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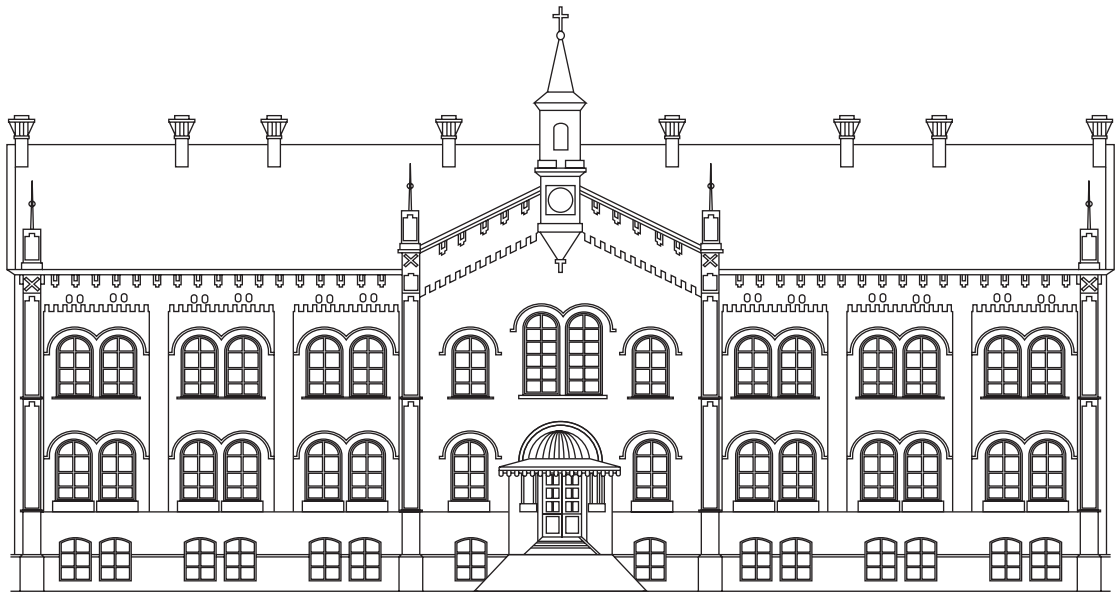

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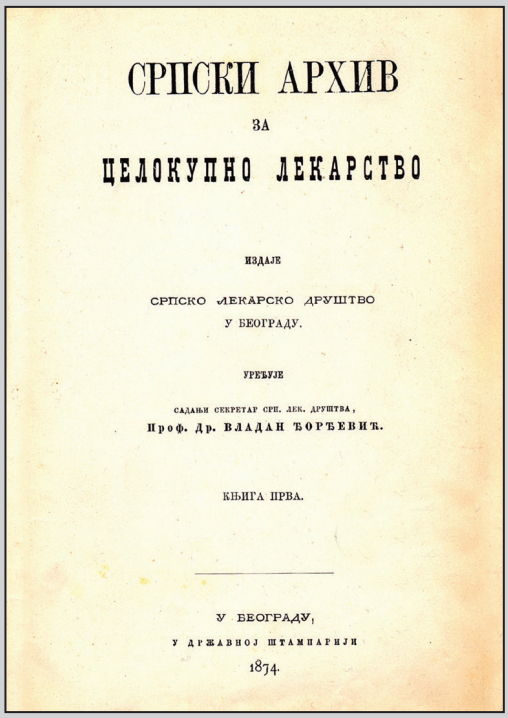


СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

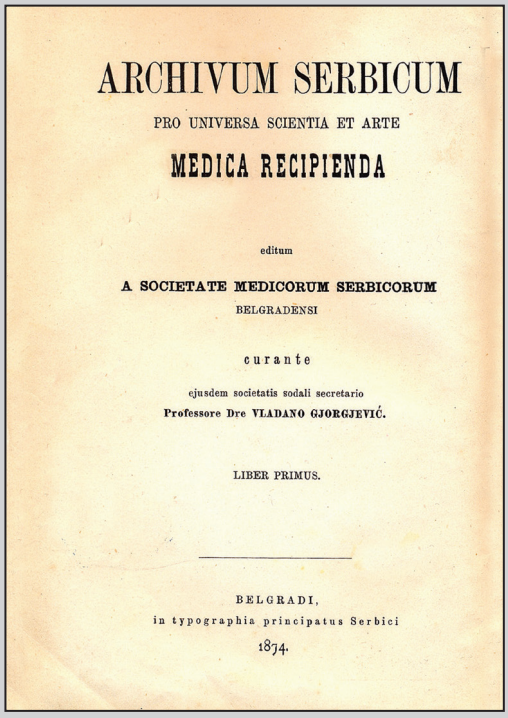
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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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).

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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.

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ГОДИШТЕ 154 ЈАНУАР–ФЕБРУАР 2026. СВЕСКА 1–2

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EDITORIAL • УВОДНИК

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

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EDITORIAL / УВОДНИК

Serbian Archives of Medicine – through trials and tribulations to new endeavors

The year behind us was full of challenges, but nonetheless one of many achieved goals. It was also the very first filled with dynamic changes. One of those was bidding farewell to many of our longstanding members of the International Editorial Board of our Journal. They have – each one in his or her way – to the best of their abilities and under the circumstances at the time, given the best they could and I take this opportunity to thank them for being with us and helping us grow (Table 1).

To the new members of our current International Editorial Board – and whose names you will find in the issue of our Journal (2025. Vol 154, Issue 1–2) – I wish a warm welcome. Furthermore, the decision of the ***Serbian Medical Society*** and its President Prof. Milan A. Nedeljković, to empower the Editorial Board with more colleagues from other medical schools nationwide appeared to be very helpful, particularly in the situation of financial adversity. Even in the face of that prolonged struggle that prevented us from expanding our technical editorial office, medical doctors and university professors serving on our boards, have generously accepted taking upon themselves providing additional technical support and administrative tasks related to meeting our bimonthly publication in a timely fashion.

As it is well known, ***Serbian Archives of Medicine*** is the official journal of the ***Serbian Medical Society***, the oldest society of its kind in modern medical Serbian history, founded in Belgrade (Serbia), on April 22, 1872 (according to the Julian calendar), i.e., May 4, 1872 (according to the Gregorian calendar), but the first issue of the ***Serbian Archives of Medicine*** was published only two years later. Then, Serbia has not yet regained its sovereignty, but even when it eventually had, the fight for its preservation shall obstruct the regular publication of our journal [1, 2, 3].

Honoring both, the legacy and postulates of the visionary and cosmopolite founders of the ***Serbian Medical Society***, as well as the demands of contemporary publishing, during 2025, not only that we have maintained the trend of growing interest of international Authors, but significantly increased it in comparison to 2024.

The COVID–19 pandemic has shown that the importance lies in emphasizing diseases and epidemics not only "where Serbs live" [1] as ***Serbian Archives of Medicine's*** first editions wished 154 years ago aiming to increase local knowledge, but in general, because advances in technology and transport have brought people together much faster than then, even when continents apart [4, 5]. We published results of national and global researchers addressing a variety of infectious and non-communicable diseases [6, 7], equally. But, in 2025 we have not neglected basic biomedical research either [8], that you can find in this issue as well (Starčević et al., 2026, pages 100–106). During the year behind us, our Journal has as well followed the technical and technological advances both in medicine and dentistry [9, 10]. Noncommunicable diseases in less affluent societies and regions have lived their own challenges since the COVID–19 pandemic and together with doctors' rights, they remain a bane of our existence. One of the papers addressing those issues can be found in this Issue of the ***Serbian Archives of Medicine*** (Galić et al., 2026, pages 107–112).

Truth be told, sometimes it is easier to find reviewers among legal minds when researchers from their field submit to our Journal, than among doctors themselves irrelevant of the fact whether the Authors are doctors or lawyers. Publishing of these papers that address usually highly sensitive topics not only in Serbia, but worldwide would not be possible without

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continuous support we get from the professors from the Faculty of Law of the University of Belgrade and other private universities as well, who have volunteered their time to participate not only as authors, but as reviewers as well.

Furthermore, in 2025 we managed to preserve the ***Serbian Archives of Medicine*** publishing on a bi-monthly basis established back in December 2018 and always on time. Besides the growing trends of submissions first noted in 2023, in 2025 we witnessed a significant increase of international authors and acceptance of international reviewers who accepted providing timely reviews *pro bono* (Table 2). We have, thus, fulfilled an important request of our external evaluators. We publish not only papers related to regional health problems that provide insights of regional relevance, but we also ensure that the reviewers of our regional submissions are international. We are as indebted to our international reviewers as we value our regional ones; it is their input that often provides valuable insight to readers and, consequently, increases our visibility worldwide.

Serbian Archives of Medicine has for the seventh year in a row provided continuous education of our authors and reviewers that helps them navigate our online submission system. Although CEON does offer a guide, and we offer instructions for authors on our journal website 24 hours, seven days a week, 52 weeks a year including holidays, a very small percentage of authors shows willingness to use either and opt for calls and emails to both, the technical office and Editorial Board members as well. Recently, the situation was further aggravated by technical difficulties experienced by several local internet providers, which made our work in that department more time-consuming and just as frustrating as it was for our authors. Last year, again, academic networks have been targeted by hackers and malware, which occasionally created unpleasant communications between the authors and the reviewers of their submissions where we aimed to mediate in the best interest of the publication.

The second year in a row, we have noticed that the use of iThenticate – introduced back in 2019 in our fight against plagiarism – has helped discourage authors to use copy/paste during editing which is a very promising sign! Unfortunately, at the end of last year iThenticate changed the interface, and the new one looks like less user-friendly than the previous one was.

With all local and global events of the 2025, our editorial policy has not failed neither our forefathers, nor the challenges that the second quarter of our century expects us to rise up to. In that regard, we have managed to encompass (1) independent research of national authors discussing statistical data of diseases in Serbia and neighbouring countries; (2) independent discussions from different medical and allied professions research fields; (3) reviews of current medical achievements worldwide; (4) critical analyses of existing national sanitary / epidemiological positions, national medical books and research [2].

I would like to take this opportunity to extend our heartfelt thanks to our partners – ***Službeni Glasnik*** and their Department in charge of our Journal's publishing process, in particular to Ms. Jasmina Živković, but also to Mr. Nemanja Anđelov who was in charge of the Journal website, for their tireless work and unending enthusiasm. Thanks to these two remarkable individuals, who have never confined their dedication to formal working hours, the ***Serbian Archives of Medicine*** continues to meet all required deadlines and reach publication on schedule. I owe a special debt of gratitude to all members of the Editorial Board, the Publisher's Advisory Board and all our reviewers for their selfless engagement during the past year.

Still, I call on your attention to another challenge ahead of us – a lovely, joyful and encouraging – but full of hopes for a better future for all of us at the ***Serbian Medical Society*** and the Editorial office of the ***Serbian Archives of Medicine*** and that is the **21st Congress of the Doctors of Serbia** scheduled to happen in Zlatibor, Serbia this Spring (May 15–17, 2026).

As I conclude this Editorial of the first issue of the ***Serbian Archives of Medicine*** for 2026, I will appeal – time and again – for the ***Serbian Medical Society*** and the **Republic of Serbia** to allocate the additional financial resources necessary to strengthen the Journal's logistical infrastructure. Such support is essential if we are to restore this national legacy – an enduring cornerstone of Serbian medical publishing – to its rightful place in the PubMed database, where it was indexed until 2017.

Conflict of interest: None declared.

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Table 1. The list of the Serbian Archives of Medicine international Editorial Board (2025)

Serbian Archives of Medicine 2025;153(1–2)

Table 2. The list of the Serbian Archives of Medicine reviewers in the year 2025

1. Akgul Turgut
2. Arsić Jasmina
3. Banko Ana
4. Banović Marko
5. Bartfai György
6. Bašić Dragoslav
7. Beatović Slobodanka
8. Begović-Kuprešanin Vesna
9. Beleslin Branko
10. Beloica Miloš
11. Belojević Goran
12. Bezmarević Mihailo
13. Bila Jovan
14. Bilanović Dragoljub
15. Bilbija Ilija
16. Bjegović-Mikanović Vesna
17. Bosić Martina
18. Brašanac Dimitrije
19. Brković Radoje
20. Brown Paul
21. Bubanja Dragana
22. Bulatović Nikola
23. Bumbaširević Marko
24. Chen Guang
25. Csiba Laszlo
26. Čolić Miodrag
27. Čolić Snježana
28. Ćeranić Miljan
29. Ćupurdija Voja
30. Dhanwal Dinesh
31. Dimić Andreja
32. Dimitrijević Milovan
33. Dinčić Evica
34. Dinić Ljubomir
35. Dmitriev Vadim
36. Dobričić-Čevrljaković Nevenka
37. Doklestić Krstina
38. Drobac Milan
39. Džatić-Smiljković Olivera
40. Đorđević-Jocić Jasmina
41. Đukanović Ljubica
42. Đukić-Ćosić Danijela
43. Erić Dražen
44. Filipović Gordana
45. Filipović Tatjana
46. Fures Rajko
47. Galunić-Bilić Lea
48. Gavrilovska-Brzanov Aleksandra
49. Giga Vojislav
50. Gojnić Miroslava
51. Gotić Mirjana
52. Gregorić Pavle
53. Hatab Nur
54. He Mu
55. Ignjatović Dejan
56. Ignjatović-Ristić Dragana
57. Ilić Branislav
58. Ilić Miroslav
59. Ilić Tatjana
60. Ilić-Živojinović Jelena
61. Ille Mihailo
62. Ille Tatjana
63. Ivanjac Filip
64. Jakjovska-Maretti Tatjana
65. Janković Radmila
66. Janjić Vladimir
67. Jeremić Jelena
68. Jeremić Rada
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72. Jovanović Tanja
73. Jovanović Zoran
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76. Jović-Vraneš Aleksandra
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78. Kalezić Nevena

79. Kalezić Tanja
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82. Knežević Aleksandar
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84. Kočica Mladen
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87. Kostić Mirjana
88. Kovačević Igor
89. Kovrigina Alla
90. Kravljanac Đorđe
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92. Kuzmanović Miloš
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95. Latas Milan
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111. Matić Aleksandar
112. Matić Slađana
113. Mesaroš Šarlota
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116. Mihajlović Goran
117. Mijović Milica
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134. Nedeljković Ivana
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189. Staletović Danijela
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191. Stamenković Miroslav
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193. Stanković Nebojša
194. Stanojević Željka
195. Stavridis Sotir
196. Stefanović Neda
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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Physical properties of different root canal sealers

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SUMMARY

Introduction/Objective Aim was to evaluate the push-out bond strength to root canal dentine and radiopacity of three different sealers: Adseal (Meta Biomed Co., Cheongju-si, South Korea), CeraSeal (Meta Biomed Co.) and control AH Plus (Dentsply Sirona, Charlotte, NC, USA).

Methods In nine dentin discs, 1 mm thickness, three holes, 1.2 mm diameter, were drilled in with a fissure carbide bur. Discs were immersed in 0.5% NaOCl and 10% citric acid respectively, for 60 seconds rinsed and dried. Every hole was filled with different sealer. Specimens were wrapped in gauze previously immersed in Hank's balanced salt solution at 37°C / seven days. The push-out test was performed using universal testing machine at a cross-head speed of 1 mm/min. The radiopacity was tested (ISO 6876/2012 standard). Three sealer specimens, 5 mm in diameter and 2 mm thick were prepared and radiographed using radiovisiography system (CCD sensor, Trophy Radiologie, Marne-la-Vallée, France) with graded aluminum step-wedge. Gray-scale value was assessed using Adobe Photoshop CS7 (Adobe Inc. San Jose, CA, USA).

Results Mean values of push-out bond strength were 5.21 ± 0.87 MPa (Adseal), 0.06 ± 0.02 MPa (CeraSeal), and 3.13 ± 0.38 MPa (AH Plus). A statistically significant difference in push-out bond strength was observed among all three sealer groups ($p < 0.05$). Adseal exhibited the strongest bond strength to root canal dentine. All sealers achieved radiopacity over 3 mm, with statistically significant difference among the groups ($p < 0.05$).

Conclusion The epoxy-based sealer Adseal showed higher bond strength compared to AH Plus and calcium silicate-based sealer CeraSeal, which, expectedly, showed the weakest dislocation resistance. All three sealers fulfilled the ISO standard to be distinguished on dental radiogram.

Keywords: root canal sealer; radiopacity; push out; calcium silicate

INTRODUCTION

Adequate root canal obturation should effectively seal the root canal system, preventing apical and coronal leakage and enable long-term success of endodontic treatment. Root canal sealers should have appropriate physical properties to achieve three-dimensional sealing [1]. One of the most important characteristics of an endodontic sealer is its capacity to adhere to radicular dentine. Adequate adhesion minimizes gap formation at the sealer–dentine interface, which could otherwise permit fluid percolation [2], and improves resistance to material displacement during functional loading or clinical procedures [3]. Likewise, materials that fill the canal space should have adequate mechanical properties that will strengthen the root canal and compensate for the reduced resistance caused by instrumentation [4].

Radiopacity is a physical property that enables radiographic visualization of the root canal filling aiding in the assessment of its quality. Furthermore, adequate radiopacity is necessary for distinction of the root canal filling material from surrounding dental and periapical tissues and for detection of voids in the root canal sealers or at the interface sealer/dentine or sealer/core material.

Epoxy resin-based sealers are known for their favorable physical properties, including extended working and setting times, low solubility, high flowability, minimal polymerization shrinkage, and excellent adaptation to dentinal walls. Their adhesion to dentine is attributed to the formation of covalent bonds between epoxide rings and exposed amino groups within the collagen network [5, 6].

Calcium silicate-based sealers are derived from mineral trioxide aggregate, which is known for its favorable clinical and biological

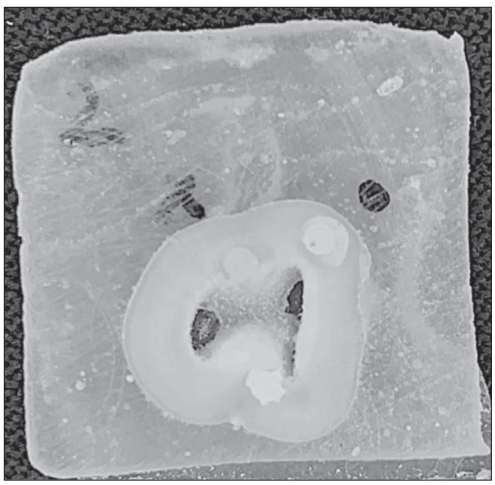

Figure 1. Dentine disk sample filled with tested sealers

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outcomes. These sealers are biocompatible [7], form a biomimetic apatite layer when interacting with phosphate-containing simulated body fluids [8, 9], release calcium [10], and exhibit excellent compatibility with various core materials due to their sufficient flow and optimal handling characteristics [11].

CeraSeal (Meta Biomed Co., Cheongju-si, South Korea) is a premixed calcium-silicate-based sealer, but unfortunately, there is very little information in literature on its properties and performance in vitro and in vivo.

Thus, the aim of this study was to evaluate the bond strength to root canal dentine and radiopacity of Adseal (Meta Biomed Co.), CeraSeal (Meta Biomed Co.) and AH Plus (Dentsply Sirona, Charlotte, NC, USA). The null hypothesis was as follows:

1) there is no statistically significant difference in the bond strength to root canal dentine among the tested sealers;

2) there is no statistically significant difference in radiopacity among the tested sealers.

METHODS

1. Three different root canal sealers were used in this study (Table 1):

- Adseal (Meta Biomed Co.) epoxy resin-based,
- CeraSeal (Meta Biomed Co.) calcium silicate-based,
- AH Plus (Dentsply Sirona) epoxy resin-based used as a control group.

Table 1. Manufacturer and composition of the tested sealers

Sealer	Manufacturer	Composition
Adseal	Meta Biomed Co., Cheongju-si, Chungcheongbuk-do, South Korea	Base -epoxy resin -NS calcium phosphate -NS zirconium dioxide -NS calcium oxide -NS ethylene glycol salicylate Catalyst -N, n-dibenzyl-5 oxanonandiamin-1,9 -amantadine
CeraSeal	Meta Biomed Co., Cheongju-si, Chungcheongbuk-do, South Korea	-calcium silicates, -zirconium oxide, -thickening agent
AH Plus	Dentsply Sirona, Charlotte, NC, USA	Paste A -bisphenol-A, -bisphenol-F calcium tungstate, -zirconium oxide, -silica iron oxide pigments Paste B -dibenzyldiamineamino adamantane tricyclodecane-diaminecalcium tungstate, -zirconium oxide, -silica, -silicone oil

2. Nine maxillary third molars from humans, extracted for orthodontic purposes, were cleaned of debris and preserved in a 0.2% thymol solution at 4°C for no more than six months. The teeth were embedded in acrylic (Duracryl plus, SpofaDental a.s., Jičín, Czech Republic) using standardized silicone molds measuring 10 × 10 × 15 mm, up to the cemento-enamel junction. The crowns were then cut off at the cemento-enamel junction with a diamond saw operating at a speed of 0.7 mm under coolant, aligned perpendicular to the tooth's long axis. A 1 ± 0.1 mm disk was sectioned from the middle segment of each tooth. Each disk had three standardized cavities, each 1.2 mm in diameter, prepared using a 1.2 mm fissure carbide bur (Dentsply Maillefer, Ballaigues, Switzerland) in a fixed handpiece to ensure uniform cavity preparation. After this, the disks were immersed in three different solutions – 0.5% sodium hypochlorite, 10% citric acid, and saline – for 60 seconds each and then blotted dry.

The cavities in each disk were randomly assigned to different groups and filled with the respective sealers, which were mixed according to the manufacturer's instructions using a probe in a vibrating motion. Any excess material was carefully removed with a plastic instrument.

The specimens were wrapped in gauze that had been soaked in Hank's balanced salt solution and incubated at 37°C for seven days. This procedure ensured that each disk contained all three sealers.

To assess the push-out bond strength of each tested sealer to the root dentine, a universal testing machine (Force Gauge PCE-FM 200, PCE Instruments, Meschede-Freienohl, Germany) was used. Each disk was placed between two supports, ensuring that the dislocation of the sealer was not obstructed. A custom-made cylindrical stainless-steel indenter, 0.8 mm in diameter, applied force to the sealer at a speed of 1 mm/min until the sealer dislodged from the root canal space. The bond strength (σ, in MPa) was calculated using a specific formula:

$$\sigma = \frac{F}{2r\pi h}$$

where F is the maximum load (N) measured at fracture, r is cavity radius (0.6 mm) and h is specimen height (1 mm).

3. The radiopacity was tested in accordance with the International Organization for Standardization (ISO 6876). The sealers were mixed following manufacturer's instructions and three specimens, 5 mm in diameter, 2 mm high, were made for each tested material.

After the setting period, the specimens were radiographed using a radiovisiography system (CCD sensor, Trophy Radiologie, Marne-la-Vallée, France) with an exposure time of 0.04 seconds, a voltage of 60 kV, and an amperage of 10 mA. The distance from the source to the object was 35 cm. Each sealer specimen was radiographed alongside an aluminum step-wedge, which was graduated from 1 to 10 mm in 1-mm increments. The gray-scale values for each step of the aluminum step-wedge and the tested materials were measured using Adobe Photoshop CS7 (Adobe Inc. San Jose, CA, USA). The correlation between the logarithm of the aluminum thickness and its corresponding gray-scale value was utilized to calculate the equivalent thickness of aluminum for each root

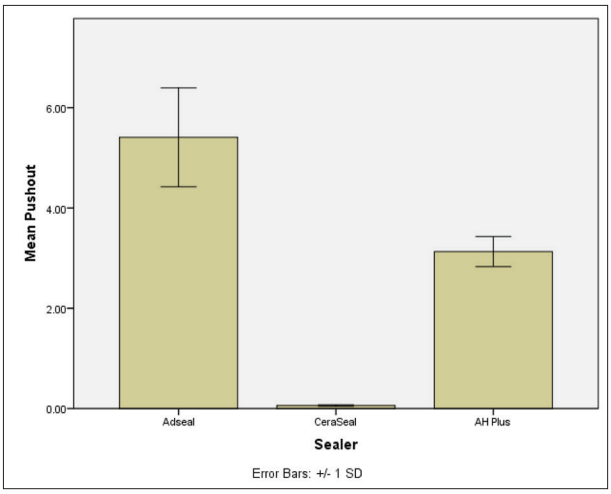

Figure 2. Push-out bond strength mean values (MPa) and standard deviation (SD)

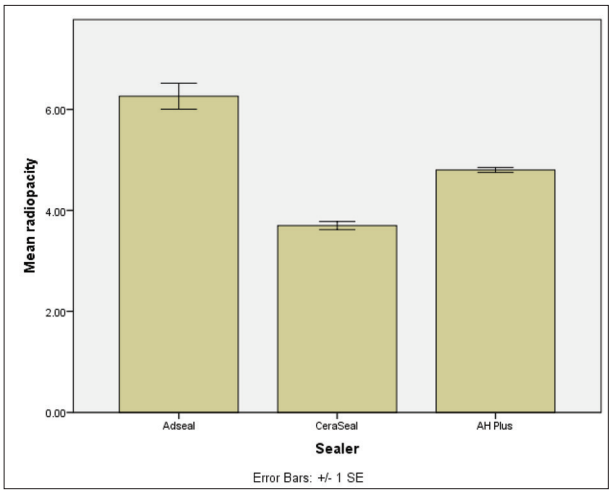

Figure 3. Different sealer radiopacity

Table 2. Push out bond strength and radiopacity

Sealer type	Push out MPa	p	Radiopacity (mm)	p
Adseal	5.21 ± 0.87	0.011*	6.26 ± 0.57	0.009*
CeraSeal	0.06 ± 0.02	0.001*	3.70 ± 0.17	0.001*
AH Plus	3.13 ± 0.38	p < 0.001*	4.80 ± 0.11	0.001*

*Statistically significant

canal sealer specimen examined. Data were compared using Welch's ANOVA with Games–Howell post-hoc test ($\alpha = 0.05$).

Ethics: This study was approved by the Ethics Committee School of dental medicine Belgrade University No 36/15.

RESULTS

Regarding the push-out bond strength of all tested sealers, Adseal demonstrated the highest mean push-out values (Mean = 5.21 ± 0.87), followed by AH Plus (Mean = 3.13 ± 0.38), whereas Ceraseal showed the lowest adhesion performance (Mean = 0.06 ± 0.02) (Figure 2.). When comparing the push-out bond strength across all groups (Adseal, AH Plus, and Ceraseal), Welch's ANOVA confirmed a statistically significant difference among the materials ($p < 0.001$). Comparing the AH Plus and Ceraseal, the difference between these two sealers was statistically significant ($p < 0.001$).

Subsequent Games–Howell post hoc analysis revealed that Adseal had significantly higher push-out bond strength than AH Plus ($p = 0.011$) and Ceraseal ($p = 0.001$), while AH Plus also exceeded Ceraseal ($p < 0.001$), Table 2.

Regarding radiopacity, Welch's ANOVA revealed a statistically significant difference in radiopacity among the tested sealers ($p < 0.001$). Games–Howell post hoc analysis showed that Adseal exhibited significantly higher radiopacity compared with AH Plus ($p = 0.009$) and Ceraseal ($p = 0.001$). AH Plus also demonstrated higher radiopacity than Ceraseal, and the difference was statistically significant ($p = 0.001$). These findings indicate that all three materials differ in radiopacity, with Adseal being the most radiopaque sealer, followed by AH Plus and Ceraseal (Table 2. Figure 3.).

All sealers showed a statistically significant difference in bond strength (0.05).

All three sealers achieved radiopacity over 3 mm Al. There was statistically significant difference in the values radiopacity of the tested sealers ($p < 0.05$) (Figure 3).

DISCUSSION

Significant differences between tested sealers were found regarding the push-out bond strength. Therefore, the first null hypothesis was rejected.

Push-out bond test is a method commonly used to evaluate the interfacial bond strength between endodontic materials and root dentine. The advantage of using the standard push-out test is that multiple slices can be derived from a single root specimen [12]. On the other hand, these slices are obtained by preparing the natural root canal of the tooth which often leads to difficulty in creating a reliable baseline due to the intricate intracanal anatomy [13]. In this study a novel set-up model, introduced by Scelza et al. [14] was used in order to increase the internal validity of the push-out test by forming artificial standard canal-like holes in dentine discs.

Resistance to dislocation of root canal sealers is conditioned by various factors such as type of sealer, presence/absence of smear layer, irrigating solutions, shape of root canals (C factor), as well as number and size of dentinal tubules [14–17].

In this study, dentinal discs were immersed in NaOCl solution and then in 10% citric acid solution with the aim of removing the smear layer. There is no uniform position in the literature on the influence of the smear layer on the push-out bond strength of the calcium silicate-based sealers to root canal dentine. The use of acids such as ethylenediaminetetraacetic can adversely affect the formation of

calcium silicate hydrate gel which is being produced during the hydration process of calcium silicate-based sealers [18].

AH Plus sealer was used as a control material in this study. This sealer epoxy resin sealer is dimensionally stable in the long term, is insoluble and has low toxicity [19]. Compared to other sealers, it has a superior dislocation resistance to root canal dentin and is considered the "gold standard" in endodontics [20, 21].

Our study showed that epoxy resin-based sealers Adseal and AH Plus demonstrated higher bond strength values than calcium silicate-based CeraSeal. High resistance to dislocation can be explained by the chemical composition of these sealers, i.e., by forming covalent bonds between open epoxy paste rings and amino groups present in dentin collagen as well as low polymerization contraction [22, 23]. Also, cohesion between paste molecules increases resistance to paste dislocation resulting in better adhesion [24].

In this study, Adseal proved to have the highest dislocation resistance to root canal dentine. Lee et al. [25] investigated physicochemical properties of epoxy resin-based and bioceramic-based root canal sealers. Flow, final setting time, radiopacity, dimensional stability, and pH change were examined according to modified ISO 6876/2012 standards and American National Standards Institute / American Dental Association specifications number 57. AdSeal showed bigger expansion rate than the favorable rate suggested by the international standards, which may partially explain very high values of bond strength in our study. The authors in the mentioned study recommended further investigation of the potential risk of inducing the vertical root fractures by the sealer expansion [25, 26].

Beautlin et al. [27] found that CeraSeal demonstrated similar values of push-out bond strength values compared to AH Plus. This experimental set up model used gutta-percha which may explain the differing distribution of bond strength values. On the other hand, a similar paper used gutta-percha while assessing bond strength and showed that bond strength values of Ceraseal were significantly lower than AH Plus [28]. These findings may be due to different protocols of root canal drying techniques used in the study. Our results are similar to the findings of Maharti et al. [29] who established that CeraSeal had lower dislocation resistance compared to AH Plus in a comparable set up model.

Radiopacity is an important feature of a sealer it helps to differ the sealer in an obturated root canal from other anatomical features on a radiogram. This property is essential to determine if there was insufficient or inadequate root canal filling or a sealer leakage. Following the ISO standards tested sealers fulfilled the standard norm of over 3 mm of radiopacity. Radiopacity of all three sealers did differ in a significant manner $p < 0.05$.

These results are in concordance with the findings of Zamparini et al. [30], where CeraSeal and AH Plus demonstrated radiopacity values above 8 mm Al.

CONCLUSION

The epoxy-based sealer Adseal showed higher bond strength compared to AH Plus and calcium silicate-based sealer CeraSeal, which, expectedly showed the weakest dislocation resistance. All three sealers achieved the ISO standard values, to be distinguished on the dental radiogram.

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Conflict of interest: None declared.

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Физичка својства различитих паста за пуњење канала корена

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САЖЕТАК

Увод/Циљ Циљ овог истраживања био је да се испита јачина везе и рендгенконтрастност три различите пасте за пуњење канала корена: *Adseal* на бази епоксидне смоле (*Meta Biomed*, Чонгћу, Јужна Кореја), *CeraSeal* на бази калцијум-силиката (*Meta Biomed*) и контролна паста *AH Plus* (*Dentsply Sirona*, Шарлот, Северна Каролина, САД).

Методе На девет дискова дентина дебљине 1 *mm* препарисана су по три кавитета пречника 1,2 *mm* карбидним сврдлом. Дискови су потопљени у 0,5% раствор *NaOCl* и 10% раствор лимунске киселине, 60 секунди, затим испрани физиолошким раствором и осушени. Сваки кавитет испуњен је различитом пастом. Узорци су умотани у газу натопљену вештачком ткивном течношћу на 37° *C* током седам дана. Тест смицања изведен је на универзалној машини при брзини наставка од 1 *mm*/мин. Радиопацитет је тестиран у складу са стандардом *ISO* 6876. Припремљена су три узорка заптивача, 5 × 2 *mm*, и радиографисана коришћењем радиовизиографског система (*CCD* сензор, *Trophy Radiologie*, Марн ла Вале, Француска) са градуисаним алуминијумским еталоном. Вредност сиве скале процењена је коришћењем софтвера *Adobe Photoshop CS7* (*Adobe Inc.*, Сан Хозе, Калифорнија, САД).

Резултати Средње вредности јачине везе износиле су 5,21 ± 0,87 *MPa* (*Adseal*), 0,06 ± 0,02 *MPa* (*CeraSeal*) и 3,13 ± 0,38 *MPa* (*AH Plus*). Уочена је статистички значајна разлика у јачини везе између свих испитиваних паста ($p < 0,05$). Све пасте су остариле рендгенконтрастност већу од 3 *mm*, са статистички значајним разликама између узорака ($p < 0,05$).

Закључак Паста на бази епоксидне смоле, *Adseal*, показала је јачу везу у односу на *AH Plus* и *CeraSeal*, који је, очекивано, показао најслабију отпорност на дислокацију. Све три пасте остариле су рендгенконтрастност прописану *ISO* стандардом.

Кључне речи: паста за пуњење канала; радиоконтрастност; јачина везе; калцијум-силикат

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Analysis of clinical characteristics and risk factors for digestive system manifestations in rheumatic diseases

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SUMMARY

Introduction/Objective The objective of the paper was to explore the risk factors and prediction models of digestive system complications in patients with rheumatic diseases.

Methods This case-control retrospective study enrolled 326 patients with rheumatic diseases (163 with digestive system involvement and 163 without), collecting demographic data, laboratory parameters (liver enzymes, lipid profiles, etc.)**,** and disease types (rheumatoid arthritis, connective tissue diseases, gout, etc.). Potential variables were screened through univariate analysis, with independent risk factors subsequently identified using multivariate logistic regression analysis.

Results Univariate analysis revealed significantly higher proportions of males (35% *vs*. 20.2%, p = 0.003), alcohol consumption history (23.9% *vs*. 14.7%, p = 0.035), triglyceride (TG) (1.59 *vs*. 1.13 mmol/L, p < 0.001), and aspartate aminotransferase (AST) (21 *vs*. 19 U/L, p = 0.005) in the digestive system involvement group compared with controls. Multivariate logistic regression confirmed male gender (odds ratio [OR] = 2.276, 95% confidence interval [CI]: 1.184–4.376), elevated AST (OR = 1.039 per U/L, 95% CI: 1.005–1.074) and hypertriglyceridemia (OR = 5.456, 95% CI: 3.217–9.252) as independent risk factors (all p < 0.05).

Conclusion Male sex, elevated AST and hypertriglyceridemia constituted core predictive factors for digestive complications in rheumatic diseases, with a 445.6% increased risk observed at TG levels > 1.6 mmol/L, necessitating targeted intensive monitoring and clinical intervention.

Keywords: rheumatic diseases; digestive system; risk factors

INTRODUCTION

Rheumatic and autoimmune diseases, characterized by chronic inflammation of joints, muscles, and connective tissues, exhibit significant global prevalence, affecting approximately 1–3% of the population [1]. This disease spectrum encompasses dozens of subtypes, including rheumatoid arthritis, systemic lupus erythematosus, sicca syndrome, and systemic sclerosis, with their complex pathological mechanisms leading to multi-system damage that has become a major contributor to patient disability, impaired quality of life, and reduced life expectancy [2, 3, 4]. Among these systemic manifestations, digestive system complications warrant particular attention. Clinical studies demonstrate that over 50% of patients with rheumatic disease experience varying degrees of digestive involvement, which not only exacerbates the primary condition but often leads to diagnostic and therapeutic delays due to nonspecific symptoms. Gastrointestinal diseases of systemic lupus erythematosus include several clinical manifestations with different frequencies (0.5–10.7% of cases), and liver involvement includes lupus-associated hepatitis (9.3%) and autoimmune hepatitis (2.3%) [5]. Patients with systemic sclerosis have gastroesophageal manifestations (93.3%), as well as intestinal manifestations (67.8%) and anorectal manifestations (18.9%) [6]. Autoimmune diseases can cause a variety of gastrointestinal manifestations, especially oesophageal motility disorder and small intestinal pseudo-obstruction [7, 8]. This high prevalence and complexity make rheumatic diseases with digestive complications a significant challenge in clinical practice.

The pathological mechanisms linking rheumatic diseases and digestive system damage are multidimensional. On the one hand, autoimmune abnormalities can directly trigger systemic vasculitis and mucosal inflammation. For example, Behçet's disease frequently involves the ileocecal region (occurring in approximately 88% of cases), manifesting as right lower quadrant pain, hematochezia, and other symptoms that closely resemble Crohn's disease, posing significant diagnostic challenges. On the other hand, secondary damage from therapeutic agents cannot be overlooked. Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids can compromise the gastrointestinal mucosal barrier, with gastric mucosal erosion observed in approximately 30% of patients undergoing long-term NSAID therapy, substantially increasing the risk of peptic ulcers and perforation. Moreover, immunosuppressants (e.g. methotrexate) and biologic agents may directly induce hepatotoxicity and pancreatitis [8, 9, 10]. This dual pathological mechanism establishes digestive complications

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as a distinctive concern in rheumatic disease management, necessitating close collaboration between rheumatology and gastroenterology specialists.

Current clinical practice faces significant challenges in diagnosing rheumatic diseases with concomitant digestive system involvement. As gastrointestinal symptoms frequently serve as the initial manifestations of rheumatic diseases yet lack specificity, misdiagnosis is common. Data indicate that approximately 23% of patients with systemic lupus erythematosus presenting with abdominal pain and diarrhoea are misdiagnosed with inflammatory bowel disease or acute abdomen, whereas the oesophageal reflux caused by salivary gland dysfunction in sicca syndrome is often mistaken for primary gastroesophageal reflux disease [11]. Such misdiagnoses not only delay treatment of the underlying disease but may also exacerbate the condition through inappropriate management. Limitations in research further constrain clinical progress. For example, critical mechanisms such as immune cross-reactivity in the gut–joint axis and the association between gut dysbiosis and rheumatic activity remain underexplored, and stratified management strategies specifically targeting digestive comorbidities are notably lacking. These issues collectively contribute to the existing knowledge gaps in current clinical practice [12].

This study systematically investigates the clinical characteristics and risk factors of digestive system manifestations in rheumatic diseases. Utilizing a rigorously designed retrospective case-control study (163 patients with digestive manifestations *vs*. 163 without), the focus is on analyzing demographic characteristics (e.g. gender differences), metabolic parameters [e.g. triglycerides (TG)], and hepatic function indices [e.g. aspartate aminotransferase (AST), alanine aminotransferase (ALT)] to identify clinical markers for high-risk populations. Concurrently, the mechanistic links between elevated liver enzymes and both intestinal barrier dysfunction and systemic inflammatory responses are explored. Ultimately, this research seeks to establish a clinical management pathway for rheumatic-digestive comorbidities, providing evidence-based support for developing individualized screening protocols (e.g. regular liver function tests and endoscopic surveillance) and optimizing therapeutic strategies. By integrating epidemiological, molecular biological, and clinical evidence, this study endeavors to address existing knowledge gaps and offer both theoretical foundations and practical guidance for reducing the incidence and mortality of digestive complications in rheumatic diseases.

METHODS

Study population

This retrospective case-control study consecutively enrolled 326 patients with rheumatic diseases admitted to the rheumatology department of a tertiary care hospital between January 2020 and December 2023, with grouping based on the presence or absence of digestive system clinical manifestations.

The study employed a sample size calculation formula for unmatched case-control studies, with the following parameter settings:

$$n=\frac{[Z_{\alpha/2}\sqrt{2\bar{P}(1-\bar{P})}+Z_{\beta}\sqrt{P_1(1-P_1)+P_0(1-P_0)}]^2}{(P_1-P_0)^2},$$

where $Z_{\alpha/2}$ and Z_{β} represent the critical values of the standard normal distribution corresponding to the significance level and statistical power ($Z_{\alpha/2}$ = 1.96 at α = 0.05; Z_{β} = 1.282 at β = 0.10); P0 denotes the estimated exposure rate of the target factor (e.g. NSAID use history) in controls, set at 20% based on literature and preliminary data; P1 indicates the exposure rate in cases, calculated as $P_1 = (OR \times P_0) / (1 - P_0 + OR \times P_0)$ = 33.3% using the anticipated odds ratio (OR = 2.0); and $\bar{P}$ represents the mean exposure rate across groups ($\bar{P}$ = 0.267). Substituting these values into the formula yielded a minimum sample size of 170 per group. Accounting for a potential 10% missing data in retrospective studies, the adjusted sample size was 189 per group (total ≥ 378). Although the actual enrolment of 326 patients (combined cases and controls) fell below this target, power analysis confirmed > 85% statistical power under α = 0.05, OR = 2.0, and P_0 = 0.20, meeting methodological requirements. Sensitivity analysis demonstrated that sample size requirements would decrease to < 150 per group if P_0 rose to 25% or the OR increased to 2.5. Given that consecutive enrolment minimized selection bias, the final sample of 326 patients remained adequate for analyzing associations between target exposures and digestive manifestations.

The inclusion criteria for the case group (with digestive manifestations) were as follows: (1) age ≥ 18 years; (2) fulfilment of international diagnostic criteria for rheumatic diseases (e.g. American College of Rheumatology / European Alliance of Associations for Rheumatology classification criteria for rheumatoid arthritis, Systemic Lupus International Collaborating Clinics criteria for systemic lupus erythematosus) [13]; (3) presence of at least one digestive system manifestation, including but not limited to gastritis, splenomegaly, hyperbilirubinemia, hyperlipidemia, hepatic steatosis, abnormal liver function, pancreatitis, gastrointestinal bleeding, or endoscopically confirmed mucosal lesions. The control group (without digestive manifestations) shared identical criteria except for the absence of the aforementioned digestive involvement. Exclusion criteria applied to both groups included (1) concurrent solid or hematologic malignancies; (2) major surgery or trauma within three months; (3) pregnancy or lactation; and (4) missing key laboratory data (e.g. TG, AST).

Data collection

Study variables were systematically collected through the hospital's electronic medical record system. Demographic characteristics included age, gender, body mass index

(BMI), smoking history (defined as continuous smoking > six months) and alcohol consumption history (ethanol intake > 30 g/day for ≥ one year). Disease characteristics encompassed rheumatic disease types (classified into 21 subtypes, as shown in Table 1) and disease duration (calculated from initial diagnosis). Laboratory measurements were uniformly performed using Beckman AU5800 automated analyzers. Liver function tests [AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)] employed rate assays, lipid profiles (TG, total cholesterol) utilized enzymatic colorimetry, immunological markers (rheumatoid factor, immunoglobulins IgG/IgA/IgM, complements C3/C4) were measured via immunonephelometry, and tumor markers (alpha-fetoprotein, carbohydrate antigen 19-9, carbohydrate antigen 72-4) were analyzed via chemiluminescence immunoassays.

Data acquisition was independently performed by two uniformly trained researchers using standardized case report forms, with all imaging results interpreted under double-blind conditions by two radiologists holding associate chief physician qualifications or higher ($\kappa = 0.84$).

Statistical analysis

Statistical analyses were performed using SPSS 26.0 software. Normality was assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent samples t-tests, whereas non-normally distributed data were presented as median (interquartile range) (M [Q1, Q3]), with Mann–Whitney U tests used for inter-group comparisons. Categorical variables were reported as frequencies (percentages) and analyzed using chi-square (χ^2) or Fisher's exact tests. Variables with $p < 0.05$ in univariate analysis were entered into multivariate logistic regression models (forward stepwise method) to calculate ORs with 95% confidence intervals (95% CI), with statistical significance set at $p < 0.05$.

Ethics: This study was conducted in accordance with the 1975 Declaration of Helsinki and approved by the Ethics Committee of The Third Affiliated Hospital of Jinzhou Medical University (Approval number: JYDSY-KXYJ-IEC-2025-051). As patient identities were anonymized and this was an observational study, the ethics committee granted a waiver of informed consent following review.

RESULTS

Distribution characteristics of rheumatic disease spectrum

Analysis of 326 patients with rheumatic diseases systematically compared the disease spectrum distribution and clinical parameters between the digestive system involvement group (n = 163) and the non-digestive involvement group (n = 163). Regarding disease type distribution (Table 1), the non-digestive group was predominantly rheumatoid arthritis (99 cases, 60.7%), followed by connective tissue diseases (17 cases, 10.4%) and ankylosing spondylitis (11 cases, 6.7%). In contrast, the digestive involvement group showed not only rheumatoid arthritis (80 cases, 49.1%) but also a significantly higher proportion of gouty arthritis (18 cases, 11%), with eight disease subtypes, including ANCA-associated vasculitis and myositis, exclusively observed in this group, suggesting unique associations between specific rheumatic conditions and digestive complications.

Table 1. Patients by type of rheumatic disease with and without gastrointestinal disorders

Type	Rheumatic diseases with digestive involvement (n = 163)	Rheumatic diseases without digestive system involvement (n = 163)
Behçet's disease	0	2
Enteropathic arthritis	0	1
Polymyalgia rheumatica	1	2
Sjögren's syndrome	8	10
Osteoarthritis	3	4
Spondylarthritis	0	1
Connective tissue diseases	12	17
Rheumatoid arthritis	80	99
Ankylosing spondylitis	11	11
Generalized osteoarthritis	1	2
Systemic lupus erythematosus	10	9
Systemic sclerosis	5	3
Psoriatic arthritis	2	2
ANCA-associated vasculitis	2	0
Adult-onset Still's disease	1	0
Takayasu arteritis	2	0
Reactive arthritis	1	0
Myositis	4	0
Gouty arthritis	18	0
Amyopathic dermatomyositis	1	0
Palmoplantar pustulosis	1	0

Univariate analysis: risk factors for digestive complications

Univariate analysis (Table 2) revealed multiple significant inter-group differences. The digestive involvement group had a higher male proportion (57 *vs.* 33 cases, $\chi^2 = 8.841$, $p = 0.003$) and more frequent alcohol consumption (39 *vs.* 24 cases, $\chi^2 = 4.427$, $p = 0.035$). Laboratory profiles demonstrated prominent metabolic and hepatic dysfunction in this group. Median TG levels were significantly elevated (1.59 *vs.* 1.13 mmol/L, $z = -7.837$, $p < 0.001$); liver enzymes were uniformly increased, including AST (21 *vs.* 19 U/L, $z = -2.839$, $p = 0.005$), ALT (20 *vs.* 16 U/L, $z = -3.039$, $p = 0.002$), GGT (29 *vs.* 22 U/L, $z = -4.360$, $p < 0.001$) and ALP (80 *vs.* 72 U/L, $z = -2.598$, $p = 0.009$). Notably, rheumatoid factor levels were paradoxically lower (20 *vs.* 22.5 IU/mL, $z = -2.485$, $p = 0.013$). No statistical differences were observed in 23 parameters, including age, BMI, and complement levels.

Table 2. Univariate factor analysis of rheumatic diseases with and without gastrointestinal involvement

Index		Rheumatic diseases with digestive involvement (n = 163)	Rheumatic diseases without digestive system involvement (n = 163)	z/t/χ^2	p
Age (year)		59.95 ± 14.05	61.77 ± 13.03	1.214	0.226
Sex	Male	57	33	8.841	0.003
	Female	106	130		
BMI		23.19 ± 3 .19	23.73 ± 3.19	1.521	0.129
Rheumatoid factor		20 (20, 55.18)	22.5 (20, 117)	-2.485	0.013
CPR		0.98 (0.34, 2.23)	0.63 (0.26, 2.07)	-1.016	0.310
ESR		35 (20, 65)	33 (15, 78)	-1.625	0.104
IGg		13.2 (10.5, 16.3)	13.7 (11.4, 17.2)	-0.383	0.702
IGa		3.51 (2.47, 4.3)	3.34 (2.34, 4.57)	-0.636	0.525
IGm		1.17 (0.75, 1.74)	1.12 (0.74, 1.82)	-0.006	0.995
C3		1.03 (0.82, 1.22)	0.99 (0.81, 1.18)	-1.041	0.298
C4		0.27 (0.22, 0.35)	0.26 (0.19, 0.33)	-1.280	0.201
AST		21 (17, 28)	19 (15, 23)	-2.839	0.005
ALT		20 (13, 32)	16 (11, 24)	-3.039	0.002
GGT		29 (19, 48)	22 (15, 34)	-4.360	< 0.001
ALP		80 (63, 95)	72 (58, 89)	-2.598	0.009
Bilirubin		10.2 (6.8, 14.5)	9.7 (7.3, 12.7)	-1.354	0.176
TG		1.59 (1.13, 2.29)	1.13 (0.85, 1.34)	-7.837	< 0.001
CHO		4.77 (4.03, 5.49)	4.56 (3.96, 5.22)	-1.840	0.066
LLLD		2.74 (2.17, 3.39)	2.57 (2.20, 3.24)	-0.625	0.532
AFP		3.12 (1.83, 6.06)	2.98 (1.81, 2.98)	-0.234	0.815
PG		6 (4.2, 8.86)	5.9 (3.85, 8.83)	-0.614	0.539
CA199		6.46 (3.73, 15.4)	7.06 (3.89, 15.08)	-0.187	0.851
CA724		3.62 (1.56, 7.3)	4.3 (1.46, 8.3)	-0.781	0.435
Disease course		5.08 ± 6.93	5.87 ± 8.06	0.950	0.343
Smoking history	No	139	135	0.366	0.545
	Yes	24	28		
Alcohol consumption history	No	124	139	4.427	0.035
	Yes	39	24		

BMI – body mass index; CPR – C-reactive protein; ESR – erythrocyte sedimentation rate; IGg – immunoglobulin G; IGa – immunoglobulin A; IGm – immunoglobulin M; C3 – complement C3; C4 – complement C4; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; TG – triglyceride; CHO – total cholesterol; LLLD – low-density lipoprotein cholesterol; AFP – alpha-fetoprotein; PG – prostaglandin; CA199 – carbohydrate antigen 19-9; CA724 – carbohydrate antigen 72-4

Table 3. Multivariate logistic analysis of rheumatic diseases combined with digestive system

Influencing factor	B	SE	Wald χ^2 value	p	OR	95% confidence interval	
						Lower limit	Upper limit
Sex*	0.823	0.334	6.082	0.014	2.276	1.184	4.376
Alcohol consumption history*	-0.035	0.363	0.010	0.922	0.965	0.474	1.964
Rheumatoid factor	0.000	0.000	0.350	0.554	1.000	0.999	1.001
AST	0.038	0.017	4.983	0.026	1.039	1.005	1.074
ALT	-0.004	0.010	0.199	0.655	0.996	0.976	1.015
GGT	0.006	0.007	0.755	0.385	1.006	0.992	1.021
ALP	0.004	0.006	0.521	0.470	1.004	0.993	1.016
TG	1.697	0.270	39.625	0.000	5.456	3.217	9.252
Constant	-3.836	0.716	28.667	0.000	0.022		

AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; TG – triglyceride; *variable assignments: sex (male = 0, female = 1); alcohol consumption history (no = 0, yes = 1); other continuous variables (e.g., AST, TG) used raw measured values

Multivariate logistic regression: identification of independent risk factors

Multivariate logistic regression analysis (Table 3) incorporating statistically significant factors from univariate analysis identified three independent risk factors. First, male gender conferred a 127.6% increased odds of digestive complications (OR = 2.276, 95% CI: 1.184–4.376, p = 0.014); second, each 1 U/L increment in AST level was associated with a 3.9% odds elevation (OR = 1.039, 95% CI: 1.005–1.074, p = 0.026); and most notably, TG demonstrated the highest OR of 5.456 (95% CI: 3.217–9.252, p < 0.001), indicating a 445.6% odds escalation among individuals with elevated TG. Although alcohol consumption history and ALT levels showed significance in univariate analysis, they lost independent predictive value after

adjusting for confounders ($p > 0.05$). Other parameters, including immunoglobulins, complements, and bilirubin, also failed to achieve statistical significance in the multivariate model.

DISCUSSION

This large-scale case-control study systematically identified independent risk factors and underlying mechanisms for digestive complications in rheumatic diseases. Male sex, elevated serum AST, and hypertriglyceridemia were established as core predictors, with OR values of 2.276, 1.039, and 5.456, respectively, providing crucial evidence for early clinical identification of high-risk patients. Notably, the heightened risk odds in male patients were closely associated with sex hormone-mediated immune dysregulation. Androgens promote Th1/Th17 cell differentiation, enhancing the release of proinflammatory factors such as tumor necrosis factor-alpha and interleukin (IL)-17 that disrupt the intestinal mucosal barrier, whereas estrogens exert anti-inflammatory protection by upregulating Treg cell function [14, 15, 16]. This immunological divergence explains male patients' increased susceptibility to drug-induced liver injury (e.g. methotrexate toxicity) and ischemic colitis, consistent with our finding of significantly higher male representation (35.0% *vs*. 20.2%) in the complication group [17].

The independent predictive value of serum AST ($p = 0.026$), surpassing that of ALT ($p = 0.655$), carries significant pathological implications. As AST is predominantly localized in mitochondria, its elevation indicates organelle-level damage, reflecting the gut–liver axis vicious cycle activated by endotoxin translocation following intestinal barrier disruption [18]. Increased intestinal permeability allows portal vein endotoxins to activate hepatic Kupffer cells, releasing pro-fibrotic factors such as IL-6 and transforming growth factor-beta that exacerbate intestinal mucosal damage. This mechanism explains the comprehensive elevation of liver enzymes (AST: 21 U/L; GGT: 29 U/L) in the digestive involvement group and confirms the 3.9% increased risk odds per 1 U/L AST rise in multivariate models. In contrast, ALT primarily reflects cytoplasmic injury and shows inadequate sensitivity for early enterogenic hepatopathy, suggesting that AST should serve as the core biomarker for monitoring intestinal complications in rheumatic diseases [19].

Triglyceride demonstrated the strongest predictive efficacy (OR = 5.456) through three pathological mechanisms. (1) Free fatty acids activate the TLR4/NF-κB pathway, inducing intestinal macrophages to secrete IL-1β and IL-18 that directly disrupt intestinal epithelial tight junctions; (2) chylomicron deposition causes mesenteric microvascular occlusion, leading to mucosal ischemic necrosis – particularly prominent in patients with systemic sclerosis; and (3) hyperlipidemic environments significantly increase local NSAID concentrations in the intestinal lumen, exacerbating chemical injury via COX-1 inhibition [20, 21]. The median TG level in our complication group reached 1.59 mmol/L (significantly higher than the 1.13 mmol/L in controls, $p < 0.001$), with gouty arthritis accounting for 11% of cases, further evidencing the synergistic activation of NLRP3 inflammasomes by hyperuricemia and hypertriglyceridemia, forming a 'metabolic-inflammatory storm.' This unique association underscores the necessity for enhanced lipid monitoring and intervention in patients with gouty arthritis.

The disease spectrum analysis revealed critical clinical patterns. Eight disease subtypes, including ANCA-associated vasculitis and myositis, were exclusively observed in the digestive involvement group, with patients with myositis exhibiting 100% complication rates attributable to anti-Jo-1 antibody-mediated smooth muscle inflammation. These patients typically presented with esophageal dysmotility (hypotensive esophagus) and delayed gastric emptying, warranting cautious use of conventional prokinetics (e.g. domperidone) due to QT prolongation risks. These findings indicate the need for disease-specific individualized management protocols for digestive complications. However, it should be noted that while alcohol consumption showed significance in univariate analysis ($p = 0.035$), it failed to maintain significance in multivariate models ($p = 0.922$), potentially reflecting confounding effects of alcohol-induced CYP450 enzyme alterations on drug metabolism, necessitating further pharmacokinetic analyses [22].

Based on these findings, we propose a three-tier prevention system. First, high-risk patients (males, or those with TG ≥ 1.6 mmol/L or AST ≥ 21 U/L) should undergo quarterly monitoring of liver enzyme profiles and fecal occult blood tests, with consideration for preventive interventions. Specifically, fibrates (fenofibrate 200 mg/day) should be the first-line treatment for hypertriglyceridemia, as they activate PPARα to downregulate the NF-κB pathway, thereby reducing intestinal inflammation. For patients with persistently elevated AST, a combination of ursodeoxycholic acid (10 mg/kg/day) and bifidobacterium preparations is recommended to restore the intestinal mucosal barrier. Male patients with gout require strict control of serum uric acid levels (< 360 μmol/L) to prevent intestinal urate crystal deposition. Notably, glucocorticoids significantly increase TG levels (by approximately 28%) – for patients with hyperlipidemia, IL-6 inhibitors such as tocilizumab should be prioritized over glucocorticoids.

This study has several limitations. First, the analysis did not account for medication exposure history (e.g. duration and dosage of NSAID use). Second, it lacked assessments of gut microbiota diversity and barrier function markers such as serum zonulin. Third, limited subgroup sample sizes (e.g. myositis) restricted stratified statistical power.

CONCLUSION

This retrospective case-control analysis of 326 patients with rheumatic diseases identified male gender (OR = 2.276), elevated serum AST (OR = 1.039 per U/L) and TG (OR = 5.456) as independent risk factors

for digestive complications in rheumatic diseases. Here, TG (≥ 1.59 mmol/L) demonstrated the most prominent predictive value, conferring a 445.6% increased risk odds, mechanistically linked to free fatty acid-mediated activation of the intestinal TLR4/NF-κB inflammatory pathway. In clinical practice, we recommend quarterly monitoring of liver enzyme profiles and fecal occult blood tests for high-risk populations (males, persistent AST > 21 U/L, or TG > 1.6 mmol/L). These findings provide critical evidence for establishing an early warning system for rheumatic-digestive comorbidities, warranting future multicenter cohort studies to validate the efficacy of interventions in reducing complication incidence.

Author contributions

Conception and design of the work: Zhu D; data collection: Hao YQ; supervision: Zhu D; analysis and interpretation of the data: Hao YQ; statistical analysis: Zhu D, Hao YQ; drafting the manuscript: Zhu D; critical revision of the manuscript: all authors; approval of the final manuscript: all authors.

Conflict of interest: None declared.

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Анализа клиничких карактеристика и фактора ризика за манифестације дигестивног система код реуматских болести

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САЖЕТАК

Увод/Циљ Циљ рада био је истражити факторе ризика и моделе предвиђања компликација дигестивног система код пацијената са реуматским болестима.

Методе Ово ретроспективно студијско истраживање случаја и контроле обухватило је 326 пацијената са реуматским болестима (163 са захваћеношћу дигестивног система и 163 без захваћености дигестивног система), прикупљајући демографске податке, лабораторијске параметре (ензими јетре, липидни профил итд.) и врсте болести (реуматоидни артритис, болести везивног ткива, гихт итд.). Потенцијалне варијабле су обрађене путем униваријантне анализе, а независни фактори ризика су накнадно идентификовани коришћењем мултиваријантне логистичке регресионе анализе.

Резултати Униваријантна анализа је показала значајно већи удео мушкараца (35% наспрам 20,2%, $p = 0,003$), историје конзумирања алкохола (24,5% наспрам 14,7%, $p = 0,035$), триглицерида (*TG)* (1,59 наспрам 1,13 *mmol/L*, $p < 0,001$) и аспартат аминотрансферазе (*AST*) (21 наспрам 19 *U/L*, $p = 0,005$) у групи са захваћеним дигестивним системом у поређењу са контролном групом. Мултиваријантна логистичка регресија потврдила је мушкарце (*OR* = 2,276, 95% *CI*: 1,184–4,376), повишен *AST* (*OR* = 1,039/*U/L*, 95% *CI*: 1,005–1,074) и хипертриглицеридемију (*OR* = 5,456, 95% *CI*: 3,217–9,252) као независне факторе ризика (сви $p < 0,05$).

Закључак Мушкарци, повишен *AST* и хипертриглицеридемија представљали су основне предиктивне факторе за дигестивне компликације код реуматских болести, са повећаним ризиком од 445,6% при нивоима *TG* > 1,6 *mmol/L*, што је захтевало циљано интензивно праћење и клиничку интервенцију.

Кључне речи: реуматске болести; дигестивни систем; фактори ризика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The influence of early operative treatment on postoperative recurrence in patients with Crohn's disease of the ileocecal region

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SUMMARY

Introduction/Objective Crohn's disease was traditionally managed by gastroenterologists, but in the past decade, the surgeon's role has expanded, with specialized inflammatory bowel disease surgeons now integral to multidisciplinary decision-making. Evidence indicates that early ileocecal resection for localized terminal ileitis with a predominantly fibrotic component, performed before complications arise, may improve outcomes and reduce disease-related morbidity. The aim of this study is to evaluate the impact of early ileocecal resection with Kono-S anastomosis on postoperative disease control in patients with localized Crohn's disease, by assessing changes in inflammatory biomarkers, clinical symptoms, and endoscopic recurrence over a two-year follow-up period.

Methods From 2021 to 2023, all patients in this study were assessed by the Inflammatory Bowel Disease Multidisciplinary Team of the University Clinical Center of Vojvodina, which determined indications for surgery. Postoperative recurrence was monitored clinically and endoscopically using colonoscopy and the Rutgeerts score. Sixty patients underwent laparoscopic ileocecal resection with Kono-S anastomosis.

Results Statistical analyses (IBM SPSS 26) used repeated-measures ANOVA at three time points: preoperatively, one year postoperatively, and two years postoperatively. Fecal calprotectin showed a strong time effect ($F(1.77, 104.51) = 300.13$, $p < 0.001$, $\eta_p^2 = 0.84$), demonstrating substantial reduction in intestinal inflammation. Defecation difficulty scores also decreased significantly ($F(1.43, 84.28) = 136.36$, $p < 0.001$, $\eta_p^2 = 0.70$). Rutgeerts scores showed no significant change between years one and two ($F(1, 56) = 3.11$, $p > 0.05$), indicating stable endoscopic findings.

Conclusion Endoscopic monitoring with the Rutgeerts score, supported by fecal calprotectin, proved most reliable for postoperative surveillance. With careful multidisciplinary selection – especially in patients with localized, fibrotic disease – early ileocecal resection using the Kono-S technique can effectively control Crohn's disease, decrease rehospitalizations and reoperations, and improve quality of life.

Keywords: Crohn's disease; surgical treatment; ileocecal resection; Kono-S anastomosis; Rutgeerts score

INTRODUCTION

The incidence and prevalence of Crohn's disease have been rising globally, with annual increases in incidence reported 4–15% over the past three decades. Crohn's disease represents a substantial socioeconomic and healthcare burden worldwide, primarily because it affects a young, working-age population and follows a chronic, relapsing–remitting course characterized by periods of exacerbation and remission [1, 2]. Despite significant advances in medical therapy, approximately 25% of patients require surgical intervention within ten years of diagnosis, and nearly 20% of those who undergo surgery require reoperation within five years [3, 4].

Historically, Crohn's disease was managed predominantly by gastroenterologists, who were responsible for diagnosis, pharmacological treatment, and follow-up, while surgeons were mainly involved in addressing acute complications. These often resulted in multiple resections, high-output ileostomies, and, in some cases, short bowel syndrome. Over the past decade, however, the surgeon's role has evolved substantially. The emergence of the inflammatory bowel disease (IBD) surgeon specialized in the surgical management of these patients has transformed Crohn's disease care into a multidisciplinary effort involving gastroenterologists, surgeons, radiologists, pathologists, and anesthesiologists [5, 6].

A major challenge in Crohn's disease management remains its nonspecific clinical presentation and delayed diagnosis. On average, two years elapse between the onset of initial symptoms (such as diarrhea, hematochezia, or nonspecific abdominal pain) and the establishment of a definitive diagnosis. This delay often results in missed therapeutic opportunities and the development of complications including stenosis, fistulas, abscesses, and perforations [7].

Histopathological examinations have demonstrated that intestinal lesions in Crohn's disease may be predominantly inflammatory, mixed, or fibrotic. While inflammatory changes may respond favorably to anti-inflammatory or biological therapy, the mixed and fibrotic types typically show poor or no response to medical treatment, necessitating interventional management such as endoscopic dilation or surgery [8]. The largest study on balloon dilation

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in Crohn's disease, conducted by Bettenworth et al. [9], included 1,493 patients who underwent 3,213 endoscopic balloon dilations. Although the initial success rate was high, 73.5% required redilation within 24 months, and 42.9% ultimately required surgical resection.

Consequently, recent studies have reconsidered early ileocecal resection for localized terminal ileitis with predominant fibrotic involvement before the onset of complications or complete obstruction. This strategy may improve quality of life and prevent disease progression to fistulizing or perforating forms that require urgent, extensive resections, high-output ileostomies, or result in short bowel syndrome [10, 11]. Increasing attention has also been directed to the potential influence of anastomotic technique and mesenteric involvement on disease recurrence. To date, no specific anastomotic configuration has been conclusively shown to reduce the rate of postoperative recurrence [12].

The Kono-S anastomosis, first described in 2011, has since demonstrated favorable outcomes worldwide. This technique forms a "supporting column" of bowel that maintains luminal diameter and prevents restenosis. The mesenteric side is positioned centrally within this column, such that even in cases of mesenteric recurrence, the anastomotic lumen remains patent, thereby reducing the risk of restenosis, a limitation observed in conventional end-to-end or side-to-side anastomoses [13].

The aim of this study is to evaluate the impact of early ileocecal resection with Kono-S anastomosis on postoperative disease control in patients with localized Crohn's disease, by assessing changes in inflammatory biomarkers, clinical symptoms, and endoscopic recurrence over a two-year follow-up period.

METHODS

Between 2021 and 2023, all patients included in this study were reviewed at the Inflammatory Bowel Disease Multidisciplinary Team (IBD-MDT) Conference of the University Clinical Center of Vojvodina, where operative management was discussed and approved.

Prior to surgery, all patients underwent colonoscopy, which confirmed stenosis with a predominant fibrotic component; in most cases, the lumen was impassable to the colonoscope. None of the patients had undergone preoperative endoscopic balloon dilation. As part of the preoperative assessment, all patients also underwent magnetic resonance enterography to determine the location and length of the affected intestinal segment.

Exclusion criteria included multiple disease localizations and previous bowel resections for Crohn's disease. The presence of fistulas or abscesses was considered a conditional exclusion criterion; in such cases, the decision regarding surgical treatment was made on a case-by-case basis after multidisciplinary discussion. For patients receiving corticosteroid therapy, tapering was performed preoperatively to minimize the risk of postoperative complications while avoiding inflammatory exacerbation. Ongoing anti-TNF therapy was not considered a contraindication for primary anastomosis formation [11].

Postoperative recurrence was evaluated by the following:

- Endoscopy, using colonoscopic findings and the Rutgeerts scoring system;
- Laboratory parameters, including complete blood count (CBC), C-reactive protein (CRP), and fecal calprotectin;
- Clinical assessment, based on patient-reported bowel function scored subjectively on a 1–10 scale.

All patients underwent laparoscopic ileocecal resection with construction of a Kono-S anastomosis (Figure 1). An Enhanced Recovery After Surgery (ERAS) protocol was applied in all cases, with oral intake initiated on the evening of surgery. Upon discharge, patients received metronidazole 400 mg twice daily for 14 days.

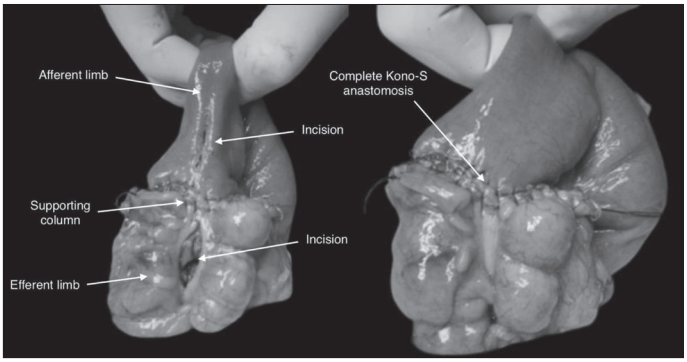

Figure 1. Kono-S anastomosis

Postoperative initiation of biological therapy was determined according to the American Gastroenterological Association risk stratification for postoperative recurrence [14].

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA). To evaluate changes over time, repeated-measures analyses of variance (ANOVA) were conducted for each inflammatory and clinical parameter, including leukocyte count, C-reactive protein (CRP), fecal calprotectin, and defecation difficulty scores. The Rutgeerts score, which was assessed postoperatively to evaluate endoscopic recurrence at the anastomotic site, was analyzed across the two available follow-up time points (T2 and T3).

Mauchly's test of sphericity was used to assess the assumption of sphericity for each repeated-measures ANOVA. When this assumption was violated ($p \leq 0.05$), the Greenhouse–Geisser correction was applied to adjust the degrees of freedom. When the assumption was met ($p > 0.05$), results from the sphericity-assumed model were reported.

If a significant main effect of time was identified, Bonferroni-adjusted pairwise comparisons were conducted to determine the specific time points between which differences occurred. Effect sizes were expressed as partial eta

Table 1. Baseline demographic and disease characteristics

Variable		Value
Number of patients		60
Sex, n (%)	Male	15 (25%)
	Female	45 (75%)
Disease location		Localized ileocecal Crohn's disease (100%)
Disease phenotype		Predominantly fibrotic stenosis
Preoperative colonoscopic finding		Stenosis in all patients
Preoperative endoscopic balloon dilation		None
Previous bowel resection for Crohn's disease		None
Multiple disease localizations		Excluded

squared (η_p^2) and interpreted according to Cohen's (1988) conventions: 0.01 = small, 0.06 = medium, and 0.14 = large effect.

Ethics: This study was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was reviewed and approved by the Ethics Committee of the University Clinical Center of Vojvodina (protocol number: 00-418).

RESULTS

A total of 60 patients were included in the study. Baseline demographic, disease, and treatment characteristics are summarized in Table 1. All patients underwent laparoscopic ileocecal resection with Kono-S anastomosis.

A repeated-measures analysis of variance (ANOVA) was performed to examine changes in inflammatory and clinical parameters across three assessment points: before surgery (T1), one year after surgery (T2), and two years after surgery (T3).

The repeated-measures ANOVA revealed a significant main effect of time for leukocyte count ($F(1, 59) = 14.75$, $p < 0.001$, $\eta_p^2 = 0.2$), indicating a postoperative reduction in leukocyte count. Bonferroni-adjusted post hoc comparisons showed a significant decrease from the preoperative assessment to one year postoperatively ($p < 0.001$), with no further significant change between one and two years after surgery ($p > 0.05$).

CRP levels also changed significantly over time ($F(1.56, 92.45) = 34.98$, $p < 0.001$, $\eta_p^2 = 0.37$), demonstrating a sustained reduction at both postoperative time points. A particularly strong time effect was observed for fecal calprotectin ($F(1.77, 104.51) = 300.13$, $p < 0.001$, $\eta_p^2 = 0.84$), indicating a marked and continuous decline in intestinal inflammation across all assessments. Defecation difficulties similarly improved over time ($F(1.43, 84.28) = 136.36$, $p < 0.001$, $\eta_p^2 = 0.7$), reflecting enhanced bowel function one and two years postoperatively (Table 2).

In contrast, the Rutgeerts score, assessed only postoperatively to evaluate endoscopic recurrence at the anastomotic site, showed no significant difference between the one-year and two-year follow-ups ($F(1, 56) = 3.11$, $p > 0.05$, $\eta_p^2 = 0.05$), suggesting stable endoscopic findings during the observation period.

Overall, effect sizes ranged from moderate (leukocytosis) to very large (fecal calprotectin and defecation difficulties), indicating substantial variation in the magnitude of postoperative improvement across parameters.

DISCUSSION

Recent studies have suggested that early ileocecal resection may lead to better disease control, a lower rate of repeat surgery, and reduced overall treatment costs compared with resections performed at more advanced stages of Crohn's disease. These findings are supported by data from Sweden and other population-based cohorts, which indicate improved surgical outcomes and a declining need

Table 2. Changes in inflammatory and clinical indicators before and after surgery: results of repeated ANOVA measures

Variable	Time	M (SD)	Mauchly W	F	df1, df2	p	η_p^2	T1	T2	T3
Leukocytosis	T1	0.3 (0.46)	0.00*	14.75	1, 59	< 0.001	0.2	–	< 0.001	< 0.001
	T2	0.1 (0.3)						–	–	
	T3	0.1 (0.3)						–		–
C-reactive protein	T1	0.6 (0.74)	0.72	34.98	1.56, 92.45	< 0.001	0.37	–	< 0.001	< 0.001
	T2	0.25 (0.44)						–	< 0.05	
	T3	0.15 (0.36)						–		–
Fecal calprotectin	T1	2.2 (0.94)	8.01*	300.13	1.77, 104.51	< 0.001	0.84	–	< 0.001	< 0.001
	T2	0.85 (0.66)						–	< 0.001	
	T3	0.4 (0.49)						–		–
Defecation difficulties score	T1	1.2 (0.76)	29.63	136.36	1.43, 84.28	< 0.001	0.7	–	< 0.001	< 0.001
	T2	0.35 (0.48)						–	< 0.01	
	T3	0.2 (0.40)						–		–
Rutgeerts score	T1	–	1.00	3.11	1, 56	0.08	0.05	–	–	–
	T2	1.16 (0.68)						–	> 0.05	
	T3	1.11 (0.65)						–		–

T1 – before surgery; T2 – 1 year after surgery; T3 – 2 years after surgery; W – Mauchly's test of sphericity; η_p^2 – partial eta squared;
M – mean; SD – standard deviation;
*p < 0.05;
p < 0.01

for re-resections in recent decades [15, 16]. Our results are consistent with these observations. In our study, all patients underwent surgery at an early disease stage before the development of complications such as abscesses, fistulas, or bowel obstruction that could otherwise necessitate multiple operations. During the follow-up period, no patient required reoperation, reflecting the potential benefit of early surgical intervention.

In all cases, a Kono-S anastomosis was performed. Because postoperative recurrence frequently develops at the anastomotic site, its configuration remains an important determinant of long-term outcome. The Kono-S technique creates a mesenteric "supporting column" designed to maintain luminal patency and potentially reduce subocclusive symptoms. In our series, patient-reported bowel function improved compared with preoperative status. However, comparative effectiveness data remain inconclusive. The large, propensity-matched KoCoRICCO study found no significant reduction in postoperative endoscopic recurrence with Kono-S compared with conventional anastomoses [17]. Conversely, other observational studies and systematic reviews, such as that of Lingam et al. [18], have reported potential functional and patency-related advantages, although the evidence quality remains low and randomized data are lacking. Our results therefore support the feasibility and functional safety of Kono-S but cannot confirm superiority in preventing recurrence.

For postoperative recurrence monitoring, inflammatory markers (CRP, leukocyte count, and fecal calprotectin) were assessed alongside scheduled endoscopic evaluations at 12 and 24 months. While systemic inflammatory markers are not sufficiently specific for detecting endoscopic recurrence, they remain useful for identifying complications such as abscesses or fistulas. In contrast, endoscopic evaluation using the Rutgeerts score, combined with fecal calprotectin values, provided a reliable measure of mucosal recurrence. A Rutgeerts score > 2 at the anastomosis clearly indicated endoscopic recurrence. When compared with the results reported by Bak et al. [19], who observed higher rates of endoscopic inflammation and re-resection during long-term follow-up, our recurrence rate was lower.

However, several factors must be acknowledged: our follow-up period was shorter (two years versus five years in their study), and our cohort was more selectively defined, excluding patients with prior resections or multiple disease localizations. These methodological differences likely contributed to the favorable outcomes observed in our patient population.

CONCLUSION

Early ileocecal resection with Kono-S anastomosis in patients with localized, predominantly fibrotic Crohn's disease provides effective postoperative disease control, demonstrated by significant improvement in inflammatory markers and stable endoscopic findings during two-year follow-up. In the authors' experience, structured postoperative surveillance based on the Rutgeerts score and fecal calprotectin represents a reliable and practical monitoring protocol.

Conflict of interest: None declared.

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Утицај раног оперативног лечења на постоперативни рецидив код болесника са Кроновом болешћу илеоцекалне регије

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САЖЕТАК

Увод/Циљ Кронова болест се традиционално лечила код гастроентеролога, али се током последње деценије улога хирурга значајно проширила, па су специјализовани хирурзи за запаљенске болести црева постали кључни део мултидисциплинарног тима. Докази указују да рана илеоцекална ресекција код локализованог терминалног илеитиса са претежно фиброзном компонентом, изведена пре појаве компликација, може побољшати исходе и смањити морбидитет повезан са болешћу.

Циљ ове студије је да се процени утицај ране илеоцекалне ресекције са *Kono-S* анастомозом на постоперативну контролу болести код болесника са локализованом Кроновом болешћу, проценом промена инфламаторних биомаркера, клиничких симптома и ендоскопског рецидива током двогодишњег периода праћења.

Методе У периоду од 2021. до 2023. сви болесници у овој студији процењени су од стране мултидисциплинарног тима за запаљенске болести црева Универзитетског клиничког центра Војводине, који је одређивао индикације за операцију. Постоперативни рецидив праћен је клинички и ендоскопски, помоћу колоноскопије и Рутгертсовог скора. Шездесет болесника је подвргнуто лапароскопској илеоцекалној ресекцији са *Kono-S* анастомозом.

Резултати Коришћен је *ANOVA* тест поновљених мерења у три временске тачке: преоперативно, годину дана постоперативно и две године постоперативно. Фекални калпротектин је показао снажан ефекат времена ($F(1,77; 104,51) = 300,13$, $p < 0,001$, $\eta p^2 = 0,84$), указујући на значајно смањење интестиналне инфламације. Скорови отежаног пражњења такође су се значајно смањили ($F(1,43; 84,28) = 136,36$, $p < 0,001$, $\eta p^2 = 0,70$). Рутгертсови скорови нису показали значајну промену између прве и друге године ($F(1, 56) = 3,11$, $p > 0,05$), што указује на стабилне ендоскопске налазе.

Закључак Ендоскопско праћење помоћу Рутгертсовог скора, уз подршку фекалног калпротектина, показало се најпоузданијим за постоперативни надзор. Уз пажљив мултидисциплинарни одабир, посебно код болесника са локализованом, фиброзном болешћу, рана илеоцекална ресекција техником *Kono-S* може ефикасно контролисати Кронову болест, смањити рехоспитализације и реоперације и побољшати квалитет живота.

Кључне речи: Кронова болест; хируршко лечење; илеоцекална ресекција; *Kono-S* анастомоза; Рутгертсов скор

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical characteristics of status asthmaticus in preschool children

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SUMMARY

Introduction/Objective Asthma is the most common chronic disease in children. Status asthmaticus is a severe exacerbation of asthma that can lead to hypoxemia and respiratory failure. Diagnosing asthma in preschool-aged children is often challenging as wheezing episodes at this age are most often caused by viral infections.

The objective was to assess this issue in our population and improve clinical practice for diagnosing and treating status asthmaticus in preschool children.

Methods A retrospective study included 200 children aged up to five years who were hospitalized with status asthmaticus during January 2019 – December 2023.

Data on patients, diagnostic procedures, therapy, and clinical course were analyzed.

Results The largest proportion of patients was aged one year (31.5%), and males predominated (60.5%). The patients were most commonly hospitalized during the fall months, with an average length of hospital stay of 6.4 days. Allergy was confirmed in 50% of the children. Family history of atopy was present in 56% of the children. Previously diagnosed asthma was present in 13.5% of the children. At discharge, asthma preventive therapy was introduced in 91.5% of the children. All the children had a favorable outcome and were discharged from the hospital.

Conclusion Status asthmaticus most commonly occurs in children in the first year of life, often presenting as the initial manifestation of asthma. More than half of the children had a family history of atopy and confirmed allergies. Timely treatment according to current protocols is crucial for a good outcome.

Keywords: asthma; children; exacerbation; allergy

INTRODUCTION

Asthma is the most common chronic disease in the pediatric population, with a prevalence of approximately 14% among children worldwide, and the prevalence is on the rise [1]. Defining asthma in preschool-aged children is challenging, as the underlying pathophysiology in this age group is not well established, primarily due to the lack of available objective pulmonary function tests [2].

A variety of risk factors may be associated with the development of asthma, including a positive personal or family history of atopy, a family history of asthma, exposure to secondhand smoke, air pollution, or premature birth [3]. The development of asthma is an interaction between genetic and environmental variables, many of which are not fully understood or identified [4].

The clinical presentation typically manifests as a triad of symptoms: cough, difficulty breathing, and wheezing [5]. The three most common phenotypes of preschool wheezing, categorized by the timing of onset, are as follows: a) transient early wheezing, which occurs before the age of three and resolves by the age of six, without any impairment of lung function; b) late-onset wheezing, which appears after the age of three, persists into childhood, and is associated with atopy. Some studies also suggest a connection with reduced lung function and bronchial hyperreactivity; c) persistent wheezing, which begins at an early age (before three years of age) and is associated with high levels of IgE, atopy, reduced lung function, and early sensitization to allergens [6].

Asthma exacerbation is an episode of worsening of the disease characterized by progressive deterioration of symptoms such as difficulty breathing, coughing, wheezing, and a decline in lung function compared to the child's usual status. It requires the use of additional treatment and changes to the existing therapy [7]. A severe asthma exacerbation that does not improve with bronchodilator use and can lead to hypoxemia, hypercapnia, and secondary respiratory failure is referred to as status asthmaticus [7, 8]. All patients with asthma are at risk of developing this condition. Even children with mild and intermittent asthma can experience serious exacerbations that require admission to intensive care units. If not recognized and treated appropriately, status asthmaticus can lead to acute respiratory failure and even death. This serious and potentially life-threatening condition remains one of the leading causes of emergency department visits [8, 9]. Rapid clinical evaluation of patients is necessary to ensure an appropriate therapeutic approach in

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Table 1. Allergy testing results

Parameter	Positive results (%)	Negative results (%)	Test was not performed (%)
IgE values	18	20.5	61.5
Skin-prick test	18.5	14	67.5
Eosinophils in nasal secretions	15	11	74

IgE – immunoglobulin E

managing status asthmaticus [9]. Viral respiratory infections are the primary cause of asthma exacerbations across all age groups [4].

Diagnosing asthma in children aged five years and younger, particularly those under the age of two, can be challenging, as episodic respiratory symptoms such as wheezing and coughing are common in this age group and are often not related to asthma but rather a result of viral respiratory infections [5]. The diagnosis of asthma in young children with recurrent wheezing episodes is more likely if they exhibit: wheezing or coughing that occurs during exercise, crying, laughing, or in the absence of obvious respiratory infections; a history of other allergic diseases (such as eczema or allergic rhinitis); sensitization to allergens; a positive family history of atopy; clinical improvement during 2–3 months of treatment with low doses of inhaled corticosteroids (ICS); and deterioration after discontinuation of therapy [5].

In a study involving children aged 2–5 years, the combination of wheezing, increased daytime cough, and nighttime use of β2-agonists was a strong predictor for developing status asthmaticus the following day. This combination of three symptoms predicted 70% of exacerbations [10].

Children with recurrent wheezing episodes and suspicion of asthma use a disproportionately large number of medications, most commonly bronchodilators and corticosteroids, as the diagnosis, as previously mentioned, is not easily established in preschool-aged children [11]. According to the 2024 Global Initiative for Asthma recommendations, asthma treatment in children aged up to five years should be implemented stepwise. Management of exacerbations in primary care or an acute care facility should include inhaled short-acting β2-agonist (SABA) every 20 minutes for the first hour, systemic corticosteroids and oxygen. Transfer to the hospital is recommended if there is no response to inhaled SABA within 1–2 hours; if the child is unable to speak or drink, has a respiratory rate > 40 breaths/min. or is cyanotic; if resources are lacking in the home; or if oxygen saturation is < 92% on room air. Additional options in the first hour of treatment could be the use of ipratropium bromide and nebulized isotonic magnesium sulfate [5].

When discussing second-line treatments for status asthmaticus, the use of intravenous magnesium sulfate is becoming increasingly common in children with asthma. This medication is generally safe with few side effects. It should be used if there is a poor response to first-line therapy and is not recommended for mild to moderate forms of asthma [12].

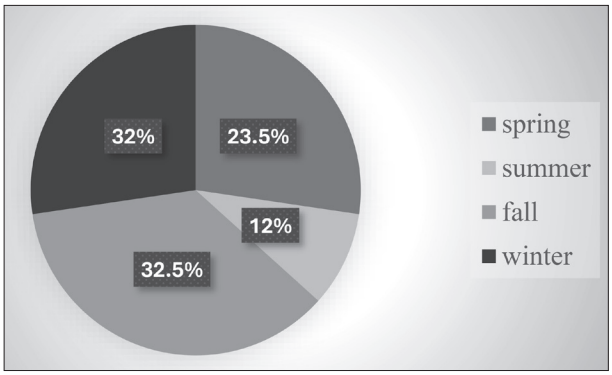

Figure 1. Distribution of hospitalized children by season

A review of the literature reveals a lack of studies focusing on status asthmaticus, the most severe and potentially life-threatening form of asthma exacerbation, and in our population, there are still no studies addressing this clinical entity. All of the above are reasons for conducting our research, which would contribute to understanding this significant health issue in the pediatric population.

METHODS

The study was a retrospective analysis of 200 children aged up to five years who were hospitalized at the Department of Pulmonary Diseases, Pediatric Clinic, Institute for Child and Youth Health Care over five years (January 2019 – December 2023) with status asthmaticus. Data concerning the patients were collected and analyzed from medical records: age, gender, anamnestic data regarding the current illness (type and duration of symptoms), asthma and atopy information (previous number of wheezing episodes, existing asthma diagnosis, use of asthma preventive therapy, presence of eczema, allergic rhinitis, or conjunctivitis, allergies to medications or food, family history of atopy). Allergy test results (total IgE, specific IgE, prick tests, eosinophils in nasal secretions) and acute-phase inflammatory markers upon admission, as well as data on the hospital course (length of hospitalization, duration of oxygen therapy, frequency of inhaled bronchodilator use upon admission, duration of systemic corticosteroid therapy, use of other therapeutic modalities and asthma preventive therapy at discharge) were analyzed.

For statistical data processing, IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA) was used. Numerical characteristics are presented as arithmetic means and ranges (minimum and maximum), while categorical characteristics are expressed in percentages. The results are presented in Table 1 and Figure 1.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as the ethical standards of institutions for each author involved. Before the start of the study, approval was granted by the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia (No.: 17/56-23).

RESULTS

Patient characteristics

In the studied sample of 200 preschool-aged children hospitalized due to status asthmaticus, there were 121 male children (60.5%) and 79 female children (39.5%).

The largest number of patients were aged one year – 63 children (31.5%). There were 20 children (10%) under one year of age, 41 children (20.5%) aged two years, 38 children (19%) aged three years, 22 children (11%) aged four years, and 16 children (8%) aged five years.

Month of hospitalization and number of hospital days

Figure 1 shows the distribution of patients by seasons. The winter months are classified as December, January, and February; the spring months are March, April, and May; the summer months are June, July, and August; while the fall months include September, October, and November. The highest number of patients was hospitalized in the fall months, while the lowest number was in the summer months.

The minimum number of hospital days was 2, while the maximum number was 22 days. The average number of hospital days was 6.4 days.

Symptoms and therapy administered prior to hospitalization

The minimum duration of symptoms prior to hospitalization for status asthmaticus was 1 day, while the maximum duration was 21 days. The average duration of symptoms was 3.5 days.

Regarding the therapy administered prior to hospitalization in the studied sample of 200 children, 155 children (77.5%) received SABA inhalations, while 45 children (22.5%) did not receive inhalations prior to hospitalization. Systemic corticosteroids were administered to 100 children (50%), while 100 children (50%) did not receive this therapy.

Previous wheezing episodes, asthma, personal and family history of atopy

In the studied sample of 200 children, 152 children (76%) had a history of previous wheezing episodes, while 48 children (24%) did not. Among the 152 children with previous wheezing episodes, 71 children (47%) experienced 1–3 wheezing episodes, 79 children (51.7%) had more than three, and data on the number of wheezing episodes were not available for two children (1.3%).

A previously diagnosed asthma was present in 27 children (13.5%), while 173 children (86.5%) had not been diagnosed with asthma prior to hospitalization. Asthma maintenance therapy was administered to 37 children (18.5%), while 163 children (81.5%) did not receive asthma maintenance therapy. The minimum duration of asthma maintenance therapy prior to hospitalization was 15 days, while the maximum duration was 450 days (15 months). The average duration of asthma maintenance therapy prior to hospitalization was 145 days.

Eczema was reported in 45 children (22.5%), while 155 children (77.5%) had not had eczema. Allergic rhinitis was present in 44 children (22%), while 156 children (78%) had not previously had allergic rhinitis. Allergic conjunctivitis was reported in 7 children (3.5%), while 193 children (96.5%) had not experienced allergic conjunctivitis.

Five children (2.5%) had a drug allergy, while 195 children (97.5%) had not reported a drug allergy. Food allergies were reported in 17 children (8.5%), while 183 children (91.5%) did not have food allergies.

A positive family history of atopy and asthma was present in 112 children (56%), while 88 children (44%) did not have a family history of atopy.

Clinical characteristics at admission

In the studied sample of 200 children hospitalized due to status asthmaticus, 123 children (61.5%) had oxyhemoglobin saturation at admission < 95%. Wheezing was present in all 200 children (100%) upon lung auscultation, while 107 children (53.5%) had both wheezing and crackles.

Diagnosis

Regarding specific IgE, it was positive in 36 children (18%), negative in 41 children (20.5%), and was not tested in 123 children (61.5%). Of the 36 children (18%) with positive specific IgE results, 13 (36%) had positive results for food allergens, while 23 (64%) had positive results for inhalant allergens.

In 37 children (18.5%), the skin prick test was positive: nine children (24.3%) were positive for food allergens, 22 (59.5%) for inhalant allergens, and six (16.2%) for both. In 28 children (14%), the test was negative, while in 135 children (67.5%) the skin prick test was not performed.

In 30 children (15%), the value of eosinophils in nasal secretions was elevated, 22 children (11%) had non-elevated values, whereas in 148 children (74%), the value of eosinophils in nasal secretions was not assessed. The allergy testing results are presented in Table 1.

Of the 200 children, allergy was confirmed in 100 children (50%) by any of the methods mentioned above (elevated total IgE and/or positive specific IgE and/or positive prick test and/or positive eosinophils in nasal secretions).

When analyzing C-reactive protein (CRP) levels in children upon hospital admission, CRP values were < 5 mg/L in 83 children (41.5 %), 5–20 mg/L in 86 children (43 %), 20–100 mg/L in 29 children (14.5 %), and > 100 mg/L in 2 children (1%).

Therapy

In the studied sample of 200 children hospitalized due to status asthmaticus, 136 children (68%) needed oxygen

treatment, while 64 children (32%) did not require oxygen therapy. Among the 136 children who required oxygen, the minimum duration of this therapy was one day, the maximum was nine days, and the average duration was 2.3 days.

Antibiotic therapy during hospitalization was administered to 136 children (68%), while 64 children (32%) were not treated with antibiotics. All patients received SABA. Inhalations were initially performed every 20 minutes for 68 children (34%), every hour for 100 children (50%), and every two hours for 32 children (16%). Inhaled magnesium sulfate ($MgSO_4$) was administered to 105 children (52.5%), while 95 children (47.5%) did not require $MgSO_4$ therapy.

Seven children (3.5%) received aminophylline, while 193 children (96.5%) did not receive aminophylline during hospitalization.

All children received systemic corticosteroids during hospitalization, with a minimum duration of one day, a maximum of 10 days, and an average duration of four days. Upon discharge, 17 children (8.5%) did not receive asthma maintenance therapy, while it was introduced for 183 children (91.5%). Among them, 121 children (66.1%) received ICS, and 62 children (33.9%) received both ICS and montelukast.

DISCUSSION

Patient characteristics

The prevalence of asthma ranges from just 1% in some countries to as high as 18%, with over 339 million people affected by this disease worldwide. This prevalence varies between genders and across different age groups. In children, asthma is more common in boys, while in adulthood, women show higher prevalence and severity of the disease. Factors contributing to gender differences in asthma prevalence and severity include sex hormones, genetics, environmental factors, and varying responses to treatment [13].

In a study conducted by Bollinger et al. [14], which included 222 children aged 3–12 years experiencing acute asthma exacerbations, a higher percentage of boys (64.8%) was observed. In the study conducted by Bisgaard et al. [15], where parents of children aged 1–5 years with respiratory symptoms resembling asthma were contacted by phone, 55.8% were boys. Similar data have been reported in other studies [16]. These trends are also confirmed in our study, which showed that 60.5% of children hospitalized due to status asthmaticus were boys, while 39.5% were girls.

Seasonality of hospitalization

The influence of seasonality on the frequency of asthma exacerbations is well-documented. The highest rate of asthma worsening in children occurs during the fall, which is thought to be related to viral infections and exposure to allergens when children return to school [17, 18]. A study by Bloom et al. [19] found that wheezing episodes were least common in August (4.1%) and most frequent in late fall and early winter (30.6%). In our study, the lowest number of patients was hospitalized during the summer (12%), while the highest number was hospitalized in the fall (32.5%), which aligns with the literature.

Symptoms and pre-hospitalization therapy

Upper respiratory symptoms often precede asthma exacerbations, highlighting the significant role of viral infections of the upper airways in triggering exacerbations in many children [5]. Most children in our study exhibited mildly elevated CRP levels (84.5% had CRP values up to 20 mg/L). Considering slightly elevated levels of acute-phase reactants, we believe that most of these patients had viral infections. Severe asthma exacerbation that does not improve with bronchodilator use is termed status asthmaticus [7]. Children exhibiting symptoms of severe exacerbation that do not regress within 1–2 hours despite repeated use of inhaled SABA require hospitalization [5]. In our research, 155 children (77.5%) received SABA prior to hospitalization, while 100 children (50%) were given systemic corticosteroids before admission.

The fact that slightly over 20% of children did not receive inhalation therapy in an outpatient setting, which is essential for those with severe asthma exacerbations, indicates the need for improvement in primary health-care to ensure timely recognition and initiation of treatment for status asthmaticus.

Previous wheezing episodes, asthma, personal and family history of atopy

Recurrent wheezing is common in preschool children, often associated with respiratory tract infections, which occur 6–8 times a year at this age. Given this, it can be challenging to determine when wheezing is a result of a respiratory infection and when it is a symptom of asthma in childhood. In a study involving children aged 12–59 months with recurrent moderate to severe wheezing episodes, 71% had at least four episodes of wheezing [20]. In our study, 76% of children had previous episodes of wheezing, and 51.7% had experienced more than three wheezing episodes.

There is no gold standard for accurately diagnosing asthma in preschool-aged children. Diagnosis is based on the presence of symptoms, evidence of airflow limitation, and response to therapy. In this age group, asthma diagnoses can sometimes be made too liberally or too conservatively, leading to significant issues in both cases. Additionally, routine lung function tests are not conducted in children under five years of age, further complicating asthma diagnosis in this age group. The response to therapy in preschool children is a useful clinical parameter for diagnosis and is recommended in numerous studies [3]. Status asthmaticus is more commonly seen in children who do not have a diagnosed asthma condition and therefore do not receive asthma therapy. This is supported by studies conducted by Bollinger et al. [14], where only

20.1% of children evaluated for acute exacerbations had a diagnosis of asthma, and by Bisgaard et al. [15], where 20% of surveyed children aged 1–5 with respiratory symptoms resembling asthma had a confirmed asthma diagnosis. The results of our study align with these findings, as only 13.5% of children had a prior asthma diagnosis, and 18.5% received preventive asthma therapy (primarily ICS) before hospitalization.

Risk factors for asthma development

It is well known that risk factors for the development of asthma include a positive personal or family history of eczema, allergic rhinitis, or nasal polyps. Epidemiological studies indicate that 15–40% of patients with allergic rhinitis also have asthma, while 76–80% of asthma patients have allergic rhinitis [21]. In a study conducted by Bollinger and colleagues, 40.5% of children evaluated for acute asthma exacerbations had allergic rhinitis, 57.7% had eczema, and 27.3% had food allergies [14]. In our study, 22% of children had allergic rhinitis, 22.5% had eczema, 8.5% exhibited food allergies, and 2.5% had drug allergies. Family history of atopy was positive in more than half of the children (56%).

Clinical characteristics on admission

Status asthmaticus can be accompanied by hypoxemia, hypercapnia, and secondary respiratory failure. In pediatric acute asthma exacerbations, the percentage of oxyhemoglobin saturation is one of the most significant factors influencing the decision to admit a child to the hospital or continue treatment at home [8]. In this study, among the sample of 200 children, 123 (61.5%) had oxyhemoglobin saturation levels of less than 95% upon admission.

Wheezing is a common clinical finding in patients with acute asthma exacerbations, resulting from turbulent airflow through narrowed airways. Diminished breath sounds, due to limited airflow, typically indicate severe bronchial obstruction. Wheezing is predominantly expiratory and is usually symmetric. Asymmetric distribution suggests the presence of atelectasis, pneumothorax, or foreign body obstruction in the airway [22]. In this study, as expected, wheezing was present in all children (100%) during lung auscultation.

Atopy assessment

Asthma is a heterogeneous disease with several underlying phenotypes. Childhood asthma, unlike adult asthma, is typically characterized by personal and family histories of atopy, along with positive markers for type 2 allergic reactions, such as elevated total or specific IgE and eosinophilia in the airways. This type of asthma responds well to treatment with ICS. Allergy testing (skin prick tests, measurement of specific IgE levels) is not routinely required for the diagnosis of asthma, but it is recommended in numerous clinical guidelines [3, 23]. Most preschool children with asthma enter remission or show significant improvement by school age [4]. In a study conducted by Bollinger and colleagues, which included 222 children aged 3–12 years who were examined in outpatient settings for acute asthma exacerbation, 82.6% of the children had positive results for various inhalant allergens [14]. In our study, we assessed atopic status through the following diagnostics: skin prick test, total IgE, specific IgE for inhalant and food allergens, and eosinophils in nasal secretions. This diagnostic workup was not performed on all patients, but only on those with personal and family histories indicating asthma. Elevated IgE levels were found in 48.7% of patients, specific IgE was positive in 18% (primarily for inhalant allergens), while 18.5% of children had a positive prick test (mainly for food allergens). Additionally, 15% of children had positive eosinophil levels in nasal secretions. In total, 50% of the tested children had at least one positive finding indicating an allergy.

Therapy

Episodes of wheezing should initially be treated with SABA, regardless of whether asthma has been diagnosed. However, this treatment may be ineffective in children under one year of age with bronchiolitis. Therefore, the response to the administered therapy should be evaluated before continuing it. If the response is incomplete or absent, it is necessary to reconsider the diagnosis and differential diagnoses [5]. The cornerstone of treatment for status asthmaticus is the administration of SABA (primarily salbutamol) at short intervals, along with systemic corticosteroids and oxygen therapy. In cases of poor response to the administered therapy, other therapeutic options, especially inhaled or intravenous magnesium sulfate, should be considered [5]. In our study, therapy was conducted according to current protocols. All patients were treated with systemic corticosteroids and SABA most commonly initiated for 20 minutes. Children with severe asthma exacerbations often experience a mismatch between pulmonary ventilation and perfusion due to airway obstruction and atelectasis, which causes hypoxemia. In such cases, the administration of oxygen is indicated to maintain oxygen saturation above 92% [22, 5]. In a study conducted by Donath et al. [23], which included children aged 1–5 years hospitalized due to asthma, 56.1% of the children received oxygen therapy. In our study, the percentage was slightly higher, at 68%.

Earlier, aminophylline was considered the first-line treatment during status asthmaticus in children, but today intravenous magnesium sulfate is recommended rather than aminophylline due to reduced side effects and comparable efficacy [12]. Nebulized isotonic magnesium sulfate can be used as an adjunctive therapy in the first hour of treatment for children aged two years or older with acute severe asthma (SaO_2 < 92%), especially if symptoms have persisted for less than six hours [5]. In our study, inhaled $MgSO_4$ was administered to 105 children (52.5%), and no child received intravenous $MgSO_4$. Seven children (3.5%) with severe clinical presentations were treated with aminophylline.

If a patient's symptoms suggest asthma, and episodes of wheezing are frequent or severe, while other alternative diagnoses have been excluded, it is recommended to start treatment with low-dose ICS as a trial therapy. The response to treatment should be assessed before deciding whether to continue therapy. The goal of asthma treatment in young children is to achieve good symptom control and maintain normal activity levels, while reducing the risk of asthma exacerbations, inadequate lung development, and adverse drug effects [5]. In this study, at discharge, 17 children (8.5%) did not receive asthma preventive therapy, while it was initiated in 183 children (91.5%); 121 (66.1%) received ICS, and 62 (33.9%) received both ICS and montelukast.

CONCLUSION

Status asthmaticus most commonly occurred in children during their early years, with a higher prevalence in boys and a significant number of cases presenting as the first manifestation of asthma. As expected, the highest incidence was noted in the fall months. More than half of the children had a family history of atopy and confirmed allergies. A significant percentage of children did not receive bronchodilator inhalations and systemic corticosteroid therapy on an outpatient basis, indicating a need for improvements in primary health-care to ensure timely recognition and initiation of treatment for status asthmaticus.

Conflict of interest: None declared.

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Клиничке карактеристике астматског статуса код деце предшколског узраста

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САЖЕТАК

Увод/Циљ Астма је најчешће хронично обољење у педијатријском узрасту. Астматски статус је тешка егзацербација астме која може довести до хипоксемије и респираторне инсуфицијенције. Постављање дијагнозе астме у предшколском узрасту често је изазовно, с обзиром на то да су епизоде визинга у овом узрасту углавном узроковане вирусним инфекцијама.

Методе Ретроспективна студија обухватила је 200 деце, узраста до пет година, која су била хоспитализована због астматског статуса у периоду од јануара 2019. до децембра 2023. године. Анализирани су подаци о пацијентима, дијагностичким поступцима, терапији и клиничком току болести.

Резултати Највећи број болесника био је узраста од годину дана (31,5%), уз предоминацију мушког пола (60,5%). Болесници су најчешће хоспитализовани током јесењих месеци, а просечно трајање хоспитализације износило је 6,4 дана. Алергија је потврђена код 50% деце. Атопију у породици имало је 56% деце. Претходно дијагностиковану астму имало је 13,5% деце. На отпусту је код 91,5% деце уведена превентивна терапија за астму. Сва деца су имала повољан исход лечења и отпуштена су из болнице.

Закључак Астматски статус најчешће се јавља код деце у првим годинама живота, при чему је код великог броја деце то прва манифестација астме. Више од половине деце има атопију у породици и потврђену алергију. За повољан исход кључно је да терапија буде започета на време и у складу са важећим протоколима.

Кључне речи: астма; деца; егзацербација; алергија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of procedural sedation using dexmedetomidine and the combination of dexmedetomidine with S-ketamine during magnetic resonance examination of the endocranium in children

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SUMMARY

Introduction/Objective There is an increasing number of children requiring magnetic resonance imaging (MRI) of the brain as a diagnostic procedure. During the scan, it is necessary for the child to remain still for an extended period. This is often challenging due to the patient's age, as well as the nature of the disease, which often makes them neurologically altered and uncooperative. The aim of this study was to evaluate the quality and safety of procedural sedation in children undergoing MRI of the brain by comparing two different sedation protocols.

Methods The study included 60 participants, aged 1–18 years, who required sedation during MRI of the brain. Using simple randomization, they were divided into two groups: the dexmedetomidine group (DEX group) was sedated with dexmedetomidine, and the dexmedetomidine/S-ketamine (DEX/KES group) received a combination of dexmedetomidine and S-ketamine.

Results Our results showed that the time to achieve adequate sedation was significantly shorter in the DEX/KES group (6.37 ± 3.62 min) compared to the DEX group (9.03 ± 3.48 min) ($p = 0.005$). During the initial 10 minutes, the average dexmedetomidine dose was identical in both groups (1.59 mcg/kg). However, during the continuous infusion phase until the end of sedation, the average dexmedetomidine dose was 1.47 mcg/kg in the DEX/KES group versus 1.60 mcg/kg in the DEX group. Analysis of hemodynamic parameters showed better stability in the DEX/KES group. Complications occurred more frequently in the DEX group.

Conclusion The dexmedetomidine/S-ketamine group provides a faster onset of sedation, better hemodynamic stability, lower total doses of sedatives, and fewer complications compared to dexmedetomidine alone.

Keywords: procedural sedation; S-ketamine; dexmedetomidine; magnetic resonance imaging

INTRODUCTION

In recent years, there has been an increasing number of children requiring magnetic resonance imaging (MRI) of the brain (endocranium) as a diagnostic procedure [1]. Children undergoing brain MRI are admitted as outpatients, and after the diagnostic procedure, they are expected to be fully awake as soon as possible and without any additional complications, as they are discharged home [2]. With the global economic downturn, financial pressures, a shortage of medical personnel, and long patient waiting lists, healthcare institutions have found it increasingly difficult to complete the necessary elective surgeries and imaging procedures. Outpatient anesthesia has provided a cost-effective and efficient way to manage scheduled patients, reduce waiting list volumes, and thereby improve patient satisfaction [3].

Procedural sedation in pediatrics poses a challenge due to the need to maintain the child's safety, comfort, and cooperation, while minimizing adverse effects. Among the available sedatives, dexmedetomidine (DEX) is increasingly used due to its combined sedative and analgesic properties [4]. One of the key advantages of DEX over other sedative agents is that it maintains spontaneous breathing and airway patency, even at higher doses. However, when administered rapidly and in higher doses, cases of bradycardia, hypotension, and sinus arrhythmia have been reported [4, 5, 6]. Continuous infusion rates of DEX can vary

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from 0.2–3 mcg/kg/h. Dose titration is not standardized [7]. Its relatively slow onset of sedation, insufficient depth, and potential for hemodynamic instability represent clinical limitations. To overcome these limitations, it is often combined with other agents.

S-ketamine is a relatively new drug used in pediatric patients. The main difference between ketamine and S-ketamine lies in the fact that ketamine is a racemic mixture, meaning it contains equal parts (50/50) of two mirror-image molecules: S-ketamine and R-ketamine. S-ketamine consists solely of the S-ketamine form [8]. It is twice as potent as ketamine and can provide more reliable sedation and analgesia with a lower risk of side effects [9]. Clinical studies have shown that S-ketamine has twice the potency of ketamine in terms of hypnotic and analgesic effects, with fewer psychiatric side effects. To achieve the same depth of sedation, the required dose of racemic ketamine is 50% higher compared to the necessary dose of S-ketamine [10]. Some findings suggest that S-ketamine provides 50% better recovery of cognitive function and the same depth of anesthesia compared to the racemic ketamine mixture [11]. Ketamine differs from other sedatives in that it has a stimulating effect on the cardiovascular system [causing increased blood pressure (BP), tachycardia, and cardiac output]. This occurs due to its sympathomimetic action on the cardiovascular system and inhibition of norepinephrine reuptake [12].

The aim of this study was to evaluate the quality and safety of procedural sedation in children undergoing brain MRI by comparing two different sedation protocols: DEX alone and a combination of DEX and S-ketamine.

METHODS

This prospective, randomized clinical study was conducted at the Clinic for Pediatric Surgery, Institute for Child and Youth Health Care of Vojvodina. The study was carried out in the period from December 1, 2024, to February 15, 2025. The study protocol complies with the Declaration of Helsinki, and the study was initiated after obtaining approval from the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina. Parents of the children included in the study signed informed consent after being properly informed about the procedure.

The study included patients aged 1–18 years who required sedation during MRI of the brain (endocranium). A total of 60 patients were enrolled. Eligible participants were under 18 years of age, regardless of sex, and classified as ASA (American Society of Anesthesiologists) I–III. Patients classified as ASA IV, as well as those hospitalized in intensive care units, intubated, sedated, or on mechanical ventilation, were excluded from the study. Patients were randomly assigned using simple randomization into one of two groups:

- group DEX sedated with DEX only
- group DEX/S-ketamine (group DEX/KES), sedated with a combination of DEX and S-ketamine.

All patients were previously evaluated in the Preoperative Anesthesia Assessment Clinic, where medical history was taken and standard examinations were conducted (clinical and pediatric examinations, electrocardiography, laboratory tests, and additional specialist consultations if needed). The MRI scans were performed under sedation, following the 1–4–6 fasting rule (clear fluids up to one hour, breast milk up to four hours, and solid food up to six hours before the procedure).

All safety measures and equipment were ensured during the procedure, including an anesthesia machine, oxygen supply, appropriately sized nasal and oral airways, a laryngoscope with different blades, endotracheal tubes, introducers, face masks, and all necessary emergency drugs and equipment.

All patients received premedication in the preoperative room 20 minutes before the MRI scan: intramuscular midazolam at 0.1 mg/kg and atropine at 0.01 mg/kg.

In group DEX (30 patients), DEX was administered at a dose of 1.5–2 mcg/kg over 10 minutes until adequate sedation (Ramsay score 6) was achieved, followed by continuous infusion at 1–2 mcg/kg/h during the procedure.

In group DEX/KES, an initial bolus dose of S-ketamine (0.5 mg/kg) was given, followed by DEX 1–1.5 mcg/kg until adequate sedation (Ramsay score 6) was reached. Then, a continuous infusion of DEX at 1–2 mcg/kg/h was maintained during the procedure.

The level of sedation was assessed using the Ramsay sedation scale, based on the patient's response to sound, verbal commands, or tactile stimulation (Table 1). Once a Ramsay score of 6 and hemodynamic and respiratory stability were achieved, patients were transferred to the MRI scanner. If a Ramsay score of 6 was not achieved after 10 ± 5 minutes of infusion or if sedation was inadequate, additional bolus doses of either DEX or ketamine were administered, depending on the group.

Table 1. Ramsay sedation scale

Response	Level
Awake and anxious, agitated, or restless	1
Awake, cooperative, accepting ventilation, oriented, or tranquil	2
Awake, responds only to commands	3
Asleep, brisk response to light, glabella tap, or loud noise	4
Asleep, sluggish response to light, glabella tap, or loud noise	5
Asleep, no response to light, glabella tap, or loud noise	6

Inadequate sedation was defined as difficulty completing the procedure due to patient movement during MRI scanning. Sedation was managed to maintain a Ramsay score of 6, with continuous infusion throughout the procedure. Monitoring included vital signs such as BP, heart rate (HR), transcutaneous oxygen saturation (SpO_2), time to achieve sedation, wake-up time, need for additional medication, and any complications.

All children breathed spontaneously throughout the procedure with oxygenation via face mask. Recovery time was defined as the period from discontinuation of the infusion until achieving a Ramsay score of 2. The quality of sedation was assessed based on the success of completing the MRI without movement and the need for additional

sedation, while safety was evaluated through vital signs and the occurrence of complications.

Ethics: The study protocol got approval from the Ethics Committee of the Institute for Child and Youth Health Care of Vojvodina (November 29, 2024; No. 17-43).

RESULTS

The average dose of DEX administered over 10 minutes to achieve sedation was identical in both groups (1.59 mcg/kg). However, the continuous DEX doses during the MRI procedure were lower in the DEX/KES group (1.47 mcg/kg) compared to the DEX group (1.60 mcg/kg). The results are presented in Table 2**.**

The time required to achieve sedation was significantly shorter (Z = -2.913; p = 0.000) in the DEX/KES group compared to the DEX group, as shown in Table 3. The median time in the DEX group was 10 minutes (range: 6.75–10 minutes), while in the DEX/KES group it was 6 minutes (range: 3–8.50 minutes).

Table 2. Dexmedetomidine dose (mcg/kg) continuously by groups

Value	DEX	DEX/KES
Average	1.60	1.47
SD	0.33	0.30
Min	1	1
Max	2.5	2
Mediana#	1.5ns	1.5
ICR (P25–P75)	0.37 (1.48–1.85)	0.20 (1.30–1.50)

SD – standard deviation; ICR – interquartile range; P25 – 25th percentile; P75 – 75th percentile;
#Mann–Whitney U test;
nsno statistically significant difference

Table 3. Time required to achieve sedation by groups

Value	DEX	DEX/KES
Average	9.03	6.37
SD	3.42	3.68
Min	2	1
Max	15	15
Mediana#	10a	6
ICR (P25–P75)	3 (6.75–10)	6 (3–8.50)

SD – standard deviation; ICR – interquartile range; P25 – 25th percentile; P75 – 75th percentile;
#Mann–Whitney U test;
a$p < 0.01$

Table 4. Systolic arterial blood pressure (mm Hg) at three examined times according to groups

Parameters	Average	SD	Min	Max	Mediana#	ICR (P25–P75)
DEX (n = 30)						
At the introduction	100.67	11.80	80	125	100ns	20 (90–110)
After 10 minutes	106.10	11.02	90	130	106.50ns	18 (95.75–113.50)
At the end	101.23	12.07	82	133	99ns	12 (92.75–104.25)
DEX/KES (n = 30)						
At the introduction	100.77	9.46	80	120	100	15 (94.75–110)
After 10 minutes	102.83	10.49	90	120	100	23 (90–113.25)
At the end	100.17	11.39	85	120	95.50	20 (90–110)

SD – standard deviation; ICR – interquartile range; P25 – 25th percentile; P75 – 75th percentile;
#Mann–Whitney U test;
nsno statistically significant difference

The comparison of systolic BP at different time intervals in both groups is presented in Table 4. In the DEX group, where continuous infusion of DEX was administered without additional sedatives, an increase in the mean systolic arterial pressure was recorded after 10 minutes; however, by the end of the procedure, the mean value had decreased. There were no clinically significant fluctuations. In the group that received the combination of DEX and ketamine, systolic arterial pressure remained highly stable throughout the procedure. After 10 minutes, the median value remained the same as at baseline, with a minimal decrease observed at the end of the procedure. Results of the Mann–Whitney U test showed no statistically significant difference between the groups in systolic arterial pressure values at any of the three time points ($p > 0.05$).

Based on the results of the Friedman test, a statistically significant difference was observed across the three time points for systolic arterial pressure in the DEX group ($\chi^2 = 6.158$; df = 2; $p = 0.046$), whereas in the DEX/KES group, no significant difference was found ($\chi^2 = 0.080$; df = 2; $p = 0.961$).

The values of Kendall's coefficient of concordance were W = 0.103 for the DEX group and W = 0.001 for the DEX/KES group, indicating that the differences were not consistent among most participants in the DEX group, while in the DEX/KES group, there was a complete absence of changes between time points.

Wilcoxon's test in the DEX group revealed a statistically significant increase in systolic arterial pressure after 10 minutes compared to the baseline (Z = -2.057; p = 0.040) and compared to the end of the procedure (Z = -2.173; p = 0.030). For all other time point comparisons, no statistically significant differences were found ($p > 0.05$).

HR values at the three measured time points by group are presented in Table 5.

Based on the results of the Wilcoxon test and data from Table 5, a statistically significant decrease in HR was observed 10 minutes after the administration of the loading dose of DEX in both the DEX group (Z = -3.776; p = 0.000) and the DEX/KES group (Z = -1.959; p = 0.049).

According to the Mann–Whitney U test, there was no statistically significant difference in HR values between the groups at baseline and at the end of the procedure. However, a statistically significant difference was found 10 minutes after drug administration (Z = -2.079; p = 0.038), in favor of the DEX/KES group.

The Friedman test showed a statistically significant difference in HR values across the three time points in both the control group ($\chi^2 = 13.270$; df = 2; p = 0.001) and the experimental group ($\chi^2 = 26.991$; df = 2; p = 0.000).

However, Kendall's coefficient of concordance was W = 0.221 in the control group, indicating that differences between the three time points existed but were not consistently present across all participants. In contrast, W = 0.450 in the group receiving the combination of DEX and ketamine indicates

Table 5. Heart rate (beats/min) at three examined times by groups

Parameters	Average	SD	Min	Max	Mediana#	ICR (P25–P75)
DEX (n = 30)						
At the introduction	107.83	15.790	75	138	106.50	21 (98.00–118.75)
After 10 minutes	90.50	17.547	57	125	88.00	26 (79.25–105.25)
At the end	95.77	13.531	68	115	97.00ns	22 (86.00–107.75)
DEX/KES (n = 30)						
At the introduction	110.27	22.095	70	160	107.50ns	27 (94.00–121.00)
After 10 minutes	104.20	24.633	60	170	100.00a	21 (90.50–111.25)
At the end	94.07		61	120	96.50	19 (84.25–102.75)

SD – standard deviation; ICR – interquartile range; P25 – 25th percentile; P75 – 75th percentile
#Mann–Whitney U test;
a$p < 0,05$;
nsno statistically significant difference

Table 6. Time of awakening from sedation by groups

Parameters	DEX	DEX/KES
Average	5.93	6.93
SD	4.21	4.74
Min	2	2
Max	16	20
Mediana#	5	6ns
ICR (P25–P75)	6 (3–8.5)	7 (2.75–10)

SD – standard deviation; ICR – interquartile range; P25 – 25th percentile; P75 – 75th percentile; #Mann–Whitney U test;
nsno statistically significant difference

Table 7. Incidence of complications during sedation in the study groups (n (%))

Complication	DEX (n = 30)	DEX/KES (n = 30)
No complication#	24 (80)	29 (96.7)ns
Bradycardia	4 (13.3)	0 (0)
Tachycardia	0 (0)	1 (3.3)
Wetting	2 (6.7)	0 (0)

Values are expressed as a number (percentage);
#χ^2 test;
nsno statistically significant difference

moderately strong and relatively uniform differences among patients.

All patients maintained spontaneous breathing throughout the procedure.

The wake-up time from sedation in both groups indicates a greater number of patients with a wake-up time shorter than 5.93 minutes in the DEX group and shorter than 6.93 minutes in the DEX/KES group. The results are presented in Table 6.

Complications were rare and occurred more frequently in DEX group.

The most common complication in the group that received only DEX was bradycardia, present in four (13.3%) patients, whereas in the DEX/KES group, no patients experienced this hemodynamic disturbance.

In the DEX group, two patients (6.7%) experienced enuresis, and one patient (3.3%) required conversion to general anesthesia. In the DEX/KES group, one patient developed tachycardia, and one patient experienced a technical error.

Nausea and vomiting were not observed in either group. Additionally, hypotension**,** hypertension, and oxygen desaturation were not observed (presented in Table 7).

DISCUSSION

There are numerous clinical studies in children that have examined sedation during MRI using DEX alone, confirming that at high doses it provides adequate sedation for pediatric MRI studies without respiratory complications, but it is associated with cardio-inhibitory changes. It leads to a lowering of BP and bradycardia [13, 14]. Some studies have also investigated combinations of DEX and ketamine for pediatric sedation, demonstrating better sedation outcomes than using DEX or ketamine alone. The onset of sedation and recovery are faster while maintaining hemodynamic and respiratory stability, with possible adverse events such as nausea, vomiting, and hallucinations attributed to the action of ketamine [15, 16]. However, to our knowledge, the use of DEX–S-ketamine has not been evaluated for MRI sedation in children.

The results of our study showed good sedation quality achieved in 26 out of 30 patients (86.7%) in both groups, indicating that both methods were highly effective in a clinical setting.

Our findings align with previous research confirming that DEX is a safe and effective option for procedural sedation in children [17, 18]. Similar findings were reported by Gao et al. [19], who demonstrated that the combination of DEX with racemic ketamine allows better sedation control and shorter time to achieve the desired sedation level compared to DEX alone.

Our results showed that the time to achieve adequate sedation was significantly shorter in the DEX/KES group compared to the DEX group, confirming our primary hypothesis that the combination of DEX and S-ketamine enables faster sedation induction. These results are consistent with previous studies in adults using the combination DEX/ketamine compared to DEX alone [20].

When observing the induction phase (initial dose during the first 10 minutes), the median DEX dose was identical in both groups. However, during the continuous infusion phase until the end of sedation, a 7.5% difference indicates a potentially lower need for additional medication in the DEX/KES group due to the additive sedative effect of S-ketamine.

Although the initial doses were identical, the reduced need for continuous DEX administration in the DEX/KES group has clinically significant potential to reduce the risk of adverse cardiovascular effects associated with higher cumulative doses [20].

Hemodynamic parameter analysis showed that changes in systolic arterial pressure were milder in the DEX/KES group. In the DEX group, after the loading dose, results showed the expected, clinically significant bradycardia, whereas changes in the DEX/KES group were milder.

These data suggest that the presence of S-ketamine contributed to a more stable hemodynamic response during sedation, likely due to its mild sympathomimetic action which mitigates the hypotensive effects of DEX.

Oxygen saturation remained stable in both groups throughout the observed period, indicating that neither DEX nor S-ketamine significantly affected respiratory function. Preserved respiratory stability, even in sedated patients, represents a key safety element of the protocol. These findings are consistent with literature data on DEX [21] and S-ketamine [22].

Regarding recovery time from sedation, although differences were present, they did not reach statistical significance, but clinically favored the group receiving only DEX. There is a study in adults comparing recovery time with ketamine combination, showing opposite results to ours, where recovery time was faster [23].

Concerning complications, excellent sedation quality was achieved in both groups. The most common complication in the DEX group was bradycardia, which in one case required medication therapy. No bradycardia was recorded in the DEX/KES group. This suggests a potential cardioprotective role of S-ketamine when combined with DEX.

Other adverse reactions (tachycardia, conversion to general anesthesia) were rare and evenly distributed among the groups. No urgent pharmacological intervention was needed in any case. In two cases in the DEX group, enuresis occurred after a bolus dose of DEX, described as a possible effect after higher doses of DEX [24, 25]. Vomiting can occur during or after procedural sedation; however, no episodes of nausea or vomiting were reported in any patient regardless of whether they received DEX or S-ketamine. There were also no cases of agitation, hallucinations, or delirium, which are commonly described complications after racemic ketamine administration [9]. Our results confirm the study by Chen et al. [26], showing that S-ketamine has fewer side effects and may reduce postoperative delirium in children.

CONCLUSION

Our study results show that the combination of DEX and S-ketamine provides faster sedation induction, better hemodynamic stability, lower total sedative dose, and fewer complications compared to DEX alone. Future research should focus on more precisely defining the optimal doses and ratios of these drugs for different types of procedures. It is particularly important to further investigate the advantages of S-ketamine over the racemic form. Additional randomized studies with larger samples would enable more precise clinical recommendations and broader application of this combination in everyday practice.

Conflict of interest: None declared.

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Поређење процедуралне седације применом дексмедетомидина и комбинације дексмедетомидина са с-кетамином током магнетнорезонантног прегледа ендокранијума код деце

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САЖЕТАК

Увод/Циљ Све је већи број деце код које се указује потреба за прегледом ендокранијума магнетном резонанцом као део дијагностичке процедуре. Током снимања потребно је да дете буде мирно дужи временски период. Отежавајућу околност чини узраст пацијента и природа болести, због које су деца често неуролошки измењена и некооперативна. Циљ ове студије био је да се испита квалитет и безбедност процедуралне седације код деце током прегледа ендокранијума магнетном резонанцом, поређењем две различите седационе шеме.

Методе Студија је обухватила 60 испитаника, узраста од 1 до 18 година, којима је била неопходна седација током прегледа ендокранијума магнетном резонанцом. Простом рандомизацијом пацијенти су подељени у две групе: група дексмедетомидин (група ДЕКС) седирана је дексмедетомидином, а група дексмедетомидин / с-кетамин (група ДЕКС/КЕС) комбинацијом дексмедетомидин / с-кетамин.

Резултати Наши резултати су показали да је време постизања адекватне седације било значајно краће у групи ДЕКС/КЕС (6,37 ± 3,62 мин.) у односу на групу ДЕКС (9,03 ± 3,48 мин.) (p = 0,005). Када се посматра иницијална доза током првих 10 минута, средња доза дексмедетомидина била је идентична у обе групе (1,59 *mcg/kg*), али у фази континуиране инфузије до краја седације просечна доза дексмедетомидина износила је 1,47 *mcg/kg* у групи ДЕКС/КЕС, наспрам 1,60 *mcg/kg* у групи ДЕКС. Анализа хемодинамских параметара показала је већу стабилност у групи ДЕКС/КЕС. Компликације су биле ретке и чешће у групи ДЕКС.

Закључак Комбинација дексмедетомидин / с-кетамин обезбеђује бржи увод у седацију, бољу хемодинамску стабилност, нижу укупну дозу седатива и мање компликација у поређењу са групом која је примала само дексмедетомидин.

Кључне речи: процедурална седација; с-кетамин; дексмедетомидин; магнетна резонанца

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparative healing outcomes after β-tricalcium phosphate grafting in pediatric aneurysmal bone cysts, simple bone cysts and non-ossifying fibroma

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SUMMARY

Introduction/Objective Aneurysmal bone cysts (ABC), simple bone cysts (SBC), and non-ossifying fibromas (NOF) are common in children. The standard treatment is curettage with defect filling. The graft selection and surgical approach vary according to the lesion type. While synthetic β-tricalcium phosphate (β-TCP) is a biocompatible graft, its efficacy in pediatric cases remains unclear. This study assessed radiographic healing, graft integration, complications, and recurrence rates after curettage and β-TCP grafting.

Methods We retrospectively reviewed 63 patients (23 ABC, 21 SBC, and 19 NOF) treated at a pediatric hospital from 2015 to 2023. All underwent intralesional curettage with β-TCP grafting. Healing was assessed using Wu, modified Irwin, and modified Neer criteria. The stable healing time, recurrence, complications, and morphometric predictors were also analyzed.

Results Radiographic healing rates were 73.9% for ABC, 85.7% for SBC, and 100% for NOF. Stable healing occurred at 13.5 ± 5.7 months for ABC and approximately 8.7–8.8 months for SBC and NOF ($p = 0.0004$). ABC healed more slowly and inconsistently; larger and relation length ratio lesions delayed healing in both ABC and SBC. Recurrence was observed in 26% of ABC cases (mean 16.7 months), 14% of SBC cases (mean 13.8 months), and none in NOF.

Conclusion β-TCP grafting is safe and effective for pediatric benign bone lesions; however, healing varies by lesion type. ABC requires longer monitoring due to a higher recurrence risk; SBC mostly stabilizes within a year; and NOF reliably remodels regardless of size. Focusing on follow-up of high-risk lesions may improve outcomes and reduce unnecessary interventions.

Keywords: aneurysmal bone cyst; simple bone cyst; non-ossifying fibroma; β-tricalcium phosphate; pediatric orthopedics; bone grafting

INTRODUCTION

Benign bone lesions frequently occur in children and adolescents and usually show characteristic features on imaging. They are often found incidentally after trauma but can also present with pain, swelling, and pathological fractures. Among the most prevalent are aneurysmal bone cysts (ABC), which exhibit local aggressiveness and can rapidly destroy bone; simple bone cysts (SBC), which tend to recur but progress at a slower rate; and non-ossifying fibromas (NOF), which are generally asymptomatic unless they compromise structural stability [1].

Their optimal management remains challenging because of the lack of standardized treatment protocols [2]. The absence of clear guidelines leads to variability in surgical approaches and reconstructive materials, posing significant challenges for pediatric orthopedic surgeons. The need for effective, safe, and reproducible treatment strategies is paramount, given the long-term growth and functional implications for young patients. Current surgical interventions typically involve curettage followed by defect filling [3, 4, 5]. Bone defects can be reconstructed using autologous, allogeneic, or synthetic grafts. There is no ideal bone graft available. Autologous bone grafting is considered the gold standard but is limited in pediatric patients because of donor-site morbidity, longer surgery times, and restricted harvest volume [6]. Allografts and xenografts serve as alternatives; however, they may produce inconsistent outcomes and pose potential immunological risks to the host, including graft rejection, inflammation, and transmission of zoonotic diseases [7]. Although synthetic bone grafts, such as beta-tricalcium phosphate (β-TCP), exhibit good biocompatibility, osteoconductivity, and predictable resorption [8, 9], clinical evidence regarding their efficacy and safety in treating benign bone lesions in children is limited. Radiological scoring systems, such as the Wu and Irwin criteria, offer a framework for assessing postoperative healing [10]. However, their usefulness is limited by the wide variation in healing rates, recurrence, and risk of complications among benign bone lesions. This variation highlights the need for direct clinical studies to understand the different outcomes and guide the treatment of specific lesions.

This study compared healing, graft integration, complications, and recurrence rates in

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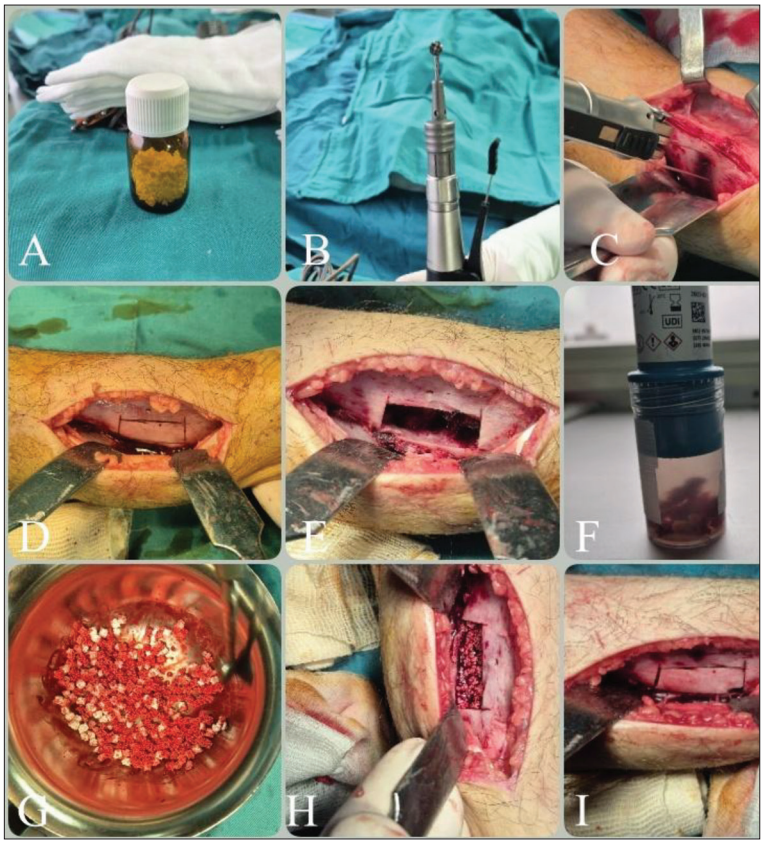

Figure 1. Surgical technique; A – β-tricalcium phosphate (β-TCP) granules; B – high-speed burr used to carefully remove bone around the lesion; C, D – Creating a cortical window to access the lesion; E – opening the cortical window and performing curettage; F – tissue obtained from the bone lesion for histopathology; G – β-TCP granules combined with patient blood; H – defect filled with granules; I – replacing and securing the cortical window after filling the defect

pediatric patients with ABC, SBC, and NOF after curettage and β-TCP grafting. The findings aim to guide better treatment and follow-up strategies for each benign bone lesion type in children and adolescents.

METHODS

Study design and population

This retrospective observational study included 63 pediatric patients (aged 4–18 years) treated at the University Clinical Center of Nis, Serbia, from January 2015 to December 2023 with standardized intralesional curettage and β-TCP filling for benign bone lesions (ABC, SBC, and NOF). Outcomes were compared among the three types of lesions. Inclusion criteria were pathohistologically confirmed ABC, SBC, or NOF; curettage with β-TCP filling; and at least 12 months' follow-up. Patients with malignant tumors, prior surgery, incomplete imaging, non-standard adjuvants, or less than 12 months of follow-up were excluded. Eligible patients were identified using ICD-10 diagnostic codes for benign bone lesions and subsequently confirmed by histopathological examination. From this initial pool, patients who met the inclusion and exclusion criteria were selected. Based on histopathological examination, there were 23 ABC, 21 SBC, and 19 NOF cases in this study.

Patient demographics, lesion details, pathological fractures, surgery data, and outcomes were obtained from records and radiographs. All patients underwent standardized intralesional curettage with β-TCP filling, as described below.

Surgical technique

All procedures were performed under general anesthesia, using a sterile technique. The lesion was located via fluoroscopy, and a cortical window, typically 1–2 cm in length, was created using an osteotome. The lesion cavity was thoroughly curetted until healthy bleeding bone was observed. A high-speed burr was used as needed to debride the cyst wall, remove the pathological lining, or enlarge cavities with thick bone septa. The cavity was thoroughly washed and packed with β-TCP granules (ChronOS™, DePuy Synthes, Raynham, MA, USA or TriOSS®, Bioceramed, Guimarães, Portugal), mixed with autologous blood. The cortical cap was returned and sealed with medical wax, if necessary. Large or unstable defects were fixed internally using plates or titanium-elastic nails. The incision was closed in layers, and the operated limb was immobilized as needed to stabilize the surgical site during early recovery (Figure 1).

Postoperative protocol and follow-up

Postoperative care involved a period of limited weight bearing, followed by gradual increases in activity and weight bearing as tolerated, guided by clinical assessment and radiographic healing. Clinical and radiographic evaluations occurred every 6–8 weeks for six months, then every 4–6 months until healing, and annually until full consolidation. Full activity and sports were permitted after adequate bone remodeling and graft integration were confirmed.

Radiological assessment

While magnetic resonance imaging or computed tomography scans were performed in certain cases for diagnostic purposes, only standard anteroposterior (AP) and lateral radiographs were used for the main outcome analysis to ensure consistency. Radiographic images, collected as part of the patient data, were analyzed using RadiAnt DICOM Viewer® 2025.2 (Medixant, Poznań, Poland) by a single experienced pediatric orthopedic surgeon. Postoperative healing was evaluated using three validated radiological scoring systems applied to standard AP and lateral radiographs.

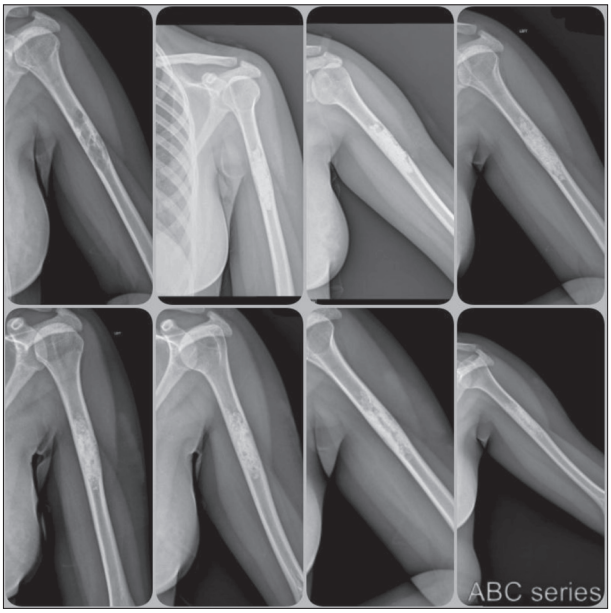

Figure 2. ABC – aneurysmal bone cyst; two years of follow-up

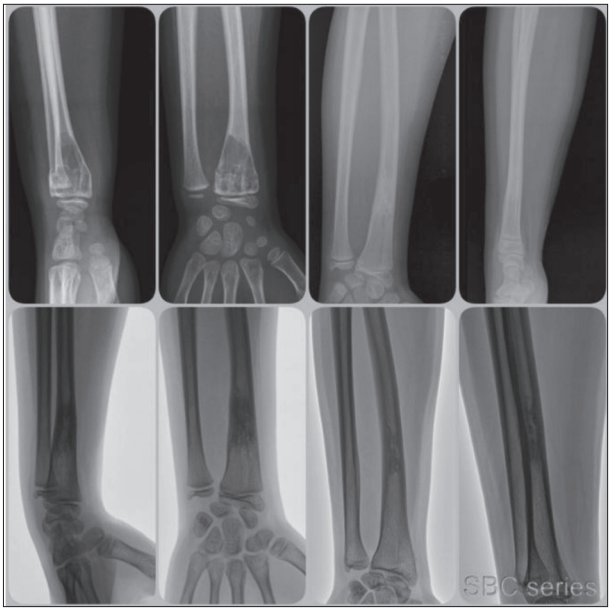

Figure 3. SBC – simple bone cyst; three years of follow-up

- Wu criteria for defect filling (quantifying cavity fill): I < 50%; II 50–75%; III 75–90%; IV > 90%;
- Modified Irwin criteria for graft incorporation (assessing biological graft integration): I clear; II hazy; III incorporation; IV remodeling;
- Modified Neer criteria for overall healing outcome: I complete healing; II healing with residual defects; III persistent defect; IV recurrence.

Outcome measures

Primary outcomes

1. Healing outcome was classified as "healed" if lesions simultaneously achieved all three criteria: a Wu Grade III or IV (for filling), an Irwin Stage III or IV (for incorporation), and a modified Neer Criteria I or II (for overall outcome);
2. Stable healing time: the number of months from surgery until X-rays first show sufficient cortical healing and trabecular bridging, along with clinical stability and no recurrence or refracture.

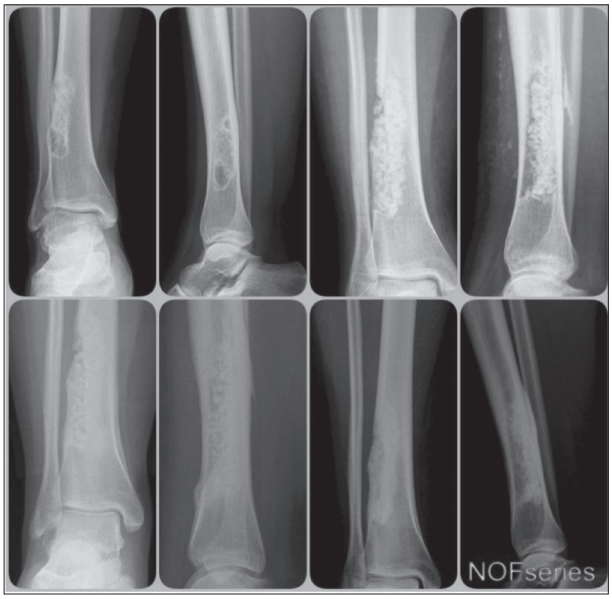

Figure 4. NOF – non-ossifying fibroma;14 months of follow-up

Secondary outcomes

1. Recurrence (radiographic evidence, symptomatic recurrence, need for re-intervention);
2. Pathological fracture;
3. Postoperative complications (infection, nerve injury, hardware failure, delayed wound healing).

Examples of all three benign bone lesions with follow-up are shown in Figures 2, 3, and 4.

Baseline characteristics

The baseline characteristics included patient age, sex, lesion location (bone and anatomical region), tumor length [$V = (\pi/6) \times \text{length} \times \text{width} \times \text{height}$], tumor volume (longest craniocaudal distance in AP or lateral radiography), relation length (lesion length divided by the total length of the affected bone), and presence of pathological fracture at presentation.

Statistical analysis

Sample size was calculated in G*Power 3.1.9.2 (one-way ANOVA, effect size 0.25, $\alpha = 0.05$, power = 0.95, three groups). Analyses were performed in IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). Variable normality was checked with the Shapiro–Wilk test. Depending on distribution, either one-way ANOVA or Kruskal–Wallis test was used. Results are shown as mean ± SD or median (range). Categorical data were analyzed with

Table 1. Demographic and anatomical characteristics of patients with ABC, SBC, and NOF

Variables	ABC (n = 23)	SBC (n = 21)	NOF (n = 19)	p
Age (years)				
Mean ± SD	11.35 ± 3.13	10.76 ± 3.36	12.32 ± 3.31	ANOVA p = 0.013
Median	11	10	14	KW p = 0.011
Range	5–17	4–18	4–17	—
Gender				
Male, n (%)	15 (65.2%)	15 (71.4%)	7 (36.8%)	$\chi^2 = 6.94$; p = 0.031
Female, n (%)	8 (34.8%)	6 (28.6%)	12 (63.2%)	—
Bone location				
Humerus	11 (47.8%)	10 (47.6%)	0 (0%)	
Femur	7 (30.4%)	4 (19%)	9 (47.4%)	
Tibia	4 (17.4%)	1 (4.8%)	10 (52.6%)	$\chi^2 = 52.8$; p < 0.0001
Radius	0	4 (19%)	0	
Fibula	0	1 (4.8%)	0	
Calcaneus	0	1 (4.8%)	0	
Foot bones (Cuboid/PxPh)	2 (8.7%)	0	0	

ABC – aneurysmal bone cyst; SBC – simple bone cyst; NOF – non-ossifying fibroma; n – number; SD – standard deviation; ANOVA – mean comparison; KW – median comparison; χ^2 – Chi-square test for categorical variables; PxPh – proximal phalanx

Table 2. Results of ABC, SBC, and NOF treated with synthetic bone graft

Variables	ABC (n = 23)	SBC (n = 21)	NOF (n = 19)	p
Initial pathological fracture (%)	15(65%)	12(57%)	5(26%)	$\chi^2 = 6.81$; p = 0.033
Healing: Healed (%)	17 (73.9%)	18 (85.7%)	19 (100%)	$\chi^2 = 4.51$; p = 0.105
Healing: Not healed (%)	6 (26%)	3 (14.3%)	0	
≤ 6 months healed (%)	0%	23.8%	21.1%	
≤ 9 months healed (%)	33.3%	57.1%	63.2%	
≤ 12 months healed (%)	58.3%	85.7%	89.5%	
Stable healing time (mean ± SD)	13.48 ± 5.68	8.67 ± 3.38	8.84 ± 2.81	ANOVA p = 0.0004
Median stable healing	12	8	9	KW p = 0.0057
Stable healing range	7–24	4–15	4–14	
Tumor length (mean ± SD)	6.25 ± 3.08	5.59 ± 2.3	4.82 ± 1.7	ANOVA p = 0.18
Tumor volume (mean ± SD)	22.31 ± 19.85	12.37 ± 9.64	7.52 ± 4.33	ANOVA p = 0.0024
Relation length (mean ± SD) (lesion to total bone length)	0.23 ± 0.14	0.22 ± 0.07	0.15 ± 0.07	ANOVA p = 0.029

ABC – aneurysmal bone cyst; SBC – simple bone cyst; NOF – non-ossifying fibroma; SD – standard deviation; χ^2 – Chi-square test; ANOVA – one-way analysis of variance; KW – Kruskal–Wallis test; p < 0.05 considered significant; relation length – lesion length/total bone length

χ^2 or Fisher's exact test. Kaplan–Meier analysis assessed recurrence time. Statistical significance was set at p < 0.05.

Ethics: The study was approved by Institutional Ethics Committees (UCC Niš: 14396/6; Medical Faculty of Niš: 12-14250-2/2) in accordance with the Declaration of Helsinki. Written informed consent was obtained from parents or guardians, and patient confidentiality was maintained.

RESULTS

Patient demographics varied across groups, with patients with ABC and SBC being notably younger (mean age 11.35 and 10.76 years, respectively) than patients with NOF (mean age 12.32 years; ANOVA, p = 0.013). Males were predominant in the ABC (65%) and SBC (71%) groups, whereas females were more prevalent in the NOF group (63%) (p = 0.031) (Table 1).

The location of the lesions also differed significantly (p < 0.0001); ABC and SBC were most frequently located in the humerus (48% each), whereas NOF was found exclusively in the femur (47%) and tibia (53%) (Table 2).

The incidence of pathological fractures as initial presentations varied significantly among the lesion types ($\chi^2 = 6.81$, p = 0.033), with a notably lower frequency observed in NOF (26%) compared to ABC (65%) and SBC (57%).

ABC lesions had significantly longer stable healing times (mean 13.5 ± 5.7 months) than SBC (8.7 ± 3.4 months) and NOF (8.8 ± 2.8 months) (ANOVA p = 0.0004; Kruskal–Wallis p = 0.0057). However, the overall healing success rates were similar (ABC: 74%, SBC: 86%, NOF: 100%; $\chi^2 = 4.51$, p = 0.105), indicating comparable long-term outcomes.

Tumor length was similar across groups (p = 0.18); therefore, initial lesion size was not a distinguishing factor. ABC lesions had the greatest volume (ANOVA p = 0.0024), whereas NOF lesions had the smallest volume. The relation index was highest in ABC and SBC and lowest in NOF (ANOVA p = 0.029; Kruskal–Wallis p = 0.0013), indicating more bone involvement in ABC and SBC.

Correlation analysis showed that stable healing time was affected by various factors across the diagnostic groups. For ABC, healing time moderately increased with larger tumor volume (r = 0.34) and relation length (r = 0.28) but decreased notably with better healing outcomes (r = -0.56); tumor length and age had a minor impact. In SBC, healing time strongly correlated with tumor volume (r = 0.63), relation length (r = 0.52), and tumor length (r = 0.45); younger age sped up healing (r = -0.36), and better outcomes shortened stabilization time (r = -0.58). NOF had mild links between healing time and tumor size, and age had minimal influence (r = 0.06).

Overall, healing time decreased from ABC to SBC to NOF, with tumor volume and size serving as the primary predictors of delayed healing. Age was insignificant, except for SBC cases (Figure 5).

The cumulative healing rates for ABC, SBC, and NOF at six, nine, and 12 months are shown in a side-by-side bar chart. ABC had the slowest healing (0%, 33.3%, 58.3%), SBC showed intermediate rates (23.8%, 57.1%, 85.7%), and NOF healed fastest (21.1%, 63.2%, 89.5%) (Figure 6).

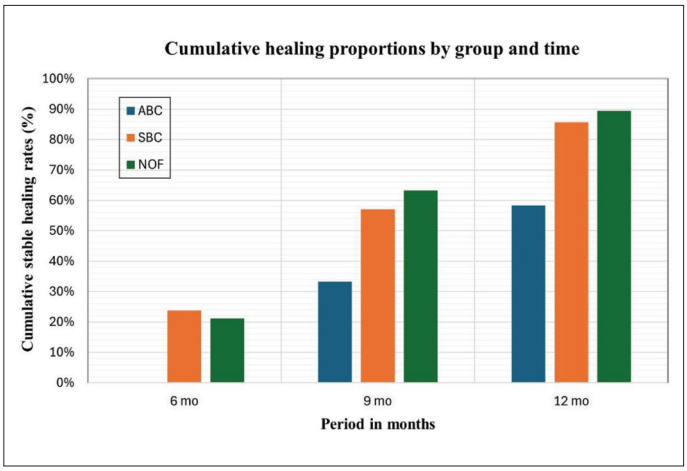

Figure 5. Cumulative healing proportions

ABC – aneurysmal bone cyst; SBC – simple bone cyst; NOF – non-ossifying fibroma; mo – months (follow-up interval)

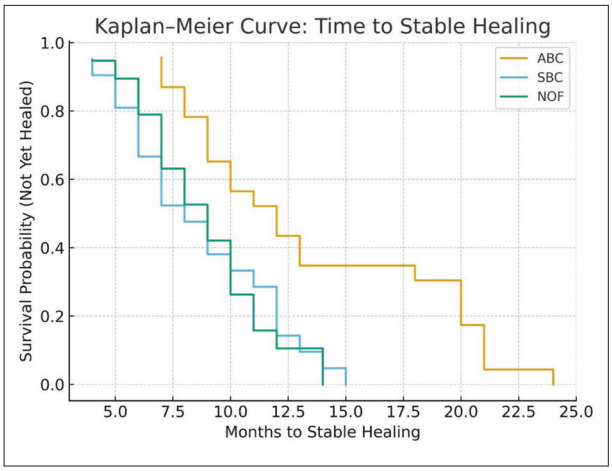

Figure 6. Kaplan–Meier curve: time to stable healing by lesion group

ABC – aneurysmal bone cyst; SBC – simple bone cyst; NOF – non-ossifying fibroma

The Kaplan–Meier curve offers a visual representation of the duration required to achieve stable healing in the ABC, SBC, and NOF groups. ABC lesions heal more slowly and unpredictably than SBC and NOF, with approximately 30% taking over 20 months to show stable radiographic healing. SBC lesions usually stabilize in 7–15 months, with approximately 80% showing variable healing. NOF lesions are more consistent, with approximately 95% stabilizing in 10–12 months and showing clear radiographic improvement.

This study evaluated the healing and complication rates for each lesion type and treatment. No major infections or adverse reactions were observed with the β-TCP grafts. For ABC, six out of 23 surgical patients had recurrences (26%) after an average of 16.7 months, and one had a pathological proximal humeral fracture. In SBC, three of 21 treated patients experienced recurrence (14.2%) after approximately 13.8 months, with one pathological distal femoral fracture reported. NOF cases showed no recurrence or significant complications.

DISCUSSION

This study evaluated the healing patterns, morphometric predictors, and recurrence rates of ABC, SBC, and NOF treated with curettage and β-TCP grafting. Although all three are benign pediatric lesions, they demonstrate distinct biological behaviors and postoperative consolidation profiles.

Demographic and anatomical features

The age distribution of our cohort (10–12 years) aligns with the known peak incidence of benign cystic and fibro-osseous lesions in late childhood and early adolescence [3, 11, 12]. ABC and SBC showed male predominance, consistent with epidemiological data reporting a higher incidence in boys. In contrast, NOF in our cohort showed female predominance, likely reflecting sample characteristics rather than a true epidemiological shift. Lesion locations were typical: ABC and SBC primarily affected the proximal humerus and femur, while NOF was confined to the femur and tibia, consistent with its preference for metaphyseal regions near the knee. Mechanical stress and high activity in boys during rapid skeletal growth can interfere with bone remodeling, making them more prone to metaphyseal lesions, benign bone cysts or fibrous conditions, and fractures [13, 14].

Healing outcomes and stable healing time

Healing rates were high across all groups (ABC 73.9%, SBC 85.7%, NOF 100%), aligning with published outcomes, where ABC demonstrated the greatest variability (65–90%), SBC typically achieved 75–90% healing, and NOF showed near-universal resolution. ABC heals more slowly and variably, reflecting its biologically active and expansile nature and the frequency of cortical destruction. SBC showed rapid and predictable healing, with most cases stabilizing within 12 months, paralleling the existing literature that highlights mechanical recovery once cortical integrity improves. NOF heals completely and predictably, as it is self-limiting [15, 16].

ABC had the slowest and most variable healing (mean 13.5 months, range 7–24 months). SBC and NOF stabilized at similar rates, with median healing times of eight and nine months, respectively. ABC requires extended osteoconduction and shows unpredictable bone growth after curettage. SBC typically heals 6–12 months post-curettage and grafting, although complications such as lesion expansion or delayed healing may occur. NOF consistently heals within 10–12 months, confirming its status as a self-limiting, reliably remodeling lesion [17].

The Kaplan–Meier further illustrated these differences: ABC demonstrated prolonged stabilization with subset healing beyond 20 months, SBC improved steadily during the first year, and NOF showed a uniform, self-limiting course.

The Kaplan–Meier curves in our study highlighted the unique healing patterns of benign pediatric bone lesions. Healing time decreased from ABC to SBC to NOF, reflecting biological differences and aggressiveness of the lesions.

Morphometric predictors of healing

Morphometric characteristics play a crucial role in determining healing kinetics. In ABC, a larger lesion volume and greater lesion-to-bone relation length were associated with delayed consolidation, supporting reports by Dormans et al. [17] and Restrepo et al. [12], who observed that cortical thinning and extensive cystic activity prolonged graft incorporation due to sustained biological turnover.

SBC showed the strongest morphometric correlations, mainly with tumor volume and relation length, indicating that mechanical factors are crucial for healing. Larger lesions increase biomechanical demands and the risk of delayed recovery or fracture [18]. Younger patients recovered faster, supporting earlier research that pediatric bones remodel more efficiently under stress [10, 14].

NOF exhibits unique remodeling, with healing being minimally affected by tumor size, location, or age. Studies have indicated that outcomes rely more on biological maturation than on graft mechanics [19].

Complications and recurrence

No significant early or late postoperative complications were observed, except for one pathological fracture in the ABC group and one in the SBC group, findings consistent with the published literature [20].

Our ABC recurrence rate was 26%, with a mean recurrence of 16.7 months, aligning with previous pediatric reports of 20–30% [17]. Most recurrences occur between 12 and 24 months, but some are observed up to 4–5 years, highlighting the need for prolonged follow-up [15]. Long-term studies (mean follow-up: 81 months) further emphasize the importance of extended monitoring for late recurrences and complications [21].

Recurrence in our SBC series was 14% with a mean time of 13.8 months, aligning with published data and likely due to residual mechanical stress and lesion size [4, 18, 22]. Larger SBCs have higher recurrence rates (41.7%), and Flont et al. [23] recommend follow-up beyond three years for early detection and management.

No recurrences or complications were reported for NOF, reflecting its benign nature and lack of aggressive postoperative outcomes in existing literature.

Comparison of synthetic grafting outcomes

β-TCP was chosen for its safety, biocompatibility, osteoconductivity, and predictable resorption, enabling effective healing. Our study found no graft-related complications, supporting β-TCP as a treatment for pediatric lesions requiring structural support [24].

Clinical implications

This study highlights the importance of lesion-specific management. The natural characteristics of the lesion play a significant role in healing patterns.

- ABC requires rigorous long-term monitoring because of its biological aggressiveness and risk of late recurrence;
- SBC benefits from early mechanical stabilization and shows rapid healing when the cortical support is restored;
- NOF requires minimal intervention and reliably remodels even when grafted, making extensive postoperative imaging unnecessary in most cases.

Morphometric assessment, particularly lesion volume and cortical involvement, provides valuable prognostic information and should be incorporated into treatment planning and follow-up scheduling.

Strengths and limitations

The strengths of this study include consistent surgical technique, standardized radiologic evaluation using multiple scoring systems, and the use of stable healing time as a quantitative endpoint. Limitations include the retrospective design, modest sample size, and lack of comparison with other graft types or adjuvant therapies. Future prospective studies with larger cohorts and comparative grafting techniques are warranted to refine the treatment guidelines.

CONCLUSION

Synthetic β-TCP demonstrated safe and effective integration across all groups, supporting its use as a valuable biomaterial for pediatric orthopedic reconstruction. Healing outcomes after curettage and β-TCP filling in pediatric benign bone lesions are strongly influenced by the lesion type and morphometric characteristics. ABC have the longest and most variable healing times and the highest recurrence rates, whereas SBC heal moderately. NOF remodel predictably, and healing remains biologically stable. Lesion-specific approaches are crucial. Patients with larger ABC and SBC require careful planning, fracture prevention, and follow-up for at least two years. In contrast, NOF generally requires minimal postoperative surveillance.

Further studies with larger cohorts are required to validate these findings and optimize the management protocols for each lesion type.

Conflict of interest: None declared.

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Ретроспективно поређење резултата реконструкције анеуризмалних и солитарних коштаних цисти и неосификујућег фиброма код педијатријских пацијената применом синтетског коштаног графта (*β-TCP*)

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САЖЕТАК

Увод/Циљ Анеуризмалне коштане цисте (АКЦ), једноставне коштане цисте (ЈКЦ) и неосификујући фиброми (НОФ) чести су у педијатријском узрасту. Стандардни третман подразумева киретажу са попуњавањем коштаног дефекта. Избор графта и хируршки приступ зависе од типа лезије. Иако се синтетски бета-трикалцијум-фосфат (*β-TCP*) користи као биокомпатибилни графт, његова ефикасност у педијатријској популацији није потпуно разјашњена. Циљ ове студије био је да процени радиографско зарастање, инкорпорацију графта, компликације и учесталост рецидива после киретаже и попуњавања *β-TCP* гранулама.

Методе Ретроспективно су анализирана 63 пацијента (23 АКЦ, 21 ЈКЦ, 19 НОФ) лечена у дечјој болници у периоду од 2015. до 2023. године. Сви пацијенти су подвргнути интралезионалној киретажи са *β-TCP* графтовањем. Зарастање је оцењивано применом *Wu*, модификованих *Irwin* и *Neer* критеријума, а анализирани су и време до постизања стабилног зарастања, рецидиви, компликације и морфометријски предиктори.

Резултати Радиографско зарастање постигнуто је код 73,9% АКЦ, 85,7% ЈКЦ и 100% НОФ. Стабилно зарастање остварено је за 13,5 ± 5,7 месеци код АКЦ и за око 8,7–8,8 месеци код ЈКЦ и НОФ ($p = 0,0004$). АКЦ је показала успоренije и варијабилно зарастање; веће и лезије са већим односом лезија–кост спорије су зарастале код АКЦ и ЈКЦ. Рецидиви су забележени код 26% АКЦ (просечно 16,7 месеци) и 14% ЈКЦ (просечно 13,8 месеци), док код НОФ није регистрован ниједан рецидив.

Закључак *β-TCP* графтовање представља безбедну и ефикасну опцију у лечењу бенигних коштаних лезија код деце, али се обрасци зарастања значајно разликују међу типовима лезија. АКЦ захтева продужено праћење због већег ризика од рецидива; ЈКЦ најчешће постиже стабилизацију у првој години; НОФ поуздано ремоделира независно од величине. Усмерено праћење високоризичних лезија може побољшати исходе и смањити непотребне интервенције.

Кључне речи: анеуризмална коштана циста; једноставна коштана циста; неосификујући фибром; бета-трикалцијум-фосфат; дечја ортопедија; коштани графт

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Anxiety and depression in children with new-onset epilepsy: parent *vs*. child perspectives – six-month follow-up study

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SUMMARY

Introduction/Objective Common internalizing symptoms, such as anxiety and depression, in school-age children with new-onset epilepsy, may not be immediately evident and can be misinterpreted by parents. This study compares how school-age children with epilepsy and their parents view the children's anxiety and depression, following previous findings that internalizing symptoms are common six months after diagnosis.

Methods The study was conducted at the University Children's Hospital in Belgrade, Serbia, with assessments performed after diagnosis and again six months later. After obtaining informed consent, children and their parents independently filled out the Revised Children's Anxiety and Depression Scale (RCADS) questionnaire. Paired t-tests assessed changes in scores from baseline to six months, with $p < 0.05$ considered significant.

Results Throughout the entire group over the six-month follow-up period, all RCADS scores, as well as self-report and parent ratings, showed significant increases. The most notable increases are seen in the subscales of social phobia from self-assessment and panic disorder from parent assessments ($p < 0.01$).

Conclusion Six-month follow-up of internalizing symptoms in our cohort of school-age patients with new-onset, uncomplicated epilepsy has shown that their parents are not sufficiently aware of the symptoms of social phobia, separation, and generalized anxiety, as well as obsessive-compulsive disorder, although their symptoms become significant after six months. Parents need to be taught to recognize their children's emotions and to seek psychological help when necessary.

Keywords: new-onset epilepsy; parents; children; anxiety; depression

INTRODUCTION

Epilepsy in the pediatric population is recognized as more than a mere tendency of the brain to generate epileptic seizures. Children with epilepsy frequently face psychological challenges, which also deeply affect their parents and families [1]. Special challenges are anxiety and depression, which may be hidden at the beginning and often misunderstood by parents [2].

Perceptions of internalizing symptoms in children with epilepsy can vary between observers, with notable differences often seen between parental assessments and the child's self-reports. Parents tend to overlook psychological symptoms, while they are more likely to recognize behavioral disorders [3]. Reilly et al. [4] showed that symptoms of anxiety and depression from self-report questionnaires are more prominent than parent reports, especially in the areas of anxiety and somatization. Children reported sudden episodes of intense discomfort and a fear of losing control, while parents expressed concern about their children's emotional vulnerability and reactions following these episodes [5]. Conversely, Bal et al. [6] found that symptoms of anxiety and depression are consistent between parents and children. Kavanaugh et al. [7] also indicated that parents often underestimate symptoms of anxiety and depression in their children with epilepsy, though it remains unclear when these symptoms become more severe. Recognizing these symptoms is crucial because unrecognized symptoms could lead to other consequences, such as reduced quality of life and poor academic performance [8]. Reilly et al. [9] showed that parents' emotional and psychological state influences their perception of internalizing symptoms in children, with parents more often reporting such symptoms than the children themselves.

Earlier, we demonstrated that in school-aged children with new-onset, uncomplicated epilepsy, there are significant levels of internalizing symptoms after six months, mainly due to psychosocial factors at the start and, to a lesser extent, the adverse effects of anti-seizure medication (ASM) [10, 11]. Seizure control, quality

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of life, cognitive function, and behavioral issues did not influence the increase in anxiety and depression symptoms. When epilepsy is present, these challenges may further add to the burden on families, who are often already dealing with parental anxiety, family functioning difficulties, and stress related to the unpredictability of seizures [12]. However, to better support both children and parents, a broader perspective is necessary. Since issues may arise early during epilepsy, it is important to examine the background. Therefore, the present study aimed to systematically explore anxiety and depressive symptoms from the perspectives of children with epilepsy and their parents to help develop guidelines for preventing internalizing symptoms in children with epilepsy.

METHODS

The research was conducted at the University Children's Hospital in Belgrade, Serbia, during the first half of 2020. It was part of a larger research project that also examined quality of life, behavior, and cognition [10, 11]. Data collection was conducted using a test–retest design in two phases: the initial assessment at the time of epilepsy diagnosis and a follow-up assessment six months later. The baseline results obtained at diagnosis served as the control for comparison with those collected after six months. The inclusion criteria included school-age children with a newly diagnosed non-structural epilepsy (confirmed by electroencephalogram and brain magnetic resonance imaging), normal psychomotor and cognitive development until then, and no other chronic illnesses. Participants in the study were all children consecutively recruited.

Children and their parents, after signing informed consent, completed the Revised Children's Anxiety and Depression Scale (RCADS) during two visits. They completed the RCADS separately to prevent influence from one on the other.

The RCADS has both self-report and parent/guardian rating versions. Each version has 47 questions evaluating symptoms: 31 for anxiety, 10 for depression, and six for obsessive-compulsive disorder (OCD). All questions are on a Likert scale from 0 (never) to 3 (always), and the total score for each subscale is the sum of responses. Six subscales measure specific symptoms: social phobia, separation anxiety disorder, panic disorder, generalized anxiety disorder, depression, and OCD. There is also a total anxiety score (sum of the first four subscales) and a total internalizing symptoms score (sum of anxiety and depression). A higher score indicates increased severity of general and specific symptoms. Psychometric research has demonstrated that the questionnaire yields reliable and valid assessments of these symptoms, and the Serbian version was employed in this study [13].

Descriptive statistics included absolute values, percentages, mean values (M), and measures of dispersion such as standard deviation (SD) and standard error (SE). Inferential statistics involved Paired t-tests to examine differences in questionnaire scores at baseline (before) and after six months (after). Normality of the data distribution was assessed using the Shapiro–Wilk test. The effect sizes of significant changes were expressed using Cohen's d coefficient and interpreted as low (< 0.5), medium (0.5–0.8), or high (> 0.8) [10]. All analyses were performed with SPSS Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, IL, USA) and p-values of less than 0.05 were considered statistically significant.

Ethics: The study adhered to ethical principles and the Helsinki Declaration, following the decision of the Ethical Committee of the University Children's Hospital, University of Belgrade, Belgrade, Serbia (No: 13/208).

RESULTS

In the research, only adequately completed data obtained from completed questionnaires were analyzed. The Shapiro–Wilk test, accompanied by visual inspection of histograms and Q–Q plots, indicated that the data met the assumption of normality. After the second visit, data were available for 60 children and their parents, because three children were lost to follow-up and five needed another ASM after the initial therapy, which was the exclusion criterion. There was no statistical difference in the results of questionnaires between those who were excluded and the included children at the first visit, as well as in age, gender, number of seizures, or levels of intelligence ($p < 0.05$).

Demographic and basic clinical details are presented in Table 1. The average age of the respondents at the time of inclusion in the study was 12.32 (SD = 3.34) years, ranging 7–18 years (Table 1). Concerning the initial number of seizures before the introduction of ASM, a statistically significant reduction is observed after six months ($z = -4.52$; $p < 0.01$), which is highly clinically relevant ($r = 0.58$).

Table 1. Basic demographic and clinical data of the subjects

Parameters	At beginning M (SD), n = 68	After six months M (SD), n = 60
Age (SD), range (yrs)	12.32 (3.34), 7–18	12.45 (3.25), 7–18
Male/female, n (%)	38 (55.9)/30 (44.1)	34 (56.7)/26 (43.3)
Seizure control		
Complete	36 (52.9)	35 (58.3)
Partial	19 (27.9)	20 (33.3)
Poor	13 (19.2)	5 (8.3)

M – mean values; SD – standard deviation

Throughout the entire group over the six-month follow-up period, all RCADS scores, along with self-report and parent ratings, showed significant increases (Tables 2 and 3). The effect sizes are high for most scales ($d > 0.8$). The most notable increases are seen in the subscales of depressive disorder and social phobia from self-assessment, and panic disorder from parent assessments. Comparison between self-reported and parent-reported RCADS scores is presented in Figure 1.

Table 2. Self-report of Revised Children's Anxiety and Depression Scale questionnaire scores in the follow-up period (n = 60)

Subscale	At beginning M (SD)	After six months M (SD), d
Self-assessment		
Social phobia	4.90 (3.58)	9.12 (4.66)*, 1.22
Panic disorder	2.15 (2.48)	5.18 (4.39)*, 1.12
Separation anxiety disorder	1.85 (2.39)	3.48 (3.42)*, 0.88
Generalized anxiety disorder	2.57 (2.63)	5.25 (3.27)*, 0.83
Total anxiety disorder	11.47 (8.54)	23.03 (13.11)*, 1.30
Depressive disorder	2.50 (2.00)	6.77 (4.64)*, 1.81
Total internalizing	13.97 (9.66)	29.80 (16.76)*, 1.52
Obsessive-compulsive disorder	1.63 (2.58)	3.53 (3.28)*, 0.74

M – mean values; SD – standard deviation; d – Cohen's coefficient;
*p < 0.01 from paired t-tests

Table 3. Parent-report of Revised Children's Anxiety and Depression Scale questionnaire scores in the follow-up period (n = 60)

Subscale	At beginning M (SD)	After six months M (SD), d
Parent-assessment		
Social phobia	5.35 (3.01)	7.73 (4.25)*, 0.97
Panic disorder	1.42 (1.29)	3.25 (3.34)*, 1.27
Separation anxiety disorder	2.00 (2.55)	2.98 (3.67)*, 0.59
Generalized anxiety disorder	2.35 (1.81)	3.90 (2.74)*, 0.78
Total anxiety disorder	11.02 (6.05)	17.87 (10.88)*, 1.22
Depressive disorder	2.93 (2.22)	6.15 (4.21)*, 1.81
Total internalizing	13.95 (7.49)	24.02 (14.33)*, 1.36
Obsessive-compulsive disorder	1.52 (1.64)	2.32 (2.38)*, 0.53

M – mean values; SD – standard deviation; d – Cohen's coefficient;
*p < 0.01 from paired t-tests

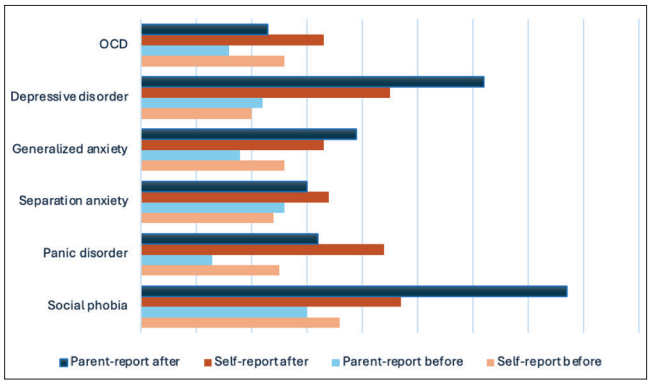

Figure 1. Comparison between Revised Children's Anxiety and Depression Scale scores from self-report and parent report

DISCUSSION

This is the first study to compare the experience of internalizing symptoms in children with new-onset epilepsy immediately after diagnosis and after six months, from both parents' and children's perspectives. We found that even at the start, parents tend to downplay their children's anxiety symptoms, which tend to become more noticeable over six months. The findings are concerning, especially as social phobias become the most common anxiety symptom in children after follow-up. Wagner et al. [14] have shown that 20% of school-aged children with epilepsy were diagnosed with clinically significant social phobia, developing after several years of living with epilepsy, primarily from the children's perspectives. Considering that social phobias in children involve an intense and persistent fear of social situations where the child expects evaluation, rejection, or ridicule, and can severely affect the child's emotional development, self-confidence, and daily functioning, particularly in school and social settings, our results highlight the need for prevention [15]. Although parents might not realize that social situations can easily trigger anxiety in their children with epilepsy, the epileptologist guiding the child has a responsibility to address it.

In the study by Redecker et al. [16], panic disorder was the most common anxiety disorder among children with epilepsy. However, we found that parents are less aware of panic disorder initially compared to children. After six months, this dynamic shift and the most significant change in children's experience of panic disorder are observed in their parents, as if they become more aware, possibly because panic disorder is more clinically visible than social phobias. This can be explained by studies from Kwong et al. [17] and Kim and Kim [18], which showed that children exhibited more severe symptoms of social anxiety and irritability, while parents focused more on the more obvious clinical symptoms.

On the other hand, the child's separation anxiety is more visible to the parents at the beginning and more pronounced after six months, which is not surprising considering that it is most often directed towards the parents. In a longitudinal study of children with recently diagnosed epilepsy, nearly one-third of children met the requirements for separation anxiety, which is significantly higher than in the general population, according to parents' reports. In contrast, the prevalence of other anxiety disorders was substantially lower, making separation anxiety the most common single type of anxiety early in the course of illness [19]. It should be highlighted that separation anxiety persists into adulthood, and overprotection is a predictor of lower quality of life [20]. Separation anxiety also reduces the caregiver's independence, highlighting a two-way relationship [21].

What is also surprising is that children are more aware of their OCD symptoms. In analogous research on pediatric OCD, parents report significant distress, uncertainty about their child's future, and burden, especially when symptom severity is high and family accommodation occurs [22]. In cases of comorbid epilepsy and pediatric OCD, parents often face compounded emotional strain, not only from managing the neurological unpredictability of epilepsy, but also from navigating their child's OCD symptoms [23]. It seems that in the case of children with epilepsy, obsessive thoughts are also conscious, and that at the beginning, and especially after six months. OCD includes not only thoughts, but also actions, which parents can misinterpret as perfectionism [24]. That emphasizes the need for psychological support. Kaşak et al. [25] found that having a child with epilepsy negatively affects parents' mental health, relationship between the parent and the child, family dynamics, and parental coping styles, so a bidirectional relationship is clear.

Even after six months, when it is significantly expressed, parents notice less generalized anxiety than their children, which is not surprising since generalized anxiety can often be hidden. Generalized anxiety disorder in children is characterized mainly by difficult-to-control worries about everyday topics (such as school performance, health, and family dynamics), often accompanied by somatic symptoms like tension, fatigue, and disturbed sleep, which seriously affect their daily functioning and psychological well-being [15].

Parents may mistake it for depressive symptoms, which, according to our results, are initially more noticeable to them than from the patients' perspective. However, after six months, children become very aware of their depressive feelings. Bearing that in mind, there is growing concern: does a parent's expression of a child's feelings influence them, passing their worries to the child? This aligns with findings from Rosic et al. [26], which show that in longitudinal studies, children's depressive symptoms are reflected in their assessments, while they initially exhibit more anxiety; conversely, parents display the opposite pattern. Additionally, Idowu et al. [27] demonstrated that over time, children's and parents' perceptions of anxiety symptoms become similar, indicating that the symptoms become interconnected.

Our findings extend previous evidence showing only moderate agreement between children and parents when reporting anxiety and depressive symptoms in pediatric epilepsy by demonstrating that these discrepancies persist and become more clinically relevant over time [28]. Reliance on parental reports alone may therefore result in under-recognition of emerging internalizing symptoms, notably less observable anxiety domains. Routine inclusion of standardized child self-report measures during early follow-up may facilitate timely identification of psychopathology. Integrating systematic psychological screening and targeted parent psychoeducation into standard epilepsy care could improve long-term mental health and overall clinical outcomes.

Unfortunately, in this study, we did not compare psychological difficulties in children with other chronic illnesses. We know that parents of children with epilepsy fear night seizures and separation, such as during school trips, and their children share these fears. However, is this fear more intense than that experienced by parents and children with asthma and diabetes mellitus? Additionally, it has been shown that parents of children with diabetes face depression or psychological stress, worries about long-term recovery, complications, and daily disease management [29]. Consequently, depression and anxiety are more common in these children than in healthy peers: about one-third display depressive symptoms and anxiety, which can significantly complicate the disease course, as psychosocial stress also worsens metabolic control and quality of life [30]. Similarly, children with asthma, along with their parents, fear asthma attacks, worry about treatment, symptoms, and physical limitations such as sports and school activities, and often experience anxiety and depression [31]. Children tend to exhibit anxiety symptoms, especially related to attacks or activity restrictions; they also face a risk for depression, although parental attitudes may influence how these symptoms are perceived [32]. Nonetheless, we can agree that no pediatric chronic illness is associated with stigma to the extent that epilepsy is.

CONCLUSION

A six-month follow-up of internalizing symptoms in our cohort of school-age patients with new-onset, uncomplicated epilepsy revealed that their parents are not sufficiently aware of symptoms like social phobia, separation anxiety, generalized anxiety, and OCD. However, these symptoms become more pronounced after six months. In this study, we did not conduct a more detailed analysis of how parents' experiences affect their children's symptoms, which we consider a significant limitation. Additionally, we did not examine other factors related to epilepsy or background factors that might contribute to internalizing symptoms. Nonetheless, we want to highlight the importance of parent education. Psychologists and epileptologists also play a role in helping parents understand their child's emotional experiences while managing epilepsy.

Conflict of interest: None declared.

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Анксиозност и депресија код деце са новодијагностикованом епилепсијом из перспективе деце и њихових родитеља – студија шестомесечног праћења

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САЖЕТАК

Увод/Циљ Уобичајени интернализујући симптоми, попут анксиозности и депресије, код деце школског узраста са новодијагностикованом епилепсијом често нису очигледни и родитељи их могу погрешно протумачити.
Ова студија упоређује перспективе деце школског узраста са епилепсијом и њихових родитеља у погледу доживљаја анксиозности и депресије код деце, имајући у виду сазнања да су интернализујући симптоми чести шест месеци након постављања дијагнозе епилепсије.

Методе Студија је спроведена у Универзитетској дечјој клиници у Београду, кроз две истраживачке визите: непосредно након постављања дијагнозе и шест месеци касније. Након добијања информисаног пристанка, деца и њихови родитељи су самостално попунили стандардизовани упитник Ревидиране скале анксиозности и депресије код деце. Упареним *t*-тестовима процењиване су промене у резултатима упитника од почетка до шест месеци, при чему се $p < 0,05$ сматрало статистички значајним.

Резултати У целој групи током шестомесечног периода праћења, сви резултати Ревидиране скале анксиозности и депресије код деце, укључујући резултате самопроцене и процене родитеља, показали су значајно повећање. Најзначајнија повећања су примећена у подскалама социјалне фобије на основу самопроцене и паничног поремећаја на основу процене родитеља ($p < 0,01$).

Закључак Шестомесечно праћење интернализујућих симптома у нашој кохорти пацијената школског узраста са новооткривеном, некомпликованом епилепсијом показало је да њихови родитељи нису довољно свесни симптома социјалне фобије, сепарационе и генерализоване анксиозности, као и опсесивно-компулзивног поремећаја, иако симптоми постају израженији након шест месеци. Родитељи треба да буду упућени у препознавање емоција своје деце како би могли да потраже психолошку помоћ када је то потребно.

Кључне речи: новооткривена епилепсија; родитељи; деца; анксиозност; депресија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Newly developed three-dimensional animation of uterine closure according to the modified technique of cesarean section by Vejnović

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SUMMARY

Introduction/Objective Information provided as both visually and verbally is learned better than information received through either pathway alone. Animation ensures this dual coding. It gives us the possibility to display abstract details of operation that cannot be observed otherwise. This is especially important for an operation as common as cesarean section (CS). Although CS is the most common operation in women, animations of uterus suturing are very few. The aim was to develop a 3D-animation of uterus suturing in CS by Vejnovic modification.

Methods The project was done 2015–2018 as collaboration between the Faculty of Medicine and the Faculty of Technical Sciences at the University of Novi Sad. The development of the animation included following steps: filming simulation of uterus suturing on sponge model, interdisciplinary discussion, making storyboard, recording sound, animating using *Blender* software (Blender Online Community, Amsterdam, Netherlands).

Results The animation lasts for 10 minutes and 17 seconds. The film was designed to be self-explanatory. In the film uterus suturing technique was presented in detail. Important segments are additionally marked in the video and stressed in the background audio explanation. The educational 3D animation of uterus suturing in cesarean section – modification Vejnovic is available from: https://youtu.be/zY98Mzyupx8.

Conclusion The animation shows advantages and benefits in surgery education, which might increase safety for the patient and the surgeon. The animation could help standardize the CS technique and disseminate precise surgical instructions, ensuring the same obstetrical outcomes.

Keywords: cesarean section; animation; uterus closure; suturing; technique; modification

INTRODUCTION

Educational animations are animations produced for the specific purpose of fostering learning. The popularity of using animations to help learners understand and remember information has greatly increased since the advent of powerful graphics-oriented computers. However, animations were used in early instructional medical films as early as 1920s. The animation enabled presentation of details and surgical sequences that were otherwise impossible to capture on film [1]. Quirino Cristiani was a pioneer of animated cinema. He directed the world's first feature-length animated film (*El Apóstol*, 1917). In 1925, he collaborated with two famous surgeons, Jose Arce and Oscar Ivanissevich, who wanted an animated film showing the technique of their work. They made two movies: *Gastrotomia* (1925) and *Rinoplastia* (1925), which Sorbonne University later bought for educational purposes. The films were praised for accuracy and realism [2]. In late 1920s, American College of Surgeons and Eastman Kodak made series of medical films and placed medical motion pictures at the center of surgical training [1]. *The Story of Menstruation* [3] is a 1946 10-minute American animated film produced by Walt Disney Productions. It was commissioned by the International Cellucotton Products Company and was shown in a non-theatrical release to approximately 100 million American students in health education classes [4]. Over time animation has become a powerful tool in education of both lay population and medical professionals. The reason for this is that animation combines two types of information that people receive and process via two distinct but interdependent pathways. The first pathway is for verbal inputs, whereas the second is for visual inputs. These pathways are additive, which means that the information provided as both images and words will be better learned than the information received through either pathway alone [5, 6].

There are over 200 video recordings and animated videos related to cesarean section available on YouTube platform [7]. However, there are few computer animations explaining the surgical procedures in cesarean section. The great majority of them were made to provide

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a description for the patients rather than detailed information for medical professionals. Some of them are very sophisticated, others are simplified. Two interactive animations can be found on the following links:

http://www.surgerysquad.com/surgeries/virtual-c-section-cesarean-surgery/,

https://www.touchsurgery.com/simulations/ain_csection.

Both of them show steps of cesarean section overall. The Surgery Squad aims to educate visitors through an interactive, personalized patient education experience. Patients can play a game about cesarean section. Through the game they get information about preoperative procedures, anesthesia, steps of operation and recovery. The presentation of operative steps is simple. The closure of the fascia layer is not included.

On Surgery Squad website visitors can also find FAQ about cesarean section and watch a live-surgery video.

The Touch Surgery platform is an interactive surgical simulator for healthcare professionals. It provides a realistic and detailed guide to the steps of different procedures. Users can quickly gain an insight into surgery watching an animation or a live surgery recording, and reading explanations written in the attachment. They can also test their knowledge and rehearse for surgery.

Animations of a new uterine suturing techniques with barbed monofilament suture were presented by Alessandri et al. [8], and from the other side by Ishchenko et al. [9] at the Third Regional Scientific Forum of Obstetricians and Gynecologists in 2019, but only the articles without videos have been published.

There are currently no available educational animations designed for medical professionals in order to elaborate on uterus suturing to the finest detail, so that it can be reproduced in clinical practice.

Cesarean section represents the most common operation in women. At the same time, it is probably an operation with the greatest performance variability, which is often overlooked. The cesarean section technique, including uterus suturing, varies dramatically. Even within the same hospital, two surgeons perform different techniques. It was hypothesized by Vervoort et al. [10] that one of the factors for developing cesarean scar defect is the way the uterus was closed. And cesarean scar defect is associated with complications in future pregnancies such as scar dehiscence, uterus rupture, placenta previa, *placenta accreta spectrum*, and scar pregnancy which can all contribute significantly to maternal morbidity and mortality [11]. There are plenty of scientific papers comparing the quality of the uterus incision site and complications depending on different uterus closure techniques.

Vejnovic modification of uterus suturing in cesarean section has been shown to preserve the thickness of the lower uterine segment measured intraoperatively in subsequent cesarean section, have less scar dehiscence and hysterectomies due to *placenta accreta spectrum* [12] and make smaller and fewer cesarean scar defect [13].

This is why the author of the modification decided to make an educational tool and provide a detailed explanation of his technique, not only to his trainees, but to all colleagues worldwide.

The aim is to standardize the technique of uterus closure in order to achieve reported outcomes in wider population. Increasing the patients' safety was the underlying incentive for creating an interdisciplinary team combining the expertise of obstetricians and professionals who deal with computer visualization, especially computer graphics.

The aim of this paper was to present a newly developed 3D animation of uterine closure by a modified technique of cesarean section – modification Vejnovic, and to discuss other available educational animations of uterus suturing.

METHODS

The development of the educational 3D animation lasted from 2015–2018 within the project "Interactive educational 3D simulation of uterus suturing during cesarean section – modification Vejnovic" granted by the Provincial Secretariat for Science and Technological Development of the Autonomous Province of Vojvodina. The project was done as collaboration between the Faculty of Medicine and the Faculty of Technical Sciences at the University of Novi Sad. The development of animation took several steps.

The first step was creating a storyboard. A storyboard is a graphic organizer in the form of illustrations or images displayed in sequence for the purpose of pre-visualizing a motion picture, animation, motion graphics or interactive media sequence. It constituted the pre-production phase of animation development.

The initial data were obtained by making a high-resolution film in which an obstetrician, instead of repairing the uterus, sutured a sponge model of the uterus that was made by the authors specifically for this purpose.

There were several reasons for this. First, when suturing the sponge model, the whole procedure was performed in a relaxed atmosphere. There was time to ask questions and discuss important aspects of the technique in order to familiarize the non-medical members of the team with the problem. In a real operation, the obstetrician must perform cesarean section in the shortest time, because of the bleeding and other risks for the patient.

The second reason was that in a real operation, the blood reduces visibility and transparency. Finally, in an operating theater the procedure is carried out by two surgeons, who stand on either side of the patient with other medical personnel (scrub-nurse, neonatologist, anesthesiologist) also present, thus making a very crowded scene. The position of the camera in such a situation would be suboptimal and would, therefore, result in bad footage.

Once the sequence of the uterus suturing was captured, from a few iterations, the first version of the storyboard was drawn. It was reviewed by the medical members of the team. Several corrections were made to the storyboard prior to finalizing the version that was used for the animation.

The comments corresponding to individual drawings, which help every reader, regardless of whether they are a medical professional, understand the procedure of uterus

closure in cesarean section – modification Vejnovic formed an integral part of the storyboard. These comments also formed the basis for the text that was prepared to be narrated in the background of the animation. In addition, the background text included important tips and observations that should help the learner to adopt the technique correctly. The text was recorded as an audio file.

The sound was recorded by a portable recorder ZOOM H6 (Zoom Corporation, Tokyo, Japan) that has six interchangeable input capsules, which makes the device the ultimate recorder for film, video, podcast and music. Raw sound processing was done in Izotope RX (iZotope, Cambridge, MA, USA), which is the industry leader in audio repair and postproduction job. Sound and image compositing was done in Steinberg Cubase software (Steinberg Media Technologies GmbH, Hamburg, Germany).

For the realization of the project's graphical elements the Blender software (Blender Online Community, Amsterdam, Netherlands) was used [14]. The Blender is an open-source software and was used for modeling, animation, simulation, rendering, compositing and editing (Figure 1).

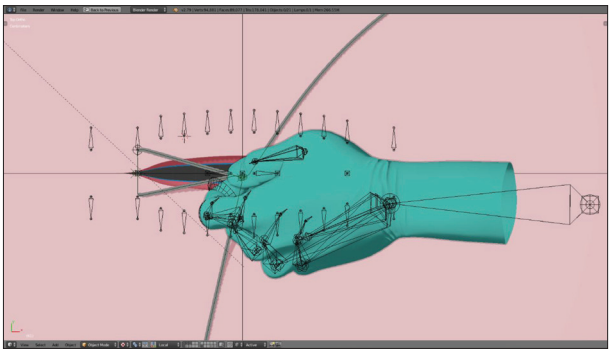

Figure 1. View of the working environment in the program *Blender* (Blender Online Community, Amsterdam, Netherlands), in which the tissue is seen with the rig, a thread with control objects and a hand with its rig

The results of the present paper were shown in the form of a storyboard and a 3D animation film.

Ethics: Ethical approval and informed consent were not needed for this research, as the entire process was performed using sponge models and computer programs, and did not involve patients.

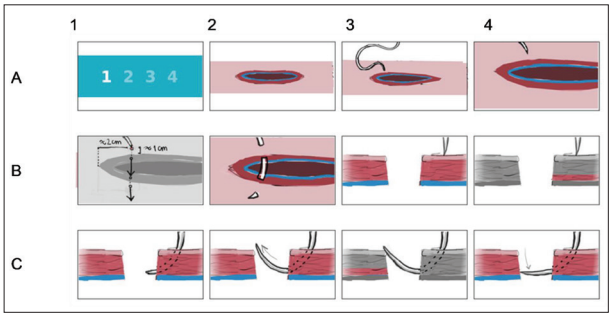

Figure 2. The first step of the repair of the uterus; important detail: the approximation of the uterine layers is better when whole thickness of the myometrium is involved into the stitch and when decidual layer is avoided; to achieve this needle should enter at the junction of serosa and myometrium, involve rich bite of myometrium and exit at the junction of myometrium and decidua from one side, then enter decidua-myometrium junction from the other side, take rich bite of myometrium and exit at the myometrium-serosa junction

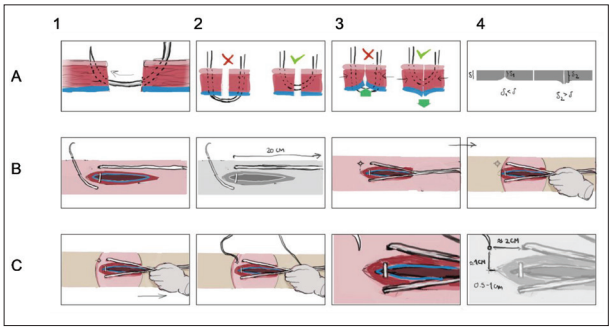

Figure 3. Creating initial suture; important detail: the first stitch is placed around 2 cm medial to the corner of the incision; thread is used as an instrument to visualize the corner of the incision and complete Z stitch safely placing the second stitch lateral to the corner in a healthy part of the wall

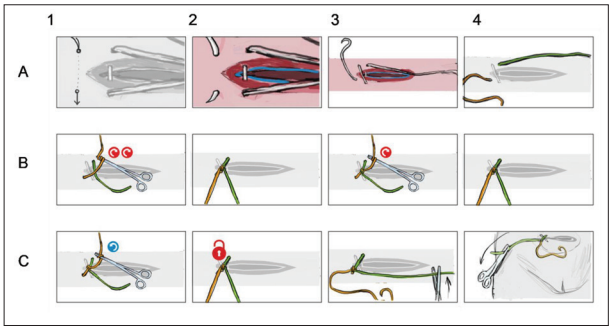

Figure 4. Creating the first knot; important detail: the knot of the first Z stitch should lie down at the cranial-medial point of the stitch if the operator works from the left side of the patient; around 10 cm of free end of the thread should be marked with Pean instrument in order to be used later

RESULTS

According to Vejnovic modification of cesarean section, there are four steps in closing the uterus incision, resulting in a modified suture, which gradually compresses the incision of the uterus. In this manner the length of the incision already intraoperatively becomes about half the size it was. This helps not only to ensure good hemostasis and uterine closure at the moment of operation, but also to maintain satisfactory approximation of the whole thickness of the uterine wall in the first days of puerperium when the uterine involution is the most prominent and the healing process is at its most vulnerable stage. It is particularly important to preserve the thickness of the lower uterine segment and thus reduce the risk of complications in the subsequent pregnancies.

The storyboard of uterus suturing in cesarean section – modification Vejnovic is presented in Figures 2–12.

The 3D animation film lasts for 10 minutes and 17 seconds. It took one month per minute on average to develop the animation. The film was designed to be

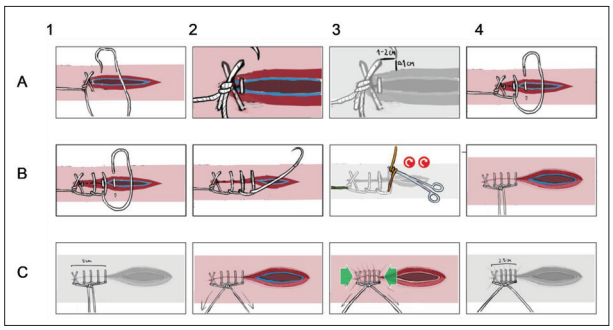

Figure 5. Making the first running-locked suture; important details: three running-locked sutures are placed towards the midline; the needle should exit from the opposite side of the incision compared to the knot of initial Z stitch; then the knot is tied using end of the thread with the needle and free end of the thread previously marked with Pean; by tightening the knot, the distance between the sutures is reduced

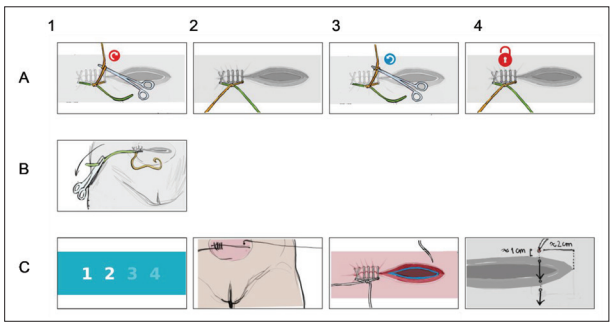

Figure 6. Finishing the first step and starting the second step of the repair of the uterus; important detail: the free end of the thread is marked with Pean; the end of the thread with the needle is left without cutting and it will be used in third step; the second step is started using a new thread

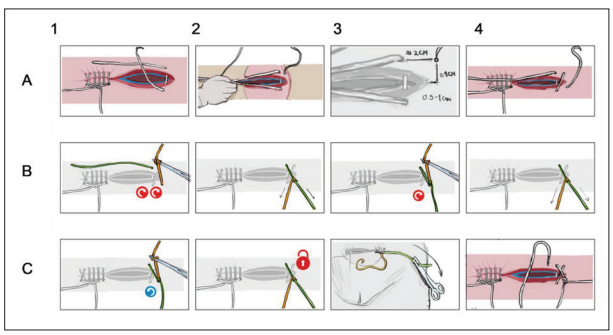

Figure 7. The second step – creating initial knot on the opposite angle of the incision; the whole procedure is the same as the first step of the repair of the uterus, except everything happens as a mirror image

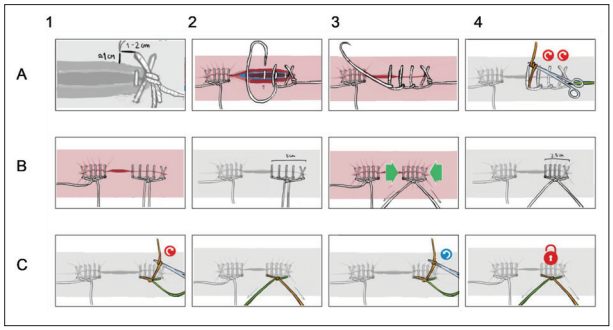

Figure 8. Making running-locked suture on the opposite angle of the uterine incision

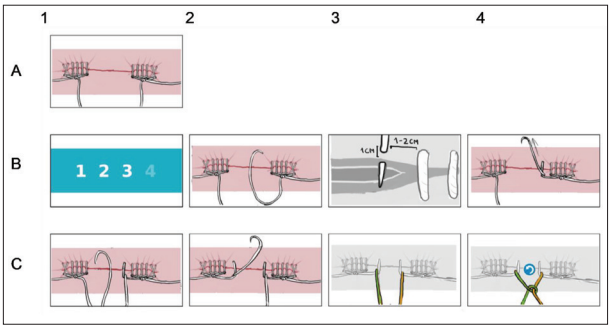

Figure 9. The third step of the repair of the uterus; the third step comprises the closure of the middle part of the incision using one to two running-locking sutures from each side

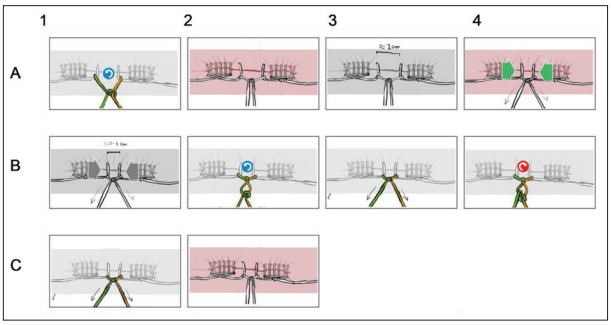

Figure 10. Making a knot in the central part of the incision; the central knot is tied using end with the needle of both threads

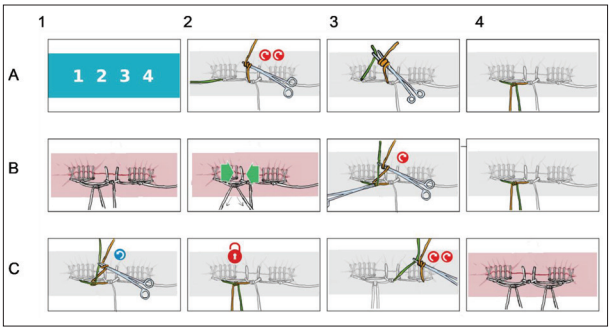

Figure 11. The fourth step of the repair of the uterus; important detail: during this step, the final shortening of the length of the sutured incision is achieved; this is done by tying one end of the thread with a needle from the middle to the free end of the thread in the corner of the incision; it is done from each side

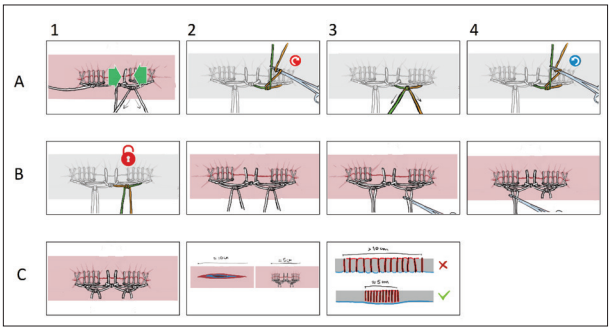

Figure 12. Finishing the repair of the uterus; this part of the storyboard shows final result of the uterus suturing according to Vejnovic modification; important effects are that the uterine layers are well approximated and that length of the sutured incision is reduced by almost 50%; this will help to maintain the approximation of the uterine layers during the dynamic period of uterine involution and improve healing process

self-explanatory. In the film uterus suturing technique was presented in detail. Important segments are additionally marked in the video and stressed in the background audio explanation. The voiceover in animation was recorded in three languages: Serbia, English and Russian. The English version of educational 3D animation of uterus suturing in cesarean section – modification Vejnovic is available from: https://youtu.be/zY98Mzyupx8.

DISCUSSION

Studies have shown that using animated movies increases motivation for learning [15, 16]. Animations are especially useful when complicated spatial structures and dynamic processes are involved [15], which can be found in surgical procedures.

Yue et al. [17] analyzed 430 instructional medical animations. They investigated degree to which these teaching tools followed empirically established learning principles outlined in the cognitive theory of multimedia learning (CTML). Meeting three main goals of CTML (managing essential processing, minimizing extraneous processing and facilitating generative processing) in the development of animation would enhance learning outcomes. There are several strategies to meet the CTML goals: words accompanying an animation should be presented aurally instead of visually; animation should contain only educationally relevant pictorial and verbal information; on-screen text should not duplicate narration [17].

Striving towards CTML goals, one of the main tasks in developing our animation was to make an optimal balance between video and audio elements in order to achieve the best learning effect in the adoption of the new technique. Simplifying the visual representation of the target structures is helping to better identify only the important elements of the technique. Audio comments provide another way to highlight crucial details and complement the explanation which would be unnecessarily complicated if shown visually.

The most important details of uterus suturing by Vejnovic modification shown in animation could be summarized as following:

The entire thickness of myometrium should be included in suture to obtain better approximation of the layers. This is achieved by the needle entering at the junction of the serosa and myometrium, richly biting the myometrial tissue, and exiting at the junction of the decidua and myometrium.

Decidual layer should not be included in suture (less than 5 mm of decidua in not considered inclusion) to avoid edge eversion.

The length of the sutured uterine incision should be approximately 50% smaller than initially and the level of sutured uterine incision should be in the level of surrounding uterine wall not above it.

The biggest challenge in the production of graphic elements for us was the animation of the threads, because of the movement of the threads through specific pathways in the tissue, a large number of stitches, and thread tightening and binding of complex knots.

The animation of the threads could be performed by 3D animation, but such an animation involves setting a large number of key frames. It would require a rig with several hundred controls, which would be hard to use and the animation process would be extremely slow and impractical. For these reasons, instead of a complex animation, a computer threads simulation was used. The thread is basically a long, curved line which is divided into several hundred segments. This line was applied with *Soft body physics* from Blender software, which is usually used to simulate soft tissue in character animation. So, the line becomes flexible and it is influenced by gravity and collision with surrounding elements, but also with itself. By using *Soft body physics*, a precise control of the movement of the thread was achieved.

The sutured tissue was animated by 3D (complex) animation using the rig, because it is a practical and reliable way to be animated in cases there is no requirement for realistic behavior of the tissue. New objects for collision in the form of tubes through which the thread passes during suturing were added to the tissue and these tubes are not visible during the rendering process and final picture creating.

For rendering *Blender Internal renderer* was used. This was our choice because it was important to achieve transparency and clarity of the image instead of a photorealistic representation. This is an unrealistic type of renderer which makes it easy to achieve a stylized image look, resembling medical illustrations. Algorithm rendering takes place at a high speed and almost in real time.

Performing cesarean section is a skill every obstetrician must be familiar with. Surgery education is specific and training in the operating room on real patients cannot be fully replaced. Features and behavior of myometrial tissue while cutting and suturing can hardly be simulated. One can feel it only when operating on a real patient on their own. To prepare for this responsibility, it is important to adopt and understand as many details as possible before entering the operating theatre. Cesarean section training using videos, simulations on mannequins and computer-enhanced visual learning module improves knowledge and confidence levels among obstetrics residents [18, 19, 20]. However, even when assisting in cesarean section, or watching a live-surgery videos, one cannot gain a complete insight into the pathway of the needle through the tissue, the depth of the suture bites etc. Those shortages can be overcome using animation. This is the first animation explaining uterus suturing in cesarean section – modification Vejnović. It complements publications that have been published so far describing the modified technique [21, 22]. It is intended to be used as a part of the curriculum about cesarean section – modification Vejnović, which comprises lectures, animation, hand-on training on sponge models and live-surgery session.

CONCLUSION

We can conclude that, after extracting the newborn, suturing the uterus is the next most crucial step in the cesarean section. This is because it is important not only for the current pregnancy, but for the following pregnancies as well. From our point of view, the way of closing the uterus directly influences the healing process, and the incidence of acute and chronic complications. This is why the modification of uterine suturing represents the biggest value of Vejnovic modification.

Our animation has several advantages in medical education. Firstly, it does not take place in the operating theatre, where the benefit of the patient always stands before education. Secondly, it provides a young doctor with an opportunity to repeatedly see the procedure on the screen, while being able to enlarge or show in slow motion many segments of the operation. Finally, the whole procedure can be watched a countless number of times. This practically means that a young doctor will be present at the real operation only after familiarizing with almost the whole procedure in the virtual world. After that, during the actual operation, they will be able to elaborate on fine details together with a senior surgeon. On the other hand, the time an experienced surgeon spends on the education of young doctors is significantly reduced and the process of education significantly increases in efficiency, speed and quality.

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Authors' contributions: R. O., A. V., and T. V. contributed to the conception and design of the work. A. V. constructed sponge models. T. V. simulated uterus suturing on the sponge models. R. O. and I. K. recorded uterus suturing and made computer animation. N. K. and N. I. recorded the narrator's voice and processed the sound of the animation. R. O. and A. V. drafted the paper. T. V., N. I., and J. V. revised paper critically for important intellectual content. All authors approved the final version of the manuscript.

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Conflicts of interest: None declared.

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Новоразвијена тродимензионална анимација затварања материце применом модификоване технике царског реза по Вејновићу

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САЖЕТАК

Увод/Циљ Информације представљене визуелно и вербално боље се усвајају од оних које су приказане само једним од два начина. Анимација пружа ово двоструко кодирање и даје могућност за приказ апстрактних детаља операције који се иначе не могу уочити. Ово је посебно важно за учестале операције као што је царски рез. Иако је царски рез најчешћа операција код жена, постоји мали број анимација шивења материце. Циљ овог рада ј био развити 3Д анимацију шивења материце током царског реза по модификацији Вејновић.

Методе Пројекат је реализован у периоду од 2015. до 2018. године у сарадњи Медицинског факултета и Факултета техничких наука Универзитета у Новом Саду. Развој анимације обухватао је следеће кораке: снимање симулације шивења материце на моделу од сунђера, интердисциплинарну дискусију, израду сценарија (сториборда), снимање звука, анимирање помоћу софтвера Блендер (*Blender Online Community*, Амстердам, Холандија).

Резултати Анимација траје 10 минута и 17 секунди. Филм је дизајниран тако да се разуме без додатних објашњења. У њему је детаљно представљена техника шивења материце. Важни сегменти су додатно назначени у видеу и наглашени у позадинском гласовном објашњењу. Едукативна 3Д анимација шивења материце при царском резу – Вејновићева модификација – доступна је на: https://youtu.be/zY98Mzyupx8.

Закључак Анимација пружа предности и користи у хируршкој обуци, што повећава безбедност пацијента и хирурга. Могла би помоћи стандардизацији технике царског реза и ширењу прецизних хируршких упутстава, обезбеђујући исте акушерске исходе.

Кључне речи: царски рез; анимација; затварање материце; шивење; техника; модификација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Staging of relapsing-remitting multiple sclerosis – the promising role of the BDNF/VEGF ratio

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SUMMARY

Introduction/Objective Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) may play important roles in the development and monitoring of multiple sclerosis (MS). BDNF is a neuroprotective factor in the process of inflammation, degeneration, and demyelination in MS. Inflammatory cells stimulate angiogenesis in demyelinating lesions through the release of VEGF, which is a proinflammatory factor.

Methods The study included 86 subjects: 20 healthy individuals and 66 patients with relapsing, who were divided into three groups: patients in remission, patients at the onset of MS relapse, and patients at the end of corticosteroid therapy for disease relapse.

Results The study showed a statistically significant difference in BDNF concentration between patient groups at baseline and at the end of therapy for disease relapse, as well as a difference in VEGF concentration between groups. The BDNF/VEGF ratio was increased in patients in remission compared with the control group; this ratio decreased significantly in patients at the onset of MS relapse compared with patients in remission.

Conclusion This study describes the BDNF/VEGF ratio for the first time as a biomarker that may be of interest in well-controlled longitudinal studies for staging relapsing–remitting multiple sclerosis and evaluating the response to therapy during relapses.

Keywords: relapsing–remitting multiple sclerosis; BDNF; VEGF; BDNF/VEGF; CRP; IL-6

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated neurodegenerative disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration [1]. There are several clinical forms of the disease: relapsing-remitting (RR-MS), primary progressive (PP-MS), and secondary progressive MS (SP-MS). The most severe form of the disease is PP-MS, which occurs in 15% of patients. In 85% of patients, the disease manifests as RR-MS. The processes of deterioration (relapse) and improvement (remission) occur at different intervals. However, on average, 50% of patients with RR-MS show clinical signs of SP-MS after a period of 10 years. Additionally, some patients experience progression independent of relapse activity, a form of disease progression in which disability worsens without relapses or inflammatory activity, highlighting the neurodegenerative nature of the disease even in the absence of acute flare-ups [2].

Inflammation is the basis of the pathogenesis of MS. Inflammation causes demyelination, and autoreactive T lymphocytes play a leading role in initiating the disease. Autoreactive T lymphocytes are activated in the peripheral circulation due to a pathogen, where clonal expansion occurs. Activated autoreactive T cells infiltrate the CNS, where they upregulate proinflammatory mediators and activate microglia/macrophages, leading to inflammation and demyelination [3]. However, besides clonal expansion, there is a significant imbalance in T cell subtypes. Th1 and Th17 subtypes become dominant and lead to microglia and macrophage activation, secretion of proinflammatory cytokines, and thus contribute to the initiation and maintenance of inflammation. The functional activity of Treg cells becomes significantly reduced, and there is no adequate inhibition of autoreactive cell activation. The lack of effective Treg cells leads to a state of chronic inflammation [4].

Various biomarkers of inflammation provide information about disease progression, remission, exacerbation, and response to therapy. The immune system response includes the production of peptides, cytokines, and free radicals, as well as increased activity of various immune cells. Proinflammatory cytokines (IL-2, TNF-alpha, IFN-gamma, IL-17) dominate and contribute to the inflammatory process, while anti-inflammatory cytokines (IL-4, IL-10, IL-13) limit the inflammatory response [5]. In addition to acquired immunity, the role of the innate immune system should be emphasized. Microglia, the primary resident immune cells of the CNS, play a pivotal role in

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neuroinflammation, tissue repair, and neural homeostasis, and their activity is altered in MS. However, under the influence of proinflammatory cytokines, microglia can also lead to neuron and oligodendrocyte damage. They increase the production of IL-6, IL-12, IL-23, and thus enhance the activation of Th1 and Th17 cell subtypes. Additionally, they begin to release reactive oxygen and nitrogen species, leading to oxidative stress [6]. Chronic inflammation leads to the overproduction of reactive oxygen and nitrogen species, which disrupt homeostasis and damage axons. Free radicals damage mitochondrial membranes, DNA, and respiratory chain enzymes. Damaged mitochondria, besides producing less ATP, produce increased amounts of free radicals, which in turn cause greater damage. Oxidative stress and metabolic dysfunction processes lead to neuronal damage and neurodegeneration [7].

Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) may play important roles in the pathogenesis of MS and monitoring disease progression [8]. BDNF, produced primarily by neurons and glial cells, is essential for neurogenesis, differentiation, and neuroprotection and serves as a key mediator of synaptic plasticity. Changes in blood and central nervous system (CNS) levels of BDNF, along with the conversion of its precursor, proBDNF, into its active, mature form, have been linked to the pathogenesis of several neurological diseases, including MS [9]. Studies have shown that BDNF levels in the blood of MS patients are significantly lower than those in healthy controls [10]. Both neurons and immune cells, including lymphocytes, macrophages, and astrocytes, synthesize proBDNF. In MS, inflammatory factors increase the production of proBDNF. However, during inflammation, the conversion of proBDNF to its active form is impaired, as inflammatory mediators decrease the activity of the enzymes responsible for this process [11].

BDNF has been confirmed to play a neuroprotective role in the subsequent processes of inflammation, degeneration, and demyelination. BDNF promotes repair, regeneration, and remyelination and prevents clinical progression of the disease [12]. BDNF exerts its effects by binding to the TrkB (tyrosine kinase B) receptor with high affinity, promoting cell survival and various trophic effects. Oligodendrocytes and their progenitors also express the TrkB receptor, through which BDNF stimulates their differentiation and myelin production, playing a key role in remyelination [13]. However, in patients with MS, lower concentrations of BDNF have been shown, and its protective role is reduced as well [10]. Proinflammatory cytokines TNF-alpha, IL-1, and IL-6 decrease the concentration of BDNF. Cytokines inhibit its transcription in neurons and glial cells by activating signaling pathways (e.g., NF-kB) and increasing oxidative stress, thereby damaging neurons and reducing BDNF production [11].

In MS, VEGF expression increases due to mitochondrial dysfunction and the higher metabolic demands of demyelinated axons. Damaged mitochondria become less efficient at producing ATP, while demyelination requires greater ATP consumption to maintain axonal conduction. As a result, even when oxygen levels are sufficient, cells experience a state of "virtual hypoxia." This condition triggers HIF-1α-dependent activation of VEGF gene transcription as a compensatory response to local metabolic stress [14]. The concept of "virtual hypoxia" and metabolic exhaustion in MS is supported by MRI spectroscopy [15] and metabolic profiling studies [7], which show altered energy metabolism in the brain.

Initiation of angiogenesis has been associated with the pathogenesis of many diseases, including MS. Previous studies have shown that proinflammatory factors within demyelinating lesions stimulate angiogenesis [16]. In the early stages of MS, VEGF acts as a proinflammatory mediator, contributing to lesion formation. Several studies have also reported significantly elevated VEGF levels at all stages of MS compared to healthy controls, reinforcing its role in the disease process [17].

Considering the protective role of BDNF and the proinflammatory role of VEGF in the areas of inflammation and neurodegeneration during the alternating phases of the disease, the aim of this cross-sectional study was to evaluate the predictive value of the ratio of these parameters in the phase of remission, that is, in the phase of relapse in patients with RR-MS.

METHODS

Subjects

The study was conducted in 2022 as a cross-sectional study in the Department of Neurology, the Central Chemical Laboratory, and the Institute of Medical Research of the Military Medical Academy in Belgrade. The Ethics Committee of the Medical Faculty of the Military Medical Academy of University of Defense confirmed the ethical acceptability of all research procedures.

The study included 86 subjects, non-smokers –20 healthy individuals and 66 patients diagnosed with RR-MS by clinical, laboratory, and radiological examinations. The participants were divided into four groups:

I – group of healthy subjects (H; n = 20); formed for research purposes, mean age 35.95 ± 8.98 years. Healthy controls were individuals without a diagnosis of multiple sclerosis or any other neurological, autoimmune, or chronic inflammatory disease, who were free from acute infection and not receiving any therapy that could affect immune function.

II – group of patients in remission (MS REM; n = 23); patients diagnosed with RR-MS who were in remission at the time of the study, mean age 42.13 ± 8.49 years. Remission is defined as the absence of disease relapse in a period of at least six months.

III – group of patients at the onset of disease relapse (MS REL1; n = 23); this group comprised patients diagnosed with RR-MS who were experiencing the onset of a disease relapse at the time of inclusion. The mean age was 36.92 ± 10.64 years. A relapse was defined with an increase of at least one point on the Expanded Disability Status Score (EDSS). Patients experiencing an acute relapse

received high-dose intravenous methylprednisolone (typically 1 g/day for five days) according to standard clinical practice. Blood samples for biomarker analysis were collected before the initiation of corticosteroid therapy.

IV – group of patients at the end of disease relapse therapy (MS REL2; n = 20); the group comprised RR-MS patients who had completed a five-day course of high-dose intravenous methylprednisolone for relapse management at the time of evaluation. The mean age was 38.67 ± 12.27 years. Sampling in this group occurred after completion of corticosteroid therapy.

Of the 66 patients enrolled in the study, 35 patients were untreated, while the remaining 31 received various forms of therapy. Specifically, 21 patients received interferon therapy (11 patients received Betaferon (interferon beta-1b, 250 μg every other day; Bayer AG, Leverkusen, Germany), four received Avonex (interferon beta-1a, 30 μg intramuscularly once weekly; Biogen Inc., Cambridge, MA, US), and six received Rebif (interferon beta-1a, 22 μg subcutaneously three times per week; Pfizer Inc., New York City, NY, US). In addition, six patients were treated with dimethyl fumarate (240 mg twice daily), two patients received monomethyl fumarate (380 mg daily), one patient received fingolimod (Gilenya, 0.5 mg once daily), and one patient was treated with mitoxantrone therapy (12 mg/m^2 intravenously per clinical protocol). The therapy is prescribed by a clinical neurologist.

Medical history data were obtained from each subject's medical record at RR-MS, and EDSS was determined by a clinical neurologist.

Biochemical analyses

Biomarkers were measured in the blood of the subjects. Blood samples were collected by venipuncture in the morning, after 12 hours of fasting. Venipuncture was performed with a vacuum system (Becton Dickinson, Plymouth, England) in vacutainers containing clot activator (serum) or vacutainers containing heparin (plasma). Blood samples were centrifuged at 2500 rpm for 15 minutes. Plasma/serum was then divided into smaller aliquots and stored at -80°C until analysis.

In patients who were in the relapse phase of the disease, blood collection was performed before the start of therapy.

The concentration of the biochemical parameters: C-reactive protein (CRP) and ferritin were measured (CRP – Advia 1800, Clinical Chemistry Analyzer System, Siemens Healthcare GmbH, Erlangen, Germany; ferritin – Siemens, Dade Behring BN II Nephelometer, Siemens Healthcare Diagnostics Ltd.). Serum BDNF, VEGF, and IL-6 concentrations were determined using commercially available ELISA kits, according to the manufacturer's instructions (BDNF – Elabscience Biotechnology Inc., Huston, TX, USA, sensitivity 3.9 pg/mL; VEGF – Invitrogen Thermo Fisher Scientific, Waltham, MA, USA, sensitivity < 5 pg/mL; IL-6 – R&D Systems, Minneapolis, MN, USA, sensitivity 0.7 pg/mL).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). Results are presented as numbers, percentages, means and standard deviations. The Shapiro-Wilk test was used to test the normality of the data distribution. A statistically significant difference between parameters that had a normal distribution was determined using the ANOVA test, followed by a Bonferroni post hoc test. For parameters that did not have a normal distribution, the Kruskal–Wallis test and the χ^2 test were used. Spearman's and Pearson's correlations were used to determine the presence of a statistically significant correlation between variables, as a function of normal distribution. The significance level for all statistical tests was set at $p < 0.05$.

Ethics: This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from patients or their representatives. The Ethics Committee of the Medical Faculty of the Military Medical Academy approved this study (No. 3/4/2023).

RESULTS

While no significant differences were found between groups in ferritin, CRP, and IL-6, a higher leukocyte count was measured in the MS REL2 (at the end of relapse treatment) than in the other three groups. Increased BDNF levels were observed in MS REL2 (after corticosteroid treatment) compared with patients in MS REL1. Significantly lower VEGF levels were observed in MS REM compared with healthy subjects. Although VEGF levels in MS REL1 were not different from those in MS REM, higher VEGF levels were measured in MS REL2 compared with MS REM after corticosteroid therapy (Table 1).

A very weak positive correlation was recorded between VEGF and leukocyte count, and a negative correlation was observed between BDNF and CRP. A weak positive correlation was also found between CRP and ferritin and IL-6 (Table 2).

The BDNF/VEGF ratio was significantly increased in MS REM patients compared with healthy subjects (H). This ratio decreased significantly in MS REL1 patients at the onset of relapse compared with patients in remission (MS REM) (Figure 1).

In the receiver operating characteristic curve (ROC) for the BDNF/VEGF ratio, the area under the curve (AUC) was greater than 0.7, indicating a suitable predictive parameter for monitoring disease progression from MS remission (MS REM) to disease relapse (MS REL1) (Figure 2).

DISCUSSION

This pilot study investigated the correlation between clinical and biochemical parameters and tissue factors (BDNF,

Table 1. Demographic, clinical, and laboratory parameters of patients divided into the following groups: healthy, patients with multiple sclerosis in remission, patients with multiple sclerosis at the beginning of relapse, and patients with multiple sclerosis at the end of therapy during disease relapse

Demographic, clinical and laboratory parameters		H n = 20	MS REM n = 23	MS REL1 n = 23	MS REL2 n = 20	p
Sex (%)	Male	60	34.8	60.9	65	0.163
	Female	40	65.2	39.1	35	
Duration of illness (years)			11.77	7.91	6.05	0.00
EDSS#			2.22	3.52	2.35	0.00
Therapy MS (yes/no)			100%	17.4%	20%	0.00
Leukocytes × 10^9/L		5.8 ± 1.16	5.4 ± 1.65	6.57 ± 2.67	**11 ± 3.55*#&**	**0.000**
CRP mg/L		0.57 ± 0.8	0.75 ± 1.48	2.47 ± 9.66	0.4 ± 1.06	0.063
IL-6 pg/mL		3.49 ± 4.29	2.2 ± 0.96	4.45 ± 7.23	2.49 ± 1.76	0.799
Ferritin ug/L		54.23 ± 50.2	69.77 ± 46.18	54.68 ± 44.37	53.29 ± 50.9	0.355
BDNF ng/mL		7.83 ± 1.83	7.67 ± 1.76	6.19 ± 2.9	**9.09 ± 3.34&**	**0.004**
VEGF A ng/mL		0.22 ± 0.09	**0.13 ± 0.04***	0.16 ± 0.06	**0.27 ± 0.22#**	0.002

MS – multiple sclerosis; H – healthy; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; MS REL2 – patients with MS at the end of therapy during disease relapse; EDSS – Expanded Disability Status Score; CRP – C-reactive protein; IL-6 – interleukin 6; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor;
*p < 0.05;
p < 0.01 statistical significance compared to group H;
#p < 0.05;
##p < 0.01 significance compared to group MS REM;
&p < 0.05;
&&p < 0.01 significance compared to group MS REL1

Table 2. Spearman's correlation analysis between brain-derived neurotrophic factor, vascular endothelial growth factor A, white blood cell count, C-reactive protein, interleukin 6, and ferritin in multiple sclerosis

	BDNF	VEGF A	Le	CRP	IL-6	Ferritin
	Rho (ρ)	Rho (ρ)	Rho (ρ)	Rho (ρ)	Rho (ρ)	Rho (ρ)
BDNF	-	0.018	0.059	-0.177	-0.067	-0.047
IL-6	-0.067	-0.026	0.085	0.163	-	0.155
VEGF A	0.018	-	0.185	0.000	-0.026	0.006
Le	0.059	0.185	-	-0.035	0.085	0.049
CRP	-0.177	0.000	-0.035	-	0.163	0.254*
Ferritin	-0.047	0.006	0.049	0.254*	0.155	-

BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor; Le – white blood cells count; CRP – C-reactive protein; IL-6 – interleukin 6;
*p < 0.05

VEGF) in a group of RR-MS patients at different stages of the disease.

The patient group MS-REL2 (at the end of corticosteroid treatment) had a significantly higher leukocyte count than the other three patient groups, which is consistent with other publications [18]. Patients were treated with i.v. corticosteroids after diagnosis of MS relapse, so leukocytosis was a sign of the effect of corticosteroids. It is already known that leukocytosis can be induced by corticosteroids. High-dose corticosteroids have been associated with the extent and earlier onset of leukocytosis [19]. Leukocytosis in MS patients is usually a byproduct of the increase in neutrophil count, and the mechanism itself is not fully understood. However, the mechanism is thought to be based on the interaction of leukocytes and endothelial adhesion molecules [20]. Although the patients in MS-REL2 received corticosteroid therapy at relapse onset, the potential immunological effects of corticosteroids on biomarker levels cannot be fully excluded.

Although an increase in inflammatory markers would be expected in MS patients, no significant differences were found between groups in ferritin, CRP, and IL-6 in this study. There was no statistically significant difference between the patients with RR-MS and the control group, and there was no difference in the concentration of these parameters during the different phases of the disease. This is in contrast to the results of other studies, in which a significantly higher concentration of ferritin [21], IL-6 and CRP was found in MS patients compared with the control group. CRP is not only an indicator of an acute phase of disease but can also indicate the location of a lesion. Studies show that the greatest increase in CRP occurs in patients with symptoms of cerebellar and brainstem damage [22].

Some other studies have shown that the concentration of BDNF decreases in MS lesions and that the concentration of this neuroprotective protein decreases with disease progression. However, in our study, no significant changes in BDNF were observed in MS REM patients and in patients at the onset of relapse compared with the control group. However, a significant increase in BDNF was observed after corticosteroid treatment compared with patients who had relapsed before treatment. Although the patient cohort was small, the observed results are consistent with earlier reports showing a significant increase in the protein concentration after relapse [23].

The inflammatory process in MS lesions leads to an increase in the concentration of VEGF, which is responsible for angiogenesis, but is itself a proinflammatory factor [14]. The study found a significantly lower concentration of VEGF in patients in remission compared with healthy individuals. These data differ from published studies that have found higher VEGF concentrations at all stages of the disease [10]. In this study, significantly higher VEGF concentrations were found at the end of MS relapse therapy compared with patients in remission, which is consistent with published data from other studies [17]. Unexpectedly, VEGF levels at the beginning of the disease relapse were not significantly different from those in remission. Unchanged VEGF levels at the beginning of relapse compared with disease remission could be due to an insufficient time interval for the full extent of VEGF increase, and the significantly higher VEGF levels at the end of MS relapse therapy could also be due to the corticosteroids, especially from the aspect of the resulting leukocytosis. It has already been shown that in many diseases whose pathogenesis is based on the process of angiogenesis, there is a correlation between a higher VEGF concentration and leukocytosis [24]. One of the possible explanations for the

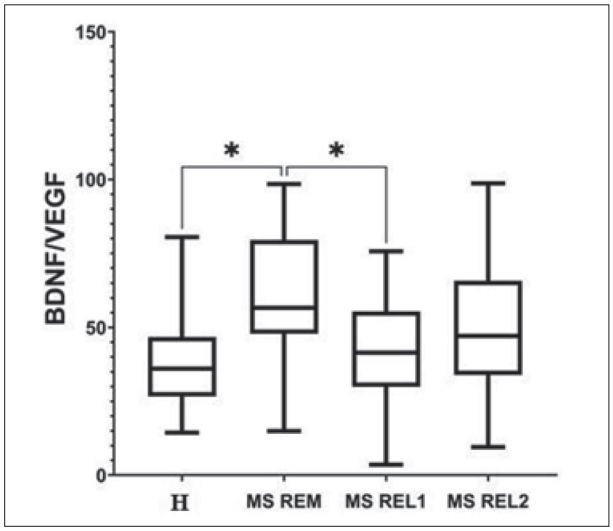

Figure 1. Brain-derived neurotrophic factor / vascular endothelial growth factor serum ratio of patients classified into the following groups: healthy, multiple sclerosis patients in remission, multiple sclerosis patients at the beginning of relapse, and multiple sclerosis patients at the end of therapy during relapse;

MS – multiple sclerosis; H – healthy; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; MS REL2 – patients with MS at the end of therapy during disease relapse; BDNF/VEGF – brain derived neurotrophic factor / vascular endothelial growth factor ratio;
*p < 0.05

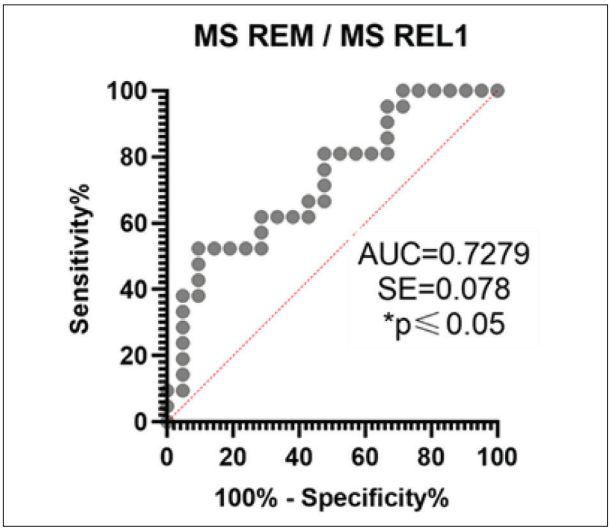

Figure 2. Receiver operating characteristic curve was analyzed to evaluate the significance of brain derived neurotrophic factor / vascular endothelial growth factor ratio in predicting disease stage; the figure shows the percentage of sensitivity and specificity; the measure of separability is expressed by the area under the curve, with a confidence interval of 95%; a ratio of AUC > 0.7 is suitable for predicting disease progression;

MS – multiple sclerosis; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; AUC – area under the curve; SE – standard error; p – statistical significance

presence of angiogenesis in MS lesions is because a large amount of ATP is needed at the sites of axon demyelination to conduct impulses and that, at the same time, ATP production at the damaged axons has been reduced. In this way, the state of hypoxia reflects the chronic demyelination of axons [14].

The data indicate that VEGF is necessary for BDNF to exert its effects. The study found that BDNF stimulates the release of VEGF, and that the effects of BDNF in the prefrontal cortex of mice depend on VEGF release. Additionally, BDNF-induced dendrite complexity is blocked by a selective VEGF-Flk-1 antagonist. VEGF infusion induced neurotrophic effects that were abolished by BDNF neutralization, indicating their reciprocal dependence [25]. The reciprocal dependence between BDNF and VEGF is based on the overlap of their signaling pathways (PI3K/Akt and MAPK/ERK) and mutual regulation of expression, enabling a synergistic effect on neuroplasticity and neuronal survival [26, 27].

Considering the interaction of these two important factors, the BDNF/VEGF ratio can be considered as an anti-inflammatory indicator showing the neuroprotective properties of BDNF and the proangiogenic and proinflammatory properties of VEGF. Considering the limitations of the study, the data indicate that the BDNF/VEGF ratio is significantly higher in patients with RR-MS, who are in remission (MS REM) compared with healthy controls. In contrast, this ratio decreases at the onset of MS relapse relative to patients in remission. All patients in the study who were in remission received therapy (17 patients received interferon therapy (Betaferon or Rebif) and six patients received dimethyl fumarate therapy) that could have anti-inflammatory and neuroprotective effects in the damaged areas. The neuroprotective and anti-inflammatory effects of this therapy have long been known. Interferon has been shown to affect the expression of certain genes, which has short- and long-term effects on the immune response in MS [28]. However, previous studies have not shown any effects of interferon therapy on BDNF [29]. At the same time, a higher ratio of BDNF/VEGF in patients in remission (MS REM) was negatively correlated with the concentration of VEGF. Moreover, ROC curve analysis indicates that the BDNF/VEGF ratio has potential as a reliable indicator of progression of RR-MS progression from remission to relapse.

Limitations of the study

This study has several limitations. The sample size was small and included patients at different clinical stages of RR-MS, resulting in biological variability and limiting the generalizability of the findings. The cohort also exhibited therapeutic heterogeneity, with multiple disease-modifying therapies represented, which restricted the ability to account for treatment effects. In addition, corticosteroid use, particularly in the MS REL2 group, may have affected BDNF and VEGF concentrations. The cross-sectional design further limits conclusions about temporal changes or predictive value, so the ROC results should be interpreted with caution. Finally, the BDNF/VEGF ratio remains an experimental parameter and requires further validation.

Overall, these factors indicate that the findings should be considered preliminary and confirmed in larger, longitudinal, and treatment-stratified studies.

CONCLUSION

The BDNF/VEGF ratio could be important for the assessment of the MS stage in patients with RR-MS, especially with regard to the prediction of the transition from the remission phase to relapse. As this relationship was described for the first time in the study conducted, the relevance of its change during the disease stage remains to be clarified.

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S.A., A.T., K.K., T.M., N.A.: writing original draft and data collection; S.I., N.M.: revising the manuscript/study supervision.

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Стадијуми у релапсно-ремитентној мултиплој склерози – перспективна улога односа *BDNF–VEGF*

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САЖЕТАК

Увод/Циљ Неуротрофни мождани фактор (*BDNF*) и васкуларни ендотелни фактор раста (*VEGF*) могу бити од значаја у развоју и праћењу тока мултипле склерозе. *BDNF* има неуропротективну улогу у процесима инфламације, дегенерације и демијелинизације код мултипле склерозе. У демијелинизационим лезијама инфламаторне ћелије подстичу ангиогенезу ослобађајући *VEGF*, који је такође проинфламаторни фактор.

Методе У студију је било укључено 86 испитаника – 20 здравих испитаника који су чинили контролну групу и 66 болесника са релапсно-ремитентном мултиплом склерозом. Болесници су били подељени у три групе: болеснике у ремисији, болеснике на почетку релапса болести и болеснике на крају кортикостероидне терапије.

Резултати Студија је показала статистички значајне разлике у концентрацији *BDNF* између болесника на почетку и на крају терапије релапса болести, као и значајне разлике у концентрацији *VEGF* између група испитаника. Однос *BDNF*/*VEGF* био је виши код болесника у ремисији у поређењу са контролном групом, док је овај однос био значајно нижи код болесника на почетку терапије релапса мултипле склерозе у односу на болеснике у ремисији.

Закључак Ова студија први пут описује однос *BDNF*/*VEGF* као биомаркер који би могао бити од интереса у добро контролисаним лонгитудиналним студијама за одређивање стадијума релапсно-ремитентне мултипле склерозе и процену одговора на терапију током релапса.

Кључне речи: релапсно-ремитентна мултипла склероза; *BDNF*; *VEGF*; *BDNF*/*VEGF*; *CRP*; *IL*-6

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Impact of sick leave on general practitioner visits among Serbia's working population

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SUMMARY

Introduction/Objective Sick leave represents an indicator of health and has multiple consequences for individuals, employers, and the health system. In Serbia, the association between sick leave and general practitioner (GP) visits has not been sufficiently explored. This study aimed to examine the association between sick leave and GP visits among the working-age population in Serbia, considering predisposing, enabling, and need factors.

Methods Data from the 2019 Serbian National Health Survey were analyzed, based on a sample of 4,652 respondents aged 18–65 years. Descriptive statistics and logistic regression methods were used to identify factors associated with GP visits in the previous 12 months, with sick leave (yes/no) included as a predictor in the model.

Results Multivariate analysis showed that sick leave was statistically significantly associated with higher odds of GP visits (OR = 2.11). The strongest enabling factor was having a chosen GP (OR = 3.95), while significant predisposing factors included marital status, education, and type of employment. Among need factors, poor self-rated health, long-term limitations, and previous hospitalization were strongly associated with GP visits. The model demonstrated good discriminatory ability (Nagelkerke $R^2 = 0.32$; ROC AUC = 0.78).

Conclusion Sick leave significantly increases the odds of GP visits. Enabling and predisposing factors play a key role, particularly having a chosen GP. The results indicate the importance of general practice accessibility as a resource for reducing inequalities in healthcare utilization among the working-age population in Serbia.

Keywords: behavior; general practice; healthcare disparities; occupational health; work

INTRODUCTION

Sick leave is an indicator of health with significant implications for individuals, employers, and healthcare systems, affecting productivity and healthcare costs [1, 2, 3]. Although studies have examined the determinants of sick leave [1–5], the relationship between sick leave and primary care utilization, particularly general practice, is less understood.

General practitioners (GPs) play crucial roles in health promotion, prevention, diagnosis, and treatment, making them pivotal in providing continuity of care [6, 7, 8] and acting as gatekeepers to specialized services [8, 9, 10]. They address socioeconomic issues, and their attitudes, practices, and recommendations for workplace adjustments can impact absenteeism [6]. Despite their multifaceted roles, the impact of GPs concerning sick leave certification remains inadequately researched [3, 6, 8].

In Serbia, GPs serve a central role in primary healthcare, with around 70% of the population using public services [11]. Since 2005, patients have been able to choose GPs, and capitation has been introduced to incentivize quality [11, 12]. General practice is delivered through 158 primary health centers [12]. By 2019, Serbia had 3,493 GPs, with a preference for public over private services (69.4% *vs.* 5.6%) [11]. GPs are responsible for certifying sick leave that validates the need for time off from work due to health issues, and influences the management of health conditions [3, 6, 8, 11]. The certification impacts an individual's access to sick leave and the workflow within general practice settings, making it a key aspect in understanding the relationship between sick leave and utilization of this sector.

This study aims to examine the impact of sick leave on the frequency of GP visits, providing insights into general practice utilization patterns among Serbia's working population.

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METHODS

This secondary data study utilized information from the 2019 Serbian National Health Survey. The survey was conducted by the Statistical Office of the Republic of Serbia, the Dr. Milan Jovanović Batut Institute of Public Health of Serbia, and the Ministry of Health of the Republic of Serbia [13]. The survey followed the methodology of the European Health Interview Survey (EHIS Wave 3), an international study aimed at assessing population health across the European Union. The methodology ensures representative data for calculating health indicators, enabling cross-national comparisons.

A stratified two-stage sampling method was used to assess health factors nationally. Out of 13,589 registered household members aged 15 and over, 11,790 completed the self-administered questionnaire (response rate 89.5%). Secondary data from 4,652 working-age individuals, aged 18–65 years, were analyzed [13]. Three types of questionnaires were employed: a household panel, face-to-face interviews, and a self-administered questionnaire.

This study followed Andersen's behavioral model [14], categorizing factors into predisposing, enabling, and need factors. Predisposing factors included demographic and socioeconomic characteristics: gender (male/female), age (18–25 to 56–65), marital status (married, single, divorced, widowed), education (college/university, secondary, primary school), employment status (self-employed, employed by an employer), and occupations classified as blue-collar (manual labor, skilled trades, service industry jobs) or white-collar (office jobs, professional roles, technical positions) [14, 15]. Enabling factors included having a chosen general practitioner (yes/no), wealth index (rich, middle, poor), and geographic region (Belgrade, Northern Serbia, Central and Western Serbia, and Southern and Eastern Serbia) [14, 15]. Need factors focused on sick leave, self-rated health, long-standing activity limitations, and hospitalization [14, 15]. Variables were coded as categorical or dichotomous. Sick leave was categorized based on whether respondents had taken sick leave in the past 12 months (yes/no). The dependent variable was whether the respondent had visited a GP in the past 12 months (yes/no).

The data were analyzed using Chi-square tests (χ^2) to examine associations between categorical variables, with significance set at $p < 0.05$. Logistic regression (univariate and multivariate) assessed the relationship between independent variables and GP visits, with sick leave included as an independent variable. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Multicollinearity was checked using variance inflation factors, all below 5. Model fit was confirmed by the Hosmer–Lemeshow test ($p > 0.05$), Nagelkerke R^2, and ROC analysis. Cross-validation confirmed the model's stability across different data subsets. Outliers and influential data points were assessed using Cook's distance, with necessary adjustments made to ensure model accuracy and validity. All analyses were performed using IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA).

Ethics: The 2019 Serbian National Health Survey adhered to international ethical standards (Declaration of Helsinki, 2008), the Decision on the Program of Official Statistics, and the Regulation on establishing the Plan of Official Statistics 2019 [13]. Privacy and data confidentiality were protected under the General Data Protection Regulation [13]. Participants received written information about the study's purpose, rights, and details for inquiries or complaints, providing written informed consent. Anonymity was ensured through data de-identification, stored securely, and results published in an aggregated form. Permission for secondary data use was obtained from the Dr. Milan Jovanović Batut Institute of Public Health of Serbia.

RESULTS

The study comprised 4,652 working individuals (mean age 42.68 ± 11.2 years). Overall, 15.8% reported sick leave in the past 12 months, with a higher prevalence among women (18.2%) than men (13.9%). Analysis of sociodemographic, economic, and health characteristics of respondents revealed statistically significant differences between individuals who used sick leave and those who did not. Sex was significantly associated with sick leave, with a higher proportion of women in the sick leave group compared to the group without sick leave (55.5% *vs*. 45.5%; $p < 0.001$). Age structure differed significantly between groups ($p < 0.001$). The sick leave group had a lower proportion of younger respondents (18–25 years), while those aged 46–55 and 56–65 years were more represented compared to the group without sick leave. Marital status also showed a significant association with sick leave ($p < 0.001$). The proportion of widowed and divorced individuals was considerably higher among those who used sick leave, while the proportion of single individuals was lower compared to the group without sick leave. Significant differences were recorded according to education level ($p = 0.044$). The sick leave group had a lower proportion of respondents with higher education, while respondents with primary education were more represented compared to the group without sick leave. Employment status was statistically significant ($p < 0.001$), with employees working for an employer using sick leave more frequently compared to the self-employed. Among enabling factors, having a chosen GP was strongly associated with sick leave ($p < 0.001$), with almost the entire sick leave group having a chosen GP. Differences were also found according to wealth index ($p = 0.049$), as well as region of residence ($p < 0.001$). Health indicators exhibited the most pronounced differences between groups. Self-rated health differed significantly ($p < 0.001$), with the sick leave group having a considerably higher proportion of respondents with poorer health status. The presence of long-term health limitations was significantly more frequent among respondents who reported sick leave ($p < 0.001$). Additionally, hospitalization in the previous 12 months was significantly more prevalent in the sick leave group ($p < 0.001$) (Table 1).

Table 1. Distribution of participants characteristics

Variable	Category	N	%	Without sick leave N (%)	With sick leave N (%)	χ^2/df/p
Sex	Male	2469	53.1	2179 (54.5)	290 (44.5)	20.99/1/ < 0.001
	Female	2183	46.9	1821 (45.5)	362 (55.5)	
Age (years)	18–25	322	6.9	301 (7.5)	21 (3.2)	33.98/4/ < 0.001
	26–35	963	20.7	859 (21.5)	104 (16)	
	36–45	1298	27.9	1127 (28.2)	171 (26.2)	
	46–55	1250	26.9	1066 (26.7)	184 (28.2)	
	56–65	819	17.6	647 (16.2)	172 (26.4)	
Marital status	Married	3420	73.5	2979 (74.5)	441 (67.6)	70.80/3/ < 0.001
	Single	836	18	749 (18.7)	87 (13.3)	
	Widowed	324	7	228 (5.7)	96 (14.7)	
	Divorced	72	1.5	44 (1.1)	28 (4.3)	
Education	College/University	1380	29.7	1,212 (30.3)	168 (25.8)	6.24/2/0.044
	Secondary school	2880	61.9	2515 (62.9)	365 (56)	
	Primary school	392	8.4	273 (6.8)	119 (18.3)	
Employment status	Self-employed	560	12	515 (12.9)	45 (6.9)	14.61/1/ < 0.001
	Employed by an employer	4092	88	3485 (87.1)	607 (93.1)	
Occupation	Blue collar	2690	57.8	2348 (58.7)	342 (52.5)	0.32/1/0.572
	White collar	1962	42.2	1652 (41.3)	310 (47.5)	
Chosen general practitioner	No	176	3.8	162 (4.1)	14 (2.1)	127.51/1/ < 0.001
	Yes	4476	96.2	3838 (95.9)	638 (97.9)	
Wealth index	Rich class	2540	54.6	2209 (55.2)	331 (50.8)	6.02/2/0.049
	Middle class	980	21.1	845 (21.1)	135 (20.7)	
	Poor class	1132	24.3	946 (23.7)	186 (28.5)	
Region	Belgrade	1157	24.9	988 (24.7)	169 (25.9)	73.15/3/ < 0.001
	Northern Serbia	1111	23.9	962 (24.1)	149 (22.9)	
	Central/ Western Serbia	1401	30.1	1215 (30.4)	186 (28.5)	
	Southern/Eastern Serbia	983	21.1	835 (20.9)	148 (22.7)	
Self-rated health	Very good / good	3450	74.2	3086 (77.2)	364 (55.8)	82.99/2/ < 0.001
	Fair	900	19.4	742 (18.6)	158 (24.2)	
	Poor / very poor	302	6.5	172 (4.2)	130 (19.9)	
Long-standing limitations	No	2950	63.4	2681 (67)	269 (41.3)	169.42/1/ < 0.001
	Yes	1702	36.6	1319 (33)	383 (58.7)	
Hospitalization	No	4000	86	3535 (88.4)	465 (71.3)	28.31/1/ < 0.001
	Yes	652	14	465 (11.6)	187 (28.7)	

In the sample of 4652 respondents, 3434 respondents (73.8%) had at least one visit to a GP in the previous 12 months (Table 2).

Table 2. General practitioner visits in the previous 12 months

General practitioner visit	N	%
No	1218	26.2
Yes	3434	73.8
Total	4652	100

The results of univariate logistic regression analysis showed that predisposing, enabling, and need factors were significantly associated with GP visits. Among predisposing factors, sex was a significant predictor, with women having higher odds of GP visits compared to men (OR = 1.35; p < 0.001). Older age groups had increased odds of visits compared to the reference group (18–25), with the most pronounced effect observed among respondents aged 56–65 years (OR = 1.95; p < 0.001).

Single individuals had significantly lower odds of visits compared to married individuals (OR = 0.54; p < 0.001), while divorced individuals had increased odds of GP visits compared to married individuals (OR = 1.91; p = 0.024). Respondents with secondary education visited GPs less frequently compared to respondents with higher education (OR = 0.84; p = 0.013). Respondents employed by an employer had higher odds of GP visits compared to self-employed individuals (OR = 1.41; p < 0.001).

Among enabling factors, having a chosen GP showed the strongest association with GP visits, with more than fourfold higher odds of visits compared to respondents without a chosen GP (p < 0.001). Respondents from the middle economic class visited GPs less frequently compared to the higher class (OR = 0.82; p = 0.014). Compared to Belgrade residents, respondents from other regions had higher odds of GP visits, with the most pronounced effect recorded in Southern and Eastern Serbia (OR = 2.32; p < 0.001).

Need factors showed associations with GP visits. Respondents who used sick leave had three times higher odds of visiting a GP compared to those without sick leave (p < 0.001). Respondents who rated their health as fair/

poor had higher odds of GP visits compared to respondents with good health (OR = 3.43; p < 0.001). The presence of long-term health limitations was strongly associated with GP visits (OR = 2.75; p < 0.001), while previous hospitalization represented the strongest single predictor (OR = 6.70; p < 0.001) (Table 3).

The multivariate logistic regression model showed satisfactory discriminatory ability (Nagelkerke R^2 = 0.32; ROC AUC = 0.78), indicating good model capability to distinguish between respondents with and without GP visits.

Among predisposing factors, marital status and education retained statistical significance in the multivariate model. Single individuals had lower odds of GP visits compared to married (OR = 0.62; p < 0.001), while respondents with secondary education visited GPs less frequently compared to respondents with higher education (OR = 0.82; p = 0.026). Employment status also showed a significant association, with respondents employed by an employer having higher odds of GP visits compared to self-employed (OR = 1.29; p = 0.014).

Among enabling factors, having a chosen GP showed the most pronounced association with GP visits, with respondents with a chosen GP having almost fourfold higher odds of visits compared to those without a chosen GP (p < 0.001).

Need factors remained statistically significant in the multivariate model. Sick leave remained a significant independent predictor of GP visits (OR = 2.11; p < 0.001). Respondents who rated their health status as fair had increased odds of GP visits compared to respondents with good or very good self-rated health (OR = 1.49; p = 0.002). The presence of long-term health limitations was associated with approximately twofold higher odds of GP visits (p < 0.001), while previous hospitalization represented a strong predictor of GP visits (OR = 3.99; p = 0.002) (Table 4).

Table 3. Univariate analysis of factors associated with general practitioner (GP) visits

Variable	OR (95% CI)	p
Predisposing factors		
Sex (female *vs.* male)	1.35 (1.19–1.53)	< 0.001
Age 36–45 (*vs.* 18–25)	1.37 (1.06–1.77)	0.017
Age 46–55 (*vs.* 18–25)	1.56 (1.20–2.03)	0.001
Age 56–65 (*vs.* 18–25)	1.95 (1.47–2.59)	< 0.001
Single (*vs.* married)	0.54 (0.47–0.63)	< 0.001
Divorced (*vs.* married)	1.91 (1.09–3.35)	0.024
Secondary education (*vs.* higher)	0.84 (0.73–0.96)	0.013
Employed by an employer (vs. self-employed)	1.41 (1.18–1.68)	< 0.001
Enabling factors		
Chosen GP (yes *vs.* no)	4.05 (3.13–5.24)	< 0.001
Middle class (*vs.* higher)	0.82 (0.69–0.96)	0.014
Northern Serbia (*vs.* Belgrade)	1.39 (1.17–1.67)	< 0.001
Central/Western Serbia (*vs.* Belgrade)	1.25 (1.05–1.47)	0.010
Southern/Eastern Serbia (*vs.* Belgrade)	2.32 (1.90–2.83)	< 0.001
Need factors		
Sick leave (yes)	2.98 (2.69–3.64)	< 0.001
Fair self-rated health (*vs.* good)	2.46 (1.98–3.06)	< 0.001
Poor self-rated health (*vs.* good)	3.43 (1.85–6.36)	< 0.001
Long-term health limitations (yes)	2.75 (2.36–3.21)	< 0.001
Hospitalization in the previous 12 months (yes)	6.7 (3.04–14.75)	< 0.001

*Reference categories: male, age 18–25 years, married, higher education, self-employed, no chosen GP, higher class, Belgrade region, no sick leave, good self-rated health, no long-term health limitations, and no hospitalization

Table 4. Multivariate logistic regression – predictors of general practitioner (GP) visits in the previous 12 months

Variable	OR	95% CI	p
Predisposing factors			
Single (*vs.* married)	0.62	0.51–0.76	< 0.001
Secondary education (*vs.* higher)	0.82	0.69–0.98	0.026
Employed by an employer (*vs.* self-employed)	1.29	1.05–1.58	0.014
Enabling factors			
Chosen GP (yes *vs.* no)	3.95	2.97–5.24	< 0.001
Need factors			
Sick leave (yes)	2.11	1.69–2.64	< 0.001
Fair self-rated health (*vs.* good / very good)	1.49	1.15–1.93	0.002
Long-term health limitations (yes)	2.06	1.71–2.49	< 0.001
Hospitalization in the previous 12 months (yes)	3.99	1.64–9.72	0.002

*Reference categories: married, higher education, self-employed, no chosen GP, no sick leave, good/very good self-rated health, no long-term health limitations, and no hospitalization

DISCUSSION

This study examined the association between sick leave use and frequency of GP visits in the working-age population of Serbia, using data from the 2019 Serbian National Health Survey. The results provide insight into patterns of primary healthcare utilization in the context of sick leave, with particular emphasis on the role of chosen GPs among the working-age population.

In our sample, 15.8% of respondents reported sick leave use [16]. Multivariate logistic regression analysis revealed that after adjusting for predisposing, enabling, and need factors, eight variables remained independently associated with GP visits: sick leave, marital status, education, employment status, having a chosen GP, self-rated health, long-term limitations, and hospitalization. Notably, sex, age, wealth index, and region – which showed significant associations in univariate analysis – did not retain significance in the adjusted model.

Sick leave emerged as a statistically significant independent predictor of GP visits. Respondents who used sick leave had more than twice the odds of GP visits compared to those without sick leave. The attenuation of the effect in the adjusted model suggests that the association between sick leave and GP visits is partially mediated by health-related factors. This finding confirms the dual role of GPs in certifying sick leave and managing health conditions [3, 6, 8].

Sex showed a significant association in univariate analysis, with women having higher odds of GP visits compared to men. However, unlike some international studies [7, 15, 16], sex did not remain significant in the multivariate model. This suggests that the observed differences between men and women can be explained by other factors

included in the model, such as marital status, education, employment type, and health status.

Similarly, age demonstrated a clear gradient in univariate analysis, with older age groups showing progressively higher odds of GP visits. However, age did not remain significant in the multivariate model after adjusting for other factors. This suggests that the age-related increase in GP visits is largely explained by the higher prevalence of health needs and greater likelihood of having a chosen GP among older individuals.

Marital status retained statistical significance in the multivariate model. Single individuals had a significantly lower odds of GP visits compared to married. This finding aligns with previous research suggesting that married individuals may have better health-seeking behavior and social support that facilitate healthcare utilization [3, 16, 17].

Education emerged as an independent predictor, with respondents with secondary education visiting GPs less frequently compared to those with higher education. Lower visit rates among individuals with lower education indicate the importance of educational status as a determinant of health literacy, which has been confirmed in previous studies [3, 16, 17].

Employment status also showed a significant association in the multivariate model, with respondents employed by an employer having higher odds of GP visits compared to self-employed individuals. This finding indicates potentially better institutional support and easier access to healthcare services in the formal employment sector [4].

Having a chosen GP emerged as the strongest predictor of GP visits in the multivariate model, with respondents who had a chosen GP showing almost fourfold higher odds of visits compared to those without one. This emphasizes the crucial role of continuity of primary healthcare in Serbia. In Serbia, as in many European countries, the GP plays a central role in assessing work capacity and certifying sick leave, which encourages contacts with the healthcare system [7, 18, 19]. This association underscores the importance of ensuring universal access to chosen GPs as a fundamental component of equitable healthcare.

The wealth index showed a significant association in univariate analysis but did not remain significant in the multivariate model. This finding, unlike the previous study [20], suggests that in Serbia's context, economic disparities in GP utilization may be mediated by other factors, indicating universal access to primary healthcare regardless of socioeconomic status.

Region of residence demonstrated significant associations in univariate analysis, with all regions outside Belgrade showing higher odds of GP visits. However, regional differences did not retain significance in the multivariate model. This suggests that the observed geographic variation in GP utilization may be explained by differences in the distribution of chosen GPs, socio-demographic characteristics, and health needs across regions [18].

Need factors remained statistically significant predictors in the multivariate model, demonstrating their fundamental role in driving GP utilization. Respondents who rated their health as fair had an increased odds of GP visits compared to those with good or very good self-rated health. The presence of long-term health limitations was associated with more than twice the odds of GP visits, while previous hospitalization represented one of the strongest predictors. These findings are consistent with studies conducted in Sweden, confirming that health needs are the primary driver of primary care utilization [2].

Although the study has the advantage of a representative sample, certain limitations should be considered. The data are based on self-reporting, which may lead to information bias, and the cross-sectional study design precludes drawing causal conclusions. Additionally, the specific mechanisms through which sick leave and the role of the chosen GP affect visit frequency were not examined in detail. Future longitudinal research could deepen understanding of these relationships.

The study identifies key factors influencing GP visits in Serbia, with sick leave playing a significant role in increasing primary healthcare utilization. The findings indicate the need to strengthen cooperation between primary healthcare and occupational medicine services to improve healthcare for the working-age population. Higher visit rates among employees on sick leave confirm the role of GPs in certifying sick leave and managing health conditions.

The observed differences in visits according to education and employment status in the multivariate model indicate the existence of inequalities in healthcare access. Particularly lower visit rates among individuals with lower education and the self-employed indicate the need to improve health literacy and reduce structural barriers to access to healthcare services. The strong independent effect of having a chosen GP emphasizes the critical importance of ensuring universal registration as a mechanism for reducing healthcare inequalities. The strong association of long-term limitations and previous hospitalizations with GP visits confirms the importance of an accessible primary healthcare system that ensures continuity of care for the working-age population of Serbia.

CONCLUSION

This study identifies the key factors influencing general practitioner visits among Serbia's working-age population, with sick leave playing a crucial role in increasing healthcare utilization. Predisposing factors such as marital status, education, and employment status, along with having a chosen GP, significantly affect the likelihood of GP visits. Need factors, including self-rated health, long-term activity limitations, and previous hospitalization, further influence healthcare-seeking behavior. General practitioners are pivotal in managing health during periods of sick leave certification. To reduce inequalities and improve access to general practice, targeted policies are essential. Ensuring universal registration with chosen GPs, improving health literacy among lower-educated individuals, and strengthening support for self-employed workers can address disparities and enhance health outcomes across Serbia's working-age population.

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Утицај боловања на посете лекару опште медицине код радно активног становништва у Србији

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САЖЕТАК

Увод/Циљ Боловање представља показатељ здравља и има вишеструке последице по појединце, послодавце и здравствени систем. У Србији повезаност између боловања и посета лекару опште медицине није довољно истражена. Циљ овог истраживања јесте да се испита повезаност боловања и посета лекару опште медицине међу радно активном популацијом у Србији, уз разматрање предиспонирајућих, омогућавајућих и фактора потреба.

Методе Анализирани су подаци из Националног истраживања здравља становника Србије 2019, на узорку од 4.652 испитаника старости 18–65 година. Коришћене су методе дескриптивне статистике и логистичка регресија ради идентификовања фактора повезаних са посетама лекару опште медицине у претходних 12 месеци, при чему је боловање (да/не) укључено као предиктор у моделу.

Резултати Мултиваријантна анализа показала је да је боловање статистички значајно повезано са већом вероватноћом посета лекару опште медицине (*OR* = 2,11). Најјачи омогућавајући фактор био је поседовање изабраног лекара опште медицине (*OR* = 3,95), док су значајни предиспонирајући фактори укључивали брачни статус, образовање и тип запослења. Међу факторима потреба, здравље процењено као лоше, дуготрајна ограниченост и претходна хоспитализација били су значајно повезани са посетама лекару опште медицине. Модел је показао добру дискриминативну способност (*Nagelkerke* R^2 = 0,32; *ROC AUC* = 0,78).

Закључак Боловање значајно повећава вероватноћу посета лекару опште медицине. Кључну улогу имају омогућавајући и предиспонирајући фактори, посебно поседовање изабраног лекара опште медицине. Резултати указују на значај доступности опште медицине као ресурса за смањење неједнакости у коришћењу здравствене заштите у радно активној популацији у Србији.

Кључне речи: понашање; општа медицина; неједнакост у здрављу; здравље на раду; посао

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Attitudes and experiences of the Serbian Medical Society members concerning the clinical practice guidelines

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SUMMARY
Introduction/Objective The Academy of Medical Sciences of the Serbian Medical Society (SMS) carried a survey on clinical practice guidelines (CPGs) among doctors, members of the SMS with the aim of examining use and attitude of doctors on CPGs.
Methods We obtained the addresses of 2876 members of 20 SMS sections randomly-selected from a total of 62 SMS sections. Out of all invited members 482 (16.8%) responded. Self-administered questionnaire survey consisted of 21 questions that included demographic information, sources of informing and doctors' experience with CPGs, their use and barriers to CPGs use.
Results Among the 482 respondents there were significantly more women (64.1%) than men, majority were aged 45–60 years, 411 (85.3%) of them were employed in public health institutions and most were specialists. Respondents were informed about CPGs at meetings (30.9%), from the literature (16.3%), from both sources (17.5%), during studies (20%), but 7% of them were not informed so far. Almost all (452) respondents agree that CPGs are useful, 150 use national, 76 international, and 213 both. During the last year, 101 (21%) of respondents did not use any CPGs. The main reasons for not using the CPGs are lack of information and difficult access to CPGs.
Conclusions The respondents consider CPGs useful for practice. Lack of information about CPGs and access to them was found as the main barrier for their use. It obligates the continuous preparation of CPGs and regular and efficient notification of doctors about them.
Keywords: clinical practice guidelines; survey; attitude; barriers

INTRODUCTION

The rapid development of medical science in recent decades is accompanied by an extremely large number of published papers from various fields of medicine. Hence, one of the biggest challenges is the transfer of scientific results into practice. Clinical practice guidelines (CPGs) are one of the tools that help to respond to that challenge. As CPGs are required to be consistent with evidence-based medicine, all guideline recommendations should be evidence-based. The authors of the CPGs find this evidence in the results of large multicenter studies, meta-analyses, and other studies that have determined that a particular diagnostic method is reliable or a particular therapeutic method is effective. In the CPGs, evidence from the literature is summarized into recommendations that enable safe, effective, ethical, and standardized health care. The World Health Organization defines evidence-based CPGs as "a set of recommendations to support informed decision-making on the desirability of carrying out specific interventions at clinical or public health level, since these guidelines provide a basis for selecting and prioritizing, among a set of possible interventions, the most appropriate" [1].

In 1990, the Institute of Medicine (US) defined in the instruction for the preparation of the CPGs that "practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [2]. Since then, numerous CPGs have been published worldwide by national and international association of health care professionals, reference health care institutions and policy makers. In Serbia, national CPGs has been issued by the Ministry of Health since 2001, and more than 50 CPGs have been published so far. In recent years, and especially during the COVID-19 epidemic, the creation of the CPGs has stalled. With the aim of ensuring continuous development of the CPGs, the Ministry of Health entrusted the Academy of Medical Sciences (Academy) of the Serbian Medical Society (SMS) to organize and manage the development of the CPGs.

Our national CPGs are developed in accordance with the principles stated in the aforementioned document of the Institute of Medicine (US) [2], as well as in the Appraisal of Guidelines for Research and Evaluation II (AGREE II) [3]. However, the development and publication of quality CPGs do not imply that they will be applied in clinical practice. Numerous papers have been published since the 1990s on the experience, interest, attitudes of doctors of various specialties on CPGs, as

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well as on the strategies of CPGs implementation and factors influencing the use of CPGs [4–8]. Although CPGs have been issued in Serbia for over 20 years, there have been no examinations of doctors' use and opinions about the CPGs. Therefore, the Academy carried out a survey on CPGs among doctors, members of the SMS with the aim of examining how many doctors used CPGs and what was their attitude and experience about CPGs.

METHODS

From the SMS secretariat, we obtained the addresses of 2876 members of 20 SMS sections randomly-selected from a total of 62 SMS sections. A self-reported cross-sectional survey among these doctors from different branches of medicine was carried out. The invitation to participate in the survey was sent via email with a link to the survey developed using Jotform platform. The email stated the purpose of the survey and pointed out that it was anonymous and voluntary. The invitation was sent on December 19, 2023 and repeated on January 15 and 26, 2024. Pre-testing of the questionnaire was carried out to check whether the questions were understandable and acceptable and whether any question was missing. Twenty doctors of different specialties were included in the pretest, thereafter several questions were corrected.

The survey tool was developed by authors who have experience in developing guidelines and survey methodology, while researching the literature and incorporating experience from previous studies into the survey development process. [5, 7, 8]. The questionnaire consisted of 21 questions. The first ones were related to the demographic characteristics of the participants and their institutions, followed by questions about the use of the CPGs, their characteristics, as well as sources of informing doctors about CPGs. The answers to the questions could be: 1) yes or no, 2) choice of one of the five-point Likert scale statements (1 = strongly agree; 5 = strongly disagree), 3) choice of several offered options. Textual answers could be given to two questions.

Statistical analysis was performed in SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Data were presented as numbers and percentages. The χ^2 or Fisher's exact test was used to evaluate differences between groups with a p value for significance of 0.05.

Ethics: The study was approved by Ethical Board of SMS (No 01/2290; Nov. 24, 2025).

RESULTS

Out of 2876 SMS members invited to participate in the survey, 482 (16.8%) responded and most of respondents were specialists in various fields of medicine (Table 1). There were significantly more women than men both among non-specialists and among specialists. The biggest

Table 1. Respondent characteristics

Variables	Total number	Employed in				Title				
		University clinic	General hospital	Health center	Other	MD	Resident	Specialist	Dr. sc.	Professor
Responded, number (% of total number)	482	161 (33.4%)	110 [a] (22.8%)	181 (37%)	30[a] (6.2%)	44 (9.1%)	35 (7.3%)	249[b] (51.7%)	65 (13.5%)	89 (18.5%)
Sex, number (%)*										
Males	173 (35.9%)	76 [a] (47.2%)	54 (49.1%)	32 (17.7%)	11 (36.7%)	8 [b] (18.2%)	15 (42.9%)	75 [b] (29%)	30 (54.5%)	45 (50.6%)
Females	309 (64.1%)*	85* (52.8%)	56* (50.9%)	149[a]* (82.3%)	19* (63.3%)	36* (81.8%)	20* (57.1%)	174 [b,]* (67.2%)	35* (45.4%)	44* (49.4%)
Age, years (%)[c]										
≤ 30	7 (1.5%)	2 (1.2%)	2 (1.8%)	3 (1.7%)	0	2 (4.5%)	4 (11.4%)	1 (0.4%)	0	0
31–45	101 (21%)	34 (21.1%)	33 (30%)	31 (17.1%)	3 (10%)	13 (29.5%)	20** (57.1%)	48 [b] (19.3%)	15 (23.1%)	5 (5.6%)
46–60	256 (53.1%)**	93 (57.8%)**	54 [a] (49.1%)**	94 (51.9%)**	15 (50%)**	16 (36.4%)	11 (31.4%)	133 [b,]** (53.4%)	36 ** (55.4%)	60 [b,]** (67.4%)
61–70	99 (20.5%)	24 (14.9%)	21 (19.1%)	47 [a] (26%)	7 (23.3%)	11 (25%)	0 [b]	60 [b] (24.1%)	11 (16.9%)	17 (19.1%)
> 70	19 (3.9%)	8 (5%)	0 [a]	6 (3.3%)	5 (1.7%)	2 (4.5%)	0 [b]	7 (2.8%)	3 (4.6%)	7 (7.9%)
Employed in, number (%)										
Public health institution	411[#] (85.3%)	150 [#] (93.2%)	96[#] (87.2%)	146 [#] (80.7%)	19[#] (63.3%)	37[#] (84.1%)	32[#] (91.4%)	211[#] (84.7%)	58[#] 89.2(%)	73[#] (82.0%)
Private health institution	42 (8.7%)	1 (0.6%)	9 (8.1%)	29[c] (16.2%)	3 (10%)	4 (9.1%)	3 (8.6%)	25 (10%)	4 (6.2%)	6 (6.7%)
Pensioners	29 (6%)	10 (6.2%)	5 (4.5%)	6 (3.3%)	8 (26.7%)	3 (6.8%)	0	13 (5.2%)	3 (4.6%)	10 (11.2%)

Data are presented as number and percentage of the number of respondents from the subgroup indicated in the column header except for the first row;
MD – doctor of medicine; dr. sc. – Doctor scientiae
*significant ($p < 0.05$) differences between males and females;
**significant difference in relation to other age groups;
[#]significant difference compared to other institution of employment;
[a]significant difference ($p < 0.05$) in relation to the other three employment institutions;
[b]significant difference in relation to other titles;
[c]significant difference ($p < 0.05$) compared to other employees in private health institution

Table 2. Sources of informing survey participants about clinical practice guidelines (CPGs)

Information about the CPGs obtained:	Number	Undergraduate study	Postgraduate study	Meetings	Literature	Meetings & literature	All 1–5	None
Total number (%)	482 (100%)	49 (10.2%)	54 (11.2%)	152 (31.5%)*	80 (16.6%)	86 (17.8%)	28 (5.8%)	33 (6.8%)
Sex, number (%)								
Males	173	20 (11.6%)	14 (8.1%)	50 (28.9%)*	31(17.9%)	34 (19.7%)	14 (8.1%)	10 (5.8%)
Females	309	29 (9.4 %)	40 (12.9%)	102 (33) *	49 (15.9%)	52(16.8%)	14 (4.5%)	23 (7.4%)
Age, years (%)								
≤ 30	7	2 (28.6%)	0	2 (28.6%)	0	0	2 (28.6%)	1 (14.3%)
31–45	101	19 (18.8%)	9 (8.9%)	29 (28.7%)*	16 (15.8%)	9 (8.9%)	9 (8.9%)	10 (9.9%)
46–60	256	23 (8.9%)	34 (13.3)	79 (30.9%) *	44 (17.2%)	46 (18%)	14 (5.5%)	16 (6.3%)
61–70	99	5 (5.1%)	11 (11.1%)	33 (33.3%)*	16 (16.2%)	26 (26.3)	3 (3%)	5 (5.1%)
> 70	19	0	0	9 (47.4%)*	4 (21.1%)	5 (26.3%)	0	1 (5.3%)
Employed in, number (%):								
University inst.	161	24 (14.9%)	16 (9.9%)	40 (24.8%)	33 (20.5%)	23 (14.3%)	15 (9.3%)	10 6.2%)
General hospital	110	12 (10.9%)	10 (9.1%)	41 (37.3%)*	14 (12.7%)	19 (17.3%)	4 (3.6%)	10 (9.1%)
Health center	181	21 (11.6%)	25 (13.8%)	61 (33.7%)*	58 (32%)	37 (20.4%)	8 (4.4%)	10 (5.5%)
Other	30	2 (6.7%)	3 (10%)	9 (30%)	7 (23.3%)	5 (16.7%)	1 (3.3%)	3 (10%)

Data are presented as number and percentage of total number of respondent group presented in this row;
*significant difference ($p < 0.05$) in relation to all other sources of informing presented in this row

Table 3. Selected questionnaire responses about the importance and characteristics of clinical practice guidelines (CPGs)

Questions	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
CPGs enable doctors to make appropriate decisions in the prevention, diagnosis, and treatment of diseases.	278 (57.5%)	174 (36.1%)	16 (3.3%)	9 (1.9%)	5 (1%)
CPGs should contain clearly highlighted recommendations, concise explanations complemented by algorithms.	284 (58.9%)	154 (32%)	22 (4.6%)	17 (3.5%)	5 (1%)
Easy to-find online CPGs are more acceptable than printed ones.	101 (21%)	187 (38.8%)	120 (24.9%)	22 (4.6%)	52 (10.8%)
Regular presentation of new national CPGs at meetings is necessary.	324 (67.2%)	133 (27.6%)	16 (3.3%)	8 (1.7%)	1 (0.2%)

Data are presented as number and percentage of the total number of respondents

difference in the proportion of women and men was found among participants from health centers (82.3% *vs*. 17.7%). Almost five times more female than male doctors work in health centers, while the majority of male doctors were employed in university clinics and general hospitals. About half of all participants were aged 45-60 and only in the subgroup of residents the majority were aged between 31 and 45. Most of the participants (41–85%) were employed in public health institutions (Table 1).

When asked how they got information about the CPGs, one third of respondents answered that they got it at meetings. It was significantly the most common type of information compared to the others mentioned, which were almost equally distributed (Table 2). A total of 33 (7%) of respondents were not informed about CPGs so far. Such a distribution can also be seen in subgroups formed according to gender and age. Nevertheless, in the small subgroup of participants under the age of 30 an equal number of respondents received information about CPGs during undergraduate studies as well as in other possible ways. It can also be noted that a higher percentage of participants younger than 45 were uninformed about CPGs compared to older ones but the difference was not significant ($p = 0.07$). Those employed at university institutions differ from others, because the number of those informed at meetings and from the literature differs insignificantly, but a significantly smaller number was informed during the studies ($p < 0.03$).

The 452 (93.6%) of respondents agreed that CPGs enable doctors to make appropriate decisions in the prevention, diagnosis, and treatment of diseases. The following responses were received to questions about the characteristics of the CPGs: 438 (90.9%) agree that each recommendation in the CPGs should be clearly highlighted and accompanied by concise explanations; 288 (59.8%) answered that online CPGs are more acceptable than printed ones (Table 3).

When asked which CPGs the participants use, 150 (31.1%) of them answered that they use national CPGs, 76 (15.8%) international, 213 (44.2%) both national and international. While the largest percentage of doctors of medicine and residents use national CPGs (52.3% and 40%), doctors of science and professors use more international ones (30.4% and 27.8%, data not presented). When asked about the CPGs use by the participants, 43 (8.9%) answered that they do not use CPGs. However, during the last year, 101 (21%) of respondents did not use any CPGs. The largest percentage of them answered that the reason was that they were not informed about the CPGs from their profession (48.5%) or that they could not easily access CPGs (25.7%). Even 385 (79.9%) of respondents did not know that the national CPGs are available on the website

Table 4. Questionnaire responses on the use of clinical practice guidelines (CPGs)

Question	Yes
So far you have used[a]	
National CPGs	150 (31.1%)
International CPGs	76 (15.8%)
Both national and international	213 (44.2%)
You have not used any CPGs	43 (8.9%)
Have you used any CPGs at least once during the last year?	381 (79%)[a]
You did not use the CPGs during the past year because	101 (21%)[a]
You were not informed about the CPGs from your profession	49 (48.5%)[b]*
You could not easily access a CPGs from your profession	26 (25.7%)[b]*
There are no new national CPGs in your profession	10 (9.9%)[b]
You feel that the CPGs cannot be helpful in your practice	10 (9.9%)[b]
You do not have time to read CPGs	6 (5.9%)[b]
Are you aware that national CPGs are available on the website of the Ministry of Health and Academy	385 (79.9%)[a]

Data are presented as number and percentage of:
[a]total number of respondents;
[b]number of respondents who did not use the CPGs during the past year;
*significantly different in relation to other reasons for not using CPGs;
Academy – Academy of Medical Sciences of Serbian Medical Society

of the Ministry of Health and Academy (Table 4). A similar percentage of respondents agreed that regular presentation of the new national CPGs at meetings is necessary (Table 3).

Respondents had the opportunity to give textual answer about how the use of the CPGs could be improved. The majority insisted on better information about the CPGs. Also, they emphasized the importance of regular updates of the CPGs and the creation of concise CPGs with clearly highlighted recommendations and algorithms that help their use. When asked which CPGs are missing, the most frequent answers (at least 10% of respondents) are lack of national CPGs from gynecology and obstetrics, pediatrics, anesthesia, rare disease, palliative treatment.

DISCUSSION

Academy of SMS carried out a self-reported cross-sectional survey among member of SMS with the aim of checking the use of CPGs and the attitude of doctors about them. Out of a total of 482 respondents, 452 (93.8%) agreed that CPGs enable doctors to make appropriate decisions in the prevention, diagnosis, and treatment of diseases. The respondents are most often informed about CPGs at meetings and from literature but 33 (6.8%) of them had not received information about CPGs so far. About 75% of respondents use national CPGs, whether they use only national (31.1%) or both national and international (44.2%). A total of 43 (8.9%) respondents answered that they do not use CPGs, but when asked if they used any CPGs during the past year, even 101 (21%) of respondents gave a negative answer. As the most common reason for not using the CPGs was lack of information about CPGs and difficulties to access them.

Out of the 2876 SMS members to whom email was sent asking them to participate in the survey, 482 (16.8%) responded. That is a lower response rate compared to those presented in similar surveys. However, it can be noted that the response to the survey on CPGs was higher in 1990s [4, 5, 9] than in the last few years [10, 11, 12]. Most of the respondents in our survey were employed and therefore burdened with numerous obligations, and the number of different surveys is constantly increasing, so this can justify the low response rate. Nevertheless, the proportion of doctors in the sample according to gender, age and employment institutions is consistent with the proportions in the health system of Serbia published by the Institute of Public Health of Serbia [13]. Respondents are mostly informed about CPGs at meetings (30.9%) and from the literature (16.3%) or from both of those sources (17.5%). Although some other authors formulated the answers to the questions on CPGs awareness a little differently compared to our questionnaire, the data about information among their respondents was similar to ours [5, 14].

About 94% of our respondents believe that CPGs are useful for diagnosing and treating patients. A similar answer was obtained in other studies [5, 9, 14, 15]. and only a small percentage of respondents in both our and these studies believe that CPGs are not useful. The answers about the use of CPGs are not in concert with the positive opinion about their usefulness obtained by majority of our respondents. While 8.9% answered that they do not use CPGs at all, even 21% did not use any CPGs during the past year. In previously published surveys, answers about the use of CPGs were defined differently. However, in several published surveys, the percentage of respondents who do not use or rarely use CPGs is about 20%, i.e., the same as in our survey, but the percentage of those who often use the CPGs is about 40% [5, 14, 15]. As the percentage of doctors who rarely use CPGs is not negligible, special attention was paid to this problem [9, 14–20]. The most common reason for not using CPGs in our and several other surveys [9, 14, 18], as well as in one analysis of 37 surveys [17] was lack of the awareness and the inability to access CPGs. Even 80% of our respondents did not know website where national CPGs are available. Among the other barriers to using the CPGs that we and others have found are lack of time, poor applicability, uselessness in practice, reduction of the doctor's autonomy, oversimplification as "cookbook," low knowledge on CPGs [6, 9, 14, 16–21]. In the textual answers participants of our survey insist on better availability and information about CPGs and publishing of CPGs from areas for which there were no national CPGs. Opinions about CPGs format, printed or electronic, are equally distributed.

Our survey showed that doctors trust the CPGs recommendations, they are interested in national CPGs and their regular updates, but they lack timely notification about new national CPGs. Respecting the opinion of the survey participants, Academy took the following measures.

In cooperation with Republics expert commissions (consisted of experts from certain fields), Academy engaged medical experts to create new CPGs/update existing ones, particularly in the field with the most interest.

The instructions for creating CPGs were innovated and precisely defined [22], with the aim of making them not only in accordance with generally accepted recommendations and rules [3, 23] but also clear and easy to understand and apply.

Associations of doctors, institutes for public health, as well as the management of health institutions participate in regular notification of doctors about new CPGs.

CPGs are readily available on multiple physician-known websites.

Academy organize the promotion of each new CPGs as well as the presentation of the CPGs at doctors' meetings and congresses.

The study has some limitations. The response rate is low, so even though the sample consists of doctors of different specialties and ages, this is a limitation of the study. Also, we do not have data on the characteristics of doctors who did not answer the questionnaire. In addition, it is a cross-sectional study and it would be important to repeat the survey in order to see the effects of the measures we have taken to improve implementation of the CPGs.

CONCLUSION

This first survey on CPGs in Serbia showed that doctors are interested in CPGs, especially national ones, and that they consider them useful for practice. Lack of information about CPGs and access to them was found as the main barrier for their use. The interest in national CPGs and their regular updating obliges all those responsible to ensure the continuous development of CPGs and their most efficient implementation.

Conflicts of interest: None declared.

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Искуства и ставови чланова Српског лекарског друштва о водичима добре клиничке праксе

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САЖЕТАК

Увод/Циљ Академија медицинских наука Српског лекарског друштва спровела је анкету о водичима добре клиничке праксе (водичи) међу члановима Српског лекарског друштва (СЛД) са циљем да се испита употреба и став лекара о водичима.

Методе У секретаријату СЛД-а добили смо адресе 2876 чланова 20 секција СЛД-а које су случајно одабране од укупно 62 секције. Од позваних лекара одговорила су 482 (16,8%). Упитник, који су самостално попуњавали учесници, састојао се од 21 питања о демографским карактеристикама учесника, изворима информација о водичима, употреби и препрекама за примену водича.

Резултати Међу 482 лекара, учесника у анкети, било је више жена (64,1%) него мушкараца, већина је била узраста од 45 до 60 година, 411 (85,3%) је било запослено у установама у јавној својини, а већина су били специјалисти. Учесници су информисани о водичима на састанцима (30,9%), из литературе (16,3%), из оба ова извора (17,5%), током студија (20%), а 7% није до тада информисано о водичима. Готово сви учесници (452) сагласни су да су водичи корисни; 150 користи националне, 76 интернационалне, а 213 и једне и друге водиче. Током претходне године 101 (21%) учесник није користио ниједан водич. Као главни разлог некоришћења навели су необавештеност и неприступачност водича.

Закључак Лекари, учесници анкете, сматрају да су водичи корисни у пракси. Као главне узроке некоришћења водича навели су недовољно обавештавање о новим водичима и неприступачност водича. То обавезује на континуирану израду водича и редовно обавештавање лекара о њима.

Кључне речи: водичи добре клиничке праксе; анкета; став лекара; препреке

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CASE SERIES / СЕРИЈА СЛУЧАЈЕВА

Adnexal torsion in pregnancy – relying on a six-year hospital experience in solving this problem

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SUMMARY

Introduction Adnexal torsion is a serious complication in pregnancy that can lead to ovarian ischemia and necrosis. This retrospective study aimed to provide clinically driven guidelines for treatment of adnexal torsion during pregnancy.

Case report We analyzed data from 10 patients who underwent surgery for adnexal torsion between 2018 and 2023. The most common symptoms were pelvic pain, nausea, and vomiting. Laparoscopy and laparotomy were equally performed, with the choice depending on factors like trimester and tumor size. Unfortunately, adnexectomy was the most common surgery due to delayed presentation and advanced necrosis. Despite this, pregnancy outcomes were favorable, with most patients delivering live babies.

Discussion The most frequent adnexal tumor in pregnancy is the corpus luteum cyst. Several studies suggest laparoscopic management of adnexal torsion in pregnancy with excellent maternal and fetal outcomes. Both delayed diagnosis and intervention can lead to adnexal necrosis and hence increase the risk of miscarriage and maternal morbidity

Conclusion Expectant management is not recommended. Due to the increased risk of miscarriage and maternal morbidity, laparoscopy (detorsion and cystectomy) is the safest and most effective type of surgery in the first trimester. Laparotomy might be more appropriate in the third or late second trimester or with a very large adnexal mass.

Keywords: adnexal torsion; pregnancy; laparoscopy; laparotomy

INTRODUCTION

Torsion of the adnexa is an acute surgical condition and potentially lethal if left to be treated inappropriately [1]. It occurs due to rotation of the adnexa (the ovary and the fallopian tube) on their vascular axis, leading to partial or complete strangulation of the blood supply. The rotation may be either incomplete or complete, and in some cases, both the ovary and the fallopian tube are involved, leading to ischemia and necrosis) [1]. Some of the causes of adnexal torsion are sexual intercourse, exercise, and sudden movement but the most common underlying cause is an ovarian cyst greater than 3 cm in size. Pregnancy and *in vitro* fertilization (IVF) are other risk factors. Pregnancy itself double the risk of torsion up to five times, and the rough estimate is five cases per 10,000 pregnancies [2, 3]. Ovarian torsion during pregnancy is an extremely emergent condition with dire consequences for both the mother and the fetus. Large ovarian cysts such as corpus luteum cysts and ovarian hyperstimulation syndrome as a result of assisted reproductive technologies (ART) are some other risk factors for adnexal torsion [4]. Torsion of the vascular pedicle leads to venous and lymphatic obstruction with resultant stasis, ischemia, and edema [5]. This ultimately results in necrosis of the tissue and can produce a local or pelvic inflammatory process. Early diagnosis and timely surgery are required to save the adnexa and their function [1, 3, 5].

Symptoms and clinical presentation of adnexal torsion are typically non-specific, making it hard to diagnose. Common presentations in pregnant patients are subacute or acute severe pelvic discomfort, often accompanied by nausea and vomiting, and signs of acute abdomen [6]. These symptoms also occur with other diseases of the gynecologic and non-gynecologic etiology including ectopic pregnancy, rupture of a cyst, appendicitis, cholecystitis, ileus, and pelvic inflammatory disease [7], and therefore lead to diagnostic misdirection and treatment delays. It is particularly difficult to diagnose adnexal torsion during the second trimester of pregnancy since its symptoms may mimic premature labor or renal colic [8]. There are no tumor markers or blood tests that can differentiate between adnexal torsion and acute conditions during pregnancy [1].

Adnexal torsion during pregnancy is also made difficult by the enlarged uterus, especially after the first trimester [9]. The enlarged uterus pushes the adnexa posteriorly, making it difficult for physical and ultrasonographic assessment [9]. Ultrasonographic evidence of adnexal torsion consists of unilaterally swollen adnexa (large ovary with stromal edema and peripherally displaced follicles) and the presence of free fluid in the cul-de-sac. Doppler

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Table 1. Clinical manifestations associated with ovarian torsion in pregnancy

Clinical manifestation	n	%
Age (y)	27.1+/-3.9	
Parity	1.1	
Adnexal mass	7	70%
Pelvic pain	10	100%
Sudden onset	6	60%
Nausea and vomiting	5	50%
WBC count > 12 × 10^9/L	4	40%
Elevated CA 125	5	50%
Elevated CRP	4	40%
Fever	3	30%
Cul de sac fluid	7	70%

WBC – white blood cell; CA – cancer antigen; CRP – C-reactive protein

Table 2. Surgical results associated with ovarian torsion in pregnancy

Operative methods	n	%
Laparoscopy	5	50%
Laparotomy	5	50%
Mass size (cm)	7.8 ± 3.6 × 5.7 ± 3.1	(4.7–12) × (1.7 × 11)
Operative time (min)	40.1 ± 28.4	20–70
Blood loss (mL)	46.5 ± 34.3	10–20
Left side of adnexal mass	3	30%
Right side of adnexal mass	7	70%
Detorsion	1	10%
Cystectomy and detorsion	1	20%
Salpingectomy and detorsion	1	30%
Adnexectomy	6	40%
Salpingectomy	1	10%

Table 3. Comparation outcome between laparoscopy and laparotomy in pregnant women with ovarian torsion

Laparoscopy (n = 5)		Laparotomy (n = 5)	p
Age (y)	32.4 ± 2.7	27.4 ± 5.98	0.127
Parity	1.20 ± 0.45	1.2 ± 0.45	1.00
BMI (%)	21.7 ± 3.1	22.8 ± 1.9	0.167
Tu mass size (cm)	6.92 ± 2.6	10.2 ± 3.39	0.123
Operative time (min)	28.2 ± 11.58	60 ± 10	0.02
Hospital stay (d)	4 ± 1.9	9.8 ± 7.1	< 0.001
Blood loss (mL)	41.8 ± 24.1	51.7 ± 58.4	0.241
Live term baby	4 (80%)	5 (100%)	0.347
Preterm delivery	1 (20%)	2 (40%)	0.312
Abortion	1 (20%)	0	

ultrasound may demonstrate diminished or no blood flow in the vascular pedicle but not always [10].

Ischemia and necrosis of the ovary and fallopian tube occur due to restricted or absent blood supply. Delayed diagnosis and surgical intervention can lead to permanent destruction of the ovaries, tissue necrosis, and signs of an acute abdomen, which may jeopardize the pregnancy with miscarriage or premature delivery [6].

Management of adnexal torsion is either expectant or, most often, surgical. They pose risks for both the fetus and the mother. Where adnexal torsion is incomplete, expectant management (wait-and-watch without treating) is acceptable because the adnexa will spontaneously untwist and improve. However, in complete and multiple torsions, expectant management will lead to irreversible damage [11].

As mentioned, the pregnant uterus with distension, and, if any, maternal obesity, can hamper diagnosis by limiting visualization under transabdominal ultrasonography [12]. In the second trimester, visualization of the adnexa by transvaginal ultrasonography may not be sufficient due to their lateral position outside the pelvis. Computed tomography scans should be avoided lest there be fetal exposure to radiation [5]. Magnetic resonance imaging is helpful if it is available, but the most accessible imaging tool remains ultrasound [13]. Bloating, limited field of view, and altered anatomy during late pregnancy can all pose challenge to ultrasound visualization of the adnexa and contribute to the challenge of diagnosing adnexal torsion [9, 13].

Once emergency diagnosis, and short incursive episode of expectant management in some, has been achieved, adnexal torsion is treated by laparoscopic or open surgery [14]. The most common surgical procedures are cystectomy, detorsion, or, in the case of tissue necrosis, salpingo-oophorectomy [14]. Compared to laparotomy (open), laparoscopy is less invasive, involves less blood loss and thromboembolic consequences, and leads to faster patient recovery [15]. However, during the second and third trimester, the distended abdomen and intraperitoneal pressure caused by pneumoperitoneum (carbon dioxide gas insufflation of the peritoneum) can complicate laparoscopic visualization and surgical management and even carry greater risk for both the mother and fetus [14, 15].

The objective of this study was to provide clinically driven guidelines for the treatment of adnexal torsion during pregnancy, based on six-year single-center clinical data. Given the rarity of adnexal torsion during pregnancy, we aimed to analyze the conditions leading to it, report on symptoms, and evaluate treatment options and their effects on pregnancy outcomes.

CASE SERIES

This retrospective study was conducted at the Narodni Front Gynecology and Obstetrics Clinic in Belgrade, Serbia. We analyzed the medical records of pregnant patients diagnosed with adnexal torsion between 2018 and 2023. During this six-year period, 10 cases were admitted and treated. We excluded patients with a preoperative diagnosis of adnexal torsion that was not confirmed during surgery.

We analyzed demographic data, including age and parity, presenting symptoms and clinical signs, surgical approach (laparoscopy *vs*. laparotomy) and type of surgery (cystectomy, salpingectomy, detorsion, adnexectomy), duration of surgery, estimated blood loss, histopathological findings, and obstetric outcomes (miscarriage, gestational age at delivery, and mode of delivery). Additionally, we analyzed laboratory data, including white blood cell (WBC) count, C-reactive protein (CRP) levels, and cancer antigen (CA) 125 levels. We also reviewed ultrasound findings, including the size and location (left or right) of the adnexal mass, ovarian stromal blood flow [resistance index (RI)], and

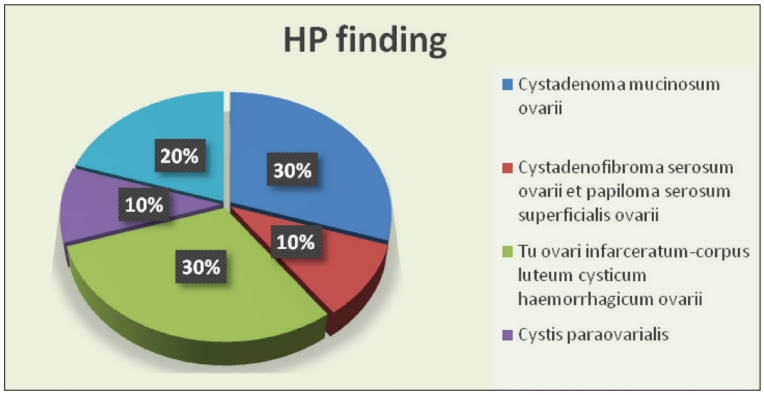

Figure 1. Histopathological (HP) finding

pregnancy status after surgery (gestational age at delivery, miscarriage, preterm delivery). Transvaginal and transabdominal ultrasound examinations were performed using the Acuson Sequoia 512 ultrasound system (Acuson, Mountain View, CA, USA; vaginal transducer 4-9 MHz; abdominal transducer 1.3 MHz. – 5.7 MHz).

Due to the small sample size, statistical analysis was limited to descriptive statistics, including mean, standard deviation (SD), standard error (SE), minimum-maximum range, median, and mode. Microsoft Excel (Microsoft, Redmond, WA, USA) was used for statistical analysis.

In 43,835 deliveries during the study period, there were 10 patients with preoperative diagnosis of adnexal torsion, which was proven by operation, with a rate of 2.3 per 10,000 pregnancies. Nine patients (90%) had adnexal torsion in the first and second trimesters, and one patient had torsion at the time of delivery. The mean age of the patients was 27.1 ± 5.1 years (18–36 years), and the mean parity was 1.1 ± 0.4 (1–3). Three (30%) of them had a history of pelvic surgery, two for ovarian cystectomy and one for an ectopic pregnancy.

The most common presenting symptom was pelvic pain (100%), which was of sudden onset in the majority, followed by vomiting and nausea (50%). Seven (70%) of the patients had palpable adnexal mass on gynecological examination, who were at the first and second trimesters of gestation. Normal blood reports were obtained in most of them, except for four of them with a mild elevation in WBC count (> 12 × 109/L) and CRP levels. CA 125 was raised in 50% of the patients. Adnexal mass was present in all (100%) patients, right-sided in 70%, with a mean diameter of 7.8 ± 3.6 × 5.7 ± 3.1 cm. Seven patients had free fluid in the cul-de-sac. Eight patients had normal uterine artery (RI) and ovarian stromal blood flow on Doppler ultrasound. In two of them, there was an undetectable blood supply to the adnexa due to necrosis of tissue and severe strangulation of the vascular pedicle.

Equal frequency was applied in using laparoscopy and laparotomy. Patients in the first trimester, particularly with a small adnexal mass, were treated by laparoscopy as the procedure of choice. Laparotomy was reserved for patients in the third trimester or for bigger adnexal masses.

Adnexectomy was the most common procedure (60%), which likely reflects referral and diagnostic delays, and, as a result, more advanced disease at surgery.

As for comparison between laparoscopy and laparotomy, we noted that hospital stay and operative time were both significantly shorter in the laparoscopy group. There was no difference between the two groups regarding the outcome of pregnancy. There was only one miscarriage (10%).

Histopathological assessment was carried out that proved that 30% of the patients had an ovary mucinous cystadenoma, 30% had a hemorrhagic corpus luteum cyst with ovarian infarction, and 20% had a large follicular cyst as the cause for adnexal torsion. There were no postoperative infections (Figure 1).

Ethics: This study was approved by the Ethics Committee of the Narodni Front Obstetrics and Gynecology Clinic, Belgrade, Serbia (No: 22008/2024/022318).

DISCUSSION

The reported incidence of adnexal torsion varies in the literature, with rates of 5.9 per 100,000 in non-pregnant women and 1.6–5 per 10,000 in pregnant women [2]. Adnexal torsion is more common during pregnancy due to the presence of corpus luteum cysts and increased ovarian mobility caused by hormonal changes [5]. Our study found a lower incidence of 0.023%, which may reflect differences in population characteristics or reporting practices.

Eight of our patients (80%) also had in the first and initial second trimester (4th to 16th week gestation) a palpable adnexal mass on one side. The smaller uterine size during this period facilitated palpation. As was previously cited [6], the first trimester was the most common presentation time for adnexal torsion (60% of our study cases). The clinical presentation of adnexal torsion in our series was similar to that seen in non-pregnant women, with non-specific symptoms most being the most common. Sudden unilateral pelvic pain was the most common symptom, most commonly worsening with time and nausea and vomiting [16]. Fever and acute abdomen can be present as necrosis of tissue progresses [7]. Differential diagnosis in pregnancy is based on gestational age and may be miscarriage, hematoma retroplacental, and rupture of the uterus [8]. In the current study, all the patients presented with acute onset of pelvic pain on one side, and 50% presented with nausea and vomiting.

A palpable adnexal mass, typically larger than 5 cm, was detected on examination in 70% of our patients, most of whom presented in the first trimester. Palpation was painful and discomforting [1]. This relatively high rate of palpable masses likely reflects the more advanced gestational age of presentation in our series. While there is no specific laboratory test for adnexal torsion, we recorded subtle increases in WBC count, CRP, and CA 125 in some patients. It is thus conceivable that subtle CRP and CA 125 increases are non-specific but possibly evocative of adnexal torsion [10]. Ultrasound remains the gold standard

for adnexal torsion diagnosis in pregnancy, with a readily available non-invasive imaging modality. Color Doppler and measurement of RI in the ovarian stroma can be employed to assess the ovarian blood supply and monitor possible ischemia. The core of ultrasound diagnosis of adnexal torsion is an edematous swollen ovary (larger than the contralateral one), low or absent blood flow, and free fluid in the pelvis [10]. Incidence of ovarian torsion after stimulation of ovaries in IVF is 0.025% to 0.2% [17]. Adnexal torsion is enhanced by assisted reproductive techniques through risk of ovarian hyperstimulation syndrome and ovarian enlargement. In our study, 40% of patients had a history of IVF, which establishes the association between ART and adnexal torsion [17].

The most common adnexal tumor in pregnancy is the corpus luteum cyst, but dermoid cysts, and cystadenomas are more common in non-pregnant women [17]. The literature suggests that the most frequent histopathological diagnoses of adnexal torsion are mature cystic teratoma (46.3%), serous cystadenoma (17.5%), and mucinous cystadenoma (11.3%) [17]. Our findings were for the most part consistent with these reports, with corpus luteum cysts being found in 40%, mucinous cystadenomas being found in 30%, and serous cystadenomas in 10%. Greater adnexal masses (greater than 5 cm) have a higher risk of torsion. Risk appears to be highest between 10- and 17-weeks' gestation [7]. The average size of the tumor was 7.8 × 5.8 cm in our experience, and 40% of patients had torsion occur between 10 and 17 weeks, consistent with this. While a few reports have suggested that cysts larger than 15 cm will be malignant [8], in our population, we could not find any malignant adnexal tumors.

Several studies suggest laparoscopic management of adnexal torsion in pregnancy with excellent maternal and fetal outcomes [11]. A meta-analysis of 163 studies by Didar et al. [15] showed laparoscopy to be the most common surgical intervention (56.88%), and open surgery was performed in only 10% of patients [16]. Detorsion with cystectomy (29.06%), salpingo-oophorectomy (27.32%), and detorsion (18.31%) were the most frequent operations [14]. Laparotomy and laparoscopy were performed with the same frequency (50% each) in our study. Laparotomy was reserved for enormous adnexal masses or late gestational ages. Adnexectomy was the most common procedure (70%), perhaps due to delay in diagnosis and presence of advanced disease (tissue necrosis or gangrene) at the time of surgery. Cystectomy, salpingectomy, or detorsion was performed in the remaining 30% of patients. A retrospective study of 60 adnexal torsion patients found the likelihood of ovarian preservation was highest if surgery were performed within four hours of symptom onset (83% *vs.* 56% > 4 hours, p = 0.39) [5, 6]. This indicates the need for urgent early diagnosis and intervention to maximize the chances of preserving the ovary. Compared to open surgery, laparoscopy has several advantages, including less invasiveness, less blood loss, less postoperative pain, faster recovery, lower risk of thromboembolism, and shorter hospital stay [15]. Pregnancy laparoscopy may also enhance visualization and minimize uterine manipulation, with potential reduction in the risk of miscarriage, preterm labor, and premature rupture of membranes. There are several studies that have established the safety and feasibility of laparoscopy during pregnancy [14]. American Society of Gastrointestinal and Endoscopic Surgeons recommendations prefer the use of laparoscopy in the management of acute abdominal conditions during pregnancy [12].

Our retrospective review of laparoscopy versus laparotomy for adnexal torsion in pregnancy revealed no marked difference in pregnancy outcome. However, patients who underwent laparoscopy experienced less pain, less blood loss, shorter hospital stay, and earlier recovery. Based on these findings, we recommend laparoscopy as the method of choice for adnexal torsion in pregnancy, especially during the first trimester.

CONCLUSION

Adnexal torsion is a pregnancy complication that, albeit unusual, is severe. The most common presenting symptoms of acute-onset unilateral pelvic pain, nausea, and vomiting should prompt urgent referral to a tertiary facility. Both delayed diagnosis and intervention can lead to adnexal necrosis and hence increase the risk of miscarriage and maternal morbidity [18, 19]. While there are no specific laboratory tests for adnexal torsion, an elevated WBC count and CA 125 can be suggestive. ART can increase the risk of adnexal torsion in pregnancy.

The most frequent underlying reason for adnexal torsion in pregnancy is the corpus luteum cyst. Expectant management is not typically recommended due to increased miscarriage and maternal morbidity. Laparoscopy appears to be the safest and most efficacious type of surgery in the first trimester [18]. Detorsion and cystectomy are the operations of choice. Laparotomy might be more appropriate in the third or late second trimester or with a very large adnexal mass. After 20 weeks of gestation, the distended uterus may complicate laparoscopic visualization and manipulation, and the Trendelenburg position may impair maternal respiratory function.

Our findings show that laparotomy and laparoscopy are equivalent in pregnancy outcome but that laparoscopy has some perioperative advantages. We would recommend a multicenter study of a larger group of patients to further evaluate the optimal management of adnexal torsion during pregnancy.

Conflicts of Interest: None declared.

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Торзија аднекса у трудноћи – ослањање на шестогодишње болничко искуство у решавању овог проблема

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САЖЕТАК

Увод Торзија аднекса је озбиљна компликација у трудноћи која може довести до исхемије и некрозе јајника. Ова ретроспективна студија имала је за циљ да пружи клинички засноване смернице за лечење торзије аднекса током трудноће. Анализирали смо податке 10 болесница које су оперисане због торзије аднекса у периоду од 2018. до 2023. године.

Прикази болесника Најчешћи симптоми били су бол у карлици, мучнина и повраћање. Лапароскопија и лапаротомија су примењиване подједнако често, при чему је избор зависио од фактора попут триместра трудноће и величине тумора. Нажалост, најчешћи захват била је аднексектомија због касног јављања пацијенткиња и узнапредовале некрозе. Упркос томе, исходи трудноће били су повољни, а већина пацијенткиња родила је живу новорођенчад.

Дискусија Најчешћи аднексални тумор у трудноћи је циста жутог тела. Више студија указује на то да лапароскопско лечење торзије аднекса у трудноћи даје одличне исходе по мајку и плод. Касно постављање дијагнозе и одлагање операције могу довести до некрозе аднекса и тиме повећати ризик од побачаја и морбидитета мајке.

Закључак Експектативно лечење се не препоручује. Због повећане могућности побачаја и мајчиног морбидитета, лапароскопија (деторзија и цистектомија) најбезбеднија је и најефикаснија врста операције у првом тромесечју. Лапаротомија може бити прикладнија у трећем или касном другом тромесечју или код великих аднексалних маса.

Кључне речи: торзија аднекса; трудноћа; лапароскопија; лапаротомија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Foreign body aspiration misdiagnosed as asthma – a case report and literature review

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SUMMARY

Introduction Foreign body aspiration (FBA) is a rare but potentially life-threatening event occurring most commonly in children and older adults. The clinical presentation of occult FBA in adults is usually subtle, manifesting as chronic cough, wheezing, and exertional dyspnea. A delay in diagnosis is not uncommon for weeks or even months due to the subtle nature of the symptoms. Direct visualization via bronchoscopy continues to be the gold standard for diagnosing and treating FBA. In this report, we present a case of a man treated for five years for difficult-to-treat asthma with unnoticed tooth aspiration.

Case outline A 63-year-old non-smoker male patient was referred to the Clinic of Pulmonology, University Clinical Center of Serbia, with chief complaints of dyspnea and chronic cough over the course of five years. He sought medical help several times and was diagnosed and treated as late-onset bronchial asthma, which failed to improve even with optimized therapy. A high-resolution CT scan was performed, which showed a calcified body in the left main bronchus measuring 16 × 13 mm, which was later extracted via flexible bronchoscopy. There was immediate symptom relief after extraction. Pulmonary function tests after the procedure showed no bronchial obstruction, with a negative bronchodilator test.

Conclusion A difficult-to-manage asthma requires a thorough workup to rule out alternative diagnoses. Foreign body aspiration, even though a rare occurrence in adults without obvious risk factors, must be considered to prevent long-term complications.

Keywords: asthma; foreign body aspiration; bronchoscopy

INTRODUCTION

Foreign body aspiration (FBA) is a rare but potentially life-threatening event occurring most commonly in children and older adults [1]. Adult patients frequently have underlying risk factors for aspiration, such as altered mental status, alcohol or drug intoxication, and neuromuscular weakness [2].

The clinical presentation of occult FBA in adults is usually subtle, manifesting as chronic cough, wheezing, exertional dyspnea, or hemoptysis. A delay in diagnosis is not uncommon for weeks or even months due to subtle symptoms [3]. In adults, aspiration occurs most commonly in the right bronchial tree [4]. These patients are frequently misdiagnosed as having pneumonia or difficult-to-treat asthma [5]. Direct visualization via bronchoscopy continues to be the gold standard for diagnosing and treating FBA [6].

In this report, we present a case of a man treated for five years for difficult-to-treat asthma with unnoticed tooth aspiration.

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CASE REPORT

A 63-year-old nonsmoker male patient was referred to the Clinic of Pulmonology, University Clinical Center of Serbia, with chief complaints of dyspnea and chronic cough over the course of five years. He sought medical help several times and was diagnosed and treated for late-onset asthma with high doses of inhaled corticosteroids / long-acting beta2-agonists and underwent multiple courses of antibiotics. During this period, the patient underwent routine laboratory tests, which did not reveal clinically significant abnormalities. While he received multiple courses of antibiotics for presumed respiratory infections, these were prescribed empirically based on clinical symptoms, without alarming laboratory findings, and no chest radiography was performed at that time. Even with optimized asthma therapy, there was no clinical improvement.

Medical history was negative for other illnesses. Subsequently, the patient reported blood-streaked sputum over the previous two months. He was admitted to our clinic for further evaluation. On physical examination performed by a pulmonologist, he was eupneic, with an oxygen saturation of 98%, and there were no obvious signs of bleeding diathesis. On auscultation, unilateral left-sided wheezing was noted with decreased breath sounds. Chest X-ray showed a focal consolidation of the left lower lobe (Figure 1). A high-resolution computed tomography (HRCT) scan was performed, which showed a calcified body in the left main bronchus measuring 16 × 13 mm with surrounding mucosal inflammation (Figure 2). A detailed medical history was retaken, during

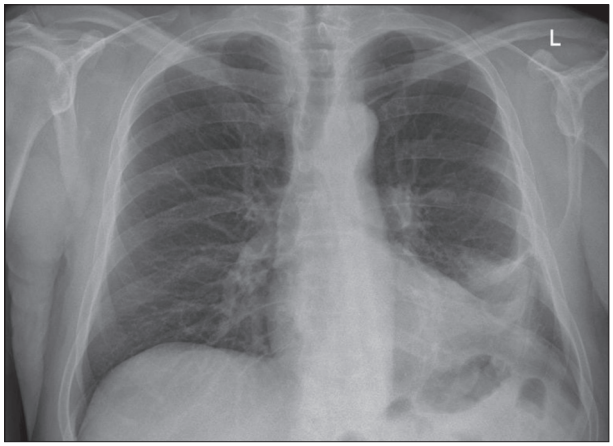

Figure 1. Chest X ray showing a focal consolidation of the left lower lobe

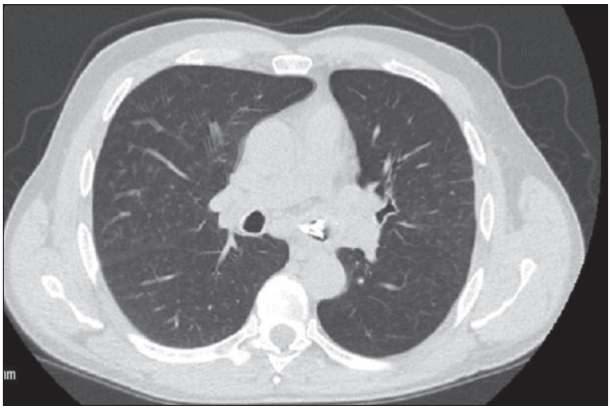

Figure 2. High-resolution computed tomography of the lungs showing a calcified body in the left main bronchus

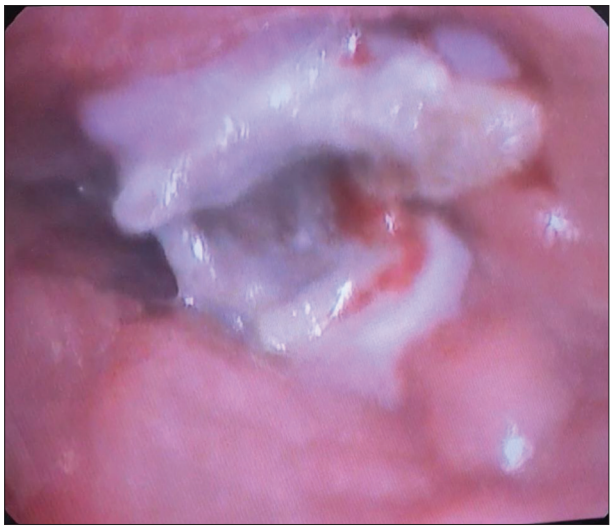

Figure 3. Bony foreign body in the left main bronchus with surrounding granulation tissue and signs of post-obstructive pneumonia

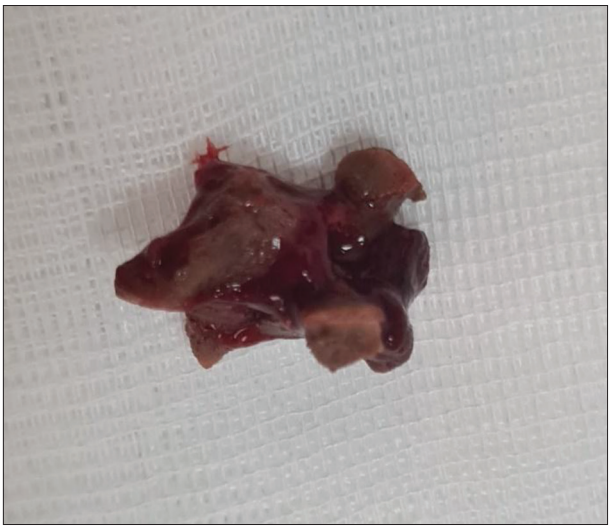

Figure 4. Extracted tooth

which he reported that approximately five years prior to presentation he awoke without a tooth (an incisor), which had previously undergone a dental procedure. Except for leukocytosis ($13.7 \times 10^3/mm^3$) and elevated C-reactive protein (53 mg/L), all laboratory parameters were normal. Flexible bronchoscopy via the transoral route was performed under local anesthesia. The entrance to the left main bronchus was found to be stenotic. Lodged in the middle part of the left main bronchus, a bony foreign body was observed just below the level of central carina with surrounding granulation tissue and signs of post-obstructive pneumonia – edematous mucosa with mucopurulent secretions (Figure 3). Mechanical extraction was performed using alligator forceps, and the foreign body was identified as a tooth approximately 20 mm in length (Figure 4). Extraction combined with partial removal of granulation tissue and secretions resulted in immediate symptom relief. Pulmonary function tests after the procedure showed no bronchial obstruction, with a negative bronchodilation test. Bronchial washings taken for Gram and Ziehl–Neelsen staining and cultures were negative. Control bronchoscopy was performed after three days, which showed small amounts of remaining granulation tissue (Figure 5). The patient was discharged and remained asymptomatic on routine follow-up. A follow-up HRCT performed after two weeks showed no signs of a foreign body.

Ethics: The principles of the Declaration of Helsinki were respected in this case report. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. All identifying details have been removed or anonymized to ensure patient privacy.

DISCUSSION

FBA is a medical emergency that necessitates prompt diagnosis and treatment [7]. A recent global epidemiological assessment demonstrated that FBA remains relatively infrequent overall, with a notably lower incidence in adult populations over recent decades despite ongoing cases being documented across age groups [8]. In contrast, another study yielded different results, demonstrating that FBA is frequently misdiagnosed as other respiratory diseases, including asthma, chronic obstructive pulmonary disease,

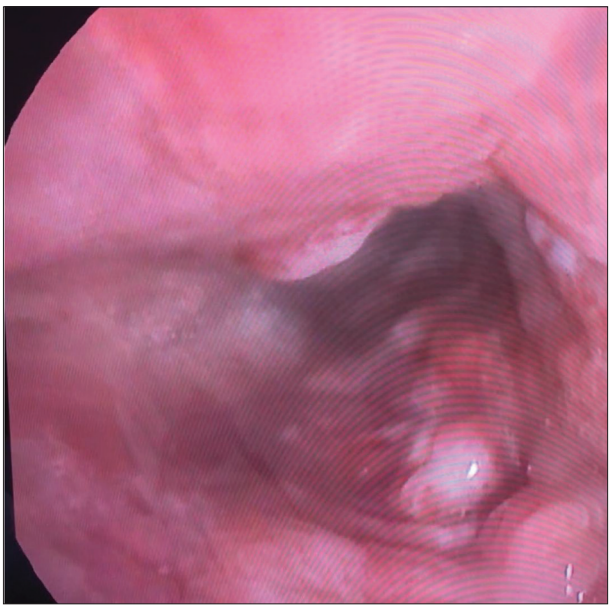

Figure 5. Follow-up bronchoscopy after the extraction, showing small amounts of remaining granulation tissue

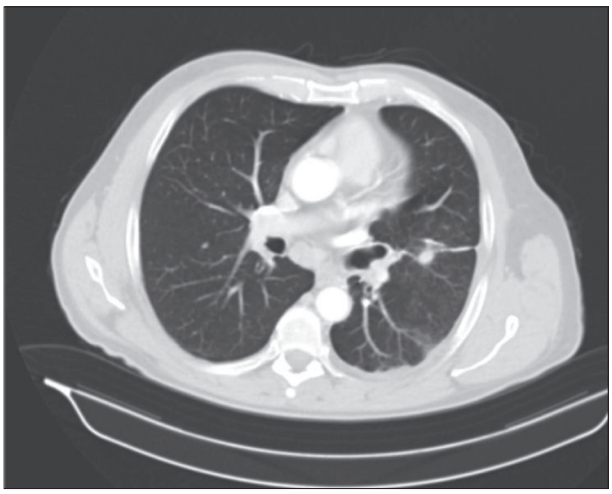

Figure 6. Follow-up high-resolution computed tomography performed two weeks later showed no signs of a foreign body

recurrent pneumonia, and bronchiectasis [6, 9, 10], similar to what has been found in our case report. We do not have precise data on the incidence of foreign body aspiration in our institution. Approximately 12 cases are diagnosed over a six-month period. As a large referral center, we encounter a relatively high number of foreign bodies. Also, this was the first case in our experience of a misdiagnosed foreign body aspiration involving a tooth. According to the most recent guidelines, difficult-to-treat asthma is defined as asthma that is uncontrolled even with high-dose inhaled glucocorticoids and a second controller therapy [11]. Walker et al. [12] highlighted the significant clinical utility of HRCT in severe asthma evaluation. In our case, the patient had been using high- dose inhaled glucocorticoids and met the criteria for difficult-to-treat asthma, but never underwent an HRCT for further evaluation. This highlights why it is crucial to maintain a high clinical suspicion for alternative diagnoses when treating difficult-to-treat asthma with a poor response to therapy. A study from 2020 showed that common reasons for poor response to asthma therapy are incorrect inhalation technique and poor patient adherence [13]. Although rare and commonly overlooked in adults, another possible differential diagnosis is occult FBA [6]. Among the most commonly aspirated objects are meat, nuts, or fish bones, as previous data suggest [14]. By contrast, in a recent multicenter study, the most common object aspirated among adults is a tooth, as an increasing number of people undergo dental treatment. Psychiatric and neurological diseases, severe trauma, alcoholism, sedative use, poor oral hygiene, and advanced age are all risk factors for airway foreign bodies in adults [8]. Our patient did not have any obvious risk factors, which suggests the importance of including FBA in the differential diagnosis of other pulmonary diseases. Symptoms associated with FBA can sometimes be non-specific, and include cough, dyspnea, wheezing, stridor, and hemoptysis [15]. A study from 2023 pointed out that the clinical presentation of FBA varies depending on the level of obstruction and the duration of foreign- body retention in the tracheobronchial tree. In patients with occult FBA, the impacted foreign body is generally small and tends to lodge distally within the airways, leading to chronic respiratory symptoms [16]. Diagnosis of FBA can be challenging, especially when it presents with chronic, nonspecific respiratory symptoms as it did in our patient. According to Bhatti et al. [17], a delay in the diagnosis of FBA can lead to complications such as recurrent pneumonias, bronchiectasis, recurrent hemoptysis, and lung abscesses. The initial step in diagnosing FBA is most commonly a chest X-ray, which can be useful; however, it is limited in specificity, as the overlying mediastinal structures can obscure the foreign body [18]. A high index of suspicion should be kept for FBA if there are secondary changes on chest X-ray, such as atelectasis or obstructive pneumonia [15]. Unlike the chest X-ray, HRCT has a reported sensitivity of 100% for detecting a foreign body, and a specificity of 66.7% according to one comparison study [19]. In our case, where the correct diagnosis was delayed, an earlier HRCT would have been crucial for prompt treatment.

Bronchoscopy has an established role in treating FBA [20]. There is no clear protocol regarding the type of initial bronchoscopy used for treating FBA. Literature data from a cohort study reports a success rate of 98% with flexible bronchoscopy, of which 75% of the cases were achieved by a single procedure, and 25% of the cases requiring more than two procedures. In the same study, formation of granulation tissue was observed in 44% of the cases [21]. In a large study consisting of 25,998 adult patients who aspirated a foreign body, treatment with flexible bronchoscopy was associated with lower rates of morbidity and mortality compared with rigid bronchoscopy, as general anesthesia is avoided [22].

Recent studies highlight that flexible bronchoscopy can be enhanced with adjunctive tools such as baskets, snares, and electrocautery to improve extraction success, especially in complex or chronically retained foreign bodies,

underscoring the evolving role of technique adaptation in adult airway management [23].

Rigid bronchoscopy can be used as a backup option if flexible bronchoscopy is unsuccessful [3]. Recent data demonstrate that when flexible bronchoscopy fails to retrieve certain airway foreign bodies, particularly those that are large or difficult to grasp, rigid bronchoscopy is frequently employed successfully as a complementary intervention, highlighting its continued importance in complex adult cases [24].

For our patient, flexible bronchoscopy with forceps extraction was sufficient for complete removal of the foreign body.

In conclusion, difficult-to-treat asthma requires a thorough workup to rule out any alternative diagnoses. Foreign body aspiration, although rare in adults without obvious risk factors, should always be considered to prevent long-term complications.

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Аспирација страног тела погрешно дијагностикована као астма – приказ болесника и преглед литературе

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САЖЕТАК

Увод Аспирација страног тела је ретко, потенцијално животно угрожавајуће стање, које се најчешће догађа код деце и старијих особа. Клиничка слика окултне аспирације страног тела је најчешће суптилна, са неспецифичним симптомима попут хроничног кашља, визинга и интолеранције напора. Постављање тачне дијагнозе се неретко одлаже недељама, понекад и месецима, услед неспецифичних симптома. Бронхоскопска директна визуелизација и екстракција представљају златни стандард у дијагнози и терапији аспирације страног тела. Приказујемо случај болесника који је пет година лечен због тешке астме са недијагностикованом аспирацијом зуба.

Приказ случаја Болесник стар 63 године, непушач, упућен је на Клинику за пулмологију Универзитетског клиничког центра Србије, са главним тегобама у виду отежаног дисања и хроничног кашља које трају пет година уназад. Прегледан је од стране лекара у више наврата, након чега је постављена дијагноза бронхијалне астме са касним почетком; међутим није имао побољшање упркос максимално оптимизованој терапији. Учињен је скенер високе резолуције грудног коша, на коме је уочено калцификовано тело у лумену левог главног бронха димензија 16 × 13 *mm*, које је накнадно извађено флексибилном бронхоскопијом. Одмах након вађења дошло је до побољшања симптома. Тестови плућне функције учињени након процедуре били су без бронхоопструкције, са негативним бронходилатацијским тестом.

Закључак Пре постављања дијагнозе тешке астме, неопходно је детаљно испитати све алтернативне дијагнозе. Аспирација страног тела, иако је ретко стање код одраслих без јасних фактора ризика, мора се узети у разматрање при диференцијалној дијагнози како би се спречиле дуготрајне компликације.

Кључне речи: астма; аспирација страног тела; бронхоскопија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Follicular lymphoma originating from the gallbladder – case report and literature review

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SUMMARY

Introduction Follicular lymphoma belongs to the group of indolent lymphoid neoplasms originating from mutated germinal center B cells, characterized by a nodular or follicular histological pattern of infiltration. Primary involvement of extranodal sites is rare. The aim of this study is to present the clinical, histological, and immunohistochemical features of a rare case of gallbladder follicular lymphoma, along with a literature review, highlighting key diagnostic and therapeutic considerations.

Case outline We present the case of a 60-year-old female patient who underwent laparoscopic cholecystectomy for ultrasound-confirmed gallbladder calculosis. Based on the morphological findings, supplemented by immunohistochemical analysis, the lesion identified in the tissue samples corresponded to follicular non-Hodgkin lymphoma.

Conclusion Gallbladder lymphoma is a rare malignancy often found incidentally. Diagnosis relies on histology and immunohistochemistry, which distinguish it from adenocarcinoma and other lymphomas. Accurate classification is essential for proper management and prognosis.

Keywords: follicular lymphoma; MALT; gallbladder; non-Hodgkin lymphoma; immunohistochemistry

INTRODUCTION

Follicular lymphoma is an indolent lymphoid neoplasm originating from mutated germinal center B-cells, characterized by a nodular or follicular histological pattern of infiltration [1]. The tumor is composed of a mixture of centrocytes and centroblasts (small cleaved follicular center cells and large noncleaved follicular center cells) (Figure 1). Follicular lymphoma is the second most common subtype of all non-Hodgkin lymphomas (NHL) and the most common indolent lymphoma. It accounts for 20–25% of adult NHL cases in the United States, with an annual incidence of approximately 14,000 new cases. The median age at diagnosis is 59 years, and it is more common in women, with a female-to-male ratio of 1.7:1.0 [2]. The classic cytogenetic abnormality in follicular lymphoma is the translocation t(14;18)(q32;q21), resulting in juxtaposition of the BCL-2 gene on chromosome 18q21 with the immunoglobulin heavy chain gene on chromosome 14 [3, 4]. Initial diagnostic workup includes a thorough medical history, detailed physical examination, laboratory tests, lymph node biopsy, bone marrow aspiration and biopsy, and computed tomography (CT) [5]. In 2004, an international cooperative group proposed the Follicular Lymphoma International Prognostic Index (FLIPI) [6, 7]. The estimated five-year overall survival for patients with high FLIPI scores is approximately 50%. Patients with follicular lymphoma may be treated with mono- or polychemotherapy [8, 9]. The introduction of rituximab has significantly altered the disease course.

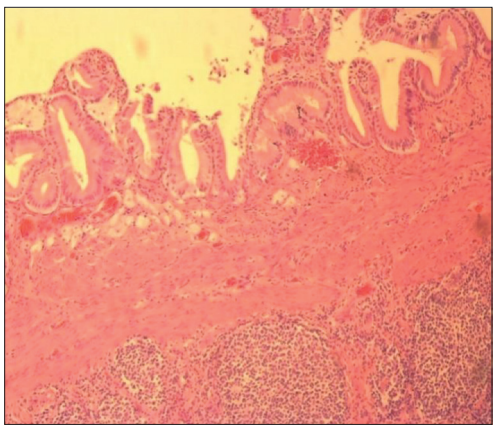

Figure 1. Follicular lymphoma of the gallbladder (H&E; × 10)

CASE REPORT

The patient was a 60-year-old woman referred to a hematologist with a diagnosis of non-Hodgkin lymphoma. Because of interscapular pain accompanied by nausea and loss of appetite, and in the context of gallbladder cholelithiasis confirmed by ultrasound one month earlier, a laparoscopic cholecystectomy was performed. Upon review of

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the histopathology report (macroscopic description): The material submitted for pathological analysis consisted of an opened gallbladder with emptied contents, measuring approximately 7 × 2 cm. The external surface was partially smooth and shiny, and partially torn. The internal surface was yellow-green and velvety. In the region of the gallbladder body, beneath the mucosa, there was a poorly demarcated thickening (lesion) measuring 2.5 × 1.3 cm, appearing whitish, solid, and shiny on the cut surface. Microscopic description is as follows: the histologically examined material consisted of gallbladder tissue samples. In the sections taken from the macroscopically described lesion within the gallbladder wall, a lesion composed predominantly of a uniform lymphoid cell population was present. The lymphoid infiltrate was made up of small to medium-sized cells with oval nuclei, granular chromatin, and visible nucleoli. The cytoplasm was scant. Focally, lymphoid cells were also present within the surface epithelium and within glandular epithelium. The described histologic appearance in the gallbladder samples was consistent with non-Hodgkin lymphoma. The differential diagnosis of gallbladder lymphoma includes several lymphoma subtypes: follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and MALT (mucosa-associated lymphoid tissue) lymphoma. Although they arise in the same organ, these different lymphoma types have distinct morphological and immunophenotypic profiles. Based on morphological findings and immunohistochemical analysis (LCA+, CD20+, CD10+, BCL2+, CK7-, synaptophysin-), the changes observed in the tissue samples were consistent with follicular non-Hodgkin lymphoma of B-cell phenotype, low-grade. To assess the extent of disease, a full clinical, laboratory, and radiological evaluation was performed, as well as PET/CT to evaluate disease activity. Laboratory findings revealed mild neutropenia, mild thrombocytopenia, and hypoalbuminemia, with normal levels of LDH, uric acid, and beta-2 microglobulin. PET/CT findings: Right occipital lymph node with an axial diameter of 10 mm and increased uptake of 18F-FDG (SUVmax 7.21). In the right axilla, multiple lymph nodes with the largest measuring 11 mm and increased uptake (SUVmax 4.21). On the left inguinal side, multiple lymph nodes with diameters up to 11 mm and increased uptake (SUVmax up to 9.6). On the right inguinal side, multiple subcentimeter lymph nodes with moderately increased uptake (SUVmax up to 2.76). Multiple foci of increased 18F-FDG uptake in almost all bones of the axial skeleton (SUVmax up to 23.46 in the body of the Th6 vertebra). Compression fractures of Th7 and Th8 were previously documented on CT. The patient was presented to the Multidisciplinary Team with a diagnosis of non-Hodgkin lymphoma (follicular grade I), clinical stage IV B, ECOG performance status: 0, FLIPI 1: 2 (intermediate risk), FLIPI 2: 1 (low risk), R-IPI: 2 (good prognostic index). The Team recommended initiation of immunochemotherapy (ICT) following the R-CHOP protocol, for eight cycles.

The patient received eight cycles of ICT per the protocol. A follow-up CT of the thorax, abdomen, and pelvis was performed. No enlarged lymph nodes were identified. Compression fractures of Th7, Th8, and Th9 were noted. Remission of the primary disease was confirmed. The patient was again presented to the Multidisciplinary Team, which recommended maintenance therapy with rituximab every three months for two years. The patient received four cycles of maintenance therapy, which was then discontinued due to COVID-19 infection. Clinical and laboratory evaluation is conducted every three months, and radiological evaluation every six months.

Ethics: Written informed consent was obtained from the patient for publication of this case report. Approval of the Ethics Committee was obtained (No. 01-19-515-2/25).

DISCUSSION

Primary extranodal involvement of follicular lymphoma is rare. In the domestic literature, there has not been a previously reported case of follicular lymphoma diagnosed by cholecystectomy. In 2003, Ferluga et al. [10] published a report describing a 63-year-old woman with symptoms of biliary obstruction. Ultrasound raised suspicion of a Klatskin tumor. Based on histopathology and immunohistochemical analysis, the tumor was classified as extranodal follicular lymphoma, grade 2. This was the first reported case worldwide of extranodal follicular lymphoma in this location. In this case, the postoperative follow-up of more than three years was completely uneventful, without any symptoms or signs of disease recurrence.

In 2004, Jelić et al. [11] published a case report describing an isolated primary extranodal lymphoma limited to the gallbladder in a 70-year-old woman with symptomatic cholelithiasis. According to the literature, the most common type of lymphoma in this location is MALT. However, this case demonstrated follicular lymphoma in an organ (gallbladder) that typically lacks lymphoid tissue. At that time, it was the 16th case described.

In 2024, Nakagaki et al. [12] published an article reporting on a 70-year-old man with an ultrasound-verified polypoid lesion in the gallbladder without specific symptoms and no abnormalities in laboratory data. Histopathology with immunohistochemistry confirmed follicular lymphoma (CD10+, CD20+, BCL2+, CD23+). This case report illustrates how difficult it can be to diagnose follicular lymphoma originating in the gallbladder.

In 2025, Myers et al. [13] presented an 82-year-old male with acute abdominal pain. Computed tomography, ultrasound, and magnetic resonance imaging detected a suspicious gallbladder mass and regional lymphadenopathy. Fine-needle biopsy and immunophenotyping confirmed a diagnosis of follicular lymphoma. Nitta et al. [14] presented a 71-year-old Japanese woman with a gallbladder polyp detected on ultrasound in 2024. Pathology revealed aggressive follicular lymphoma of the liver and gallbladder. Immunohistochemical staining was positive for CD10, CD20, CD23, CD79a, BCL2, and BCL6. Nishida et al. [15] presented a male patient in his 70s. During follow-up, a gallbladder tumor was detected on CT scans. Immunohistochemical staining demonstrated that lymphocytes were positive for CD10, CD20, and BCL2. The final

pathological diagnosis was primary follicular lymphoma of the gallbladder.

Gallbladder lymphoma is a rare malignancy, most often discovered incidentally after cholecystectomy. Clinically and radiologically, it can mimic benign conditions or adenocarcinoma, making histological and immunohistochemical analysis essential for diagnosis. The differential diagnosis includes follicular lymphoma, MALT lymphoma, and diffuse large B-cell lymphoma, each distinguishable by morphology and immunophenotype. Timely recognition and accurate classification of the lymphoma are crucial for guiding appropriate management and prognosis. Future research should focus on optimizing diagnostic techniques, refining therapeutic strategies, and conducting longer-term follow-up studies to better assess patient outcomes in such a rare disease. This case highlights the need for heightened clinical suspicion and comprehensive evaluation in atypical presentations of extranodal lymphoma.

Conflict of interest: None declared.

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Фоликуларни лимфом пореклом из жучне кесе – приказ болесника и преглед литературе

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САЖЕТАК

Увод Фоликуларни лимфом спада у групу индолентних лимфоидних неоплазми пореклом од мутираних Б ћелија герминалног центра, са карактеристичним нодуларним или фоликуларним хистолошким типом инфилтрације. Примарно захватање екстранодалних локализација је ретко. Циљ рада је приказати клиничке, хистолошке и имунохистохемијске карактеристике ретког случаја фоликуларног лимфома жучне кесе, уз преглед литературе, са нагласком на кључне, дијагностичке и терапијске аспекте.

Приказ болесника Представљен је случај болеснице старе 60 година код које је због ултразвучно верификоване калкулозе жучне кесе урађена лапароскопска холецистектомија. На основу морфолошког налаза употпуњеног имунохистохемијском анализом, описана промена у добијеним исечцима одговара фоликуларном нехочкинском лимфому.

Закључак Лимфом жучне кесе је малигна болест која се често открива случајно. Дијагноза се заснива на хистологији и имунохистохемији, што га разликује од аденокарцинома и других лимфома. Прецизна класификација је неопходна за правилно лечење и прогнозу.

Кључне речи: фоликуларни лимфом; *MALT* лимфом; жучна кеса; нехочкински лимфом; имунохистохемија

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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Invasive diagnostic procedures for early-stage lung cancer – the clinical significance of novel navigational techniques in interventional bronchoscopy

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SUMMARY
Long-term statistical data worldwide on lung cancer (LC) show an overall 34% reduction in mortality compared to 1991. The primary reasons for this decline include a reduced smoking rate, earlier diagnosis, advancements in invasive diagnostic methods, and the introduction of low-dose computed tomography screening. These factors have contributed to detecting LC at earlier stages of the disease and improving timely treatment. The diagnostic sensitivity of conventional bronchoscopy for peripheral pulmonary lesions (PPL), representing early-stage LC, has historically been relatively low, ranging 30–60%. Over the past two decades, diagnostic sensitivity for PPL has improved with the development of advanced navigational techniques, such as virtual bronchoscopic navigation, electromagnetic navigation bronchoscopy, radial endobronchial ultrasound, cone-beam computed tomography, and ultrathin bronchoscopy. In the past two to three years, robotic-assisted bronchoscopy has further enhanced diagnostic navigation capabilities to their current maximum potential.
Keywords: bronchoscopy; early detection of cancer; lung neoplasms; smoking; video-assisted techniques and procedures

INTRODUCTION

Global data on lung cancer (LC) incidence and mortality have become increasingly refined in recent years and demonstrate significant geographical heterogeneity [1–4]. In the period following the COVID-19 pandemic, studies reported an increase in LC incidence and mortality worldwide, largely due to delayed diagnostic evaluation and detection at more advanced stages, which negatively affected treatment outcomes. Overall cancer incidence in 2020 was 9% lower than in 2019, with the most substantial decrease observed in asymptomatic (*in situ* and localized) disease, attributable to reductions in screening and incidental detection during routine medical visits [5]. However, when long-term LC statistical data are considered, there is a continued decrease in mortality, amounting to 34% compared with 1991 (US data). The main reasons for the reduced LC mortality are the decline in the smoking rate, earlier detection, advances in invasive diagnostic modalities, and the implementation of low-dose computed tomography (LDCT) screening, all contributing to earlier-stage diagnosis and timely treatment [6]. Obtaining an adequate bronchial or pulmonary tissue sample is crucial not only for establishing a diagnosis of LC but also for determining the molecular and immunologic profile of the lung tumor [7]. When the objective of invasive pulmonary diagnostics is early-stage diagnosis, sampling typically involves small peripheral pulmonary lesions (PPL), where flexible bronchoscopy has replaced rigid bronchoscopy completely. New image-guided bronchoscopic techniques have increased diagnostic yield and reduced complication rates compared with conventional bronchoscopy. These include virtual bronchoscopic navigation (VBN), electromagnetic navigation bronchoscopy (ENB), radial endobronchial ultrasound (R-EBUS), cone-beam computed tomography (CBCT), ultrathin bronchoscopy (UTB), and robotic bronchoscopy [8]. Advanced bronchoscopic imaging techniques

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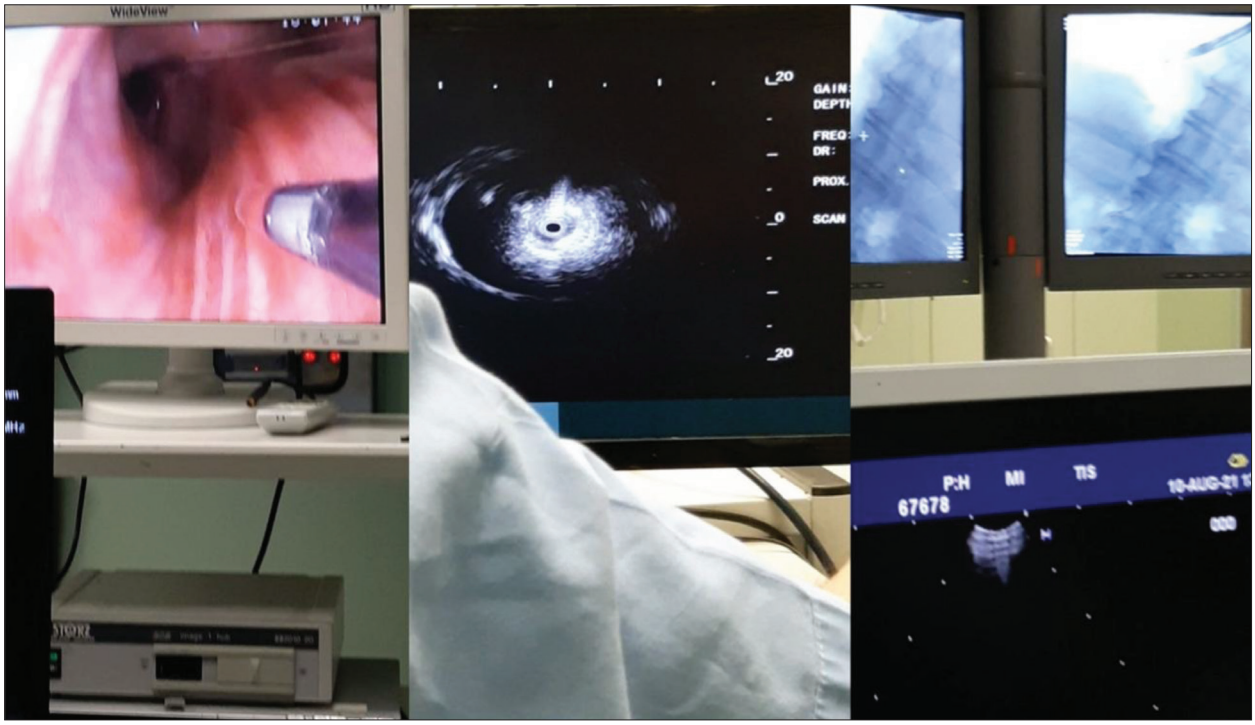

Figure 1. Radial endobronchial ultrasound [16]

such as autofluorescence imaging and narrow-band imaging can also detect changes in the bronchial epithelium, including carcinoma *in situ*, 40% of which may progress to invasive carcinoma. Early detection allows these lesions to be treated endoscopically, for example, by endobronchial brachytherapy or photodynamic therapy [9].

Transthoracic needle aspiration and biopsy (TTNA/TTNB)

TTNA/TTNB are well-established and safe diagnostic techniques for obtaining cytologic or histologic samples from PPL. Over time, several imaging modalities have been used to guide needle placement, including plain radiography, fluoroscopy, computed tomography (CT), ultrasound, and electromagnetic-navigated TTNA [10]. These TTNA/TTNB methods have become procedures of choice for diagnosing peripheral pulmonary nodules due to their high diagnostic yield. A sample can be obtained via needle biopsy or fine needle aspiration for cytology and cell-block preparation, and both sample types are suitable for molecular analysis. The CT-guided TTNA and TTNB demonstrate diagnostic yields ranging from 64% to 97% [11]. The most common complications include pneumothorax (rate to ~25%, with ~5–6% requiring intervention) and hemoptysis (5% prevalence) [12]. Thoracic oncologists generally avoid TTNA/TTNB for PPL because these lesions are potentially resectable. However, this approach is preferred for suspected small cell lung carcinoma, for which surgery is not indicated. When surgery is contraindicated for any reason, TTNA/TTNB method is strongly recommended.

Bronchoscopy – new diagnostic procedures

Interventional pulmonology has expanded rapidly since the first groundbreaking studies in 2004 which demonstrated the usefulness of R/L-EBUS for diagnosing pulmonary lesions and LC staging. The development of interventional pulmonology has significantly improved the management of LC, particularly early-stage non-small cell LC [12, 13].

R-EBUS with and without guide sheath (GS)

Although conventional flexible bronchoscopy can be used for diagnosing PPL, its diagnostic yield is variable and generally lower than that of CT-guided TTNA/TTNB. This limitation facilitated the development of newer bronchoscopic techniques, such as R/L-EBUS [14]. Several studies have confirmed that a multimodal approach that combines R-EBUS with VBN or ENB has an improved diagnostic yield when compared to using only R-EBUS, as navigational systems compensate for instances in which R-EBUS fails to reach the lesion [15]. The key limitation of R-EBUS is the lack of real-time tissue sampling, as the radial probe (RP) must be removed from the bronchoscope's working channel before biopsy instruments are introduced. Maintaining a consistent position of the RP withdrawal and instrument insertion is challenging (Figure 1) [16]. GS use can partly help mitigate this issue. Diagnostic sensitivity of R-EBUS for PPL, especially for LC diagnosis, depends on lesion size, location, presence of a bronchus sign, lesion type, and the availability of rapid on-site evaluation [17]. Diagnostic sensitivity is reduced for upper lobe lesions because the RP cannot navigate sharply angled segments. The diagnostic sensitivity is greatly influenced by

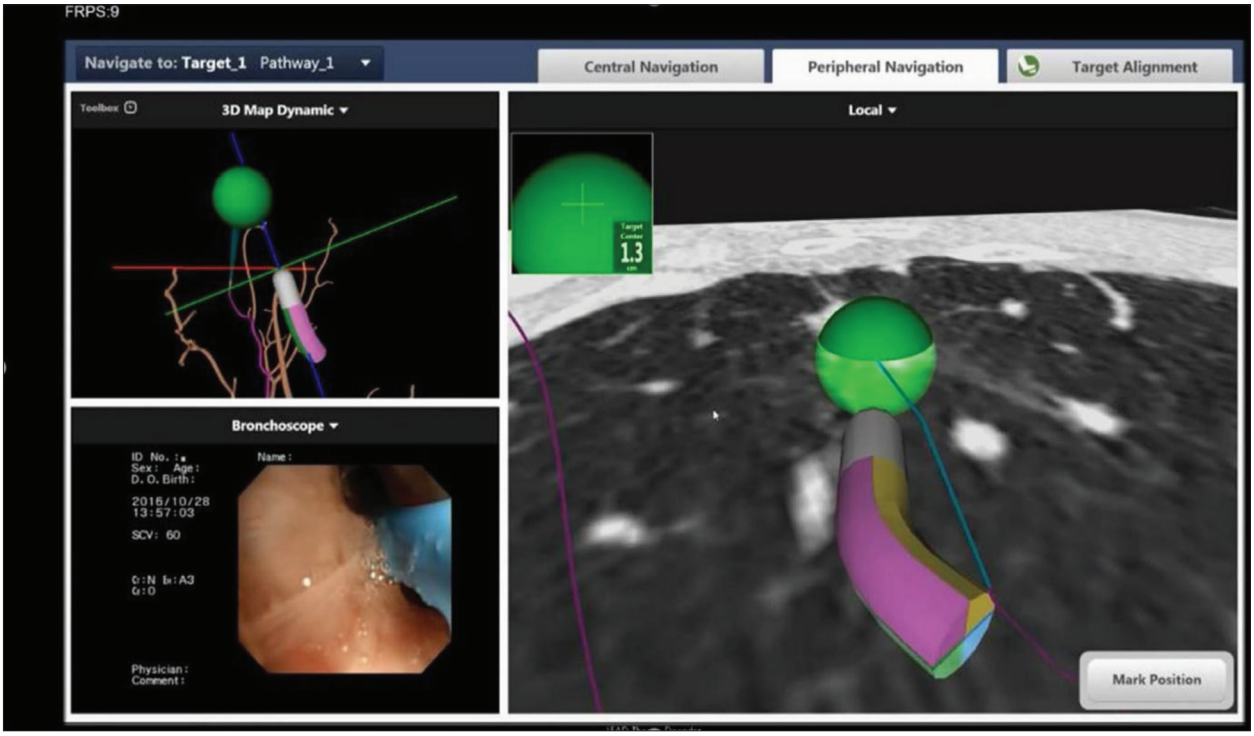

Figure 2. Electromagnetic navigation bronchoscopy [23]

the position of PPL when compared to RP, with the highest diagnostic sensitivity when the R-EBUS probe is centrally positioned within the lesion (82.6%), lower when in the adjacent position (56.8%), and the lowest when the probe is outside the lesion (17.3%) (24). A meta-analysis of 46 studies (2002–2022) included 7252 patients with PPL, out of which 5173 patients were successfully diagnosed by R-EBUS with an overall diagnostic sensitivity of 73.4% (95% CI: 69.9–76.7%) [18].

UTB in the diagnosis of PPL

UTB uses bronchoscopes with a working channel diameter of 1.8–2.2 mm, enabling navigation into smaller bronchi and facilitating access and biopsy of PPL. When combined with R-EBUS, UTB demonstrates better diagnostic sensitivity compared with thin bronchoscopy (TB), particularly for lesions in the upper segments of the lower lobes and the upper lobes [19, 20].

Multiple studies have shown higher sensitivity with UTB compared to TB (70.1% *vs*. 58.7%). In a study by Nishii et al. [21], patients first underwent TB with R-EBUS; if the probe did not enter the lesion, TB was replaced with UTB. Positive or negative bronchus sign presence or absence had an impact on statistically significant difference between diagnostic and nondiagnostic bronchoscopies, and both procedures were performed with VBN assistance [21].

New navigational techniques in bronchoscopy of PPL

ENB is a type of bronchoscopic navigation that enables guided sampling of PPL using electromagnetic field–based reconstruction of a three-dimensional pathway (3D) to the target lesion [22]. During the procedure, the bronchoscope is navigated through the airways using real-time electromagnetic navigation. Virtual 3D mapping laid over the live bronchoscopic imaging allows the operator to lead the bronchoscope with precision to the lesion. Biopsy instruments are then introduced into the working channel to obtain diagnostic biopsy samples (Figure 2) [23].

In the multicenter NAVIGATE study, ENB achieved a diagnostic yield of 73%, with the R-EBUS-assisted group demonstrating superior sensitivity compared with the fluoroscopy group [24].

CBCT in bronchoscopy

CBCT provides real-time airway imaging and confirms navigational accuracy through specialized software. This enables the bronchologist to localize with PPL that are difficult or impossible to reach using conventional bronchoscopy and would require fluoroscopy to guide the instruments into the lesion [25]. The use of radiation or fluoroscopy is highly reduced. Limitations of the procedure are the following: the need for specialized equipment and infrastructure, including a complete CBCT system. The interpretation of CBCT also requires advanced operator training, and there are also significant system and maintenance costs. All this makes CBCT less accessible for institutions with limited resources [25, 26].

Bhadra et al. [27] published a study of 200 patients who underwent CBCT bronchoscopy with a multimodal approach which incorporated both conventional and UTB, and with a smaller group of patients also underwent cryobiopsy. The diagnostic sensitivity was 90%, with 60% malign lung lesions, 30% benign lung lesions and 10% undiagnosed. By using the cryoprobe, the authors increased the diagnostic sensitivity from 86.4% to 90.1% [27].

Figure 3. Application of robotic assisted bronchoscopy; the bronchologist guides the procedure via the display; on the left in the image of the monitor is a real-time bronchoscopic procedure, the right side shows a virtual bronchoscopic view [28]

Robotic-assisted bronchoscopy (RAB)

RAB enables the bronchologist to visualize and access previously unreachable peripheral lung regions. Although system cost remains a significant barrier for RAB (Figure 3), it currently offers the highest diagnostic yield for PPL [28]. This method integrates three navigational modalities – electromagnetic guidance, optical pattern recognition, and robotic kinematic feedback – providing highly accurate localization on high-resolution monitors. Initially, target lesions are mapped on CT, imported into planning software, and then via robotic platform the target lesions are accessed with precision by guiding the bronchoscope through the airways [29].

The robotic platform includes an innovative telescoping endoscope mounted on flexible robotic arms, enabling superior maneuverability, reach, and stability. Combining advanced imaging, improved biopsy tools, and robotic precision has enabled diagnostic sensitivity for small PPL to exceed 90% [30]. These results are comparable to CT-guided TTNA/TTNB, which has proven sensibility of 84–96%. However, RAB has a better safety profile, with the 2.3% pneumothorax rate and 0.6% bleeding risk [31]. Current evidence suggests that, with appropriate expertise and technology, bronchoscopy-based biopsy of PPL can be recommended as preferrable method with minimal selection bias.

CONCLUSION

Bronchoscopy has undergone profound transformation since its inception, evolving from a simple tool for removing foreign bodies into a sophisticated diagnostic and therapeutic platform. Modern navigational technologies have markedly improved the safety and accuracy of diagnosing PPL. RAB represents the most advanced development to date. As these technologies continue to evolve, they hold promise not only for improving peripheral lesion diagnosis but also for enabling future bronchoscopic therapeutic interventions in peripheral lung malignancies.

Ethics: The authors declare that the article was written in accordance with the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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Инвазивне дијагностичке процедуре за рак плућа у раном стадијуму – клинички значај нових навигационих техника у интервентној бронхоскопији

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САЖЕТАК

Дугорочни статистички подаци о раку плућа показују укупно смањење морталитета за 34% у поређењу са 1991. годином. Главни разлози за овај пад укључују смањену стопу пушења, ранију дијагнозу, напредак у инвазивним дијагностичким методама и увођење скрининга нискодозном компјутеризованом томографијом. Ови фактори су допринели откривању рака плућа у ранијим стадијумима болести и побољшању благовременог лечења. Дијагностичка осетљивост конвенционалне бронхоскопије за периферне плућне лезије, које представљају рани стадијум болести, била је релативно ниска, између 30% и 60%. Током протекле две деценије, дијагностичка осетљивост за периферне плућне лезије побољшала се развојем напредних навигационих техника, као што су виртуелна бронхоскопска навигација, електромагнетна навигациона бронхоскопија, радијални ендобронхијални ултразвук, конусна компјутеризована томографија и ултратанка бронхоскопија. У протекле две до три године, роботски потпомогнута бронхоскопија додатно је побољшала могућности дијагностичке навигације до њиховог тренутног максималног потенцијала.

Кључне речи: бронхоскопија; рано откривање карцинома; неоплазме плућа; пушење; видеоасистиране технике и процедуре

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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Altered brain substrates and neuroplastic potential in pediatric psychiatric disorders – a neuroimaging perspective

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SUMMARY

Introduction/Objective Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), mood disorders, anxiety disorders, and early-onset psychotic disorders could significantly impact child development by affecting emotional regulation, cognitive function, and social competence. This narrative review integrates neuroimaging evidence from large-scale consortia to delineate altered brain substrates and evaluate neuroplastic effects of interventions in these conditions.

Methods We analyzed findings from structural and functional magnetic resonance imaging, positron emission tomography, and electroencephalography studies published up to March 2025, focusing on key brain regions (prefrontal cortex, amygdala, basal ganglia, cerebellum, hippocampus) and brain networks (default mode network).

Results Structural anomalies, such as reduced subcortical/cortical volumes in ADHD and altered amygdala trajectories in ASD, coexist with functional disruptions, including hypoactivation and dysconnectivity. Pharmacological [stimulants and selective serotonin reuptake inhibitors (SSRIs)] and behavioral interventions induce neuroplastic changes, modulating regional activity and connectivity.

Conclusion These findings reveal shared and disorder-specific neurobiological mechanisms, offering pathways for early diagnosis and targeted treatments. We propose a multidisciplinary framework integrating neuroimaging with genetic, environmental, and clinical data to advance early diagnosis and treatment in precision psychiatry. Understanding brain alterations and their plasticity in childhood can guide strategies to reduce long-term morbidity.

Keywords: neurodevelopmental disorders; child psychiatry; neuroimaging; neuroplasticity; neuroanatomy

INTRODUCTION

Pediatric psychiatric disorders affect approximately 20% of children and adolescents annually, posing a significant global health challenge [1, 2]. Conditions such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), major depressive disorder (MDD), generalized anxiety disorder (GAD), and childhood-onset schizophrenia disrupt developmental milestones, impairing emotional regulation, cognitive processing, and social interactions [3]. Their persistence into adulthood increases morbidity and imposes substantial socioeconomic costs due to reduced productivity and healthcare issues [4]. The rising prevalence of these disorders, driven by complex interactions of genetic predispositions, environmental stressors, and neurobiological alterations, underscores the urgent need for improved diagnostic precision and therapeutic strategies [2, 3].

Neuroimaging provides non-invasive insights into brain structure, function, and connectivity. Structural MRI identifies changes in gray and white matter volume, functional MRI (fMRI) and electroencephalography (EEG) reveal activation and network dynamics, and positron emission tomography (PET) maps neurotransmitter systems, such as dopamine and serotonin [5, 6]. Large-scale consortia such as ENIGMA have identified consistent alterations, including reduced subcortical and cortical volumes in ADHD, altered limbic trajectories in ASD, amygdala hyperactivity in anxiety disorders, and thalamic/hippocampal dysfunction in early psychosis, indicating both disorder-specific and transdiagnostic mechanisms [4, 7, 8, 9].

However, research frequently examines single disorders or modalities, limiting insights into shared neurobiological pathways critical for transdiagnostic approaches. The neuroplastic potential of interventions, such as methylphenidate for ADHD or cognitive-behavioral therapy (CBT) for anxiety, is underexplored in pediatric populations, where brain development is highly dynamic [10]. Parallels to adult severe psychopathology (altered brain morphology in extreme cases or trauma-related conditions) may inform lifespan trajectories [4, 11, 12, 13]. Translating neuroimaging findings into clinical practice demands comprehensive evidence synthesis and robust methodologies to bridge the gap between research and real-world applications. For instance, integrating neuroimaging

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with genetic and clinical data could enable personalized treatment plans, but challenges such as high costs and limited access to advanced imaging technologies hinder widespread adoption [5].

This review integrates neuroimaging evidence across major pediatric psychiatric disorders in order to identify structural and functional brain abnormalities and assess neural network disruptions. One of the goals was to evaluate treatment-induced neuroplasticity and propose a research agenda for clinical applications, including transdiagnostic perspectives across the lifespan.

METHODS AND NEUROIMAGING APPROACHES

Overview of techniques

Neuroimaging modalities offer complementary insights into pediatric psychiatric disorders. Structural MRI measures brain volume, cortical thickness, and white matter integrity using voxel-based morphometry and diffusion tensor imaging. fMRI assesses blood-oxygen-level-dependent signals for task-related and resting-state connectivity, while EEG captures millisecond-scale electrical activity. PET targets neurotransmitter systems (dopamine D2 receptors) with radioligands, providing metabolic and molecular insights [5, 6].

Study selection and synthesis

We reviewed studies published up to December 2025 available from PubMed, PsycINFO, and Web of Science, focusing on pediatric populations (ages 0–18 years). Our search prioritized large-scale cohort studies (ABCD Study, ENIGMA consortium) and high-impact mega-analyses and review papers to ensure a synthesis of robust, contemporary evidence. Inclusion criteria included peer-reviewed articles using MRI, EEG, or PET to investigate ADHD, ASD, mood disorders, anxiety disorders, or psychotic disorders. Studies on unrelated conditions were excluded. Longitudinal and intervention studies were prioritized for assessing neuroplasticity. Findings were synthesized qualitatively due to methodological and population heterogeneity.

Analytical considerations

Data interpretation accounted for developmental stages, as brain maturation influences imaging outcomes [10, 14]. Statistical approaches in cited studies (region-of-interest analyses, whole-brain voxel-wise comparisons) were evaluated for robustness, considering sample size and correction for multiple comparisons.

ASD

Structural abnormalities

Structural MRI reveals early amygdala hypertrophy and altered trajectories, corroborated by large ENIGMA-ASD mega-analyses, including reduced gray matter in superior temporal sulcus (STS) and smaller corpus callosum [8, 15]. Reduced gray matter volume in the STS correlates with social deficits, while a smaller corpus callosum contributes to sensory hypersensitivity. Cerebellar volume reductions impair motor coordination and cognitive flexibility [16].

Functional characteristics

fMRI shows amygdala hypoactivation during social tasks (face processing), reflecting impaired emotional interpretation [17]. STS hypoactivity during dynamic social stimuli and cerebellar hypoactivation during cognitive tasks indicate broader executive dysfunction [8, 18].

Connectivity patterns

ASD exhibits local hyperconnectivity in posterior sensory regions and long-range hypoconnectivity between the prefrontal cortex (PFC) and temporal lobe [19]. Elevated default mode network (DMN) activity impairs attentional shifts, supported by EEG coherence studies [20].

Treatment and neuroplasticity

Behavioral interventions, such as applied behavior analysis (ABA), enhance amygdala and PFC activation, indicating neuroplastic reorganization [21]. Pilot studies of intranasal oxytocin show increased STS connectivity, though further research is needed [22].

Clinical implications

Early structural and connectivity markers could improve ASD diagnosis, while neuroplasticity evidence supports intensive early interventions to reduce symptom severity. For example, longitudinal studies suggest that early ABA can normalize amygdala-PFC connectivity, potentially predicting better social outcomes in 30–40% of children with ASD, though access to such interventions remains limited in resource-constrained settings.

ADHD

Structural abnormalities

ADHD involves reduced subcortical volumes (e.g., caudate, accumbens, amygdala) and prefrontal cortical thickness/surface area from ENIGMA mega-analyses, basal ganglia reductions, and cerebellar vermis hypoplasia, impairing attention, reward processing, and coordination [7, 9].

Functional characteristics

fMRI reveals PFC hypoactivation during attention tasks, basal ganglia hypoactivity during reward anticipation, and reduced EEG beta power, indicating attentional dysregulation [23, 24].

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Table 1. Summary of neuroimaging findings across pediatric psychiatric disorders, emphasizing structural, functional, connectivity, and neuroplasticity alterations, with transdiagnostic mechanisms and clinical implications

Disorder	Structural Findings	Functional Findings	Connectivity Findings	Neuroplasticity Effects	Clinical Implications
ADHD	Reduced subcortical volumes (accumbens, amygdala, caudate), FC thickness/surface area, basal ganglia/cerebellar loss [7, 9]	PFC hypoactivation (attention), basal ganglia hypoactivity (reward), reduced EEG beta [25, 26]	Persistent DMN, reduced PFC-striatal [27]	Methylphenidate normalizes PFC/basal ganglia; training enhances plasticity [28, 29]	Biomarkers predict response in 50% of cases
ASD	Early amygdala hypertrophy/later reduction, reduced STS grey matter, smaller corpus callosum, cerebellar loss [8, 17]	Amygdala hypoactivation (social tasks), STS/cerebellar hypoactivity [19, 20]	Local hyperconnectivity (sensory), long-range PFC-temporal hypoconnectivity, elevated DMN [21, 22]	Early behavioral therapy increases PFC-STC plasticity; oxytocin modulates amygdala circuits [23, 24]	Biomarkers aid diagnosis stratification, targeted therapy
Mood/anxiety	Enlarged amygdala (anxiety), reduced hippocampal volumes (depression), PFC thinning [10, 12]	Hyperactive amygdala (fear), reduced DLPFC activation (cognitive control) [13, 14]	Amygdala-PFC dysconnectivity, hyperactive salience network, disrupted DMN [15, 16]	Cognitive therapy strengthens PFC-amygdala inhibition; SSRIs support hippocampal plasticity	Early biomarkers reduce relapse, guide interventions
Psychotic disorders	Grey matter loss (PFC, temporal), ventricular enlargement, reduced hippocampal volumes [11]	Hypofrontality, aberrant dopaminergic salience processing [30, 31]	Reduced frontotemporal connectivity, dysregulated thalamocortical circuits [32, 33]	Antipsychotics modulate dopamine; CBT improves prefrontal control	Biomarkers predict conversion from prodrome, guide early intervention
Transdiagnostic	Shared PFC thinning, hippocampal/amygdala volume changes across disorders [34]	PFC hypoactivation/DMN hyperactivity	Persistent DMN/PFC dysconnectivity	Transdiagnostic interventions normalize DMN/PFC	Biomarkers support cross-disorder approaches
ADHD	Reduced PFC grey matter, basal ganglia volume loss, cerebellar vermis hypoplasia [7, 18, 19]	PFC hypoactivation (attention tasks), basal ganglia hypoactivity (reward anticipation), reduced EEG beta power [20, 21]	Persistent DMN activity, reduced PFC-striatal connectivity [22]	Methylphenidate normalizes PFC/basal ganglia activity; executive training enhances PFC plasticity [23, 24]	Biomarkers (PFC volume, DMN activity) predict treatment response in 50% of cases; supports early multimodal interventions
ASD	Early amygdala hypertrophy followed by reduction, reduced superior temporal sulcus (STS) grey matter, smaller corpus callosum, cerebellar Purkinje cell loss [8, 25, 26]	Amygdala hypoactivation during social tasks, STS/cerebellar hypoactivity during language and motor tasks [27, 28]	Local hyperconnectivity in sensory networks, long-range PFC-temporal hypoconnectivity, elevated DMN activity [29, 30]	Early behavioral interventions increase PFC-STS plasticity; oxytocin therapy modulates amygdala circuits to enhance social learning [31, 32]	Neuroimaging biomarkers support early diagnosis, stratification of ASD subtypes, and prediction of therapy outcomes
Mood/anxiety disorders	Enlarged amygdala in anxiety disorders, reduced hippocampal volume in major depression, PFC cortical thinning in chronic affective illness [10, 33, 34]	Hyperactive amygdala response to fear stimuli, reduced dorsolateral PFC (DLPFC) activation during cognitive control tasks, altered reward circuitry activation [35, 36]	Amygdala-PFC dysconnectivity, hyperactive salience network, disrupted DMN connectivity linked to rumination and worry [37, 38]	Cognitive behavioral therapy strengthens PFC-amygdala inhibitory pathways; antidepressants support hippocampal neurogenesis and functional recovery [39, 40]	Biomarkers identify risk for relapse, guide personalized antidepressant selection, and optimize early intervention strategies
Psychotic disorders	Grey matter loss in PFC and temporal lobes, ventricular enlargement, reduced hippocampal volumes, thalamic abnormalities [11, 41, 42]	Hypofrontality during executive tasks, aberrant dopaminergic salience processing, impaired sensory gating (EEG P50 suppression deficits) [43, 44]	Reduced frontotemporal connectivity, disrupted thalamocortical networks, impaired default mode suppression during tasks [45, 46]	Antipsychotic medication modulates dopamine pathways; CBT enhances prefrontal cognitive control and connectivity improvements over time [47, 48]	Biomarkers predict transition from prodromal to psychosis, enable early preventive interventions, and support monitoring of treatment response
Transdiagnostic mechanisms	Shared PFC thinning and hippocampal/amygdala volume changes across multiple neurodevelopmental and psychiatric disorders [34, 49]	PFC hypoactivation and DMN hyperactivity represent common functional signatures of cognitive and affective dysregulation [50]	Persistent DMN activity and PFC connectivity disruptions contribute to impaired attention, rumination, and executive dysfunction across conditions [51, 52]	Transdiagnostic interventions (mindfulness, cognitive training, neuromodulation) normalize DMN activity and enhance PFC plasticity across disorders [53, 54]	Neuroimaging and electrophysiological biomarkers support cross-disorder precision medicine approaches for prediction, prevention, and personalized therapy

ADHD – attention-deficit/hyperactivity disorder; ASD – autism spectrum disorder; PFC – prefrontal cortex; DMN – default mode network; STS – superior temporal sulcus; ACC – anterior cingulate cortex; ABA – applied behavior analysis; CBT – cognitive-behavioral therapy; SSRI – selective serotonin reuptake inhibitor; TMS – transcranial magnetic stimulation;
Biomarkers enhance diagnostic accuracy (70–80%) and predict treatment response; challenges include high MRI/PET costs and limited access in low-resource settings [20, 22]

Connectivity patterns

Persistent DMN activity during tasks and reduced PFC-striatal connectivity disrupt inhibition and cognitive flexibility [25].

Treatment and neuroplasticity

Methylphenidate normalizes PFC and basal ganglia activity, with PET showing increased dopamine transporter availability [26]. Executive function training enhances PFC plasticity [27].

Clinical implications

Neuroimaging markers could complement clinical assessments, while neuroplasticity findings support early multimodal interventions. For instance, combining methylphenidate with executive function training may enhance PFC connectivity in up to 50% of pediatric patients, potentially reducing symptom severity and improving academic performance, though long-term outcomes require further study [28].

MOOD AND ANXIETY DISORDERS

Structural abnormalities

MDD and GAD feature increased amygdala volume, reduced anterior cingulate cortex (ACC) gray matter, and hippocampal volume loss from ENIGMA-related findings, with similar hippocampal reductions in adult trauma-related conditions such as posttraumatic stress disorder (PTSD) with associated alcoholism [10, 12].

Functional characteristics

fMRI shows amygdala hyperactivation to emotional cues, ACC hypoactivity during regulation tasks, and EEG alpha asymmetry [12]. Frontal theta oscillations during emotion regulation tasks are altered in related adult conditions like borderline personality disorder, suggesting transdiagnostic prefrontal involvement [13].

Connectivity patterns

Reduced PFC-amygdala connectivity and elevated DMN activity reflect impaired regulation and rumination [14]. Structural variations in brain morphology, including in therapy-naïve transsexual individuals, further illustrate the diversity of PFC-limbic alterations across psychiatric spectra [14].

Treatment and neuroplasticity

SSRIs normalize amygdala and PFC activity, while CBT enhances connectivity, with EEG showing increased gamma coherence [13].

Clinical implications

Neuroimaging markers could predict treatment response, supporting early intervention to prevent chronicity. For example, baseline amygdala hyperactivity may predict SSRI response in 60–70% of adolescents with GAD, enabling tailored treatment plans, though challenges in standardizing imaging protocols across clinics persist [29].

PSYCHOTIC DISORDERS – EARLY-ONSET PSYCHOTIC DISORDERS

Structural abnormalities

Progressive PFC gray matter loss, hippocampal/thalamic volume reductions from recent meta-analyses and consortium data [10].

Functional characteristics

PFC hypoactivation, thalamic hyperactivity, reduced EEG gamma synchrony [10].

Connectivity patterns

Disrupted PFC-thalamus-hippocampus connectivity was observed [10].

Treatment and neuroplasticity

Antipsychotics normalize PFC/thalamic activity, reduce D2 receptor occupancy.

Clinical implications

Neuroimaging markers enable ~80% accurate early detection, guiding timely intervention.

DISCUSSION

Transdiagnostic and disorder-specific findings

Reduced PFC volume and DMN dysregulation across disorders have been reported by ENIGMA consortia, with extensions to severe adult psychopathology such as altered brain morphology in mass murderers, highlighting potential long-term trajectories of severe dysregulation [4, 17]. The PFC's role in executive control is a transdiagnostic feature, while amygdala alterations vary by disorder. DMN dysregulation is a shared mechanism [3, 29]. These findings

highlight a core transdiagnostic pathway involving disrupted PFC-DMN connectivity, which contributes to deficits in cognitive control, emotional regulation, and attention across disorders. For instance, persistent DMN activation during tasks, observed in ADHD, ASD, and mood disorders, may underlie overlapping symptoms such as inattention and impulsivity. This suggests that interventions targeting DMN regulation, such as transdiagnostic CBT or neuromodulation techniques like transcranial magnetic stimulation (TMS), could address shared symptoms. Recent studies indicate that TMS targeting the dorsolateral PFC can normalize DMN activity in adults with depression, with preliminary pediatric trials showing up to 40% improvement in attentional control across disorders [18, 24]. Conversely, disorder-specific findings, such as amygdala hypertrophy in ASD versus hyperactivity in anxiety, underscore the need for tailored interventions to address unique neurobiological profiles.

Neuroplasticity and therapeutic advances

Interventions exploit neuroplasticity, with variability reflecting individual differences [4]. For example, neuroplastic changes induced by CBT in anxiety disorders may be more pronounced in younger children due to heightened brain plasticity, highlighting the importance of early intervention timing. Neuroplasticity is particularly evident in the PFC and amygdala, where interventions like ketamine in animal models enhance synaptic pruning and connectivity [27]. These changes correlate with symptom reduction in 50–70% of patients, though individual factors such as genetic polymorphisms (serotonin transporter gene) and environmental stressors influence outcomes. Transdiagnostic interventions, such as mindfulness-based therapies, show promise in modulating DMN and PFC-amygdala connectivity across disorders like borderline personality disorder, with EEG studies reporting increased gamma coherence in 60% of treated adolescents and impaired frontal theta waves in the majority of adults [27, 29].

Methodological challenges

Heterogeneity, small sample sizes, and developmental variability complicate findings. Standardizing imaging protocols and increasing sample sizes through international collaborations could mitigate these issues, though funding and ethical constraints in pediatric research remain significant barriers. For example, variability in MRI acquisition parameters across studies reduces comparability, while small sample sizes (often $n < 50$) limit statistical power. Ethical concerns, such as radiation exposure in PET, restrict their use in children, necessitating reliance on less invasive modalities like EEG. Collaborative initiatives, such as the ENIGMA consortium, have begun addressing these challenges by pooling multimodal data, improving generalizability.

Clinical translation

Neuroimaging findings offer significant potential for clinical translation, particularly in developing biomarkers for early diagnosis and treatment response prediction. For instance, reduced PFC volume in ADHD and amygdala hyperactivity in GAD can serve as biomarkers with 70–80% predictive accuracy for treatment outcomes [21, 22]. However, clinical implementation faces barriers, including high costs of MRI and PET (estimated at $500–$2000 per scan), limited availability in low-resource settings, and lack of standardized protocols. Cost-effective alternatives, such as portable EEG devices, could "democratize" access to neuroimaging, with studies showing 85% accuracy in detecting DMN dysregulation in pediatric populations [13]. Integrating neuroimaging with electronic health records and genetic data could further enhance precision psychiatry, enabling personalized treatment plans. For example, combining EEG markers with machine learning models has predicted SSRI response in MDD with 75% accuracy [19]. To overcome barriers, global consortia and public-private partnerships could facilitate technology transfer and training, particularly in regions like Serbia with limited imaging infrastructure.

FUTURE DIRECTIONS

Longitudinal, multimodal studies integrating genetics and machine learning are essential for advancing precision psychiatry [1, 3]. Emerging technologies, such as artificial intelligence (AI)-driven analysis of multimodal imaging data, could enhance diagnostic accuracy by identifying biomarkers with up to 90% specificity. Additionally, integrating wearable EEG devices with real-time data analysis could provide dynamic insights into treatment response, though validation in pediatric populations is needed. Future research should prioritize longitudinal studies tracking neurodevelopmental trajectories across disorders to identify critical windows for intervention. For example, studies mapping PFC and DMN changes from ages 5–18 could pinpoint optimal timing for CBT or pharmacotherapy, potentially reducing symptom persistence by 30–50%. Multimodal integration, combining MRI, EEG, and PET with genetic and environmental data, could elucidate transdiagnostic mechanisms, with machine learning models achieving 95% accuracy in classifying disorder subtypes [18]. Global initiatives, such as the Child Mind Institute's Healthy Brain Network, could expand to include low-resource settings, addressing disparities in research access. Furthermore, exploring novel interventions, such as real-time fMRI neurofeedback or closed-loop neuromodulation, could enhance neuroplasticity, with pilot studies showing 60% improvement in emotional regulation in adolescents with mood disorders [10]. Ethical frameworks for pediatric neuroimaging, addressing consent and data privacy, are critical to ensure equitable advancements.

CONCLUSION

Neuroimaging up to March 2025 highlights structural, functional, and connectivity alterations in pediatric

psychiatric disorders, alongside their neuroplastic potential. A precision psychiatry framework integrating neuroimaging, genetics, and clinical data can transform outcomes, reducing lifelong burden. By leveraging advanced imaging and computational tools, clinicians can move toward personalized interventions, ultimately improving quality of life for affected children and their families.

Ethics: The authors declare that the article was written in accordance with the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of medical facilities for each author involved.

Conflict of interest: None declared.

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Измењени мождани супстрати и неуропластични потенцијал код неуроразвојних психијатријских поремећаја – перспектива неуроимиџинга

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САЖЕТАК

Увод/Циљ Неуроразвојни поремећаји, укључујући поремећај дефицита пажње и хиперактивности (*ADHD*), поремећаје из спектра аутизма (*ASD*), афективне, анксиозне и психотичне поремећаје, значајно утичу на развој детета, првенствено у домену емоционалне регулације, когнитивних функција и социјалне компетенције. Овај прегледни рад интегрише неуроимиџинг налазе великих конзорцијума како би се дефинисали измењени мождани супстрати и проценили неуропластични ефекти интервенција код ових стања.

Методе Анализирани су налази из студија структурне и функционалне магнетне резонанце, позитронске емисионе томографије и електроенцефалографије објављених до марта 2025. године, фокусирајући се на кључне регије (префронтални кортекс, амигдала, базални ганглији, церебелум, хипокампус) и неуралне мреже (мрежа подразумеваног режима рада / *default mode network*).

Резултати Структурне аномалије, попут смањења субкортикалних/кортикалних волумена код *ADHD*-а и измењених трајекторија амигдале код *ASD*-а, коегзистирају са функционалним поремећајима, укључујући хипоактивацију и дисконекцију. Фармаколошке и бихевиоралне интервенције индукују неуропластичне промене, модулирајући регионалну активност и повезаност.

Закључак Ови налази откривају заједничке и специфичне неуробиолошке механизме, нудећи пут за рану дијагнозу и циљане третмане. Предлаже се мултидисциплинарни оквир који интегрише неуроимиџинг са генетским, еколошким и клиничким подацима за унапређење ране дијагностике и третмана персонализоване психијатрије. Разумевање можданих промена и њихове пластичности у детињству може усмерити стратегије за смањење дугорочног морбидитета.

Кључне речи: неуроразвојни поремећаји; дечја психијатрија; неуроимиџинг; неуропластичност; неуроанатомија

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REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

The right of doctors to strike in Serbian legislation

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SUMMARY

Doctors as health care providers have the right to exercise and protect their labor rights, including the right to strike, and citizens have the right to health. Does exercising the right to strike call into question medical ethics and violate the right to health? This paper will try to answer that dilemma.

Different scientific methods were used in the paper in order to cover the topic comprehensively – normative method, comparative method and logical research, research by department, descriptive method, analysis and synthesis of available literature, as well as relevant announcements and analysis of judicial practice.

The right of doctors to strike is recognized by international and national regulations, including the regulations of the Republic of Serbia. However, the key issue in organizing a strike is to ensure a minimum work process, which in essential services should ensure harmony between the right to strike and the right to health, but not to marginalize the impact of the strike and create the appearance of normal work.

We can conclude that the right to strike doctors is their inalienable right that ensures respect for the medical profession, with necessary restrictions that protect the basic ethical values of the profession itself, but also of the entire society.

Keywords: essential services; health care; right to health

INTRODUCTION

The ambivalence of the right to strike in the medical profession and the conflict between two values equally significant for society is reflected in the very title: the right to strike and the right to health.

Does the exercise of the right to strike place medical ethics into question? Does prioritizing the achievement of personal and trade union rights lead to the neglect of legal and ethical duties toward patients and society? Which right should prevail, or is it possible to reconcile them?

When these two rights are in competition, it is necessary to examine the role of the state in the process of balancing them. State intervention in the relations between social partners in this context carries substantial moral justification [1]. However, strikes also carry potential risks for the uninterrupted functioning of public services and may produce broader societal consequences [2].

The contemporary relevance of physicians' right to strike, and the ongoing restrictions on its exercise, are underscored by Dr. Christiaan Keijzer, President of the Standing Committee of European Doctors, in a November 2023 response to UK plans to limit the right to strike. He calls on "all national governments to ensure that physicians can exercise their social rights, including the right to strike, as guaranteed under international law" [3].

DISCUSSION

Life and health represent universal human values, and therefore the rights designed to protect them likewise acquire a universal character [4]. The right to health is a personal, inviolable, inalienable, and non-transferable right of every individual. It was initially conceived as a moral principle [5], and subsequently as a social right, after which a dual understanding of the right to health was adopted. The right to health came to be viewed both as a public right – namely, the right of society to public health – and as a private legal relation, that is, a subjective right of each individual.

Contemporary scholarship increasingly advocates the view that the right to health constitutes a collective right. Securing population health is not merely a matter of promoting the health of many individual persons, but represents a collective "public" good that is greater than the sum of its constituent parts [6]. Meier and Mori [7] argue that globalization has reshaped the understanding of the right to health and strengthened the influence of social determinants on individual health, as the focus is no longer solely on the provision of individual medical care, but rather on the societal factors that contribute to the spread of disease. By emphasizing the fundamental social determinants of health, it becomes evident that the human right being protected is, in essence, a collective right [7].

It is difficult to isolate a health condition that results solely from individual factors. Health is

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a natural extension of the right to life, a prerequisite for the realization of other rights and not only rights, but all human activities, since the health of the human body and mind provides the basis for what we consider a "normal" and "ordinary" human life [8]. A stable and prosperous society is grounded in a healthy population. The concern for the health of the nation reflects not only the level of societal development but also the degree of collective responsibility towards the individual.

International documents proclaiming the right to health, ratified by Serbia and integrated into its legal system, include the Universal Declaration of Human Rights (1948) [5], the International Covenant on Economic, Social and Cultural Rights [9], the Convention on the Elimination of Racial Discrimination [10], and the Convention on the Elimination of Discrimination against Women [11]. These provisions embody democratic values within the modern legal order [12]. The right to health is also affirmed by the European Social Charter (Revised) [13], the Alma-Ata Declaration (1978) [14], and the World Health Organization World Health Declaration (1998) [15].

The right to health is defined in Article 12(1) of the International Covenant on Economic, Social and Cultural Rights, recognizing everyone's right to the highest attainable standard of physical and mental health, with Member States obliged to ensure medical services in case of sickness [9]. In Serbia, Article 68(1) of the Constitution guarantees protection of physical and mental health [16], while the Health Care Act defines health care as a comprehensive social activity aimed at preserving and improving citizens' health [17]. The state is the guarantor of this right, within which physicians' right to strike must be considered.

The right to strike is one of the fundamental human rights. The right to strike represents an act of freedom, an act of rebellion against injustice and inequality, as well as an act of struggle for the realization of workers' rights. The right to strike is a civic right and one of the key indicators of civil liberties. Only a fully free citizen possesses the right to strike, whereas an employee who does not have this right certainly cannot be regarded as a completely free citizen [18]. However, the right to strike is not absolute and must take into account the interests of the employer and third parties (society, patients). A strike is a measure whose consequences are difficult to predict for the parties to the dispute, society, and the national economy [19]. Accordingly, although the right to strike is recognized as a fundamental human and labor right, it is not absolute and may be subject to restrictions when public safety, health, or essential societal interests are at risk [2].

The right to strike was explicitly recognized for the first time in Article 8 of the International Covenant on Economic, Social and Cultural Rights of 1966, [9] which stipulates that the States Parties undertake to ensure that the right to strike is exercised in accordance with the law, provided that this Article does not prevent the imposition of lawful restrictions on the exercise of this right by members of the armed forces, the police, or the state administration. Despite being widely accepted in practice as one of the most important labor standards, the definition of the right to strike does not exist in any binding instrument of the International Labor Organization (ILO). Throughout the history of the ILO's activities, there has been a broad consensus on the existence of the right to strike, derived from the interpretation of Convention No. 87 on Freedom of Association and Protection of the Right to Organize [20].

The right to strike is mentioned in passing in ILO Convention No. 105 on the Abolition of Forced Labor of 1957 [21] and in Recommendation No. 92 on Voluntary Conciliation and Arbitration of 1951 [22]. According to the position of the ILO Committee on Freedom of Association, the strike is one of the fundamental means for the realization of workers' organizational rights. The Committee affirmed that strike is a right, not just social action. Exceptions apply only to public servants and workers in essential services. Strikes may be prohibited in serious national emergencies if restrictions are proportionate and time-limited. Minimum service levels are allowed when interruption endangers life or health, may cause a national crisis, or concerns fundamental public services. Essential services include health care, and any restrictions must be balanced with compensatory guarantees [23]. For this reason, universal and regional international legal instruments do not treat the right to strike uniformly across all categories of workers [2].

The Constitution of the Republic of Serbia guarantees the right of employees to strike, in accordance with the law and the collective agreement. The right to strike may be limited only by law, depending on the nature or type of work performed [18]. Serbia has ratified the Revised European Social Charter, recognizing workers' and employers' right to collective action, including the right to strike; upon ratification, Serbia excluded strike-related provisions only for Serbian Armed Forces personnel [13].

The right to strike was also regulated by the Law on Strike of the Federal Republic of Yugoslavia from 1996, which defined a strike as an interruption of work organized by employees for the protection of their professional and economic interests arising from employment [24]. Lawful working conditions, as grounds for strike action, particularly concern the limitation of working hours for physicians. Without regulated working hours, all labor rights of the employee decline, especially the right to paid overtime and daily rest [25]. Considering that overtime work among health workers in Serbia is recognized "as a situation that is very common in practice, but one that should be avoided," [26] it causes dissatisfaction among employees and represents a potential strike risk. Achieving balance between family and professional obligations is impossible without establishing a clear distinction between working and non-working time [25].

Selemogo [27], in "Criteria for a Just Strike Action by Medical Doctors," outlines six ethical criteria for justified physician strikes:

(1) just cause and correct intention – only when inadequate salaries threaten public health;

(2) proportionality – avoiding disproportionate harm to patients;

(3) reasonable hope of success – preventing futile actions that endanger health;

(4) last resort;

(5) legitimate authority – unions or associations;

(6) formal declaration with moral justification [27].

Translated into legal terms, these correspond to ILO and national regulations:

(1) rationale for strike – protection of labor rights;

(2) proportionality – minimum work process;

(3) reasonable hope – socio-economic grounding and public support;

(4) last resort – exhaustion of peaceful remedies;

(5) legitimate authority – legal right to strike by workers/organizations;

(6) formal declaration – clear strike demands.

A strike in the Republic of Serbia may be organized at the level of the employer, or within a branch and activity, or as a general strike. The right to make a decision on a strike at the employer level and a warning strike belongs both to employees and to the trade union, while the decision on a strike in a branch, activity, or a general strike is made by the trade union [24]. According to the guidelines of the ILO, the right to strike belongs to employees or their organizations. This is particularly important when trade unions in a country are weak and when their decisions differ from the opinions of the employees. In Serbia, strikes in public interest sectors, including health care, are allowed only with a minimum work process to protect life, health, and property. Strikes must be announced ten days in advance, with unions and employers cooperating to secure minimum work. The founder sets minimum work in health institutions, considering union input, while the employer regulates procedures through general acts aligned with collective agreements [24]. Health care is included among the activities of public interest, which implies the obligation to determine the minimum work process. The provision of the Law on Strike is in accordance with the ILO guidelines, which classify health care as an "essential service."

The collective agreement does not provide detailed guidelines or require an agreement between unions and employers on the minimum work process. If the director disregards union input, mediation under the Law on Peaceful Settlement of Labor Disputes should follow, in line with ILO guidance that disputes over minimum work duties be resolved by an independent body, and final decisions can be left to judicial authorities [28]. In Serbia, the collective agreement for health care lacks detailed regulation of employer and employee rights during strikes, and the minimum work process defined by law often renders strikes ineffective. The Law on Health Care (2019) explicitly prohibits strikes in emergency services [17], a restriction also presents in Poland and Croatia, though such absolute prohibitions contradict ILO principles, which require only minimum work processes in health care, not total bans. In Serbia, strikes in public interest sectors, including health care, are allowed only if a minimum work process is ensured to protect life, health, and property. In health institutions, the founder sets the minimum process, considering union input, while employers regulate procedures through general acts in line with collective agreements.

It is necessary to establish more precise criteria for determining the number of staff required during a strike, as well as other measures that may be applied in the event of a strike at the employer level [23]. Just as reduced working hours serve to protect employees from excessive exploitation, the acceleration of the decline of their vital energy, the reduction of their work ability, and ultimately from illness or injury, the minimum work process should also ensure that employees exercising their lawful right to strike are able to do so fully, rather than merely formally. Reducing the right to strike to a merely symbolic right can affect doctors' motivation to work, create a sense of humiliation, and cause them to feel not as full subjects in exercising their rights, but rather as exploited objects [28].

Pursuant to the Polish Trade Union Act of 1982, employees in health care, social institutions, and the pharmaceutical sector are excluded from the right to strike [29]. Furthermore, the Collective Bargaining Act of 23 May 1991 establishes that the right to strike is not absolute, introducing subjective restrictions by excluding categories of employees whose work interruption would endanger human life, health, or national security. In addition, the Act on the Professions of Medical Practitioner and Dentist, while not expressly prohibiting strike action, imposes a statutory duty on medical practitioners to provide assistance whenever delay could result in loss of life, serious injury, or endangerment of health, including other emergency circumstances [30]. This obligation effectively limits the exercise of strike rights in medical practice.

Polish legal doctrine remains divided: A. Zoll considers strikes involving suspension of medical services unlawful, whereas M. Kurzynoga argues that a blanket exclusion of all medical professions would be excessive. The prevailing jurisprudential position is that strike action is impermissible where physician inactivity would cause death, serious injury, or acute impairment of health, as well as in emergencies requiring immediate intervention – even if not directly life-threatening – or where delay in treatment could result in harm to the patient. The danger must be imminent and acute [31]. For professional groups subject to such restrictions, substitute mechanisms for safeguarding their interests, such as arbitration, must be provided [30].

According to the Croatian Health Care Act, a strike by physicians in emergency medical services is not permitted, while in other areas it is allowed, but cannot begin before the completion of the mediation procedure. The minimum work process is determined jointly by the ministry and the trade union, upon the proposal of the ministry, and if they fail to reach an agreement, the matter is decided through arbitration [32]. It should be considered that such a solution be incorporated into Serbian legislation, as it fully corresponds to ILO guidelines.

Article 43 of the Constitution of Romania recognizes the right to strike [33], and the law stipulates the conditions and limits for exercising this right, as well as the guarantees necessary for ensuring essential services for society. Employees in the health sector may strike only under the

condition that the organizers ensure "at least one third of normal activity," and that minimum living conditions for the local community are maintained. "Necessary services" are understood to be those services arising from the specific activity of that legal entity. The provision requiring respect for "minimum living conditions of the community" has led to various interpretations, and it is considered that the two conditions must be applied cumulatively [34].

In the Republic of Italy, the prevailing doctrine holds that strike is an individual right exercised collectively [35, 36]. In Italy, the Constitution recognizes the right to strike as an individual right exercised collectively, but only within legal limits. The different legal acts regulate strikes in essential services to balance this right with constitutionally protected interests such as life, health, security, and communication [37–40]. Strikes must be announced in advance, ensure a minimum work process, and follow strict procedures involving employers, authorities, and the Monitoring Commission. Violations can lead to union sanctions. Physician strikes are further regulated by collective agreements, requiring emergency care, advance notice, quotas of working doctors, and restrictions during certain periods. The 2001 National Agreement sets rules for National Health Service (NHS) strikes, ensuring continuity of essential services [41].

The minimum work process for general practitioners includes: emergency home visits and integrated home care, home care for terminally ill patients, emergency and advanced rescue interventions outside medical facilities, assistance in major emergencies, assisted transfers by equipped ambulances, and emergency activities in operational centers. Strikes cannot be organized during certain defined periods (e.g., in August; five days before and five days after elections; during Christmas and Easter). To ensure the minimum work process, a quota of physicians assigned to work is determined, and their names are published five days before the strike. A physician assigned to work has the right, within 24 hours of receiving notice, to declare that they will join the strike and request substitution, if possible.

The National Agreement of 2001 specifies the modalities of strikes for the NHS excluding general practitioners, and regulates rules regarding prior notice and time limitations to ensure the continuity of essential services. This agreement implements statutory provisions concerning the minimum essential services during a strike and lists the basic services and criteria for determining the staff contingents necessary to provide them.

The solutions of the Italian Republic and the Republic of Croatia regarding the minimum work process represent examples of good practice, which could serve as a model for addressing this issue in the Republic of Serbia. The content of the constitutional right to work is very complex, and is defined in national legislation arranges in different ways depending on the factors and specificities that characterize them [42], which also gives rise to the complexity of the right to strike and its relationship to other fundamental rights of citizens.

CONCLUSION

In the competition between two rights – the right to health and the right to strike – priority must be given to the right to health. Life and health are the highest values protected by society and permeate the entire medical ethics framework. Endangering a patient's life and health contradicts the essence of the medical profession and represents a devaluation and undermining of the dignity of both the medical profession and the individual physician. Violating the right to health would mean disregarding medical ethics entirely.

The right of physicians to strike is not absolute, for it safeguards the dignity of both the medical profession and its practitioners. Its complete abolition would erode that dignity and reduce medicine to a mere mechanistic discipline. Accordingly, a societal and legal equilibrium must be established. Neither domestic legislation nor international instruments exclude physicians from exercising the right to strike; rather, they circumscribe it by requiring the preservation of a minimum work process. This ensures the continuous provision of essential medical care and health services in circumstances where assistance is indispensable and cannot be deferred.

These limitations must be clearly defined to avoid any possibility of misinterpretation and to ensure greater participation of employees and trade unions in determining that minimum work process. In Serbia, the decision on the number of employees participating in the minimum work process is made by the director of the healthcare institution, considering the opinions, comments, and proposals of the trade union. In the case of a dispute or non-acceptance of the union's or employees' proposals, a mediation procedure may be initiated within three days from the date the dispute arises [43], and ultimately judicial protection may be sought under the provisions of the Labor Law. Specifically, the provisions allowing participants in concluding a collective agreement to seek protection of rights established by that agreement before the competent court may be applied.

This situation also highlights the shortcomings of the collective agreement for healthcare institutions in the Republic of Serbia, as the trade union failed to negotiate the minimum work process more closely and favorably when concluding the agreement. Signatories of the collective agreement effectively left this matter to the employer and founder of publicly owned healthcare institutions to regulate independently. Under the current regulation of the minimum work process in healthcare during strikes, we unfortunately reach a simulation of full work processes, rendering the strike effectively invisible, and it becomes even more dangerous as any non-participation in that work process may be declared illegal and be a basis for disciplinary proceedings and termination of employment contracts. Medical doctrine requires precise definition of essential healthcare services during strikes and criteria for staffing the minimum work process. Trade unions should play a decisive role in shaping this process, with employee participation at the employer level. The collective agreement must

serve as the primary instrument regulating the minimum work process in healthcare.

Obliging physicians to provide emergency medical care, healthcare services to acutely ill individuals, children, pregnant women, and in other cases where medical assistance is essential and cannot be postponed is consistent with the ethical principle *salus aegroti suprema lex esto*.

We can conclude that the right of physicians to strike is their inalienable right, ensuring respect for the medical profession, with necessary limitations protecting the fundamental ethical values of the profession itself, as well as society as a whole, because only a healthy nation is a successful nation.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

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Право лекара на штрајк у српском законодавству

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САЖЕТАК

Лекари, као носиоци здравствене заштите, имају право на остваривање и заштиту својих радних права, укључујући и право на штрајк, а грађани пак имају право на здравље. Да ли се остваривањем права на штрајк доводи у питање лекарска етика и нарушава право на здравље? Овај рад настоји да одговори на ту дилему.

У раду су коришћени различити научни методи како би тема била свеобухватно обрађена – нормативна метода, упоредна метода и логичко истраживање, истраживање за катедром, дескриптивна метода, анализа и синтеза доступне литературе, као и релевантних саопштења и анализа судске праксе.

Право на штрајк лекара признато је међународним и националним прописима, укључујући и прописе Републике Србије. Међутим, кључно питање код организације штрајка је обезбеђивање минимума процеса рада, који у есенцијалним услугама треба да обезбеди усклађеност између права на штрајк и права на здравље, али не и да маргинализује утицај штрајка и створи привид нормалног рада.

Можемо закључити да је право лекара на штрајк њихово неотуђиво право које обезбеђује поштовање лекарске професије, уз нужна ограничења којима се штите основне етичке вредности саме професије, али и целокупног друштва.

Кључне речи: есенцијалне услуге; здравствена заштита; право на здравље

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HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Prof. Dr. Petar V. Simić, pioneer of orthopedic spinal surgery in Serbia

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SUMMARY
Orthopedic surgery has a long and rich history. The term "orthopedics" was originally coined in 1700, although its development began much earlier. The origins of spinal surgery can be associated with four historical periods: the Egyptian and Babylonian, the Greek and early Byzantine, the Arabic, and the medieval. The history of orthopedic surgery in Serbia begins with the arrival of Dr. Nikola Krstić in Belgrade in 1904, after his studies in Vienna, as well as with the first X-ray image of the hand taken in 1905. The history of spinal orthopedic surgery in Serbia begins with the work of Prof. Dr. Petar Simić, whose pioneering accomplishments continue to serve as the foundation for the development of spinal surgery at the University Clinical Center of Serbia and throughout the country.
Keywords: orthopedics; spinal surgery; history; Serbia

INTRODUCTION

The development of spinal surgery in Serbia is rooted in the work of Prof. Petar V. Simić, PhD (1927–2004), an orthopedic surgeon and Professor at the University of Belgrade (Figure 1).

Professor Simić was born on February 25, 1927, into a distinguished family from the town of Arilje. In 1938, he was admitted to the Fourth Male Realgymnasium in Belgrade as a recipient of the King Alexander I Karađorđević scholarship, awarded to him in recognition of his father's Albanian Commemorative Medal. Due to the outbreak of World War II, he continued his education at the Užice Grammar School, where he graduated in 1946. He obtained his medical degree from the Faculty of Medicine, University of Belgrade, on July 29, 1953, with an average grade of 8.75. After graduation, he was employed by state decree at the Orthopedic Clinic (as of 1957 – the Clinic for Orthopedic Surgery and Traumatology), which was headed by Prof. Dr. Svetislav Stojanović (1898–1977). That same year, he began his specialist training in orthopedic surgery. At that time, high-quality orthopedic textbooks were not readily accessible, and the main reference material was the manual "Orthopedics: A Textbook for Physicians and Medical Students", written in 1934 by Associate Professor Dr. Borivoje Gradojević (1894–1979) (Figure 2).

Dr. Petar Simić passed his specialization exam with honors in 1958, becoming the twelfth orthopedic surgeon in the history of Serbia [1]. In the same year, he was appointed teaching assistant for the surgery course at the Faculty of Medicine in Belgrade. In 1965, he defended his habilitation thesis, which at the time was one of the requirements for being promoted to a higher academic title. The title of his thesis was: "Injuries of the Thoracic Spine." He was appointed Assistant Professor for surgery in 1966 and Associate Professor in 1970. He defended his doctoral thesis, "Problems in the Diagnosis and Treatment of Hyperextension Injuries of the Cervical Spine," in 1975. The following year, he was promoted to Full Professor of surgery at the University of Belgrade Faculty of Medicine [2].

Figure 1. Prof. Petar V. Simić, PhD (1927–2004), founder of spinal surgery in Serbia and Full Professor at the University of Belgrade Faculty of Medicine

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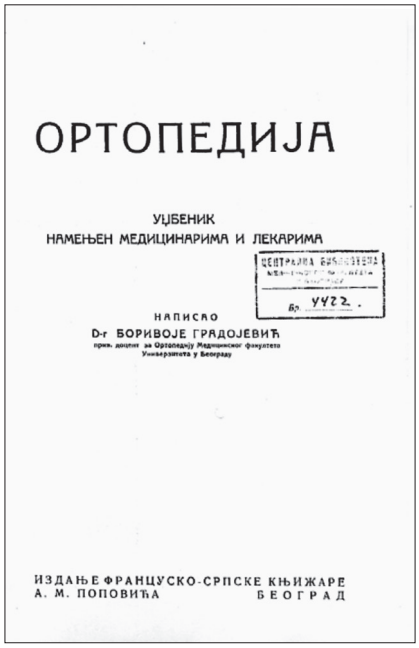
ОРТОПЕДИЈА

УЏБЕНИК
НАМЕЊЕН МЕДИЦИНАРИМА И ЛЕКАРИМА

НАПИСАО
D-r БОРИВОЈЕ ГРАДОЈЕВИЋ

ИЗДАЊЕ ФРАНЦУСКО-СРПСКЕ КЊИЖАРЕ
А. М. ПОПОВИЋА БЕОГРАД

Figure 2. The first orthopedic textbook, written by Dr. Borivoje Gradojević in 1934

Figure 3. Clinic for Orthopedic Surgery and Traumatology, Belgrade, circa 1960

Prof. Simić became a full member of the Academy of Medical Sciences of the Serbian Medical Society in 1978. He also served as Head of the Department of Postgraduate Studies in Orthopedic Surgery and Traumatology at the Faculty of Medicine in Belgrade. From 1978 to 1983, he was the Director of the Clinic for Orthopedic Surgery and Traumatology at the University Clinical Center of Serbia in Belgrade and is on record as the first director to resign from the position.

He was fluent in English and had a working knowledge of French and German.

Professor Simić's surgical work

The origins of spinal orthopedic surgery in Serbia date back to 1964, when the Department of Neuro-orthopedics was established within the Clinic for Orthopedic Surgery and Traumatology – an institution now known as the Department of Spinal Surgery (Figure 3). This department was founded through the perseverance, enthusiasm, and vision of Prof. Simić, who at the time recognized the need for a specialized center devoted exclusively to spinal pathology. Prof. Simić remained the Head of the department until his retirement in 1993. During that period, patients with tuberculous spondylitis – Pott's disease – presented a particular challenge, as did patients with spinal cord injuries, whose numbers were steadily increasing each year, primarily as a consequence of traffic-related trauma.

Prof. Simić was the first in our country and the region to introduce into surgical practice – and personally perform – a number of operative procedures on the spinal column, having carried out more than 6000 complex spinal surgeries. Considering that the surgical microscope was introduced into spinal surgery only in 1977, computerized tomography in 1973, and discography and magnetic resonance imaging in 1980, one can only imagine the level of courage and determination that Prof. Simić demonstrated when he began performing spinal surgery, a discipline that is still regarded as exceptionally demanding. He made a significant contribution to advancing the diagnosis and surgical treatment of various pain syndromes associated with the spinal column. For several surgical procedures, he refined operative approaches, facilitating their easier and faster execution.

Pain syndromes of the spine are today the leading cause of morbidity among the working-age population and are the reason for the existence of numerous associations and organizations. Sessions on spinal pain syndromes are among the most attended and most engaging at all major international congresses. We are increasingly witnessing adolescents seeking medical attention for cervical or lumbar syndromes, while spinal stenosis remains the predominant problem among the elderly population.

Prof. Simić designed and patented an implant for the stabilization of unstable spinal injuries in cases of vertebral fractures and dislocations, which is still known worldwide as the "Simić Apparatus".

In diagnosing spinal diseases, he relied primarily on clinical examination – a practice that has become quite rare today, as surgeons generally depend on nuclear magnetic resonance imaging (NMRI) findings and radiologists' opinions. The importance of the clinical examination is best illustrated by a quotation from Prof. Simić's book: "… certain physicians neglect the classical clinical examination and hesitate to perform certain tests, disregarding the well-known fact that more errors have been made due to inadequate examination than for any other reason. This should be emphasized, because there is a tendency to overlook the taking of anamnesis and classical clinical examination, in the hope that some of the modern diagnostic methods,

such as NMRI and other techniques, will resolve the diagnosis."

Professor Simić's professional development

Professor Simić underwent professional training at renowned clinics in England – the National Spinal Injuries Centre in Aylesbury in 1959 and the Royal National Orthopaedic Hospital in London in 1979. As part of his study visits, he spent time at the Central Institute of Traumatology and Orthopedics (*Национальный медицинский исследовательский центр травматологии и ортопедии имени Н.Н. Приорова*) in Moscow, in 1964 and 1968; at the Karolinska Hospital (*Karolinska sjukhuset*) and Huddinge University Hospital (*Huddinge universitetssjukhus*) in Stockholm in 1979; and at Northwestern Memorial Hospital in Chicago in 1981. From each of these visits, he brought back new knowledge and practices, which he applied in the treatment of his patients. He continuously kept up with professional literature and often emphasized that in medicine, one must read and learn constantly. As a long-standing member of the International Society of Orthopedic Surgery and Traumatology *(Société Internationale de Chirurgie Orthopédique et de Traumatologie* – SICOT), he actively participated in its work, delivering lectures and presenting his papers at nearly all SICOT congresses.

Professor Simić's scientific contributions

Professor Simić was the author of more than 150 scientific and professional papers published in both domestic and international journals, including The Journal of Bone and Joint Surgery, The Serbian Archives of Medicine, Acta Orthopaedica Iugoslavica, the proceedings of the International Society of Orthopedic Surgery and Traumatology, the proceedings of the Yugoslav Association of Orthopedic Surgeons and Traumatologists (JUOT) congresses, and others. He also wrote several books, the most significant being *Trauma – Local and General Disorders in the Organism* [3] and *Diseases of the Spine* [4], comprising about 750 pages (Figure 4). For the book *History of Surgery*, which he co-authored with his son, Prof. Dr. Aleksandar Simić, he was posthumously awarded the Belgrade City Award in Medicine for 2008 [5].

In addition to his exceptional professional achievements, he was also a talented painter and exhibited his artwork at several solo exhibitions (Figures 5 and 6).

Figure 4. Title page – *Diseases of the Spine*

Global development of spinal surgery in the 20th century

To fully appreciate the significance of Prof. Simić's pioneering work and the establishment of the Department of Neuro-orthopedics, it is essential to consider the level of development of spinal orthopedic surgery in the world at the time.

Spinal surgery was revolutionized in the 20th century. This was fueled both by a deeper understanding of spinal anatomy and surgical approaches, and by the introduction of new diagnostic techniques and implants [3].

The origins of spinal surgery can be traced back to Hippocrates (460–370 BC), often referred to as the "father of spinal surgery." Hippocrates devoted serious attention to spinal deformities, which remain a challenge to treat even today, as differing opinions persist regarding operative versus non-operative management. The Hippocratic bench and ladder form the basis of all modern methods of indirect decompression – spinal traction (Figure 7). This method appears to be more widely used today than ever before in the treatment of various spinal pathologies, yet few practitioners are aware that the concept originated with

Figure 5. Prof. Petar Simić's work of art

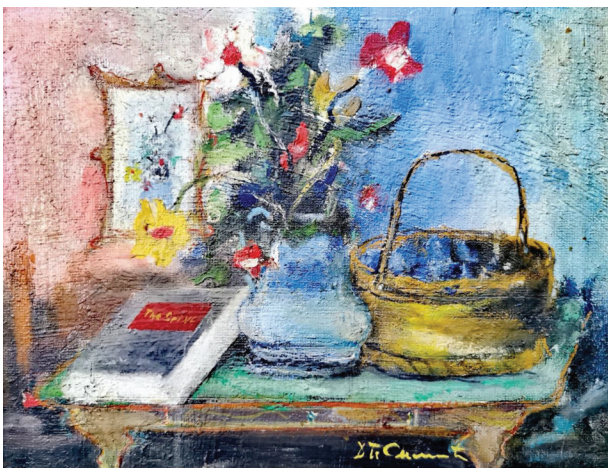

Figure 6. Prof. Petar Simić's work of art

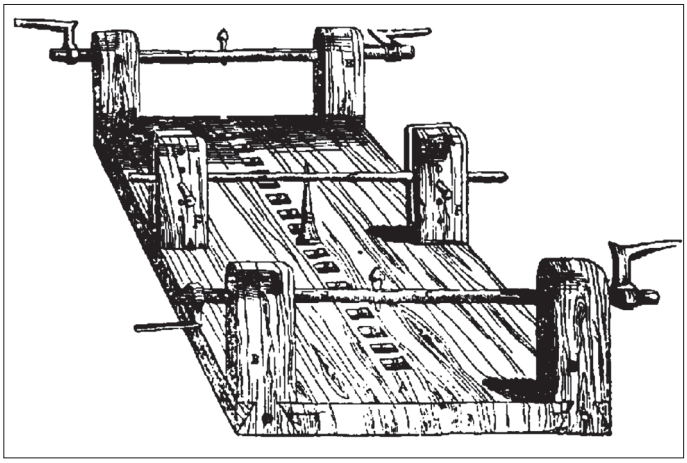

Figure 7. The Hippocratic bench (source: *Loeb Classical Library*)

Hippocrates [6]. One of the most prominent followers of Hippocrates, the Greek physician of the Roman Empire period, Galen (129–c. 216), was the first to define scoliosis, kyphosis, and lordosis. The French military surgeon Ambroise Paré (1510–1590) was the first to introduce braces in the treatment of these deformities, which remain the foundation of non-operative management even today. The French surgeon Jules René Guérin (1801–1886) performed the first official surgical correction of scoliosis in 1865 [7].

Spinal surgery achieved its most significant and rapid advancements in the 20th century, driven by the introduction of the surgical microscope, X-rays, discography, computed tomography scanning, NMRI [8], and implants for internal fixation. The earliest internal fixations targeted the posterior structures of the cervical spine, likely due to anatomical accessibility, with the first successful posterior cervical fixation at C6–C7 using figure-of-eight silver wiring documented in 1891 [9]. The anterior approach to the cervical spine was introduced in 1890, but the first anterior cervical discectomy and fusion was performed in 1958 by George W. Smith (1916–1964) and Robert A. Robinson (1914–1990), as well as by Ralph Bingham Cloward (1908–2000), independently of each other. Surgical approaches and instruments for the anterior approach continue to bear the names of these surgeons today [10]. During this period, Prof. Simić also began introducing these procedures at the Clinic for Orthopedic Surgery and Traumatology in Belgrade.

The first official description of lumbar-sacral spine fixation using screws dates back to 1948, when the first fixation through the facet joints was performed (Figure 8). In 1970, Raymond Roy-Camille (1927–1994) introduced the current gold standard for spinal fixation – transpedicular fixation. He also devised a method for posterior cervical spine fixation with lateral mass screws, which also remains the gold standard to this day [11].

Prof. Simić was perhaps most profoundly influenced by the work of Paul Randall Harrington (1911–1980), an American surgeon who introduced the Harrington rod fitted with hooks in 1955 (Figure 9). This system was originally designed for open correction of spinal deformities but came to be used for dislocation fractures of the thoracolumbar spine after 1969, when modified instrumentation combining hooks and transpedicular screws was developed [12]. A modified version of this system is still in use today for the treatment of kyphoscoliotic deformities, although hooks are now employed far less frequently. Modern spinal surgery routinely integrates posterior, lateral, and anterior approaches – something that would have been unthinkable in the 20th century.

During Prof. Simić's era, patients with tuberculous spondylitis – Pott's disease – posed a major therapeutic challenge both in our country and worldwide [13]. Both then and

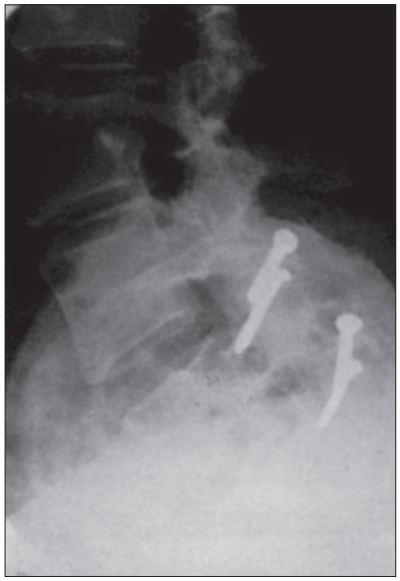

Figure 8. Source: King D. Internal fixation for lumbosacral fusion. J Bone Joint Surg Am. 1948;30A(3):560–5. [PMID: 18109577]

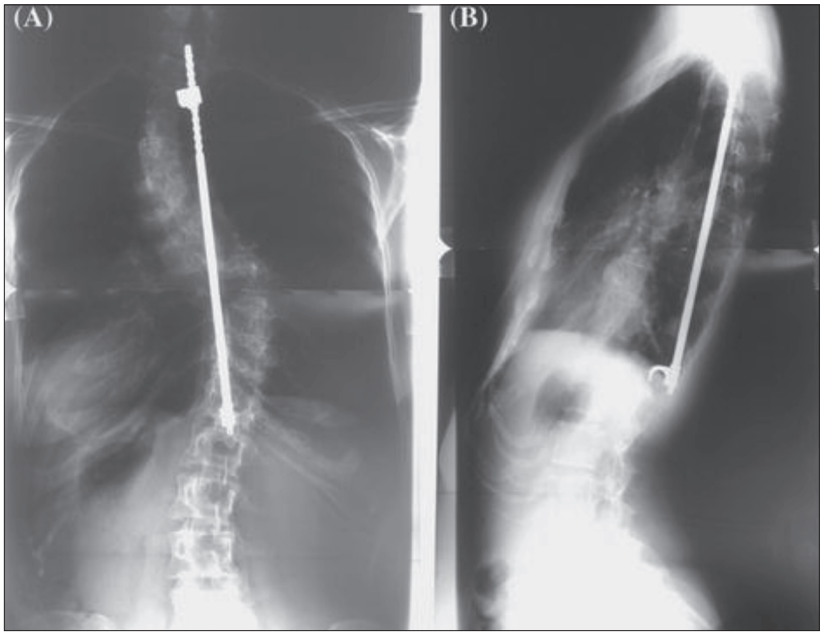

Figure 9. The Harrington rod fitted with hooks; source: Hasler CC. A brief overview of 100 years of history of surgical treatment for adolescent idiopathic scoliosis. J Child Orthop. 2013;7(1):57–62. [DOI: 10.1007/s11832-012-0466-3] [PMID: 24432060]

now, the guiding principle of treatment remained the same: a combination of medication, as the foundation of treatment, and surgery. Interestingly, early surgical management of these patients involved radical (excisional) surgery – a practice introduced in our country by Prof. Simić himself. Among senior orthopedic surgeons who had the privilege of witnessing his pioneering work, the first associations that come to mind are the Dott and Alexander procedures (anterolateral thoracic decompression). Today, the treatment of tuberculous spondylitis is based on the so-called "middle-path regime," which combines antituberculous drug therapy with conservative surgery focused not on removing the pathological substrate, but primarily on preventing deformity and neural damage.

Figure 10. The *Eurospine Surgical Center of Excellence* certificate

The 21st century has brought numerous groundbreaking innovations, all within the realm of minimally invasive surgery. These include integrating diagnostic technologies (the endoscope, the 3D microscope, the exoscope) with instruments for minimally invasive fusion, introducing biologically compatible implants, and incorporating robotics and navigation – advancements that are ushering us into a new, still largely unexplored world of artificial intelligence [14].

After Prof. Petar Simić's retirement, the development of spinal surgery in Serbia continued and has persisted to this day. The department's leadership was assumed by Dr. Slobodan Šljivar. It was later renamed the Department of Acute Spinal Trauma of the Clinical Center of Serbia, initially headed by Dr. Branislav Pešić, alongside Dr. Nebojša Lozo and a group of young orthopedic residents who were increasingly showing interest in spinal pathology and surgery. Today, the department is officially known as the Department of Spinal Surgery, as it treats not only patients with spinal injuries from across the country and the region, but also those with tumors, infections, degenerative diseases, and deformities of the spine (with the exception of pediatric deformities, for which the Banjica Institute for Orthopedic Surgery remains the national referral center).

Over the past ten years, more than 15 new procedures in the domain of spinal surgery have been introduced at the University Clinical Center of Serbia, the most significant of which include: vertebral cementing (vertebroplasty and sacroplasty) for fractures and tumors; minimally invasive surgery (tubular and endoscopic); percutaneous stabilization of the spine and sacroiliac joints; vertebral body replacement (corpectomy); occipito-cervical fusion and C1–C2 fusion; spinopelvic stabilization; cervical and lumbar disc prosthesis; intrathecal and intralesional administration of bone marrow aspirate concentrate, mesenchymal stem cells in patients with spinal cord injury; and radiofrequency tumor ablation.

Among the procedures performed for the first time at the University Clinical Center of Serbia were awake spine surgery ("awake spine") and navigation-assisted stabilization. Culminating decades of spinal surgery in Serbia – beginning with Prof. Simić's pioneering surgeries and the founding of the Department of Neuro-orthopedics to the present – in May 2025, the Department of Spinal Surgery of the University Clinical Center of Serbia was designated a *Eurospine Surgical Center of Excellence* (Figure 10), performing over 500 procedures annually.

Although successors will never fully grasp the challenges of being a leader and pioneer of spinal surgery, today's spinal surgeons can appreciate how difficult it was to operate on the spine in an era without tools such as the surgical microscope, computed tomography scanner, NMRI, modern anesthesia, and contemporary implants. For this reason, profound gratitude and deep respect are owed to surgeons such as Prof. Petar Simić.

In conclusion, another quote from Prof. Simić's book, *Diseases of the Spine*: "It has been said that humankind had to leave Paradise behind because of the desire for knowledge, but whether this be true or not, it is certain that our desire for knowledge will secure Paradise for us in the future" [4].

Ethics: The authors declare that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

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Проф. др Петар В. Симић, оснивач ортопедске спиналне хирургије у Србији

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САЖЕТАК

Ортопедска хирургија има дугу и богату историју. Термин „ортопедија" првобитно је настао 1700. године, иако је њен развој почео много раније. Порекло спиналне хирургије може се повезати са четири историјска периода: египатским и вавилонским, грчким и рановизантијским, арапским и средњовековним. Историја ортопедске хирургије у Србији почиње доласком др Николе Крстића у Београд 1904. године, након студија у Бечу, као и првим рендгенским снимком шаке, који је начињен 1905. године. Историја спиналне ортопедске хирургије у Србији почиње радом проф. др Петра Симића, чија пионирска достигнућа и даље служе као темељ за развој спиналне хирургије у Универзитетском клиничком центру Србије и широм земље.

Кључне речи: ортопедија; спинална хирургија; историја; Србија

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HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Presidents of the Serbian Medical Society as leading figures in its development (1872–2025)

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SUMMARY
Dr. Vladan Đorđević, together with fourteen other colleagues, founded the Serbian Medical Society in 1872, which has been publishing the journal *Serbian Archives of Medicine* since 1874. From its founding and the adoption of the first Constitution (June 8, 1872) to the most recent amendments and supplements to the Statute (February 6, 2025), the Society has adopted a total of 29 highest-level normative acts. In the initial period these were titled *Constitution* (1872–1884), followed by *Rules* (1905–1963), while since 1970 the term *Statute* has been used. The Statute regulates the manner of election of the President of the Society and the scope of his duties. From its founding to the present day, the Serbian Medical Society has had a total of 40 Presidents, or Presidents of the Presidency during the period from 1980 to 1991. This paper presents the rudimentary biographical data of the presidents of the Society who, through their work or by initiating statutory changes, contributed to the advancement of the Society's activities.
Keywords: Serbian Medical Society; founders; statutory changes; honorary Presidents

INTRODUCTION

From the founding of the Serbian Medical Society and the adoption of its first Constitution (June 8, 1872) to the most recent amendments and supplements to the Statute (February 6, 2025), the Society has adopted a total of 29 highest normative acts. In the initial period, these acts were entitled *Constitution* (1872–1884), followed by *Rules* (1905–1963), while since 1970 the title *Statute* has been used to denote the highest normative act.

Under the Constitution of the Serbian Medical Society of 1872, the competencies of the President of the Society were precisely defined, establishing the President as both its executive and representative authority. A constitutional provision stipulated that the President managed the Society's overall operations, ensured the implementation of constitutional norms, signed all official documents (diplomas, records, decisions, official correspondence, and financial instruments), determined the agenda of meetings, and was authorized to convene extraordinary sessions [1].

The competencies of the President, as defined in the earliest normative acts, did not undergo substantial changes in their basic features throughout the historical development of the Society. Given that the President's powers included proposing the program of activities and initiating amendments and supplements to the fundamental act, the President played a key role in directing the Society's activities and functioning. It may therefore be concluded that the work of the Serbian Medical Society was, to a significant extent, shaped by the actions and engagement of its President.

From its founding to the present day, the Serbian Medical Society has had a total of 40 Presidents, or Presidents of the Presidency in the period from 1980 to 1991. The duration of their terms of office and the scope of their powers was regulated by the highest valid acts of the Society.

From the founding of the Society until the adoption of the Statute in 1983, the President's term of office lasted one year. The Statute of 1983 established that the term of office of the President of the Presidency would last two years.

The Statute adopted in April 1974 was aligned with the Constitution of the Socialist Federal Republic of Yugoslavia adopted in February of the same year. Further changes in the organizational structure and management of the Society, as well as a more explicit alignment with the doctrine of self-managing socialist governance and the prevailing ideological and political orientation of the time, were incorporated into the Statute of 1980. This act established the Presidency of the Assembly as the executive governing body, replacing the former Executive Board, and transferred the authority to elect the President of the Society from the Assembly to the Presidency. (This provision was also retained in the statutes of the Serbian Medical Society adopted during the period of transition and the abandonment of the ideology of socialist self-management.) At the same time, the title of the office was changed, replacing the designation President of the Society with President of the Presidency of the Society. The Statute of 1983 extended the term of office of the President of the Presidency from one to two years. The Statute adopted

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Figure 1. Dr. Aćim Medović (1815–1893)

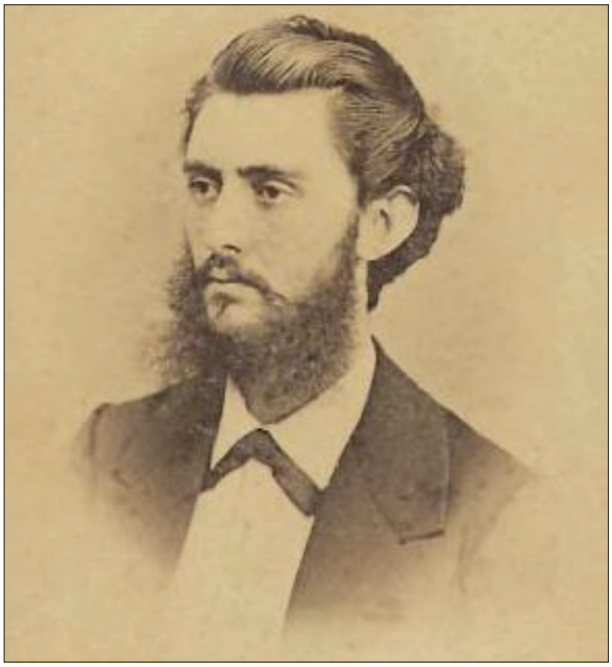

Figure 2. Dr. Vladan Đorđević (1844–1930)

in 1991 reinstated the title President of the Society and extended the term of office to four years. The Statute of 2010 allowed one consecutive re-election to the office of President, while the Statute of 2018 abolished the limitation on the number of terms for which officials of the Society may be elected [2].

PRESIDENTS OF THE SERBIAN MEDICAL SOCIETY

Owing to the efforts of Dr. Vladan Đorđević, the Serbian Medical Society was founded in 1872. At the so-called "First Preliminary Meeting," held on May 4, 1872, the following physicians were present: Carlo Belloni, Jovan Valenta, Joachim Medowicz (Aćim Medović), Petar Ostojić, Josif Holec, Sava Petrović, Đorđe Klinkovski, Jan Mašín (Jovan Mašin), Panayotis Papakostopoulos, Bernhard Brüll, Julius Lenk, Marko Polak, and Vladan Đorđević, as well as the dentist Ilija Ranimir. At this meeting, a provisional governing board of the Society was elected: Dr. Aćim Medović was chosen as provisional president, Dr. Jovan Mašin as vice-president, and Dr. Vladan Đorđević as secretary [3].

Of the fourteen Belgrade physicians who participated in founding the Society, four later also served as presidents of the Serbian Medical Society: Aćim Medović, Panayotis Papakostopoulos, Đorđe Klinkovski, and Vladan Đorđević.

The first president of the Serbian Medical Society was **Dr. Aćim Medović** (1815–1893) (Figure 1). He served as president from May 4, 1872 to April 26, 1873.

Dr. Aćim Medović was the first advocate of establishing a medical society in the Principality of Serbia. In an article published in *Srbske novine*, he expressed hope and expectation that the sanitary administration would "find the means to unite all physicians in our country into a single medical society," which would keep medical annals and systematically collect and preserve experience gained from individual clinical cases, forensic-medical issues, and monitoring of the population's health status, so that the observations of individual physicians might become useful to the entire medical corps and be preserved "from oblivion" for the benefit of science [4, 5].

Dr. Medović's mandate as president of the Society ended with his resignation, which resulted from a personal conflict with the vice-president, Dr. Jovan Mašin.

In addition to his significant role in the founding and early development of the Serbian Medical Society, Dr. Aćim Medović was a corresponding member of the Society of Serbian Letters, a full member of the Serbian Learned Society, and an honorary member of the Serbian Royal Academy, thereby institutionally affirming his contribution to Serbian science and culture [6, 7].

After Vice-President Dr. Jovan Mašin withdrew from the Serbian Medical Society, the chairmanship was assumed by the oldest member of the Society, **Dr. Panayotis Papakostopoulos** (1820–1879). Dr. Papakostopoulos served as president until the annual assembly held on November 4, 1873. In addition to his medical profession, Dr. Papakostopoulos was also a professor of Greek at the Belgrade High School. He belonged to a circle of members of the Serbian Medical Society who, in addition to professional work, made a significant contribution to the development of Serbian culture. In the history of Serbian literature, he is recorded as one of the early translators of works of ancient Greek literature into Serbian, including Homer's *Odyssey* [8, 9].

Dr. Đorđe Klinkovski (1827–1905) served as the fourth president of the Serbian Medical Society from May 6, 1886 to February 16, 1890.

The founder of the Serbian Medical Society, **Dr. Vladan Đorđević** (1844–1930) (Figure 2) was the fifth president

from February 16, 1890 to October 3, 1892. Immediately after the founding of the Society, he served as secretary and subsequently became the initiator and first editor of the journal *Srpski arhiv za celokupno lekarstvo* (*Serbian Archives of Medicine*). The strength of the foundations on which Dr. Vladan Đorđević built the Serbian Medical Society is evidenced by the fact that, despite numerous historical trials, the Society preserved continuity in its work. Over more than a century and a half of existence, it survived eight wars, including the NATO bombing of the Federal Republic of Yugoslavia, as well as profound changes in state systems and territorial frameworks. From 1872 to the present day, the Serbian Medical Society has operated within six different state formations, retaining its status as the most important medical organization in Serbia and, in terms of continuity of existence, one of the oldest in Europe.

Appointed by decree of Prince Milan on April 13, 1879 as head of the Sanitary Department of the Ministry of the Interior, Dr. Vladan Đorđević undertook the drafting of key legislative acts in the field of public health. The Law on the National Sanitary Fund was adopted in 1879, and the Law on the Organization of the Sanitary Profession and the Protection of Public Health in 1881, thereby laying the institutional foundations of the modern health service in Serbia.

Dr. Vladan Đorđević served as Minister of Education and Ecclesiastical Affairs, as well as acting Minister of National Economy, in the government of Nikola Hristić from April 1888 to February 1889. He held the office of Prime Minister and Minister of Foreign Affairs of the Kingdom of Serbia from October 1897 to 1900.

He was a full member of the Serbian Learned Society from 1869, a full member of the Serbian Royal Academy of Sciences, and a corresponding member of several international professional associations. He was promoted to the first honorary Doctor of Medical Sciences of the University of Belgrade on September 17, 1925.

In addition to his medical and political engagement, Dr. Vladan Đorđević had been active in literary work since his secondary-school days. He wrote plays, short stories, travelogues, and novels, leaving behind a voluminous and genre-diverse opus.

Viewed in its entirety – as physician, reformer, statesman, and writer – Dr. Vladan Đorđević ranks among the most prominent figures of Serbian history from the late nineteenth and the first decades of the twentieth century [10].

The First Congress of Serbian Physicians was held jointly with Serbian natural scientists in Belgrade from 18 to 20 of September 1904, as part of the celebration of the centenary of the First Serbian Uprising and the coronation of King Peter I Karađorđević, who was also the patron of the Congress. The president of the Organizing Committee was Dr. Jovan Danić, president of the Serbian Medical Society and Editor-in-Chief of the *Serbian Archives of Medicine*.

Dr. Jovan Danić (1854–1924) was the eighth president of the Serbian Medical Society. He served his first term from January 23, 1899 to May 7, 1905, and his second from September 26, 1907 to October 25, 1910. After the expiration of his second term, he was elected lifetime honorary president of the Society. He edited four journals, including *Serbian Archives of Medicine* (from the second issue in 1896 until 1924) and *Narodno zdravlje. Lekarske pouke narodu* (from the second issue in 1896 until 1914). In 1885, he was elected an honorary member of the Royal Medical Academy in Rome and an honorary member of the Association of Physicians of Croatia, Slavonia, and Međimurje county.

He published more than 200 works, including books, original articles, health-education papers, translations, adapted translations, and travelogues [11].

As previously noted, over more than a century and a half of its existence, the Serbian Medical Society adopted a total of 29 highest legal acts, mostly minor amendments. A turning point was marked by the *Rules* adopted in 1905, based on a proposal submitted on behalf of five members of the Society by Dr. Mita Nikolić and Dr. Đoka Nikolić, which initiated the "second period" of the Society's development. These *Rules* created conditions for expanding membership, improving the work of governing bodies, enhancing the material position of members, and strengthening the role of the Society in the organization and functioning of the health service. The Rules established new bodies and institutions of the Society: The Executive Board, the Court of Honor, and the Fund for Assisting Poor Physicians, Their Widows, and Orphans. The Executive Board consisted of nine members, one of whom had to be a military physician. From among its members, the Board elected the president, vice-president, and secretary [12].

Dr. Đorđe–Đoka J. Nikolić (1863–1940) served as president of the Serbian Medical Society in two terms: from May 7, 1905 to October 6, 1907, and from January 11, 1914 to December 5, 1919. He was an energetic advocate of establishing a Faculty of Medicine in Belgrade.

He was president of the Society during the First World War. He chaired the commemorative extraordinary session of the Society, at which he stated:

"In vain today do our eyes search among the ranks for old acquaintances – there are none, we do not see them. We shall find them among those who have repaid their debt to the fatherland. When the balance of the fallen and the survivors began to be drawn up, it became clear that the medical profession occupied first place among the fallen" [13].

From 1921 until his retirement in 1923, he served as Assistant Minister of Health. In 1922, he was elected an honorary member of the Royal Sanitary Institute in London.

In addition to his professional work, he engaged in literary activity and translation. He translated from English and German not only medical works but also literary texts, among which Henrik Ibsen's drama *John Gabriel Borkman* stands out [14].

Two significant amendments to the Rules of the Serbian Medical Society date from 1911 and 1919. The first was adopted at the XXXIX Annual General Assembly in 1911, when it was decided to establish subcommittees of the Society in every district town. One of the proponents of

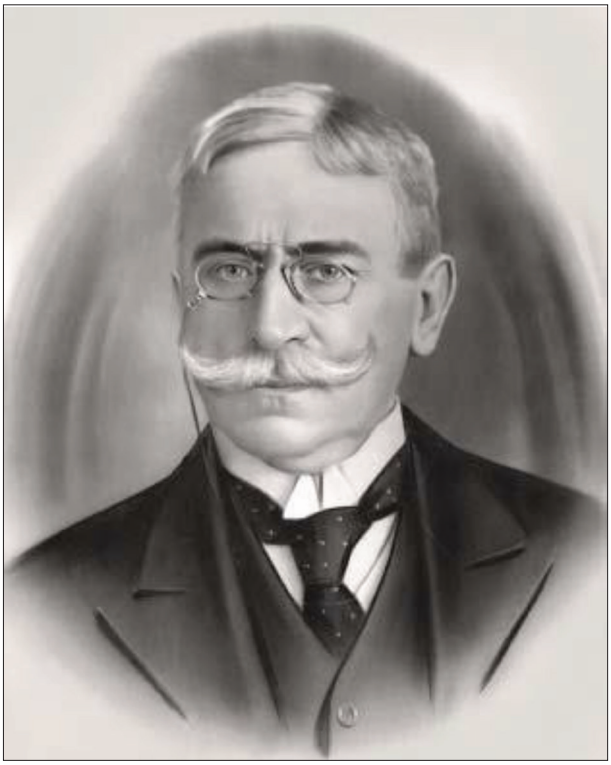

Figure 3. Dr. Vojislav J. Subbotić (1859–1923)

this amendment, Dr. Aleksa Stojković, called the subcommittees "the cornerstone for the future building of our organization" [15].

The second amendment was adopted at the Annual General Assembly of the Society held on November 22, 1919, on the proposal of Dr. Vojislav J. Subbotić, who, together with 23 other members, proposed enabling the establishment of professional sections. The need for their establishment was justified as a measure for the "differentiation of professional work and the deepening of studies and discussions" [16]. These amendments later enabled the development of the Society through the establishment of numerous branches and sections as forms of territorial and professional organization.

Dr. Vojislav J. Subbotić (1859–1923) (Figure 3) served as president of the Society from October 12, 1910 to December 29, 1913 and from November 22, 1919 to September 3, 1921. From his arrival in Belgrade in May 1889, he was very active in the work of the Society, which he regarded as crucial for the postgraduate education of Serbian physicians. In his first year at the General State Hospital, he delivered around 60 reports. He organized meetings of surgeons, including the First Meeting of Serbian Surgeons (1907) and the First Yugoslav Meeting for Operative Medicine (1911).

Dr. Bukić Pijade described the period of his presidency as a "period of scientific momentum". Dr. Vojislav J. Subbotić was one of the founders of the Faculty Medicine, the first full professor of surgery, the first vice-dean, and the second dean. He was also a member of numerous prestigious foreign societies, including the French, German, and International Surgical Societies, the Pest Medical Society, the Paris Medical Academy, and the Societies of War Surgeons of the USA and England [17, 18].

Two presidents of the Serbian Medical Society from the interwar period are of particular importance for the institutional and material development of the Society: Dr. Vojislav M. Subotić Jr., founder of the largest endowment administered by the Society, and Dr. Svetislav Stefanović, during whose presidency the Society, after more than six decades as a tenant, began holding professional meetings and annual assemblies in its own building.

Dr. Vojislav M. Subotić (1866–1922) served as president of the Serbian Medical Society from September 3, 1921 to February 4, 1922. His public and professional engagement was primarily directed toward work in the Serbian Red Cross Society and the Serbian Medical Society. He was a member of the Red Cross administration from 1898 to 1921, initially as secretary and, from July 1914, as vice-president.

He had been active in the Serbian Medical Society since May 18, 1902 as a board member, secretary, and treasurer. He was elected president at the 43rd Annual General Assembly held on September 3, 1921 and submitted his resignation from membership and the presidential office on February 4, 1922.

During the Great War, he experienced two severe personal tragedies. First, he lost his only son Luka, who, as a volunteer hospital orderly, contracted typhoid fever and died on December 27, 1914. On May 30, 1915, his wife Melanija died "of excessive, immeasurable grief" for their son.

These events directly influenced the establishment of the "Endowment of Medical Student Luka and His Parents Melanija and Dr. Vojislav Subotić," of which Dr. Subotić informed the Ministry of Education and Ecclesiastical Affairs on June 8, 1915.

Significant real estate assets in Belgrade were transferred to the Endowment: a house in Takovska 19 and two plots of land, one near the Tobacco Factory and the other in Bulver Despota Stefana near the Pančevo Bridge, as well as plots in Vrnjačka Banja and Banja Koviljača. The founding act also defined the obligations of the Serbian Medical Society, which assumed care for the family tomb and the obligation to hold annual professional meetings dedicated to the memory of Luka Subotić. This practice was continuously maintained even after the founder's death.

The funds of the Endowment of Dr. Vojislav M. Subotić played a significant role in financing the construction of the Home of the Serbian Medical Society, the Endowment of Dr. Steva Milosavljević, at Zeleni Venac (Kraljice Natalije 1–3). Due to a lack of funds to complete the construction, the Society used loans from the Subotić Endowment capital totaling 1,250,000 dinars, with the obligation to repay the principal and accrued interest. With the nationalization of property in 1960, by decision of the Nationalization Commission of the People's Committee of Stari grad municipality, the entire property of the Serbian Medical Society, including the Home, passed into state ownership.

Dr. Vojislav M. Subotić also left a significant written legacy, publishing a total of 44 works, including studies

Figure 4. The Home of the Serbian Medical Society, Endowment of Dr. Steva Milosavljević

of lasting value for research into the history of Serbian medicine and the Serbian Medical Society [19, 20].

Dr. Svetislav Stefanović (1877–1944) served as president of the Serbian Medical Society for six terms, from September 6, 1928 to October 25, 1934. During his presidency, legal and organizational issues concerning endowments, funds, and legacies were intensively addressed, enabling the start of construction of the Society's Home in 1931. Financial resources were secured through endowments and legacies of several benefactors, as well as voluntary contributions and loans from physicians. The 60th anniversary of the founding of the Society was celebrated on May 5, 1932 in the newly constructed Home (Figure 4) [21].

In addition to his medical work, Dr. Svetislav Stefanović was active in literature and culture. He studied English and comparative literature, engaged in literary translation – particularly of the works of William Shakespeare – and published poetry and prose in periodicals and separate collections.

From June 1942 until the liberation of Belgrade, he headed the Serbian Literary Cooperative as president of its Commissarial Administration. He followed the work of the International Commission for the Investigation of War Crimes, formed in July 1943 to determine the circumstances of mass executions near Vinnytsia in Ukraine. In the article "Lesson and Message from Vinnytsia," [22] he conveyed the position of forensic experts, formed on the basis of material evidence, that the crimes were committed in 1937–1938 and carried out by members of the People's Commissariat for Internal Affairs during the mass purges conducted throughout the Soviet Union in those years.

After the liberation of Belgrade, he was arrested on October 22, 1944 and sentenced to death. By a decision of the Plenum of the Serbian Medical Society in 1946, he was declared unworthy of membership, primarily for ideological reasons. At a joint session held in December 2021, the Assembly of the Serbian Medical Society annulled this decision and posthumously restored all his membership rights [23, 24, 25].

After the end of the Second World War, the Serbian Medical Society resumed its work. On the role of the Society in the postwar period, Dr. Uroš Jekić, then Minister of Public Health of Serbia, wrote in the editorial of the first postwar issue of *Serbian Archives of Medicine*:

"The renewal of the work of the Serbian Medical Society, which fundamentally changes the essence of its activities; the gathering and linking of all medical forces in the country through the Serbian Medical Society; the relaunch of the *Serbian Archives*, through whose pages the spirit of the new era should flow – these are further proofs of a fortunate development of our medical service" [26].

The first postwar assembly of the Society was held from 14 to 16 April 1946 in the hall of the Society's Home. The election of Prof. Dr. Kosta Todorović as president indicated the desire of the delegates not to interrupt the continuity of the Society's work even under the new circumstances created by the revolutionary change of the social system. The previous president, Dr. Milan Petrović, was elected president of the Supervisory Board. The "Rules of the Serbian Medical Society" were unanimously adopted, enabling the Society to "turn inward and devote itself to organizational and professional issues" [27].

Speaking about the importance of establishing branches in all places in the Republic of Serbia where conditions existed, Dr. Čedomil Plavšić stated:

"In the Society's branches, the entire social life should take place, and the *Rules* therefore state that the tasks of the branches are in fact the tasks of the Society. (…) It is necessary that all physicians in the interior, with full attention and love, make efforts not only to establish branches but also to cooperate intensively within them, to elevate and improve them, because the people and our small state will benefit from this, as will we ourselves" [28].

The Assembly also adopted a Resolution which, among other things, called for the establishment of a School of Dental Medicine [29].

Academician Kosta Todorović (1887–1975) (Figure 5) was the first postwar president of the Society, from April 14, 1946 to March 20, 1949. He had been a long-standing member of the Society and, in the interwar period, vice-president under Svetislav Stefanović and Momčilo Ivković. His election as president marked the beginning of the "golden age" of the Serbian Medical Society. Thanks to his work – which Dr. Vladimir Stanojević said "served

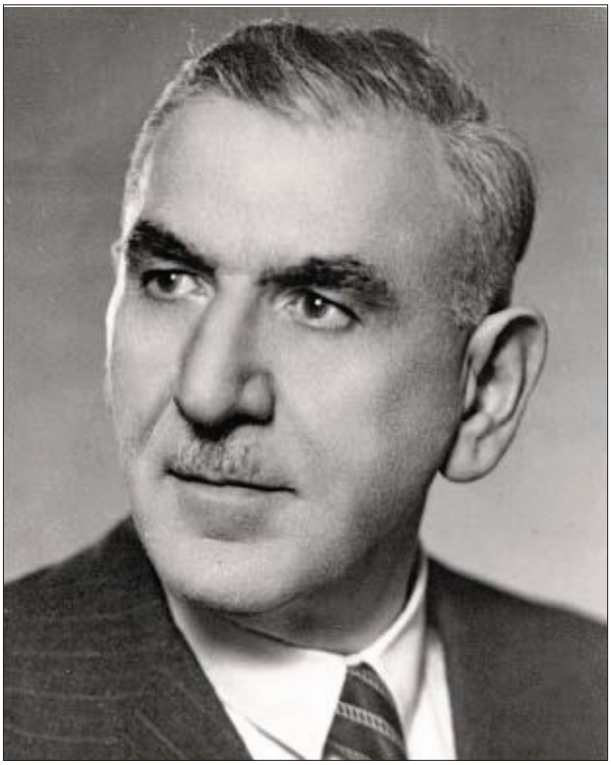

Figure 5. Academician Kosta Todorović (1887–1975)

as a bridge for the transition from our rich cultural heritage to contemporary creativity" – the Society managed to preserve its identity in the early postwar years, when organizations originating in the old regime were not viewed favorably [30]. He also succeeded in having the Society recognized by the new authorities as a partner in addressing numerous health problems that had persisted in Serbia for decades. During his mandate, the more extensive establishment of branches and specialist sections began.

As part of the revitalization of the Society's work, the series "Library of the Serbian Medical Society" was founded. All professional publications of the Society, except *Serbian Archives* and the *Annual Reports*, were included in this series. During Todorović's presidency, numerous branches were established, the work of sections founded before the Second World War was renewed, and new ones were created (cardiology, neuropsychiatry, gynecology and obstetrics, otorhinolaryngology, dermatovenereology, and others). The proposal to establish a Section for the History of Medicine and Pharmacy was "enthusiastically welcomed by Prof. Dr. Kosta Todorović" [31].

This section would in 1955 establish the Museum of Serbian Medicine of the Serbian Medical Society. During Todorović's mandate, the Dental Section launched a formal initiative to establish the School of Dental Medicine in Belgrade (1948).

The second postwar president of the Society, from March 20, 1949 to March 28, 1954, was **Prof. Dr. Uroš Jekić** (1896–1980). As Minister of Health in the Government of the Republic of Serbia, he contributed to the renewal of the Society's work, and as its president he organized the first postwar Congress of Physicians of Serbia (1952), which "represented one of the most significant events in the postwar history of the Society and made a major contribution to solving health problems throughout the Republic" [32].

In April 1974, the Serbian Medical Society held its 87th regular assembly and adopted a new statute, harmonized with the *Constitution* of the Socialist Federal Republic of Yugoslavia adopted in February of the same year. The new Constitution imposed a model of collective governance, so that instead of a president, the Society elected a Presidency with a one-year rotating chairmanship. In such a short mandate, it was not possible to implement more substantial activities. Enthusiasm for work in the branches began to weaken, and membership declined, so that by 1980 it had fallen to a quarter of the total number of physicians. By comparison, in 1963 the proportion of members relative to the total number of physicians and dentists was 92%, and in 1973 it was 75%.

The presidents of the Presidency of the Serbian Medical Society were: Petar Stefanović (1924–1999), Borislav Najdanović (1916–1987), Aleksandar Dimitrijević (1942–2012), Milenko Lalić (1922–2004), and Dragan Kuburović (born 1935). Professor Dragan Kuburović is the only dentist to have headed the Society in its more than century-and-a-half-long existence.

From the Assembly held in 1983, the Serbian Medical Society abandoned the concept of "presidencies" and once again elected a president of the Society, leading to a series of positive changes that revitalized the Society.

Professor Petar Korolija (1925–2004) served as president from October 7, 1983 to November 13, 1987. During his mandate, the City Assembly of Belgrade granted the Society the building of the Eye Clinic in Džordža Vašingtona street for permanent use. The organization of multi-day symposia titled "Advances in Diagnosis and Treatment" was initiated, the practice of the professors of the Faculty of Medicine delivering lectures in branches outside Belgrade was renewed, and a larger number of specialist sections were established.

The political disintegration of Yugoslavia, initiated by the adoption of the 1974 Constitution, led to the collapse of the state in the bloody civil war of the 1990s. The Serbian Medical Society suffered severe consequences. Sanctions, inflation, and war led to a decline in membership and activity. A major credit goes to **Academician Vojin Šulović** (1923–2008), president of the Society from November 13, 1987 to April 1, 1996, for preserving the Society even under such extremely unfavorable conditions. Despite the difficult situation, Congresses of Physicians of Serbia were held in 1992, 1993, and 1996, and five specialist sections were established.

The true revival of the Serbian Medical Society began with the election of **Academician Radoje Čolović** (born 1944) (Figure 6) as its president on January 30, 2009. During 14 years at the helm of the Society, until November 17, 2023, he made a significant contribution to its reputation. Thanks to his charisma and enthusiasm, numerous branches were founded, doubling the number of members; the work of sections that had been dormant for years, even

Figure 6. Academician Radoje Čolović (1944)

decades, was revitalized and renewed. During his mandate, the Society was awarded the Order of Sretenje, Second Class, and the Order of Saint Sava, Second Class (2012), and in 2022, on the occasion of the 150th anniversary of the Society, the Order of Sretenje, First Class. At the Assembly held on November 17, 2023, he was elected an honorary member and honorary president of the Society.

Through his work in the Society, Academician Radoje Čolović "raised for himself a monument more lasting than bronze" (*Exegi monumentum aere perennius* – Horace, *Ode* 3.30). In addition to strengthening the Society, his engagement was marked by the renovation of the Society's headquarters building in Džordža Vašingtona street, as well as the Home of the Serbian Medical Society in Kraljice Natalije street.

The current leadership of the Serbian Medical Society, headed by President Prof. **Dr. Milan A. Nedeljković** (born 1957) (Figure 7), elected on November 17, 2023, has defined as the main goals of its mandate the positioning of the Society within the Law on Health Care, increasing membership, and encouraging branches and sections to engage more actively in continuing education. At the Assembly session held on February 6, 2025, two important decisions were adopted: to define the Serbian Medical

Figure 7. The leadership of the Serbian Medical Society in 2025 (from the right: Prof. Dr. Milan A. Nedeljković, President of the Serbian Medical Society; Dr. Zoran Vacić, Secretary General of the Serbian Medical Society; Prof. Dr. Dragoslav Bašić, Vice President of the Serbian Medical Society; Prof. Dr. Nebojša Stanković, President of the Academy of Medical Sciences of the Serbian Medical Society; Prof. Dr. Nebojša Radovanović, Secretary General of the Academy of Medical Sciences of the Serbian Medical Society)

Society as a scientific society through amendments to the statute, and to initiate the procedure for returning the Museum and Library from the Museum of Science and Technology to the Society.

The presidents of the Serbian Medical Society also included: Mladen Janković (1831–1885), Lazar Dokić (1846–1893), Mihailo Mika Marković (1847–1911), Mihailo Petrović (1863–1934), Momčilo K. Ivković, Đorđe Joanović (1871–1932), Milan Jovanović Batut (1847–1940), Svetozar Moačanin (1884–1962), Milan Petrović (1886–1963), Radivoje Berović (1900–1975), Jezdirmir Studic (1902–1960), Čedomil Plavšić (1902–1986), Dragomir Karajović (1899–1964), Vojislav Danilović (1910–1981), Aleksandar Mezić (1910–1973), Srboljub Stojiljković (1922–1974), Dragomir Mladenović (1919–2017), Vladimir Paunović (1942–2007), Zoran Ivanković (born 1951), and Vojkan Stanić (born 1950).

CONCLUSION

The historical development of the Serbian Medical Society, viewed through the prism of its highest normative acts and the activities of its presidents, demonstrates an institution of exceptional stability, adaptability, and continuity. From the adoption of the first Constitution in 1872 to the most recent amendments to the Statute in 2025, the Society's normative framework has changed in accordance with social, political, and ideological circumstances, while its fundamental objectives – professional cohesion of physicians, advancement of the health service, and development of medical science – have remained unchanged.

A special place in the history of the Society is occupied by the office of president, whose powers, despite numerous statutory changes, have always played a key role in directing the Society's work. Although the title of the office, the method of election, and the length of the mandate have changed – from one-year terms, through collective governance during the period of self-management socialism, to the contemporary model of multi-year mandates – the influence of the individuals who led the Society has remained decisive. The history of the Society clearly shows that periods of greatest progress and institutional strengthening are associated with strong, visionary, and authoritative presidents.

From founders and early presidents such as Aćim Medović and Vladan Đorđević, through reformers of the early twentieth century, interwar builders of the Society's institutional and material foundations, to postwar restorers and contemporary leaders, the presidents of the Society were not merely administrators but also bearers of broader social, scientific, and cultural initiatives. Their actions enabled the Society to survive wars, changes of state systems, ideological breaks, and economic crises, while retaining its status as the oldest and most prestigious medical organization in Serbia.

The contemporary development of the Serbian Medical Society – grounded in the restoration of a strong presidential function, the strengthening of branches and sections, and clearer positioning within the legal system of the Republic of Serbia – represents a logical continuation of its historical tradition. It is precisely in the combination of normative continuity and strong personal engagement of the leadership that the key to the longevity and social significance of the Serbian Medical Society lies.

Ehics: The authors declare that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved.

Conflict of interest: None declared.

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Председници Српског лекарског друштва као водеће личности његовог развоја (1872–2025)

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САДРЖАЈ

Доктор Владан Ђорђевић са четрнаесторицом колега 1872. године оснива Српско лекарско друштво, које од 1874. издаје часопис „Српски архив за целокупно лекарство". Од оснивања и доношења првог Устава (8. јуна 1872) до последњих измена и допуна Статута (6. фебруара 2025), Друштво је усвојило укупно 29 највиших нормативних аката, који су у почетном периоду носили назив *Устав* (1872–1884), затим *Правила* (1905–1963), док се од 1970. године до данас користи назив *Статут*. Статутом је регулисан начин избора председника Друштва и делокруг његовог рада. Од оснивања до данас Српско лекарско друштво имало је укупно 40 председника, односно председника Председништва у периоду од 1980. до 1991. године. У овом раду дати су основни биографски подаци председника Друштва који су својим радом или иницирањем статутарних промена доводили до напретка у раду Друштва.

Кључне речи: Српско лекарско друштво; оснивачи; статутарне промене; заслужни председници

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 хонорарише. 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, коментари по позиви, 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, *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 (https://www.nlm.nih.gov/mesh/meshhome.html)*.

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 се означавају 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 видео-приказа у е-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 публикације 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. Примери навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *https://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/en/submission-letter/SubmissionLetterForm2023.pdf*).

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 И НАКНАДЕ ЗА ОБРАДУ И ОБЈАВЉИВАЊЕ ЧЛАНКА. Да би рад био разматран за објављивање 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 9 Статута Друштва) у години у којој рад предају на разматрање.

Следеће накнаде су обавезне како би рад био прегледан, обрађен и потенцијално објављен у *Српском архиву за целокупно лекарство*:

- накнада за преглед сваког примљеног рада домаћих аутора: 6.000 динара по раду;
- накнада за прихваћен рад, односно накнада за објављивање рада домаћих аутора: 12.000 динара по раду;
- накнада за преглед сваког примљеног рада страних аутора: 75 евра (или 9000 динара) по раду;
- накнада за прихваћен рад, односно накнада за објављивање рада страних аутора: 150 евра (или 18000 динара) по раду.

Накнаде се плаћају пре прегледања, односно пре објављивања рада. Радови за које нису плаћене накнаде неће бити прегледани, односно објављени.

Треба напоменути да уплата накнаде за преглед рада није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*.

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 накнаду за преглед чланка, као доказ о уплатама. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за преглед чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Онлајн систем за подношење радова водиће вас кроз поступак уноса података о чланку и отпремања ваших датотека. 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 бројеве телефона.

АДРЕСА:
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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., ^{99}Tc, IL-6, O_2, 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.

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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.

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