, Muszytowski M, Ostrowski J. Nicolaus Copernicus: not only a great astronomer but also a physician. J Nephrol. 2011;Suppl 17:S25–32. [DOI: 10.5301/JN.2011.6490] [PMID: 21614776]
14. Rudowski W. [Nicolaus Copernicus as a physician]. NOWOTWORY J Oncol. 2002;52(4):342–7. (Polish)
15. Śliwiński M. Doctor Copernicus. In: The Magazine of the World Health Organization. Geneva: the World Health Organization; June 1973. p. 12–5.
16. Bogdanowicz W, Allen M, Branicki W, Lembring M, Gajewska M, Kupiec T. Genetic identification of putative remains of the famous astronomer Nicolaus Copernicus. PNAS. 2009;106(30):12279–82. [DOI: 10.1073/pnas.0901848106] [PMID: 19584252]
17. Piasecki K, Zajdel D. Anthropological research in Frombork. Tomb No. 13. Reconstruction of the appearance of the head on the basis of the skull. In: Gassowski J, editor. The search for Nicolaus Copernicus' Tomb. Pultusk: Wyższa Szkola Humanistyczna; 2006. p. 21–36.
18. Porzionato A, Macchi V, Stecco C, Parenti A, De Caro R. The Anatomical School of Padua. Anat Rec (Hoboken). 2012;295(6):902–16. [DOI: 10.1002/ar22460] [PMID: 22581496]
19. Rebollo RA. The Paduan School of Medicine: medicine and philosophy in the modern era. Hist Cienc Saude Manguinhos. 2010;17(2):307–31. [DOI: 10.1590/s0104-59702010000200003] [PMID: 21461471]
20. Furlan S, Mazzola RF. Alessandro Benedetti, a fifteenth century anatomist and surgeon: his role in the history of nasal reconstruction. Plast Reconstr Surg. 1995;96(3):739–43. [DOI: 10.1097/00006534-199509000-00032] [PMID: 7638303]
21. Mallek J. Copernicus medical education and practice [accessed 27.10.2023]. Available from: https://webs2.uci.umk.pl/nct/en/science/medicine/3/
22. de la Croix D, Vitale M. Scholars and literati at the University of Padua (1222–1800). RETE. 2021;3:33–42 [accessed 27.10.2023]. Available from: https://doi.org/10.14428/rete.v3i0/Padua
23. Popowska-Drojecka J, Muszytowski M, Rutkowski B. Was the famous astronomer Copernicus also a nephrologist. J Nephrol. 2011;Suppl 17:S33–6. [DOI: 10.5301/JN.2011.6459] [PMID: 21614777]
24. Ilić M. Kopernik. Drame o velikanima. 1st ed. Beograd: Albatros plus; 2014.
25. Stracenski I. Postupci likova kao okvir za razvoj drame „Kopernik" Miodraga Ilića [accessed 27.10.2023]. Available from: https://www.kcns.org.rs/agora/postupci-likova-kao-okvir-za-razvoj-drame-kopernik-miodraga-ilica/
26. Sikorski J. Nicolaus Copernicus in Warmia and his travel to Vilnius and Königsberg. In: Sikorski J, Jasiński J, editors. On the trail of outstanding historic personages – Nicolaus Copernicus and Immanuel Kant, two of the greatest figures of science on once prussian lands. Olsztyn: „ElSet" Publishing Studio; 2020. p. 15–45 [accessed 27.10.2023]. Available from: https://zamkigotyckie.org.pl/archiwalne/orgpl/wp-content/uploads/2020/08/Kopernik_Kant_wer_ang.pdf
27. Stimmer T. Portrait of Nicolaus Copernicus, 1587 [accessed 27.10.2023]. Available from: https://polsca.pan.pl/exhibition/kopernik/5.pdf
28. Manjunath R. Letter from Nicolaus Copernicus to Duke Albrecht of Prussia [accessed 27.10.2023]. Available from: https://www.linkedin.com/pulse/letter-from-nicolaus-copernicus-duke-albrecht-prussia-manjunath-r

Никола Коперник и медицина – 550 година од рођења и 480 година од смрти научника који је преокренуо поглед на свет

Данијела Вучевић[1], Милица Радосављевић[2], Јанко Самарџић[2], Мирослав Раденковић[2], Татјана Радосављевић[1]

[1]Универзитет у Београду, Медицински факултет, Институт за патофизиологију „Љубодраг Буба Михаиловић", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Институт за фармакологију, клиничку фармакологију и токсикологију, Београд, Србија

САЖЕТАК

Ове године се навршава 550 година од рођења и 480 година од смрти Николе Коперника, међународно признатог оца модерне астрономије, који је „зауставио Сунце, покренуо Земљу" и преокренуо поглед на свет. Међутим, слава Николе Коперника се не односи само на области астрономије, математике, црквеног и цивилног права, као и на теологију, економију и дипломатију; овај ерудита из доба ренесансе је такође био и један од најцењенијих лекара практичара у то време. Важно је истаћи да је Никола Коперник посебну пажњу посвећивао сиромашним људима, пружајући им бесплатне медицинске савете, помоћ и лекове. Стога се наш рад бави овим мање познатим аспектом живота славног научника.

Кључне речи: Никола Коперник; медицинско образовање; медицинска пракса; историја медицине

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh).*

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

Before submitting their paper to the Editorial Office of the Serbian Archives of Medicine, authors should read the Instructions for Authors, where they will find all the necessary information on writing their manuscript in accordance with the journal's standards. It is essential that authors prepare their manuscript according to established specifications, as failure to do so will result in paper being delayed or rejected. Serbian Archives of Medicine provides no fee for published articles. By submitting a paper for publishing consideration, authors of a paper accepted for publication in the Serbian Archives of Medicine grant and assign all copyrights to the publisher – the Serbian Medical Society.

GENERAL INSTRUCTIONS. *Serbian Archives of Medicine* publishes papers that have not been, either in their entirety or partially, previously published, and that have not been accepted for publication elsewhere. *Serbian Archives of Medicine* publishes papers in English and Serbian. For better availability and citation, authors are encouraged to submit articles of all types in English. The journal publishes the following article types: editorials, original papers, preliminary and short communications, case reports, video-articles, images in clinical medicine, review articles, current topics, articles for practitioners, history of medicine articles, language of medicine articles, medical ethics (clinical ethics, publication ethics) and regulatory standards in medicine, congress and scientific meeting reports, personal view articles, invited commentaries, letters to the editor, book reviews, professional news, In memoriam and other articles. Original papers, case reports, preliminary and short communications, review articles, current topics, video-articles and images in clinical medicine are published in English only, while other article types may be published in Serbian if the Editorial Office reaches such decision.

The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors (contained within the Submission Letter) declaring any potential interest or stating that the authors have no conflict of interest. For additional information on different types of conflict of interest, please see World Association of Medical Editors (WAME, *www.wame.org*) policy statement on conflict of interest.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*http://www.nlm.nih.gov/mesh*) are to be used for selection of the keywords.

TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

STRUCTURE OF THE MANUSCRIPT. All section headings should be in capital letters using boldface. Original articles and preliminary and short communications should have the following section headings: Introduction (objective is to be stated in the final paragraph of the Introduction), Methods, Results, Discussion, Conclusion, References. A review article and current topic include: Introduction, corresponding section headings, Conclusion, References. The firstly named author of a review article should cite at least five auto-citations (as the author or co-author of the paper) of papers published in peer-reviewed journals. Co-authors, if any, should cite at least one auto-citation of papers also published in peer-reviewed journals. A case report should consist of: Introduction (objective is to be stated in the final paragraph of the Introduction), Case Report, Discussion, References. No names of patients, initials or numbers of medical records, particularly in illustrations, should be mentioned. Case reports cannot have more than five authors. Letters to the editor need to refer to papers published in the *Serbian Archives of Medicine* within previous six months; their form is to be comment, critique, or stating own experiences. Publication of articles unrelated to previously published papers will be permitted only when the journal's Editorial Office finds it beneficial.

All enclosures (tables, graphs, photographs, etc.) should be placed at the end of the manuscript, while in the body of the text a particular enclosure should only be mentioned and its preferred place indicated. The final arrangement (position) of the enclosures will depend on page layout.

ABBREVIATIONS. To be used only if appropriate, for very long names of chemical compounds, or as well-known abbreviations (standard abbreviations such as DNA, AIDS, HIV, ATP, etc.). Full meaning of each abbreviation should be indicated when it is first mentioned in the text unless it is a standard unit of measure. No abbreviations are allowed in the title. Abbreviations in the summary should be avoided, but if they have to be used, each of them should be explained when first mentioned in the text of the paper.

DECIMAL NUMBERS. In papers written in English, including text of the manuscript and all enclosures, a decimal point should be used in decimal numbers (e.g. 12.5 ± 3.8), while in Serbian papers a decimal comma should be used (e.g. 12,5 ± 3,8). Wherever applicable, a number should be rounded up to one decimal place.

UNITS OF MEASURE. Length, height, weight and volume should be expressed in metric units (meter – m, kilogram – kg, gram – g, liter – l) or subunits. Temperature should be in Celsius degrees (°C), quantity of substance in moles (mol), and blood pressure in millimeters of mercury column (mm Hg). All results of hematological, clinical and biochemical measurements should be expressed in the metric system according to the International System of Units (SI units).

LENGTH OF PAPER. The entire text of the manuscript – title page, summary, the whole text, list of references, all

enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian – must not exceed 5,000 words for original articles, review articles and articles on history of medicine, and 3,000 words for case reports, preliminary and short communications, current topics, articles for practitioners, educational articles and articles for "Language of medicine", congress and scientific meeting reports; for any other section maximum is 1,500 words.

Video-articles are to last 5–7 minutes and need to be submitted in the flv video format. The first shot of the video must contain the following: title of the journal in the heading (*Serbian Archives of Medicine*), title of the work, last names and initials of first and middle names of the paper's authors (not those of the creators of the video), year of creation. The second shot must show summary of the paper, up to 350 words long. The final shot of the video may list technical staff (director, cameraman, lighting, sound, photography, etc.). Video-articles need to be submitted along with a separate summary (up to 350 words), a single still/photograph as an illustration of the video, and a statement signed by the technical staff renouncing copyrights in favor of the paper's authors. To check the required number of words in the manuscript, please use the menu *Tools-Word Count*, or *File-Properties-Statistics*.

ARTICLE ENCLOSURES are tables, figures (photographs, schemes, sketches, graphs) and video-enclosures.

TABLES. Each table, with its legend, should be self-explanatory. The title should be typed above the table and any explanatory information under the table. Tables should be numbered in Arabic numerals in order of citation in the text. Use *MS Word*, the menu *Table-Insert-Table*, inserting the adequate number of rows and columns. By the right click of the mouse, use the options *Merge Cells* and *Split Cells*. Use *Times New Roman*, font size 12 pt, with single line spacing and no indent to draw tables. Abbreviations used in tables should be explained in the legend below each respective table.

If the manuscript is entirely in the Serbian language, tables and corresponding legend should be both in Serbian and English. Also, the table cells should contain text in both languages (do not create two separate tables with a single language!).

FIGURES. Figures are all types of visual enclosures, and photographs, schemes, sketches and graphs are published as 'figures' in the *Serbian Archives of Medicine.* Figures should be numbered in Arabic numerals in order of citation in the text. Only original digital photographs (black-and-white or color), of minimum 300 dpi, and *jpg* or *tiff* format, are acceptable (small, blurry and photographs of poor quality will not be accepted for publishing!). If authors do not possess or are not able to provide digital photographs, then the original photos should be scanned in 300 dpi, and saved in original size. If a paper needs to be illustrated with a considerable number of figures, several figures will be published within the paper, and the rest will be available in the electronic version of the paper as a PowerPoint presentation (every figure needs to be numbered and be accompanied by legend). Video-enclosures (illustrations of a paper) can last 1–3 minutes and are submitted in the *flv* format. Along with the video, a still/photograph representative of the video is also needed, as it will be used as a placeholder in the electronic version of the paper, and as an illustration in the printed version.

If the manuscript is entirely in the Serbian language, photographs and corresponding legend should be both in Serbian and English.

Photographs may be printed and published in color, but possible additional expenses are to be covered by the authors.

GRAPHS. Graphs should be plotted in *Excel* in order to see the respective values distributed in the cells. The same graphs should be copied and pasted to the *Word* document, numbered in Arabic numerals by order of citation in the text. The text in the graphs should be typed in *Times New Roman*. Abbreviations used in graphs should be explained in the legend below the respective graph. In the printed versions of papers, graphs are generally published in black-and-white; therefore, it is suggested to avoid the use of colors in graphs, or to utilize colors of significant difference in brightness.

If the manuscript is entirely in the Serbian language, graphs and corresponding legend should be both in Serbian and English.

SCHEMES (SKETCHES). Schemes and sketches are to be submitted in *jpg* or *tiff* format. Schemes should be drawn in *CorelDraw* or *Adobe Illustrator* (programs for drawing vectors, curves, etc.). The text in the schemes should be typed in *Times New Roman*, font size 10 pt. Abbreviations used in schemes should be explained in the legend below the respective scheme. If the manuscript is entirely in the Serbian language, schemes and corresponding legend should be both in Serbian and English.

ACKNOWLEDGMENT. List all those individuals having contributed to preparation of the article but having not met the criteria of authorship, such as individuals providing technical assistance, assistance in writing the paper or running the department securing general support. Financial aid and all other support in the form of sponsorship, grants, donations of equipment and medications, etc., should be mentioned too.

REFERENCES. The reference list is the responsibility of the authors. Cited articles should be readily accessible to the journals readership. Therefore, following each reference, its DOI number and PMID number (if the article is indexed for MEDLINE/PubMed) should be typed. References should be numbered in Arabic numerals in order of citation in the text. The overall number of references should not exceed 30, except in review articles, where maximum of 50 is acceptable, and in meta-analysis, where up to 100

references are allowed. The number of citations of original articles must be at least 80% of the total number of references, and the number of citations of books, chapters and literature reviews less than 20%. If monographs and articles written by Serbian authors could be included in the reference list, the authors are obliged to cite them. The majority of the cited articles should not be older than five years. Use of abstracts as references is not allowed. If it is important to comment on results published solely in the form of an abstract, it is necessary to do so within the text of the article. The references of articles accepted for publication should be designated as *in press* with the enclosed proof of approval for publication.

The references are cited according to the Vancouver style (*Uniformed Requirements for Manuscripts Submitted to Biomedical Journals*), rules and formats established by the International Committee of Medical Journal Editors (*http://www.icmje.org*), used by *the U.S. National Library of Medicine* and scientific publications databases. Examples of citing publications (journal articles, books and other monographs, electronic, unpublished and other published material) can be found on the web site *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. In citation of references, the defined standards should be strictly followed, because it is one of the essential factors of indexing for classification of scientific journals.

SUBMISSION LETTER. The manuscript must be accompanied by the Submission Letter, which is signed by all authors and includes the following: 1) statement that the paper has never been published and concurrently submitted for publication to any other journal; 2) statement that the manuscript has been read and approved by all authors who have met the criteria of authorship; and 3) contact information of all authors of the article (address, email, telephone number, etc.). Blank Submission Letter form can be downloaded from the journal's web site (*http://srpskiarhiv.rs/global/pdf/SubmissionletterformFINAL.pdf*).

Additionally, the authors should submit the following copies of all permits for: reproduction of formerly published material, use of illustrations and publication of information on known people or disclosure of the names of people having contributed to the work.

MEMBERSHIP FEE AND SUBSCRIPTION RATES. In order to publish their article in the *Serbian Archives of Medicine*, all authors and co-authors, medical doctors and doctors of dental medicine, must be members of the Serbian Medical Society (according to the Article #6 of the Statute of the SMS) for the year in which the manuscript is being submitted. All authors pay an "Article Processing Charge" for the coverage of all editing and publishing expenses. Domestic authors pay 3,000 RSD, and those from abroad €35. The editing and publishing fee is required for substantive editing, fact and reference validations, copy editing, and publishing online and in print. An author who had already paid the fee can have more articles submitted for publishing consideration in the year the fee was paid. All authors who pay this fee may, if they desire so, receive the printed version of the journal in the year when the fee is paid. Please note that the payment of this charge does not guarantee acceptance of the manuscript for publication and does not influence the outcome of the review procedure, in accordance with good publishing practice. The journal accepts donations from sponsors to create a sum for payment reductions or waivers for authors unable to cover the Article Processing Charge (a justification of the inability to pay should be provided in such cases).

The requirement for paying the Article Processing Charge does not apply to students or to journal subscribers. Institutions (legal entities) cannot by their subscription cover this condition on behalf of the authors (natural persons). Copies of deposit slips for membership and Article Processing Charge should be enclosed with the manuscript. Foreign authors are under no obligation to be members of the Serbian Medical Society. All the relevant information can be obtained via email address of the Editorial Office (*office@srpskiarhiv.rs*) and on the journal's web site (*http://srpskiarhiv.rs/en/subscription/*).

SUBMISSION. Our online submission system will guide you through the process of entering your article details and uploading your files. All correspondence, including notification of Editorial Office, requests for revision and Editor's decision will be sent by e-mail.

Please submit your manuscript and all enclosures via: ***http://www.srpskiarhiv.rs***.

NOTE. The papers not complying with these instructions will not be reviewed and will be returned to the authors for revision. Observing the instructions for preparation of papers for the *Serbian Archives of Medicine* will shorten the time of the entire process of publication and will have a positive effect on the quality and timely release of the journal's issues.

For further information, please contact us via the following address:

ADDRESS:
Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Website: *www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

CIP – Каталогизација у публикацији
Народна библиотека Србије, Београд

61(497.11)

СРПСКИ архив за целокупно лекарство : званичан часопис Српског лекарског друштва = Serbian Archives of Medicine : official journal of the Serbian Medical Society / главни и одговорни уредник Гордана Теофиловски-Парапид. - Књ. 1 (1874)-књ. 2 (1875) ; књ. 3 (1879)- књ. 8 (1881) ; књ. 9 (1887)-књ. 10 (1888) ; књ. 11 (1894)-књ. 12 (1895) ; год. 1, бр. 1/2 (1895)- . - Београд : Српско лекарско друштво, 1874-1875; 1879-1881; 1887-1888; 1894-1895; 1895-(Београд : Службени гласник). - 29 cm

Двомесечно. - Текст на енгл. језику. - Има суплемент или прилог: Српски архив за целокупно лекарство. Суплемент = ISSN 0354-2793. - Друго издање на другом медијуму: Српски архив за целокупно лекарство (Online) = ISSN 2406-0895
ISSN 0370-8179 = Српски архив за целокупно лекарство
COBISS.SR-ID 3378434

The Journal Serbian Archives of Medicine is indexed in: Science Citation Index Expanded, Journal Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journal, DOI Serbia

CONTENTS