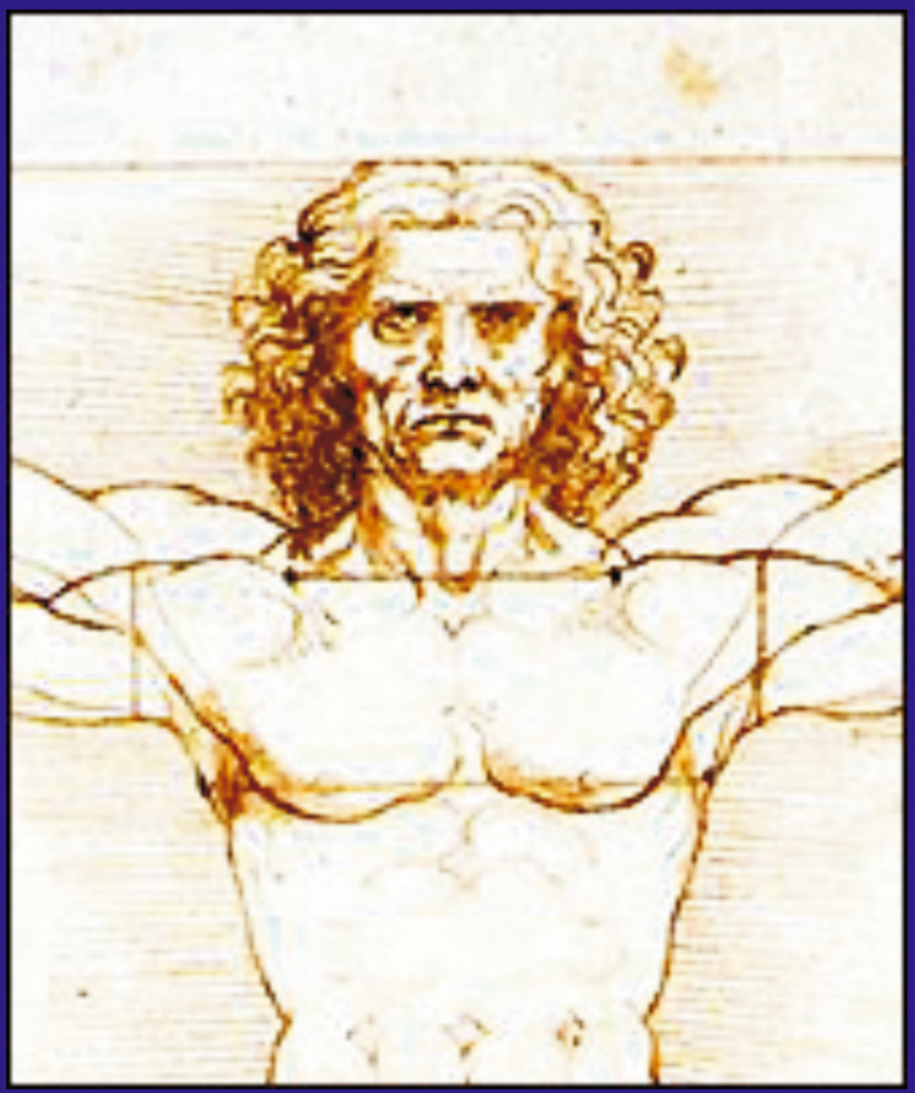
SANAMED

ISSN-1452-662X



Vol 20 (2) 2025.

MEDICAL JOURNAL

ISSN-1452-662X

IZDAVAČ
Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

ADRESA UREDNIŠTVA
„SANAMED“,
Ul. Palih boraca 52, 36300 Novi Pazar, Srbija,
email: sanamednp2006@gmail.com, www.sanamed.rs

ŠTAMPA
„OFSET“, Kraljevo

TIRAŽ
500

PRETPLATA
Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

ISSN-1452-662X

PUBLISHER
Association ofmedical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

EDITORIAL ADDRESS
“SANAMED”,
St. Palih boraca 52, 36300 Novi Pazar, Serbia,
email: sanamednp@gmail.com, www.sanamed.rs

PRINT
“OFSET”, Kraljevo

CIRCULATION
500

SUBSCRIPTION
Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

SANAMED

Number 20(2)/2025

CONTENT

SANAMED

Number 20(2)/2025

SADRŽAJ

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

SANAMED
2025; 20(2): 123–124
ISSN-1452-662X

DOI: 10.5937/sanamed0-59086
UDK: 615.214:577.171.5
ID: 174720777
Letter to the Editor

REVISITING A COMPARATIVE STUDY OF MELATONIN WITH PLACEBO IN ATTENUATION OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPY AND INTUBATION

Sengul Ilker,[1, 2] Sengul Demet[3]

[1] Giresun University Faculty of Medicine, Division of Endocrine Surgery, TR28100 Giresun, Turkey
[2] Giresun University Faculty of Medicine, Department of General Surgery, TR28100 Giresun, Turkey
[3] Giresun University Faculty of Medicine, Department of Pathology, TR28100 Giresun, Turkey

Primljen/Received: 25. 05. 2025. Prihvaćen/Accepted: 12. 07. 2025. Published online first 21. 07. 2025.

Dear Editor,

An indolamine called melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone primarily synthesized and secreted by the pinecone-shaped gland of the cerebrum, named the conarium or epiphysis cerebri, from the amino acid tryptophan. Melatonin itself was first isolated in 1958 from the bovine pineal gland by Lerner et al., while the 17th-century philosopher René Descartes hypothesized the pineal gland of the brain (epiphysis cerebri) as the seat of the human soul—a structure paleontologists have described as an ancestral "third eye" (1–5). We do pen these lines concerning the article entitled *"A comparative study of melatonin with placebo in attenuation of hemodynamic responses to laryngoscopy and intubation,"* published in *Sanamed*, volume 19 (6). Jamwal et al. (6) reveal and address an important clinical issue—the attenuation of hemodynamic responses during laryngoscopy and endotracheal intubation—and explore the potential role of oral melatonin as premedication.The findings suggest that oral melatonin at doses of 3 mg and 6 mg effectively attenuate these pressor changes and also provides analgesic and anxiolytic effects, with the 6 mg dose showing greater effectiveness.These outcomes are valuable and align with other research indicating melatonin's potential benefits in the perioperative period. However, while the results are promising, we wish to highlight a significant methodological aspect mentioned by the authors themselves, which warrants careful consideration when interpreting the findings. The study design allocated patients to Melatonin 3 mg, Melatonin 6 mg, and Placebo groups at the discretion of the attending anesthesiologist, rather than through a formal randomization process. As the authors correctly point out, this lack of randomization might introduce selection bias due to subjective considerations during allocation. Although the demographic characteristics, ASA grade, and Mallampati grading were reported as comparable across the groups at baseline, the non-random allocation method means that other potentially confounding factors, not explicitly measured or reported, could have differed systematically between the groups, influencing the outcomes observed. Furthermore, the study population was limited to patients undergoing elective surgery for supratentorial tumors. While this provides a focused cohort, it also limits the generalizability of these findings to patients undergoing other types of surgery or those with different underlying pathological conditions or comorbidities beyond those listed as exclusion criteria.In addition, the authors acknowledge that the size and location of these specific tumors could potentially influence postoperative recovery characteristics. Moreover, they appropriately suggest that future studies should be conducted using randomized controlled trials with larger sample sizes and standardized methodologies to further assess melatonin's efficacy and establish dose-response relationships. We support this recommendation. As such, a robust randomized design is crucial to minimize bias and provide more definitive evidence regarding melatonin's role in attenuating hemodynamic responses and providing anxiolysis and analgesia in a broader surgical population. In essence, the study provides interesting preliminary evidence supporting the use of oral melatonin premedication. Nevertheless, the methodological limitation regarding the lack of randomization may be a critical factor when interpreting

these findings. To this end, we look forward to future research, ideally using randomized controlled trial designs, that will build upon these findings and provide more explicit guidance on the clinical application of melatonin in perioperative care. This issue merits further investigation. We thank Jamwal et al. (6) for their valuable study on melatonin.

Acknowledgments: We thank all participants in the study.

Authors' contribution: IS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing-original draft, Writing-review&editing. **DS:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing-original draft, Writing-review&editing. All authors have read and approved the final and published version of the manuscript.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: This research received no external funding.

Note: Artificial intelligence was not utilized as a tool in this study.

REFERENCES

1. Maliki OF, Alagbon AI, Ibitoye CM, Olayaki LA. Melatonin and Vitamin C modulate cassava diet-induced alteration in reproductive and thyroid functions. Niger J Exp Clin Biosci. 2021; 9(3): 133-43. doi: 10.4103/njecp.njecp_9_21.

2. Lane R. Of sight, and insight. The Lancet. 2023: 401(10371): 97. doi: 10.1016/S0140-6736(22)02589-2.

3. Soares Júnior JM, Kesicioglu T, Sengul D, Sengul I. Of sight, and insight into melatonin's role in breast cancer? Rev Assoc Med Bras. 2023; 69(7): e697EDIT. doi: 10.1590/1806-9282.697EDIT.

4. Soares Junior JM, Detanac D, Sengul I, Dugalic S, Sengul D, Detanac D. Melatonin, menopause, and thyroid function in gynecologic endocrinology: what is the role? Rev Assoc Med Bras. 2024; 70(1): e701EDIT. doi: 10.1590/1806-9282.701EDIT.

5. Soares Junior JM, Sengul I, Sengul D. Melatonin, programmed death ligand-1, programmed death ligand-1, and cancer: imagine beyond the future? Rev Assoc Med Bras. 2025; 71(3): e0713EDIT. doi: 10.1590/1806-9282.0713EDIT.

6. Jamwal P, Zulfiqar A, Mohinder C, Singh CM, Deepika J, Iqra N, et al. A comparative study of melatonin with placebo in attenuation of hemodynamic responses to laryngoscopy and intubation. Sanamed. 2024; 19(1): 25-32. doi: 10.59437/sanamed19-49613.

Correspondence to/Autor za korespondenciju
Prof. Demet Sengul, M.D.
Founder & Chair, Department of Pathology,
Founder, Scientific and Research Laboratories,
Giresun UniversityFaculty of Medicine,
TR28100, Giresun, Turkey
email: demet.sengul.52@gmail.com
WoS, A-3035-2019; Scopus, 22938589200

ORCID numbers
Sengul Demet 0000-0002-0416-0621
Sengul Ilker 0000-0001-5217-0755

***How to cite this article**:* Sengul I, Sengul D. Revisiting a comparative study of melatonin with placebo in attenuation of hemodynamic responses to laryngoscopy and intubation**.** Sanamed. 2025; 20(2): 123-124. doi: 10.5937/sanamed0-59086.

SANAMED
2025; 20(2): 125–130
ISSN-1452-662X

DOI: 10.5937/sanamed0-58635
UDK: 616.711-001.4-08; 37.016:61-057.875
ID: 174728713
Original article

ARE WE TRAINING MEDICAL STUDENTS TO MANAGE AUTONOMIC DYSREFLEXIA IN SPINAL CORD INJURY? A STUDY

Alfallaj Ibrahim Muath, Salati Ahmad Sajad

Qassim University, College of Medicine, Department of Surgery, Kingdom of Saudi Arabia

Primljen/Received: 05. 05. 2025. Prihvaćen/Accepted: 28. 06. 2025. Published online first 30. 06. 2025.

Abstract: **Background:** Autonomic dysreflexia (AD) is a potentially life-threatening complication of spinal cord injury (SCI), characterized by sudden, paroxysmal episodes of hypertension. Healthcare professionals and family members caring for individuals with SCI must be able to recognize and manage AD promptly and appropriately. This study aimed to assess the level of knowledge about AD among final-year medical students, evaluate their preparedness to manage AD, and highlight the importance of educating families of SCI patients on its recognition and management.

Methods: A questionnaire-based, descriptive cross-sectional study was conducted among final-year (MD-4) medical students at the College of Medicine, Qassim University. Data were collected, cleaned, and analyzed using Microsoft Excel 2021. Students were then categorized into three groups based on their knowledge level: poor, fair, and good.

Results: Significant gaps were identified in students' knowledge of AD. Out of 68 students initially surveyed, 24 (35.3%) had not heard of AD and were excluded. Among the 44 participants included in the final analysis, scores ranged from 4 to 12 out of a maximum of 21, with a mean score of 7.02 (33.4%). A total of 27 students (61%) were classified as having poor knowledge, and 17 (39%) as fair. None of the students qualified for the "good" knowledge category.

Conclusions: The findings underscore the need for incorporating autonomic dysreflexia into the undergraduate medical curriculum. Early education would ensure that medical graduates are better prepared to manage AD and can help prevent complications by educating patients' families.

Keywords: spinal cord injury, autonomic dysreflexia, stroke, hypertension, pain, fecal impaction, pressure ulcer, Foley catheter.

INTRODUCTION

Spinal cord injury (SCI) is a life-altering condition with devastating consequences, resulting in the loss of motor, sensory, and autonomic functions. In addition to the primary injury, patients are at risk for a range of secondary health complications. One such complication is autonomic dysreflexia (AD), a potentially life-threatening medical emergency that affects individuals with SCI. It is characterized by sudden, paroxysmal hypertensive episodes and typically presents with symptoms such as a pounding headache, bradycardia, flushing and sweating of the face and neck, piloerection (goosebumps), and shivering (1, 2).

If not recognized and treated promptly, AD can lead to serious cardiophysiological and systemic complications (3), including seizures (4), recurrent cardiac arrest (5), retinal or subarachnoid hemorrhage (6, 7), stroke (4, 6), and even death (3, 7, 8, 9).

AD most commonly occurs in individuals with SCI at or above the T6 spinal level, where supraspinal control of the sympathetic preganglionic neurons (SPNs) involved in blood pressure regulation—particularly in the splanchnic circulation—is interrupted (10). Without descending inhibitory control from the brain, these SPNs become hyperreactive to noxious stimuli originating below the level of injury. This hyperactivity causes vasoconstriction and a dangerous rise in blood pressure. The brain detects this sudden increase in BP through baroreceptor input from the aortic arch and carotid sinuses, transmitted via cranial nerves IX and X. In response, the brainstem sends descending parasympathetic inhibitory impulses to counteract the hypertension. However, due to the spinal lesion, these impulses are blocked at the injury level, resulting in vasodilation (manifesting as headache, flushing, and diaphoresis) only in the upper body (Figure 1), and failing to reduce systemic blood

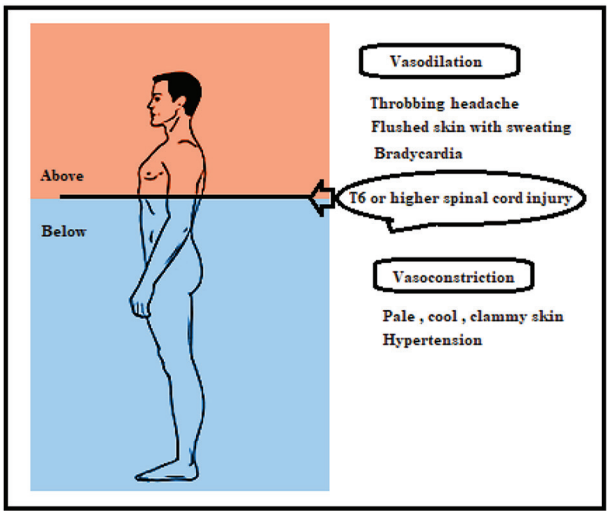


Figure 1. *Pathophysiology of autonomic dysreflexia. (Image credits: Sajad Ahmad Salati)*

pressure. Additionally, stimulation of the vagus nerve (cranial nerve X) leads to secondary bradycardia (10, 11, 12).

Although AD is more commonly associated with complete spinal cord lesions, studies have shown that individuals with motor-incomplete injuries are also at risk (10, 11, 12).

The peer-reviewed literature indicates that health-care professionals often possess limited knowledge of autonomic dysreflexia (AD), and many physicians not directly involved in rehabilitation may be unfamiliar with the condition. This knowledge gap is largely attributed to the minimal emphasis placed on AD during undergraduate medical education. In this context, the present study was conducted to assess the level of awareness and understanding of AD among final-year undergraduate medical students.

MATERIALS AND METHODS

Study Design

A cross-sectional descriptive study was conducted to assess the level of knowledge related to autonomic dysreflexia among medical students. Pre-validated

Table 1. *Questionnaire for assessment of knowledge related to Autonomic Dysreflexia*

Questions		Yes	No	Not sure
PART 1: Have you heard about Autonomic Dysreflexia (AD) in Spinal Cord Injured patients?				
PART 2: If answer is YES, then please answer the following questions.				
1.	**Which of the following are the symptoms of AD?**			
i.	Pounding headache			
ii.	Profuse Sweating over the face and neck			
iii.	Goose-bumps			
iv.	Flushing over face and neck			
v.	Blurred vision			
2.	**Which of the following can precipitate AD?**			
i.	Blocked urinary catheter			
ii.	Faecal impaction / constipation			
iii.	Anal fissure			
iv.	Pressure ulcers			
v.	In growing nail			
vi.	Gallstones			
vii.	Tight clothing, stockings /straps			
viii.	Sexual stimulation			
3.	What happens to the blood pressure in AD?			
i.	Increases			
ii.	Decreases			
iii.	Stays normal			
4.	**What happens to the heart rate in AD?**			
i.	Increases			
ii.	Decreases			
iii.	Stays normal			
5.	**Which of the following are the possible complications of AD?**			
i.	Seizures			
ii.	Intracerebral haemorrhage			
iii.	Retinal haemorrhage			
iv.	Arrythmias			
v.	Death			
6.	**What level of injury to the spinal cord is crucial in predicting the development of AD?**			
i.	Cervical			
ii.	Midthoracic			
iii.	Lumbar			

questionnaires from previous studies by Kaydok (13), Tederko (14), Strcic and Marki (15), and McGillivray et al. (16) were selected and appropriately modified for this purpose (Table 1).

Sampling and Study Population Definition

Total sampling coverage was employed to include all students who consented to participate in the study. The enrolled cohort consisted of final-year (MD-4) undergraduate medical students from the male campus of the College of Medicine (Unaizah), Qassim University, Kingdom of Saudi Arabia.

Exclusion Criteria:

Participants were excluded if they (i) had not yet reached the final year (MD-4) and therefore had not completed all curriculum blocks covering spinal trauma, or (ii) were MD-4 students who responded negatively to Part A of the questionnaire, indicating they had never heard or read about autonomic dysreflexia (AD).

Execution:

After consultation with two medical education specialists, a content expert (MIF, the first author and board-certified neurosurgeon) evaluated the questionnaire for criterion validity. Reliability and face validity were confirmed through an offline pilot study involving eight students. Subsequently, enrolled students completed an anonymous online survey. Only those who answered "yes" to the initial question regarding familiarity with the term "autonomic dysreflexia" proceeded to the second section, which assessed their knowledge of AD's pathophysiology, contributing factors, symptoms, and complications.

Data Handling and Analysis:

Data were collected, cleaned, and analyzed using Microsoft Excel 2021 (Data Analysis ToolPak). Descriptive statistics, including frequency distributions and percentages, summarized participant responses and knowledge levels. Results were presented in tables and figures. Statistical significance was considered at $p < 0.05$ or $p < 0.01$.

Scoring Scheme:

Each correct answer was awarded one point; no points were awarded or deducted for incorrect or "not sure" responses. The questionnaire comprised 21 items, setting the maximum achievable score at 21 and the minimum at zero. Based on total scores, participants were categorized as shown in Table 2.

Table 2. *Categorization of students based upon the score achieved in the questionnaire*

Category	Score
Poor Knowledge	0-7
Fair Knowledge	8-14
Good Knowledge	15-21

Ethical Considerations

Participation in the study was entirely voluntary. Students who declined to participate were assured that their decision would not result in any negative consequences. The questionnaire was administered anonymously. In accordance with the principles of the Declaration of Helsinki, all data were kept confidential, not disclosed to third parties, and used solely for the purposes outlined in the study protocol.

RESULTS

A total of 68 students participated in the study. Of these, only 44 students (22 males and 22 females) had heard or read about AD, responding affirmatively in Part 1 of the questionnaire and thus proceeding to Part 2. Consequently, 24 students (35.3%) were excluded at this stage. Overall scores among the 44 participants ranged from 4 to 12 (Figure 2), with a mean score of 7.02 out of 21 (33.4%). The mean scores for male and female students were 6.95 and 7.09, respectively, with no statistically significant difference observed between genders.

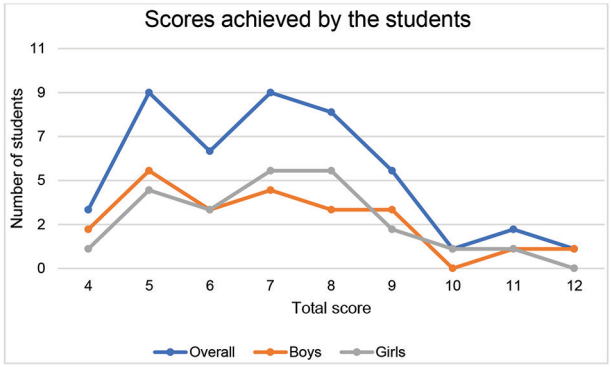


Figure 2. *Scores achieved by the students in the questionnaire. (Image credits: Sajad Ahmad Salati)*

Accordingly, the level of knowledge was categorized as shown in Figure 2, with 27 students (61%) classified as having poor knowledge and 17 students (39%) as having fair knowledge. None of the students met the criteria for the good knowledge category.

The percentage of correctly identified symptoms and precipitating factors was only 32% and 27%, respectively. Similarly, 39% of students knew that SCI cases above the midthoracic level are vulnerable to

Figure 3. *Level of knowledge related to autonomic dysreflexia. (Image credits: Sajad Ahmad Salati)*

AD. Only 41% were aware that heart rate can decrease, while 75% correctly recognized that blood pressure increases during AD. No student knew that AD could result in death, although 33% identified other possible complications.

DISCUSSION

Autonomic dysreflexia (AD) is a serious and potentially life-threatening complication that can occur following spinal cord injury (SCI) (17, 18). According to peer-reviewed studies, the prevalence of AD among patients with SCI above the sixth thoracic level ranges from 48% to 90%. The condition may occur as often as 40 times a day and significantly increases the risk of stroke—by 300% to 400% (18–20). The likelihood of experiencing AD and its complications increases with the severity and extent of the spinal lesion (1, 2, 3, 18, 19, 20).

This study reveals notable gaps in knowledge about AD among final-year medical students, who will soon assume clinical roles as interns or residents responsible for educating caregivers of SCI patients. These findings are consistent with other research, which shows that many healthcare professionals have limited understanding of AD, and that physicians outside rehabilitation specialties may be unfamiliar with this condition. A major reason for this gap appears to be the limited emphasis on AD during undergraduate medical education, despite its clinical importance.

This issue is particularly relevant in the Kingdom of Saudi Arabia (KSA), where the incidence of spinal cord injuries is among the highest worldwide—approximately 62 cases per million residents—raising the risk of AD considerably (12, 21, 22, 23). Around 25% of SCI patients develop neurological deficits such as quadriplegia or paraplegia, and about 68% sustain injuries involving the cervical and thoracic spine. Complete neurological injuries are more common than incomplete ones (23, 24, 25). Al-Habib et al. found that cervical spine injuries are more frequent in younger patients, while thoracic injuries are predominant in older individuals (23).

Several studies involving healthcare providers working with SCI patients have confirmed that AD remains a largely under-recognized complication, with widespread knowledge gaps. For example, Kaydok et al. (13) surveyed nurses and physiotherapists at a rehabilitation center and found low awareness of AD among both groups. They emphasized the need for standardized training programs worldwide to raise awareness among patients, caregivers, and medical professionals.

Similarly, Tederko et al. (14) studied undergraduate and postgraduate physiotherapists in Poland and found poor knowledge of AD. Their findings showed that lower test scores were linked to limited professional education and clinical exposure to SCI, leading them to recommend enhanced teaching on AD at both undergraduate and postgraduate levels.

Strcic and Marki (15) assessed nursing and physiotherapy students in Croatia and discovered that despite 57% having clinical contact with SCI patients, 74% demonstrated poor knowledge of AD regardless of their experience. They concluded that targeted educational initiatives are necessary to improve understanding.

McGillivray et al. (16) surveyed community-dwelling individuals with SCI and their families, revealing significant knowledge gaps. Notably, 41% had never heard of AD despite being at high risk, and 22% reported symptoms consistent with the condition. The authors recommended that education on AD be provided during rehabilitation by qualified healthcare professionals.

Limitations and Significance Statement

The small number of students included in the study is a major limitation; hence, the outcomes cannot be generalized and require larger, more robust studies to establish a true state of affairs. The average knowledge level and real-world readiness may have been artificially inflated by excluding students who had not heard of or read about AD; the overall statistics might have been lower if all students had been included rather than only the remaining participants.

However, this study revealed the need to incorporate AD into the undergraduate curriculum. Accordingly, the departmental curriculum committee approved teaching this topic through a team-based learning (TBL) session in the next academic year (2026). A follow-up study will be undertaken to assess the impact of this curriculum change.

CONCLUSION

Medical students are not adequately equipped with knowledge related to autonomic dysreflexia. For students assuming the role of junior healthcare providers to effectively manage this potentially fatal condition and educate families of spinal cord injury patients on first aid and preventive measures for skin, bladder,

and bowel care, this topic must be included in the undergraduate medical curriculum.

Abbreviations

SCI - Spinal cord injury
AD -Autonomic dysreflexia
TBL - Team-based learning
KSA - Kingdom of Saudi Arabia
BP - Blood pressure
SPN - Sympathetic preganglionic neurons

Acknowledgements: The authors express gratitude to the students who participated in the survey; without their active participation, this study would not have been possible.

Source of funding: The authors declare that they did not receive any funds or support for this study from any public, private, or nonprofit funding organizations.

Conflicts of Interest: None.

Authors' contributions: SAS conceived the project and conducted the literature review. MIF conducted the survey and performed the data analysis. Both authors approved the final draft of the manuscript.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

DA LI SE STUDENTI MEDICINE ADEKVATNO OSPOSOBLJAVAJU ZA LEČENJE AUTONOMNE DISREFLEKSIJE KOD POVREDE KIČMENE MOŽDINE?

Alfallaj Ibrahim Muath, Salati Ahmad Sajad

Univerzitet Qassim, Medicinski fakultet, Katedra za hirurgiju, Unaizah, Saudijska Arabija

Uvod: Autonomna disrefleksija (AD) je ozbiljna komplikacija povrede kičmene moždine (PKM), karakterisana iznenadnim, paroksizmalnim epizodama hipertenzije. Zdravstveni radnici i članovi porodice koji se brinu o osobama sa PKM moraju biti u stanju da pravovremeno i adekvatno prepoznaju i tretiraju AD. Cilj ove studije bio je da se proceni nivo znanja o AD među studentima završne godine medicine, oceni njihova spremnost za lečenjem AD, kao i da se istakne značaj edukacije porodica pacijenata sa PKM o prepoznavanju i lečenju ovog stanja.

Metode: Deskriptivna studija preseka zasnovana na upitniku sprovedena je među studentima završne godine medicine (MD-4) na Medicinskom fakultetu Univerziteta Kaseem. Podaci su prikupljeni, obrađeni i analizirani korišćenjem Microsoft Excel 2021. Studenti su zatim svrstani u tri grupe na osnovu nivoa znanja: loš, zadovoljavajući i dobar.

Rezultati: Identifikovani su značajni nedostaci u znanju studenata o AD. Od ukupno 68 anketiranih studenata, 24 (35,3%) nisu bili upoznati sa pojmom AD i isključeni su iz analize. Među preostalih 44 učesnika, rezultati su se kretali od 4 do 12 bodova od maksimalnih 21, sa prosečnim rezultatom od 7,02 (33,4%). Ukupno 27 studenata (61%) svrstano je u kategoriju sa lošim znanjem, dok je 17 (39%) imalo zadovoljavajuće znanje. Nijedan student nije ispunio kriterijume za dobar nivo znanja.

Zaključak: Rezultati ukazuju na potrebu uključivanja teme autonomne disrefleksije u osnovni medicinski kurikulum. Rano obrazovanje osiguralo bi da budući medicinski stručnjaci budu bolje pripremljeni za lečenje AD i da mogu doprineti prevenciji komplikacija edukacijom porodica pacijenata.

Ključne reči: povreda kičmene moždine, autonomna disrefleksija, moždani udar, hipertenzija, bol, fekalna impakcija, dekubitus; Foley kateter.

REFERENCES

1. Cowan H, Lakra C, Desai M. Autonomic dysreflexia in spinal cord injury. BMJ. 2020 Oct 2;371:m3596. doi: 10.1136/bmj.m3596.

2. Morgan S. Recognition and management of autonomic dysreflexia in patients with a spinal cord injury. Emerg Nurse. 2020; 28(1): 22-7. doi: 10.7748/en.2019.e1978.

3. Lakra C, Swayne O, Christofi G, Desai M. Autonomic dysreflexia in spinal cord injury. Pract Neurol. 2021; 21(6): 532-8. doi: 10.1136/practneurol-2021-002956.

4. Colachis SC, Fugate LP. Autonomic dysreflexia associated with transient aphasia. Spinal Cord. 2002; 40(3): 142-4. doi: 10.1038/sj.sc.3101251.

5. Colachis SC , Clinchot DM. Autonomic hyperreflexia associated with recurrent cardiac arrest: case report. Spinal Cord. 1997; 35(4): 256-7. doi: 10.1038/sj.sc.3100359.

6. Pan SL, Wang YH, Lin HL, Chang CW, Wu TY, Hsieh ET. Intracerebral hemorrhage secondary to autonomic dysreflexia in a young person with incomplete C8 tetraplegia: A case report. Arch Phys Med Rehabil. 2005; 86(3): 591-3. doi: 10.1016/j.apmr.2004.03.021.

7. Vaidyanathan S, Soni BM, Hughes PL, Oo T. Fatal cerebral hemorrhage in a tetraplegic patient due to autonomic dysreflexia triggered by delay in emptying urinary bladder after unsuccessful intermittent catheterization by carer: lessons learned. Int Med Case Rep J. 2018; 11: 53-8. doi: 10.2147/IMCRJ.S143077.

8. Eker A, Yigitoglu PH, Ipekdal HI, Tosun A. Acute onset of intracerebral hemorrhage due to autonomic dysreflexia. J Korean Neurosurg Soc. 2014; 55(5): 277-9. doi: 10.3340/jkns.2014.55.5.277.

9. Wan D, Krassioukov AV. Life-threatening outcomes associated with autonomic dysreflexia: a clinical review. J Spinal Cord Med. 2014; 37(1): 2-10. doi: 10.1179/2045772313Y.0000000098.

10. Phillips AA, Krassioukov AV. Contemporary cardiovascular concerns after spinal cord injury: Mechanisms, maladaptations, and management. J Neurotrauma. 2015; 32(24): 1927-42. doi: 10.1089/neu.2015.3903.

11. Rempel L, Sachdeva R, Krassioukov AV. Making the invisible visible: understanding autonomic dysfunctions following spinal cord injury. Phys Med Rehabil Clin N Am. 2025; 36(1): 17-32. doi: 10.1016/j.pmr.2024.07.002.

12. Alwashmi AH. Spinal cord injury and autonomic dysreflexia: a case report on an overlooked complication of spinal cord injury. Cureus. 2022; 14(10): e30259. doi: 10.7759/cureus.30259.

13. Kaydok E. Nurses and physiotherapists' knowledge levels on autonomic dysreflexia in a rehabilitation hospital. J Spinal Cord Med. 2023; 46(4): 569-73. doi: 10.1080/10790268.2021.1983313.

14. Tederko P, Ugniewski K, Bobecka-Wesołowska K, Tarnacka B. What do physiotherapists and physiotherapy students know about autonomic dysreflexia? J Spinal Cord Med. 2021; 44(3): 418-24. doi: 10.1080/10790268.2019.1645966.

15. Strcic N, Markic D. The knowledge about autonomic dysreflexia among nursing and physiotherapy students. J Spinal Cord Med. 2019; 42(6): 791-6. doi: 10.1080/10790268.2018.1439432.

16. McGillivray CF, Hitzig SL, Craven BC, Tonack MI, Krassioukov AV. Evaluating knowledge of autonomic dysreflexia among individuals with spinal cord injury and their families. J Spinal Cord Med. 2009; 32(1): 54-62. doi: 10.1080/10790268.2009.11760753.

17. Trueblood CT, Singh A, Cusimano MA, Hou S. Autonomic dysreflexia in spinal cord injury: mechanisms and prospective therapeutic targets. Neuroscientist. 2024; 30(5): 597-611. doi: 10.1177/10738584231217455.

18. Sharif H, Hou S. Autonomic dysreflexia: a cardiovascular disorder following spinal cord injury. Neural Regen Res. 2017; 12(9): 1390-1400. doi: 10.4103/1673-5374.215241.

19. Squair JW, Phillips AA, Harmon M, Krassioukov AV. Emergency management of autonomic dysreflexia with neurologic complications. CMAJ. 2016; 188(15): 1100-3. doi: 10.1503/cmaj.151311.

20. Caruso D, Gater D, Harnish C. Prevention of recurrent autonomic dysreflexia: a survey of current practice. Clin Auton Res. 2015; 25(5): 293-300. doi: 10.1007/s10286-015-0303-0.

21. Bakhsh A, Aljuzair AH, Eldawoody H. An Epidemiological overview of spinal trauma in the Kingdom of Saudi Arabia. Spine Surg Relat Res. 2020; 4(4): 300-4. doi: 10.22603/ssrr.2019-0118.

22. Alshahri SS, Cripps RA, Lee BB, Al-Jadid MS. Traumatic spinal cord injury in Saudi Arabia: an epidemiological estimate from Riyadh. Spinal Cord. 2012; 50(12): 882-4. doi: 10.1038/sc.2012.65.

23. Al-Habib A, Alaqeel A, Marwa I, Almohammadi M, Al Shalaan H, AlEissa S, et al. Causes and patterns of spine trauma in children and adolescents in Saudi Arabia: implications for injury prevention. Ann Saudi Med. 2014; 34(1): 31-7. doi: 10.5144/0256-4947.2014.31.

24. Lucci VM. Recent updates in autonomic research: advances in the understanding of autonomic dysfunction after spinal cord injury. Clin Auton Res. 2023; 33(2): 83-5. doi: 10.1007/s10286-023-00944-y.

25. Krassioukov A, Stillman M, Beck LA. A primary care provider's guide to autonomic dysfunction following spinal cord injury. Top Spinal Cord Inj Rehabil. 2020 Spring; 26(2): 123-7. doi: 10.46292/sci2602-123.

Correspondence to/Autor za korespondenciju
Muath Ibrahim Alfallaj
Demonstrator, Department of Surgery, College of Medicine, Qassim University
Kingdom of Saudi Arabia
Email: MI.ALfallaj@qu.edu.sa
Phone: +966561833888
ORCID: 0009-0006-6174-4793
Present Address: Qassim, Qassim University, BuraydahCity 52571.
ORCID
Salati Ahmad Sajad 0000-0003-2998-7542

How to cite this article: **Alfallaj IM,** Salati AS. Are We Training Medical Students to Manage Autonomic Dysreflexia in Spinal Cord Injury? A Study. Sanamed. 2025; 20(2): 125-130. doi: 10.5937/sanamed0-58635.

SANAMED
2025; 20(2): 131–137
ISSN-1452-662X

DOI: 10.5937/sanamed0-57836
UDK: 616.718.19-001.5-08
ID: 174733577
Original article

COMPARATIVE ANALYSIS OF SURGICAL OUTCOMES IN AO-OTA 31-A2 FRACTURES: TWO-HOLE VS. FOUR-HOLE DYNAMIC HIP SCREW

Mesanovic Edin,[1] Fajic Fikret,[1] Mesanovic Mirza[2]

[1] Cantonal Hospital "Dr. Safet Mujic", Department of Orthopedic Surgery and Traumatology, Mostar, Bosnia and Herzegovina
[2] University Clinical Center Tuzla, Orthopedic Surgery and Traumatology Clinic, Tuzla, Bosnia and Herzegovina

Primljen/Received: 27. 03. 2025. Prihvaćen/Accepted: 14. 06. 2025. Published online first 30. 06. 2025.

Abstract: **Background:** The choice of implant for the treatment of multifragmentary pertrochanteric fractures AO-OTA 31-A2 is complex, and the dynamic hip screw (DHS) can be used as a biomechanically safe and cost-effective option. Surgeons typically choose between DHS plates with two or four holes. The primary aim of this study was to determine whether there is a difference in surgery time, hospital stay, intraoperative blood loss, and incision length in patients with AO-OTA 31-A2 fractures treated with two-hole or four-hole DHS. The secondary aim was to compare the rate of complications, including fracture nonunion, implant breakage (DHS plate, sliding screw, compression screw, or cortical screws), cut-out, fracture collapse, and avascular necrosis.

Methods: This retrospective study included 94 patients with AO-OTA 31-A2 fractures treated with DHS implants containing either two or four holes. Patients were divided into two groups: Group A, which included 60 patients treated with a two-hole DHS plate, and Group B, which included 34 patients treated with a four-hole DHS plate.

Results: Group A had a significantly shorter surgery time (44.80 ± 8.01 minutes) compared to Group B (48.12 ± 5.43 minutes; $p < 0.05$). Group A also had a significantly smaller incision ($p < 0.05$). There were no significant differences between the two groups in terms of the remaining outcomes.

Conclusion: The absence of significant differences in complication rates supports the conclusion that both DHS types are viable options for the treatment of AO-OTA 31-A2 fractures.

Keywords: dynamic hip screw, femur, hip fractures.

INTRODUCTION

Hip fractures are a prevalent injury that continues to rise with projections suggesting that by 2050, their incidence will nearly double compared to 2018 (1). These fractures can be categorized into two primary types: intracapsular and extracapsular. Extracapsular hip fractures predominantly occur in the elderly, often resulting from low-energy mechanisms, while younger individuals may experience these fractures due to high-energy trauma (2).The AO-OTA classification system is widely utilized to classify extracapsular hip fractures, which include trochanteric fractures, which are further divided into three categories: simple pertrochanteric fractures (AO-OTA 31-A1), multi-fragmentary pertrochanteric fractures (AO-OTA 31-A2), and intertrochanteric fractures (AO-OTA 31-A3) (3).

In the management of trochanteric hip fractures, surgical intervention is the primary treatment modality, with implant selection depending on the specific fracture type. The most commonly used implants are the dynamic hip screw (DHS) and the proximal femoral nail (PFN) (4, 5, 6). Numerous studies and systematic reviews have confirmed that DHS remains the preferred implant for treating simple pertrochanteric fractures (AO-OTA 31-A1), due to favorable outcomes in terms of fracture healing, biomechanical stability, and cost-effectiveness (7, 8).

The treatment of multifragmentary pertrochanteric fractures (AO-OTA 31-A2) requires more complex decision-making, as both DHS and PFN have demonstrated satisfactory outcomes in clinical practice (8, 9). Several studies have reported good results in treating AO-OTA 31-A2 fractures with DHS (10–14). In a sys-

tematic review, Zhang et al. compared intramedullary nails and extramedullary fixation methods, concluding that both DHS and PFN can yield favorable outcomes in the treatment of unstable intertrochanteric fractures. The study emphasized that although PFN may offer advantages in terms of stability, DHS remains a reliable option, particularly in less complex cases. This underscores the importance of considering fracture morphology when selecting an implant (15).

Bone quality is another important factor in the decision-making process, as osteoporosis can adversely affect surgical outcomes (16, 17).The DHS system consists of a barrel plate, a sliding screw positioned at a fixed angle (typically 135 degrees), and a compression screw. DHS plates are available in various configurations, typically featuring two, four, or six holes for cortical screw placement. Biomechanical studies have shown that a two-hole DHS plate offers a level of safety comparable to that of four-hole plates, suggesting that fewer screws may be sufficient for effective stabilization (18-20). On the other hand, Wang et al. claimed that the length of DHS plate has a significant effect on stress on the screws and may contribute to side plate pull-out (20).

AIM

The primary aim of this study was to determine whether there is a difference in surgery time, hospital stay, intraoperative blood loss, and incision length in patients with AO-OTA 31-A2 fractures treated with either a two-hole or a four-hole dynamic hip screw (DHS).

The secondary aim was to compare the rate of complications, including fracture nonunion, implant breakage (DHS plate, sliding screw, compression screw, or cortical screws), cut-out, fracture collapse, and avascular necrosis.

MATERIALS AND METHODS

After obtaining approval from the Ethics Committee, we conducted a retrospective analysis of patients hospitalized in the Department of Orthopedic Surgery and Traumatology at Cantonal Hospital "dr. Safet Mujic" Mostar with a diagnosis of multi-fragmentary trochanteric fracture (AO-OTA 31-A2) treated with Dynamic Hip Screw Plate (Marquard, Spaichingen, Germany). We analyzed cases from January 2014 to January 2021.

For the primary outcomes, we reviewed patients' medical histories and the hospital's electronic database. For secondary outcomes, we used the Picture Archiving and Communication System (PACS) to review radiographic images (X-rays) obtained at the last follow-up examination, one year post-injury.

The inclusion criteria were: 1) multi-fragmentary trochanteric fracture (AO-OTA 31-A2); 2) patients treated with DHS with 2 or 4 holes; 3) complete medical history; 4) minimum follow-up of one year.

Exclusion criteria were: pathological fractures, multiple fractures, previous proximal femoral fracture, and psychiatric diagnosis.

A total of 94 patients were included in the study. Patients were divided into two groups: Group A (60 patients treated with two-hole DHS plates) and Group B (34 patients treated with four-hole DHS plates). All surgeries were performed by orthopedic surgeons with comparable levels of expertise.

All patients were placed in the supine position on a traction table after administration of general anesthesia. Closed reduction of trochanteric fracture was performed under the C-arm. In case of inadequate reduction, open reduction of fracture was done during the surgery. An incision was made at the level of the greater trochanter and extended distally. We used a muscle-splitting technique which includes a sharp incision of the fascia lata and sharp dissection between muscle fibers of the vastus lateralis muscle. A guide pin was inserted through the femoral neck to the edge of the cartilage of the femoral head with a 135° angle guide. The length of the screw was determined to be 10 mm shorter than the guide pin. We used a reamer and tap over the guide wire and after that, the screw was placed 5-10 mm beneath the surface of the femoral head cartilage. The DHS plate was placed over the screw close to the femoral surface and secured to the bone with either two or four cortical screws. The compression screw was placed and cortical screws were tightened. We retained the compression screw in order to increase construct stability (21).

Our hospital protocol for hip fracture patients includes administration of low molecular weight heparin subcutaneously on the day of admission, continued daily until discharge. After discharge, patients received Rivaroxaban 10 mg for 30 days. Two grams of Cefazolin were given as antibiotic prophylaxis. Physical therapy began on the first postoperative day, starting with sitting and bed exercises. On the second day, patients were assisted by a physiotherapist to ambulate using a walker with no weight bearing. At the first postoperative follow-up one month after surgery, radiographs were obtained, and patients were instructed to begin partial weight bearing (touching the ground). At two months, follow-up radiographs were repeated, and patients were advised to increase weight bearing to 20 kg. Full weight bearing was allowed after three months. The final follow-up examination with radiographs occurred one year after surgery.

Primary outcome data were collected from patient records and included surgery time, length of hospital stay, intraoperative blood loss, and incision length.

For secondary outcomes, radiographs from the first (one month), second (two months), third (three months), and last (one year) follow-up examinations were analyzed to identify nonunion, breakage of the DHS plate, sliding screw, compression screw, or cortical screws, cut-out, fracture collapse, and avascular necrosis.

Surgery time was defined as the interval between the initial incision and placement of the final suture. Blood loss included the sum of measured blood collected in the vertical drape pocket, blood on surgical gowns and drapes, sponges, gauzes, and suction drainage.

Nonunion was defined as a fracture persisting for at least nine months without signs of healing for three consecutive months (22). Fracture collapse was assessed by comparing radiographs from the first postoperative day and the one-year follow-up or at the time mechanical failure was detected (23). Only fracture collapse greater than 1 cm was included.

Statistical analysis was performed using GNU PSPP 2.0.1. Continuous data were presented as mean ±standard deviation (SD). Histograms were used to assess normality. Differences between normally distributed continuous variables were analyzed using independent samples t-test; for non-normally distributed variables, the Mann–Whitney U test was applied. Differences in categorical variables were analyzed using the chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS

In this study, 60 patients were treated with two-hole DHS (Group A) and 34 patients with four-hole DHS (Group B). The mean age was 73.5 ± 12.66 years in Group A and 76.26 ± 9.94 years in Group B. Group A included 18 males and 42 females, while Group B had 8 males and 26 females. There were no significant differences between the groups regarding age or sex ($p > 0.05$).

The time from injury to surgery did not differ significantly between the two groups ($p = 0.552$). However, Group A had a significantly shorter surgery time (44.80 ± 8.01 minutes) compared to Group B (48.12 ± 5.43 minutes) ($p < 0.05$).

No significant difference was observed in the length of hospital stay between the groups ($p > 0.05$). The mean intraoperative blood loss was 240.50 ± 53.22 mL in Group A and 231.18 ± 46.11 mL in Group B, with no significant difference ($p > 0.05$).

The mean incision length was significantly smaller in Group A (7.84 ± 0.52 cm) compared to Group B (9.79 ± 0.77 cm) ($p < 0.05$) (Table 1).

Regarding complication rates, Group A experienced 4 cases of nonunion, 3 cases of implant breakage, 1 case of cut-out, 12 cases of fracture collapse, and no cases of avascular necrosis. In Group B, there were 2 cases of nonunion, no implant breakages, 1 case of cut-out, 11 cases of fracture collapse, and 1 case of avascular necrosis. None of these complications showed a statistically significant difference between the two groups ($p > 0.05$) (Table 2) (Figures 1-4).

Table 1. *Comparison of primary outcomes between two groups*

	Group A (2 holes)	Group B (4 holes)	P value
Number of patients	60	34	
Mean age ± SD	73.50 ± 12.66	76.26 ± 9.94	0.276
Sex (male/female)	18/42	8/26	0.500
Time until surgery (days)	1.95 ± 0.87	1.82 ± 0.76	0.552
Surgery time (minutes)	44.80 ± 8.01	48.12 ± 5.43	**0.034***
Hospital stay (days)	12.80 ± 1.34	12.32 ± 1.12	0.086
Blood loss during surgery (mL)	240.50 ± 53.22	231.18 ± 46.11	0.395
Incision length	7.84 ± 0.52	9.79 ± 0.77	**< 0.05***

Table 2. *Comparison of number of complications in each group (secondary outcome)*

	Group A (2 holes)	Group B (4 holes)	P value
Nonunion	4	2	0.881
Implant breakage	3	0	0.185
Cut-out	1	1	0.681
Fracture collapse	12	11	0.181
Avascular necrosis	0	1	0.182

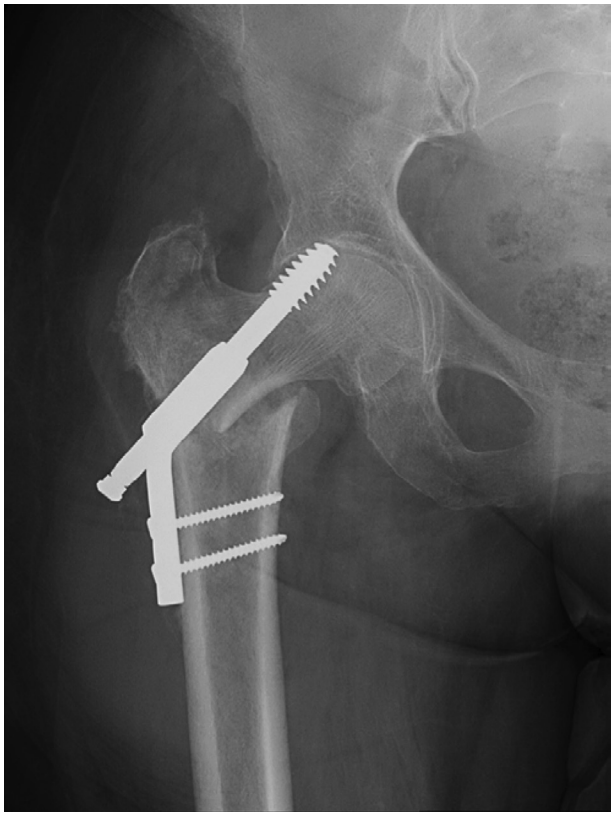


Figure 1. *X-ray showing fracture collapse and cut-out in 2-hole DHS system (from author's personal archive)*

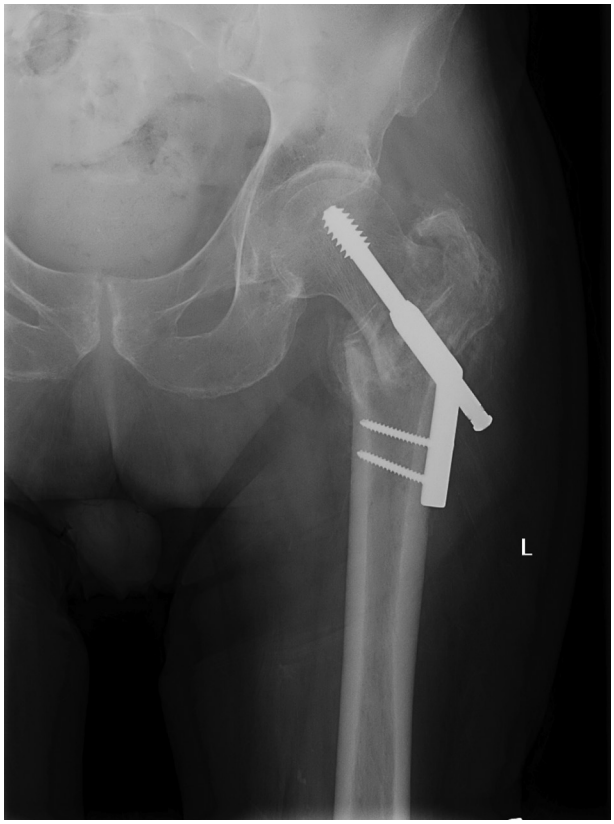


Figure 2*. X-ray showing fracture collapse in 2-hole DHS system (from author's personal archive)*

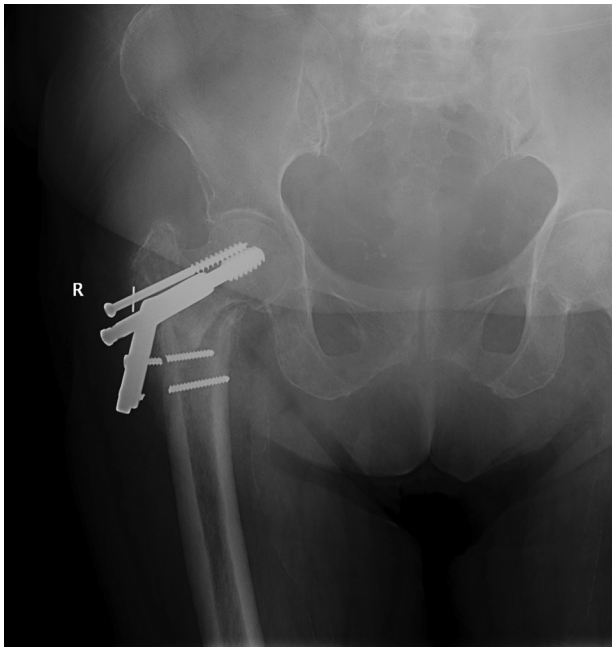


Figure 3. *X-ray showing implant breakage (cortical screws) in 2-hole DHS system (from author's personal archive)*

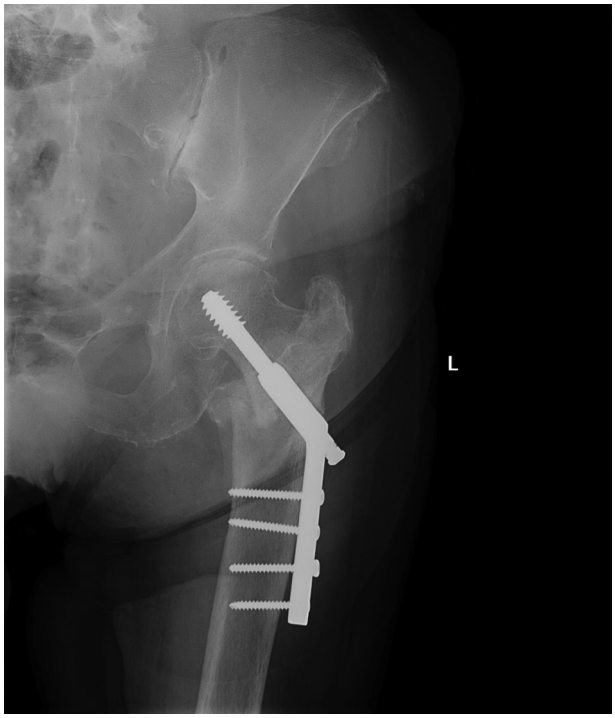


Figure 4*. X-ray showing fracture collapse in 4-hole DHS system (from author's personal archive)*

DISCUSSION

Dynamic Hip Screw (DHS) remains a key implant for treating AO-OTA 31-A2 fractures despite advances in implant technology over recent decades. Its low cost makes it particularly favored in developing countries. However, surgeons often face uncertainty

when deciding the appropriate DHS plate length, with concerns mainly revolving around clinical outcomes and biomechanical stability.

Our results showed that the four-hole DHS group had less intraoperative blood loss. However, this difference was not statistically significant. This finding contrasts with most recently published studies, which report that patients treated with four-hole DHS typically experience greater blood loss due to longer incisions and more extensive soft tissue dissection (24, 25). This discrepancy may be explained by meticulous surgical technique, including careful hemostasis, gentle handling of soft tissues, and minimal muscle stripping. Additionally, we did not use surgical drains in any patient.

We found no significant difference between the two groups in terms of time until surgery or length of hospital stay. The average waiting time between hospital admission and surgery was around two days in both groups. This delay is often related to the patients' age and existing comorbidities, which frequently necessitate consultations with other specialties (internal medicine, cardiology, neurology, etc.), thus postponing surgery.

However, the two-hole DHS group had a significant advantage in terms of shorter surgical time and smaller incision length. This supports findings from previous studies suggesting that longer plates require longer incisions for proper positioning, which can influence patient outcomes (26, 27).

Although the two-hole DHS group had a higher number of complications, the difference was not statistically significant. This suggests that both DHS configurations are comparably effective in preventing adverse outcomes, consistent with literature indicating that implant design does not significantly affect complication rates (28, 29). The similar rates of complications can be attributed to the comparable biomechanical stability of both plate types. Rog et al. demonstrated that two-hole and four-hole DHS plates had similar axial and torsional stiffness and load to failure (19).

The stability provided by DHS appears adequate to promote healing and maintain femoral head integrity, thereby reducing the risk of common postoperative complications (8, 30). A study by Akinyemi et al. also found that using a four-hole DHS plate is not necessary to achieve good outcomes in both stable and unstable trochanteric fractures (31).

On the other hand, Ceynowa et al. claimed that four-hole DHS demonstrated greater strength compared to the two-hole variant, particularly in resisting rotational forces at the fracture site, which is crucial during weight-bearing activities (32). Similarly, a systematic review by Soni et al. concluded that while two-hole DHS plates offer lower biomechanical stability, other parameters such as fracture healing time, infection rates, radiation exposure, analgesic use, hospital stay, and failure rates were comparable between the two groups. They recommend the use of four-hole DHS (28).

Ultimately, achieving an optimal balance between surgical efficiency and biomechanical stability is essential for successful fracture fixation.bute to the overall success of fracture fixation.

CONCLUSION

In conclusion, although much of the literature supports the view that four-hole DHS offers greater biomechanical stability, the two-hole DHS remains a compelling option due to its advantages in surgical time and incision length. The absence of significant differences in complication rates further supports the notion that both DHS types are viable choices for the treatment of AO-OTA 31A2 fractures. The decision between using a two-hole or four-hole DHS should be based on a comprehensive assessment of the fracture pattern, the patient's overall medical condition, and the biomechanical demands on the fixation device.

Future studies should continue to investigate the long-term outcomes of these two DHS types to further refine treatment protocols and support clinical decision-making in orthopedic practice.

Abbreviations:

DHS – Dynamic hip screw

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: This research received no external funding.

Author contribution: All authors have made substantial contributions to all parts of the manuscript. Also, all authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained by the hospital's ethical board.

Data Availability Statement: All data generated or analyzed for this report are included in the published article.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

KOMPARATIVNA ANALIZA HIRURŠKIH ISHODA KOD PRELOMA AO-OTA 31-A2: DINAMIČKI ZAVRTANJ ZA KUK SA DVA OTVORA U ODNOSU NA DINAMIČKI ZAVRTANJ SA ČETIRI OTVORA

Mesanovic Edin,[1] Fajic Fikret,[1] Mesanovic Mirza[2]

[1] Kantonalna bolnica „Dr. Safet Mujić“, Odeljenje za ortopedsku hirurgiju i traumatologiju, Mostar, Bosna i Hercegovina
[2] Univerzitetski klinički centar Tuzla, Klinika za ortopedsku hirurgiju i traumatologiju, Tuzla, Bosna i Hercegovina

Uvod: Izbor implantata za lečenje multifragmentarnih pertrohanteričnih preloma AO-OTA 31-A2 je složen, a dinamički zavrtanj za kuk (DHS) može se koristiti kao biomehanički siguran i jeftin implantat. Hirurzi obično imaju izbor između DHS ploča sa dva ili četiri otvora. Primarni cilj ove studije bio je utvrditi postoji li razlika u vremenu operacije, dužini hospitalizacije, intraoperativnom gubitku krvi i dužini incizije kod pacijenata sa AO-OTA 31-A2 prelomima lečenih DHS-om sa dva otvora ili DHS-om sa četiri otvora. Sekundarni cilj je uporediti stopu komplikacija koje uključuju nezarastanje preloma, lom implantata (DHS ploča, klizni zavrtanj, kompresioni zavrtanj ili kortikalni zavrtnji), cut-out, kolaps preloma i avaskularnu nekrozu.

Metode: U našu retrospektivnu studiju uključili smo 94 pacijenta sa AO-OTA 31-A2 prelomima lečenih pomoću DHS-asa 2 ili 4 otvora. Pacijenti su podeljeni u dve grupe: grupu A koja je uključivala 60 pacijenata lečenih DHS pločicom sa dva otvora i grupu B koja je uključivala 34 pacijenta lečena DHS pločicom sa četiri otvora.

Rezultati: Grupa A imala je značajno kraće vreme operacije 44,80 ± 8,01 minuta u odnosu na grupu B 48,12 ± 5,43 minuta ($p < 0,05$). Grupa A je takođe imala značajno manju dužinu incizije ($p < 0,05$). Preostali ishodi nisu imali značajnu razliku između dve grupe.

Zaključak: U zaključku, odsustvo značajnih razlika u stopama komplikacija podržava ideju da su oba tipa DHS-a održive opcije za lečenje AO-OTA 31A2 preloma.

Ključne reči: dinamički zavrtanj kuka, femur, prelomi kuka.

REFERENCES

1. Sing CW, Lin TC, Bartholomew S, Bell JS, Bennett C, Beyene K, et al. Global epidemiology of hip fractures: secular trends in incidence rate, post-fracture treatment, and all-cause mortality. J Bone Miner Res. 2023; 38(8): 1064-75. doi: 10.1002/jbmr.4821.

2. Li M, Lv HC, Liu JH, Cui X, Sun GF, Hu JW, et al. Differences in bone mineral density and hip geometry in trochanteric and cervical hip fractures in elderly Chinese patients. Orthop Surg. 2019; 11(2): 263-269. doi: 10.1111/os.12456.

3. Meinberg E, Agel J, Roberts C, Karam M, Kellam J. Fracture and dislocation classification compendium—2018. J Orthop Trauma. 2018; 32(1): S1-S10. doi: 10.1097/bot.0000000000001063.

4. Baldock TE, Dixon JR, Koubaesh C, Johansen A, Eardley WGP. Variation of implant use in A1 and A2 trochanteric hip fractures : a study from the National Hip Fracture Database of England and Wales. Bone Jt Open. 2022; 3(10): 741-5. doi: 10.1302/2633-1462.310.bjo-2022-0104.r1.

5. Mitković M, Milenković S, Micić I, Kostić I, Stojiljković P, Mitković M. Hip function and health-related quality of life in intramedullary and extramedullary internal fixation of trochanteric fractures. Srp Arh Celok Lek. 2020; 148(7-8): 451-4. doi: 10.2298/sarh200301029m.

6. Palm, H. Hip Fracture: The Choice of Surgery. In: Falaschi, P., Marsh, D. (eds) Orthogeriatrics. Practical Issues in Geriatrics. Springer, Cham. 2021: 125-41. doi: 10.1007/978-3-030-48126-1_9.

7. Kumar R, Menyah E, Thahir A, Thakur R, Malindzisa L, Relwani J. Management of trochanteric fractures: are we NICE compliant? Cureus. 2023; 15(10): e47038. doi: 10.7759/cureus.47038.

8. Grønhaug KML, Dybvik E, Matre K, Östman B, Gjertsen JE. Intramedullary nail versus sliding hip screw for stable and unstable trochanteric and subtrochanteric fractures. Bone Joint J. 2022; 104-B(2): 274-82. doi: 10.1302/0301-620x.104b2.bjj-2021-1078.r1.

9. Wang D, Zhang K, Qiang M, Jia X, Chen Y. Computer-assisted preoperative planning improves the learning curve of PFNA-II in the treatment of intertrochanteric femoral fractures. BMC MusculoskeletDisord. 2020; 21(1): 34. doi: 10.1186/s12891-020-3048-4.

10. Woldeyesus TA, Gjertsen JE, Dalen I, Meling T, Behzadi M, Harboe K, et al. Preoperative CT improves the assessment of stability in trochanteric hip fractures. Bone Jt Open. 2024; 5(6): 524-31. doi: 10.1302/2633-1462.56.bjo-2023-0177.r1.

11. Andriollo L, Fravolini G, Sangaletti R, Perticarini L, Benazzo F, Rossi SMP. Angle-adjustable dynamic hip screw plate for unstable trochanteric fractures in middle-aged patients: mid-term outcomes and return to sport. J Clin Med. 2024; 13(4): 988. doi: 10.3390/jcm13040988.

12. Schemitsch EH, Nowak LL, Schulz AP, Brink O, Poolman RW, Mehta S, et al.; INSITE Investigators. Intramedullary nailing vs sliding hip screw in trochanteric fracture management: the INSITE randomized clinical trial. JAMA Netw Open. 2023; 6(6): e2317164. doi: 10.1001/jamanetworkopen.2023.17164.

13. Wessels JO, Bjarnesen MP, Erichsen JL, Palm H, Gundtoft PH, Viberg B. Sliding hip screw vs intramedullary nail for AO/OTA 31-A1–A3: a systematic review and meta-analysis. Injury. 2022; 53(3): 1149-59. doi: 10.1016/j.injury.2021.12.034.

14. Mellema JJ, Janssen S, Schouten T, Haverkamp D, van der Bekerom MPJ, Ring D, et al. Intramedullary nailing versus sliding hip screw for A1 and A2 trochanteric hip fractures. Bone Joint J. 2021; 103-B(4): 775-81. doi: 10.1302/0301-620x.103b.bjj-2020-1490.r1.

15. Zhang C, Xu B, Liang G, Zeng X, Zeng D, Chen D, et al. Optimizing stability in AO/OTA 31-A2 intertrochanteric fracture fixation in older patients with osteoporosis. J Int Med Res. 2018; 46(5): 1767-78. doi: 10.1177/0300060518761504.

16. Makridis KG, Badras LS, Badras SL, Karachalios TS. Searching for the 'winner' hip fracture patient: the effect of modifiable and non-modifiable factors on clinical outcomes following hip fracture surgery. Hip Int. 2019; 31(1): 115-24. doi: 10.1177/1120700019878814.

17. Lu Y, Uppal HS. Hip fractures: relevant anatomy, classification, and biomechanics of fracture and fixation. Geriatr Orthop Surg Rehabil. 2019; 10: 2151459319859139. doi: 10.1177/2151459319859139.

18. McLoughlin SW, Wheeler DL, Rider J, Bolhofner B. Biomechanical evaluation of the dynamic hip screw with two- and four-hole side plates. J Orthop Trauma. 2000; 14(5): 318-23. doi: 10.1097/00005131-200006000-00002.

19. Rog D, Grigsby P, Hill Z, Pinette W, Inceoglu S, Zuckerman L. A biomechanical comparison of the two- and four-hole side-plate dynamic hip screw in an osteoporotic composite femur model. J Orthop Surg (Hong Kong). 2017; 25(2): 2309499017717199. doi: 10.1177/2309499017717199.

20. Wang CC, Lee CH, Chin NC, Chen KH, Pan CC, Su KC. Biomechanical analysis of the treatment of intertrochanteric hip fracture with different lengths of dynamic hip screw side plates. Technol Health Care. 2020; 28(6): 593-602. doi: 10.3233/thc-202248.

21. Feng X, Qi W, Fang CX, Lu WW, Leung FKL, Chen B. Can barb thread design improve the pullout strength of bone screws? Bone Joint Res. 2021; 10(2): 105-12. doi: 10.1302/2046-3758.102.bjr-2020-0072.r2.

22. Vanderkarr MF, Ruppenkamp JW, Vanderkarr M, Holy CE, Blauth M. Risk factors and healthcare costs associated with long bone fracture non-union: a retrospective US claims database analysis. JOrthop Surg Res. 2023; 18(1): 745. doi: 10.1186/s13018-023-04232-3.

23. Fang C, Gudushauri P, Wong TM, Lau TW, Pun T, Leung F. Increased fracture collapse after intertrochanteric fractures treated by the dynamic hip screw adversely affects walking ability but not survival. Biomed Res Int. 2016; 2016: 4175092. doi: 10.1155/2016/4175092.

24. Říha D, Bartoníček J. Internal fixation of pertrochanteric fractures using DHS with a two-hole side-plate. Int Orthop. 2009; 34(6): 877–82. doi: 10.1007/s00264-009-0840-z.

25. Dar FA, Iqbal Z, Lone AH, Ali N. Clinical and radiological results of minimally invasive two-hole dynamic hip screw fixation of stable intertrochanteric fractures: a prospective study of 50 patients. Int J Recent Surg Med Sci. 2023; 10(1): 67-74. doi: 10.1055/s-0043-1761618.

26. Baird RP, O'Brien P, Cruickshank D. Comparison of stable and unstable pertrochanteric femur fractures managed with two- and four-hole side plates. Can J Surg. 2014; 57(5): 327-30. doi: 10.1503/cjs.026113.

27. Ravikumar D, George U, Shetty DS. A comparative study of functional outcome between DHS and PFN in basicervical femur fracture. Int J Orthop Sci. 2023; 9(2): 1-15. doi: 10.22271/ortho.2023.v9.i2a.3347.

28. Soni A, Munshi S, Radhamony NG, Nair R, Sreenivasan S. Dynamic hip screw plate length in stable intertrochanteric fracture neck of femur: a systematic review. Cureus. 2022; 14(3): e23138. doi:10.7759/cureus.23138.

29. Bombah FM, Diawara M, Ekani BY, Nana T, Mikiela A. Complications after dynamic hip screw osteosynthesis of proximal femoral fractures at Army Instructional Hospital-Libreville. Case Rep Orthop. 2021; 2021: 4177203. doi: 10.1155/2021/4177203.

30. Hsu CE, Chiu YC, Tsai SH, Lin TC, Lee MH, Huang KC. Trochanter stabilising plate improves treatment outcomes in AO/OTA 31-A2 intertrochanteric fractures with critical thin femoral lateral walls. Injury. 2015; 46(6): 1047-53. doi: 10.1016/j.injury.2015.03.007.

31. Akinyemi TO, Mannan S, Ayeni FA. Pertrochanteric hip fracture fixation with 3 hole and 4 hole DHS side plates: a retrospective patient record review. Niger J Med. 2022; 31(2): 144-8. doi: 10.4103/NJM.NJM_120_21.

32. Ceynowa M, Zerdzicki K, Kłosowski P, Pankowski R, Rocławski M, Mazurek T. The early failure of the gamma nail and the dynamic hip screw in femurs with a wide medullary canal: a biomechanical study of intertrochanteric fractures. Clin Biomech. 2020; 71: 201-7. doi: 10.1016/j.clinbiomech.2019.11.006.

Correspondence to/Autor za korespondenciju
Edin Mesanovic
Address: Tekija 43, Mostar 88000, Bosnia and Herzegovina
Tel. number: +38761642143
Email: edin_mesanovic@yahoo.com
ORCID No:
Edin Mesanovic 0000-0002-1730-7223
Fikret Fajic 0009-0005-5357-2226
Mirza Mesanovic 0009-0004-4636-6996

***How to cite this article**:* Mesanovic E, Fajic F, Mesanovic M. Comparative Analysis of Surgical Outcomes in AO-OTA 31-A2 Fractures: Two-Hole vs. Four-Hole Dynamic Hip Screw. Sanamed. 2025; 20(2): 131-137. doi: 10.5937/sanamed0-57836.

SANAMED
2025; 20(2): 139–145
ISSN-1452-662X

DOI: 10.5937/sanamed0-58886
UDK: 616.155.194-055.26
ID: 174748937
Original article

IMPACT OF MATERNAL ANAEMIA ON NEONATAL OUTCOMES: A SINGLE-CENTRE EXPERIENCE

Dostović Hamidović Lejla,[1] Skokić Fahrija,[1] Muratović Selma,[2] Terzić Asja[2]

[1] University Clinical Center of Tuzla, Pediatric Clinic, Tuzla, Bosnia and Herzegovina
[2] University Clinical Center of Tuzla, Clinic of Gynecology and Obstetrics, Tuzla, Bosnia and Herzegovina

Primljen/Received: 15. 05. 2025. Prihvaćen/Accepted: 12. 07. 2025. Published online first 15. 07. 2025.

Abstract: **Background:** Maternal anaemia is one of the most common complications of pregnancy and is associated with adverse outcomes such as preterm delivery, impaired fetal development, and increased risks of morbidity and mortality in the perinatal period. The high prevalence of anaemia in pregnancy and its impact on fetal development represents a significant public health issue. The aim of this study was to analyze the influence of maternal anaemia on neonatal outcomes.

Patients and Methods: In a two-year prospective study conducted at the Clinic of Gynecology and Obstetrics and the Clinic of Children's Diseases of the University Clinical Center Tuzla, 177 newborns and their mothers were analyzed—127 in the experimental group (mothers with anaemia) and 50 in the control group (without anaemia). Sociodemographic and clinical data of the mothers and newborns were collected. Data were processed using conventional statistical techniques. Ethical approval was obtained from the relevant institutional review board.

Results: Of the 120 (70.58%) mothers with anaemia included in the study, 106 (88.3%) were between 18 and < 35 years of age. Working mothers had lower odds of anaemia ($p = 0.025$), while mothers who did not use supplements during pregnancy had higher odds ($p = 0.001$). Maternal anaemia was significantly associated with smoking or tobacco use ($p = 0.015$). Mothers living outside of marriage were more likely to be anaemic. A higher percentage of vaginal bleeding ($p = 0.0001$), uncontrolled pregnancies ($p = 0.011$), and caesarean section as the mode of delivery ($p = 0.000$) were recorded among anaemic mothers. Babies born to anaemic mothers had lower birth weight compared to those born to non-anaemic mothers ($p = 0.004$). Maternal anaemia significantly affected gestational age ($p = 0.024$) and Apgar scores in the 1st ($p = 0.006$) and 5th minutes ($p = 0.0031$). In this study, maternal anaemia during pregnancy had a statistically significant impact on perinatal outcomes including perinatal asphyxia, respiratory distress syndrome, neonatal infections, icterus neonatorum, intracranial hemorrhage, and hypoxic-ischemic encephalopathy.

Conclusion: In developing countries, current strategies for the prevention of anaemia in pregnancy have had limited success. Programs for careful monitoring and management of anaemia during pregnancy need to be developed in order to prevent poor perinatal outcomes.

Keywords: neonatal outcome, anaemia, pregnancy.

INTRODUCTION

Anaemia in pregnancy is a global health concern. While mild dilutional anaemia is considered a normal physiological adaptation during pregnancy, more pronounced anaemia can negatively affect both maternal and neonatal health. Therefore, recognising iron deficiency anaemia and distinguishing it from normal physiological changes is essential, along with identifying rarer causes that may require clinical intervention (1).

According to the World Health Organization (WHO), haemoglobin levels below 11 g/dL during gestation are indicative of maternal anaemia. Maternal anaemia is classified as mild, moderate, or severe based on haemoglobin levels: 10–10.9 g/dL for mild, 7–9.9 g/dL for moderate, and below 7 g/dL for severe cases (2).

In 2019, the global prevalence of anaemia among women of reproductive age was 29.9%, translating to more than half a billion women aged 15 to 49. Among pregnant women, the prevalence was 36.5%, compared to 29.6% in non-pregnant women of reproductive age (3). These differences across regions are largely influ-

enced by socioeconomic conditions and related nutritional deficiencies (4).

Maternal anaemia is one of the most common complications of pregnancy, associated with adverse outcomes such as preterm delivery, restricted fetal growth, and increased perinatal morbidity and mortality (5).

Additionally, anaemia is linked to a higher risk of maternal mortality in developing countries, as well as a variety of complications, including infections, pregnancy-induced hypertension, preeclampsia, eclampsia, premature rupture of membranes, and postpartum depression. Adverse pregnancy outcomes occur 30–45% more frequently in anaemic mothers (6, 7).

Due to its high prevalence and impact on fetal development, anaemia in pregnancy remains a significant public health issue.

The aim of this study was to analyse the perinatal risks in anaemic pregnant women and associated neonatal outcomes.

PATIENTS AND METHODS

This prospective study was conducted over a two-year period (from January 1, 2020, to January 1, 2022) at the Clinic of Gynecology and Obstetrics and the Clinic of Pediatrics of the University Clinical Center Tuzla. The study included 177 neonates and their mothers, with 127 in the test group (born to mothers with confirmed anaemia) and 50 in the control group (mothers without anaemia). Twin pregnancies were also included in the analysis.

Data were collected using a pre-designed proforma that included sociodemographic and clinical parameters of both mothers and neonates. Maternal parameters included age, place of residence, employment status, marital status, education level, type of diet, smoking/tobacco use, and haemoglobin concentration. Neonatal parameters included sex, gestational age, birth weight, Apgar scores, and overall health status. Obstetric history was also recorded, including parity, twin pregnancy, vaginal bleeding, antenatal care, and mode of delivery.

Maternal anaemia in pregnancy was categorised as mild (10–10.9 g/dL), moderate (7–9.9 g/dL), or severe (below 7 g/dL), depending on haemoglobin concentration (2).

Blood samples for haemoglobin measurement were collected in heparinised tubes and analysed using a Sysmex XE-2100 haematological analyser (TOA Medical Electronics Co., Ltd., Kobe, Japan) at the Department of Biochemistry, Polyclinic for Laboratory Diagnostics, University Clinical Center Tuzla.

The New Ballard Score was used to assess neonatal postnatal gestational age (8). Gestational age was categorised as preterm (< 37 weeks), term (37 to <42 weeks), and post-term (≥ 42 weeks) (8).

The Apgar score was recorded at 1 and 5 minutes after birth, assessing five vital signs: respiration, heart rate, muscle tone, reflexes, and colour (9). Birth weight (BW) was measured in grams (g) using a Libela Celje weighing scale and categorised into four groups: < 2500 g, 2500–3499 g, 3500–4000 g, and > 4000 g.

All data were entered into a Microsoft Excel spreadsheet. Data analysis, including descriptive statistics and the chi-squared test, was performed using SPSS software version 20.0. Differences were considered statistically significant at $p < 0.05$. All analyses were conducted using a 95% confidence interval.

The study followed ethical principles outlined by institutional and/or national ethics committees, in accordance with the 1964 Declaration of Helsinki and its subsequent amendments (10). Ethical approval was obtained from the Institutional Ethics Committee.

RESULTS

Of the 120 (70.58%) mothers with anaemia included in the study, 106 (88.3%) were between the ages of 18 and < 35 years. The mean maternal age was 27.94 years, the mean body weight was 80.39 kg, and the mean height was 167.44 cm. The mean body mass index (BMI) was 28.62 kg/m².

In the control group of 50 (29.41%) mothers without anaemia, 44 (88%) were also of middle age. The mean maternal age was 28.52 years, mean body weight was 78.96 kg, and mean height was 166.22 cm. The mean BMI in this group was 28.61 kg/m².

Among the 177 newborns observed, the majority were born to mothers with moderate anaemia—109 (61.60%).

The association between maternal anaemia and the sociodemographic characteristics of mothers is summarised in Table 1. Employed mothers had lower odds of being anaemic ($p = 0.025$), while mothers who did not use supplements during pregnancy had higher odds ($p = 0.001$). In our study, no statistically significant association was found between maternal educational status and anaemia. A significant association was observed between anaemia and smoking/tobacco use ($p = 0.015$). The most common marital status in both groups was married, and a statistically significant association was found between marital status and group ($p = 0.026$). Mothers who were unmarried were more likely to be anaemic.

Additionally, a statistically significant association was observed between anaemia and the presence of vaginal bleeding, antenatal care, and mode of delivery ($p < 0.05$). A higher proportion of vaginal bleeding

***Table 1**. Sociodemographic parameters of mothers (n = 170)*

Clinical parameters	Anemic mothers		Non-anemic mothers		χ^2	P value
	f	%	f	%		
Age groups (years)						
18 to < 35	106	88.33	44	88.00	0.038	0.950
≥ 35-49	14	11.67	6	12.00		
Place of living						
Urban	56	46.67	25	50.00	0.157	0.691
Rural	64	54.17	25	50.00		
Employment						
Employed	84	70.00	26	52.00	5.007	0.025
Un-employed	36	30.00	24	48.00		
Marital status						
In marriage	109	90.83	50	100.00	4.900	0.026
Common-law marriage	11	9.17	0	0		
Mother's education						
Primary school	12	10.00	3	6.00	1.794	0.180
Middle school	70	58.33	32	64.00		
High school	10	8.33	6	12.00		
Graduate	28	23.33	9	18.00		
Use of supplements						
No	23	19.17	1	2.00	10.386	0.001
Yes	7	5.83	1	2.00		
First trimester only	90	75.00	48	96.00		
Smoking/tobacco abuse						
Yes	54	45.00	13	26.00	5.847	0.015
No	66	55.00	37	74.00		

χ^2 - chi-squared test; p - probability value

***Table 2.** Obstetric parameters of mothers (n = 170)*

Obstetric parameters	Anemic mothers		Non-anemic mothers		χ^2	P value
	f	%	f	%		
Parity						
Parity 1	62	51.69	27	54.00	1.294	0.255
Parity 2	49	33.33	19	38.00		
Parity ≥ 3	18	15.00	4	8.00		
Twin pregnancy						
No	113	94.17	50	100.00	3.041	0.081
Yes	7	5.43	0	0.00		
Vaginal bleeding						
Yes	29	24.17	0	0.00	14.56	0.0001
No	91	75.83	50	100.00		
Pregnancy control						
Optimal	98	81.67	48	96.00	6.462	0.011
Suboptimal	13	10.83	2	4.00		
No control	9	7.50	0	0.00		
Mode of delivery						
Vaginal	48	40.00	38	76.00	18.398	0.000
Vacuum exstractio	1	0.83	0	0.00		
Sectio Caesarea	71	59.17	12	24.00		

χ^2 - chi-squared test; p - probability value

Table 3. *Association of maternal anemia with clinical parameters of neonates (n = 177)*

Clinical parameters	Anemic mothers		Non-anemic mothers		χ^2	P value
	f	%	f	%		
Gender						
Male	57	44.88	23	46.00	0.0181	0.893
Female	70	55.12	27	54.00		
Gestational age						
Preterm (< 37)	25	19.69	3	6.00	5.045	0.024
Term (37 to 42)	102	80.31	47	94.00		
Post-term (> 42)	0	0.00	0	0.00		
Birth Weight for Gest. age						
Eutrophic	112	88.19	48	96.00	3.333	0.067
Hypotrophic	7	5.51	0	0.00		
Hypertrophic	8	6.30	2	4.00		
Birth weight (grams)						
< 2500	22	17.32	1	2.00	8.266	0.004
2500-3500	58	45.67	29	58.00		
3500-4000	39	30.71	15	30.00		
> 4000	8	6.30	5	10.00		
APGAR score in the 1st minute						
8-10	93	73.23	46	92.00	7.498	0.006
4-7	34	26.77	4	8.00		
≤ 3	0	0. 00	0	0.00		
APGAR scorein the 5th minute						
8-10	116	91.34	50	100.00	4.617	0.031
4-7	11	8.66	0	0.00		
≤ 3	0	0.00	0	0.00		

χ^2 - chi-squared test; p - probability value

Table 4. *Association of maternal anemia with perinatal outcome in neonates (n = 177)*

Perinatal outcome	Anemic mothers		Non-anemic mothers		χ^2	P value
	f	%	f	%		
Perinatal asphyxia						
No	103	88.03	43	94.00	4.616	0.031
Yes	24	20.51	3	6.00		
RDS						
No	110	94.02	49	98.00	5.091	0.024
Yes	17	14.53	1	2.00		
Neonatal infection						
No	100	85.47	46	92.00	4.366	0.036
Yes	27	23.08	4	8.00		
Icterus neonatorum						
No	108	92.31	48	96.00	4.062	0.043
Yes	19	16.24	2	4.00		
HIC						
No	101	86.32	48	96.00	7.310	0.006
Yes	26	22.22	2	4.00		
HIE						
No	108	92.31	50	100.00	8.379	0.003
Yes	19	16.24	0	0.00		

χ^2 - chi-squared test; p - probability value; RDS - Respiratory distress syndrome; HIC - Haemorrhagia intracranialis; HIE - Hypoxic-ischemic encephalopathy

($p = 0.0001$), lack of antenatal care ($p = 0.011$), and caesarean section as the mode of delivery ($p = 0.000$) were recorded among mothers with anaemia. Table 2 summarises the obstetric parameters.

The association between maternal anaemia and neonatal clinical parameters is presented in Table 3. Newborns of anaemic mothers had significantly lower birth weights compared to those of non-anaemic mothers ($p = 0.004$). Maternal anaemia also had a significant effect on gestational age ($p = 0.024$), as well as Apgar scores at both 1 minute ($p = 0.006$) and 5 minutes ($p = 0.0031$).

In our study, maternal anaemia during pregnancy had a statistically significant impact on perinatal outcomes such as perinatal asphyxia ($p = 0.031$), respiratory distress syndrome ($p = 0.024$), neonatal infections ($p = 0.036$), icterus neonatorum ($p = 0.043$), intracranial haemorrhage ($p = 0.006$), and hypoxic-ischemic encephalopathy ($p = 0.003$). The results detailing the association between maternal anaemia and perinatal outcomes are shown in Table 4.

DISCUSSION

Data on the age of pregnant women in this study show that the majority of both anaemic (88.3%) and non-anaemic (88%) mothers were in the middle-age category, with average ages of 27.94 and 28.52 years, respectively. A notable proportion—11.6%—were older pregnant women (≥ 35 years). Previous studies have shown that advanced maternal age is associated with increased risks, partly due to pre-existing conditions such as chronic hypertension or hypothyroidism. These risks include EPH gestosis, gestational diabetes, miscarriage, chromosomal abnormalities, macrosomia, low birth weight, and an increased likelihood of caesarean delivery (11).

In our study, the participants were evenly distributed by place of residence, with a slightly higher proportion of anaemic mothers living in rural areas (54.17%). Most pregnant women in both groups had a secondary education, with a substantial proportion (23.33%) of anaemic women having higher education. Anaemic mothers were more frequently unemployed (30%). Regarding marital status, the majority of mothers in both groups were married; however, anaemia was more common among those who lived outside of marriage (9.17%). Existing research shows that better socioeconomic conditions—such as higher levels of education and income—are linked to healthier dietary habits during pregnancy (12).

In this study, maternal anaemia was significantly associated with a vegetarian diet. Similar findings were reported by Bansal et al. and Bhaware et al. (13, 14). Smoking or tobacco use was also significantly associated with anaemia in pregnancy ($p = 0.015$). Likewise, Mistry et al. found a relationship between tobacco abuse and maternal anaemia (15). Smoking during pregnancy is a well-established risk factor for complications in the pregnancy course and for impaired fetal growth and development.

A higher percentage of vaginal bleeding ($p = 0.0001$), inadequate antenatal care ($p = 0.011$), and caesarean section as the mode of delivery ($p = 0.000$) were observed in anaemic mothers.

Among neonatal clinical parameters, maternal anaemia was significantly associated with lower birth weight ($p = 0.004$), shorter gestational age ($p = 0.024$), and lower Apgar scores at both 1 and 5 minutes. These findings are consistent with those of Adhikari et al., who reported a significant association between maternal anaemia and reduced gestational age ($p = 0.033$), lower birth weight ($p = 0.04$), and shorter neonatal length ($p = 0.003$) (16). Similarly, the study by Bakhtiar et al. showed that maternal anaemia is associated with preterm birth, low birth weight, and low Apgar scores at one minute (17).

Reduced maternal haemoglobin levels impair placental angiogenesis, thereby limiting oxygen delivery to the fetus and contributing to intrauterine growth restriction (18).

In our study, maternal anaemia had a statistically significant impact on adverse perinatal outcomes, including perinatal asphyxia, respiratory distress syndrome (RDS), neonatal infections, neonatal icterus, haemorrhagia intracranialis (HIC), and hypoxic-ischemic encephalopathy (HIE) ($p < 0.05$).

The findings confirm the hypothesis of a statistically significant interdependence between maternal anaemia and perinatal outcomes. The percentage of newborns with unfavourable outcomes was significantly higher among those born to anaemic mothers compared to those born to non-anaemic mothers.

These results highlight the complex relationship between anaemia in pregnancy and perinatal health—an area that warrants further research. Future studies should consider larger and/or higher-risk populations, utilise a broader range of anaemia biomarkers, and assess maternal and neonatal anaemia across multiple time points.

CONCLUSION

Anaemia during pregnancy is recognised as a global public health concern. While mild dilutional anaemia may occur as a normal physiological adaptation, more severe forms can have detrimental effects on both maternal and neonatal health. In developing countries, current strategies for the prevention of anaemia in pregnancy have had limited success. Therefore, comprehensive

programmes for the careful monitoring and management of anaemia during pregnancy should be developed to reduce the risk of adverse perinatal outcomes.

Abbreviations

BMI – Body mass index
EPH gestosis – Edema, proteinuria, hypertension gestosis
HIE – Hypoxic-ischemic encephalopathy
HIC – Haemorrhagia intracranialis
p – Probability value
RDS – Respiratory distress syndrome
WHO – World Health Organization
χ^2 – Chi-squared test

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: This research received no external funding.

Author contribution: All authors have made substantial contributions to all parts of the manuscript. Also, all authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained by the hospital's ethical board.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

UTICAJ ANEMIJE U TUDNOĆI NA NEONATALNI ISHOD - ISKUSTVO JEDNOG CENTRA

Dostović Hamidović Lejla,[1] Skokić Fahrija,[1] Muratović Selma,[2]Terzić Asja[2]

[1] Univerzitetski klinički centar Tuzla, Klinika za dečije bolesti, Tuzla, Bosna i Hercegovina
[2] Univerzitetski klinički centar Tuzla, Klinika za ginekologiju i akušerstvo, Tuzla, Bosna i Hercegovina

Uvod: Anemija majke je jedna od najčešćih komplikacija u trudnoći, koja je povezana s negativnim ishodima trudnoće poput prevremenog porođaja i poremećajima razvoja fetusa, kao i povećanim rizikom obolevanja i smrti u vreme porođaja. Zbog svoje visoke učestalosti, uticaj anemije u trudnoći na fetalni razvoj ostaje značajan javno zdravstveni problem. Cilj rada je bio ispitati uticaj majčine anemije na neonatalni ishod.

Metode: U dvogodišnjoj prospektivnoj studiji sprovedenoj u Klinici za ginekologiju i akušerstvo i Klinici za dečije bolesti, Univerzitetskog kliničkog centra Tuzla analizirano je 177 novorođenčadi i njihovih majki-127 u eksperimentalnoj grupi (majke sa anemijom) i 50 u kontrolnoj grupi (bez anemije). Evaluirani su sociodemografski i klinički podaci majki i novorođenčadi. Podaci su obrađeni korišćenjem konvencionalnih statističkih metoda. Etičko odobrenje za studiju dobijeno je od nadležnog institucionalnog odbora.

Rezultati: Od 120 (70.58%) majki sa anemijom u trudnoći, 106 (88.3%) je bilo u dobi od 18 do < 35 godina. Zaposlene majke su ređe bile anemične u odnosu na nezaposlene (p = 0.025), dok je kod majki koje nisu koristile suplemente tokom trudnoće zabeležen veći procenat anemije (p = 0.001). Anemija je bila značajnija kod trudnica koje su pušile tokom trudnoće (p = 0.015) kao i kod onih koje su živele u vanbračnoj zajednici. Veći procenat vaginalnog krvarenja (p = 0.0001), nekontrolisanih trudnoća (p = 0.011) i carskog reza kao načina dovršetka porođa (p = 0.000) zabeležen je kod majki sa anemijom. Novorođenčad majki sa anemijom imala su nižu porođajnu težinu u odnosu na novorođenčad majki bez anemije (p = 0.004). Anemija majke značajno je uticala na rađanje novorođenčadi niže gestacijske dobi (p = 0.024) i nižeg Apgar skor u 1. (p = 0.006) i 5. minuti (p = 0.0031). U našem istraživanju, anemija majke tokom trudnoće imala je statistički značajan negativan uticaj na perinatalni ishod kao što su neonatalna asfiksija, respiratorni distres sindrom, neonatalna infekcija i ikterus novorođenčadi, pojava intrakranijalne hemoragije i hipoksično ishemijska encefalopatija.

Zaključak: U zemljama u razvoju trenutna strategija prevencije anemije u trudnoći ima malo uspeha. Trebalo bi razviti programe pažljivog praćenja kriterijuma vezanih za anemiju tokom trudnoće da bi se pravovremenim delovanjem izbegli loši perinatalni ishodi.

Ključne reči: neonatalni ishod, anemija, trudnoća.

REFERENCES

1. Auerbach M, Landy HL. Anemia in pregnancy. UpToDate. Available at https://www.uptodate.com /contents/anemia-in-pregnancy. Accessed on 19 September 2024.

2. World Health Organization. Guideline on haemoglobin cutoffs to define anaemia in individualsand populations. 2024. Available at: https://www.who .int/publications/ i/item/9789240088542.

3. World Health Organization. Anaemia in women and children. Available at: https://www.who.int/data/gho/data/themes/topics/anaemia_in_women_and_children. Accessed on 19 September 2024.

4. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Anemia in Pregnancy: ACOG Practice Bulletin, Number 233. ObstetGynecol 2021; 138: e55.doi: 10.1097/AOG.0000000000004477. PMID: 34293770.

5. Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2020; 188(6): 819-30. doi: 10.1111/bjh.16221.

6. Bone JN, Bellad M, Goudar S, Mallapur A, Charantimath U, Ramadurg U, et al. Anemia and adverse outcomes in pregnancy: subgroup analysis of the CLIP cluster-randomized trial in India. BMC Pregnancy Childbirth. 2022; 22(1): 407. doi: 10.1186/s12884-022-04714-y.

7. Shi H, Chen L, Wang Y, Sun M, Guo Y, Ma S, et al. Severity of anemia during pregnancy and adverse maternal and fetal outcomes. JAMA Netw Open. 2022; 5(2): e2147046. doi: 10.1001/jamanetworkopen.2021.47046.

8. Mehta VR, Parmar HR, Khandwala AB, Kakkad KM, Vekaria VV, Bhatt JV. A study of postnatal assessment of gestational age of neonates by new Ballards and Parkins score. Int J Contemp Pediatr. 2022; 9(1): 32-8. doi: 10.18203/2349-3291.ijcp20214849.

9. Simon LV, Shah M, Bragg BN. APGAR Score. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024.

10. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 310(20): 2191-4. doi: 10.1001/jama.2013.281053.

11. Hsieh TT, Liou JD, Hsu JJ, Lo LM, Chen SF, Hung TH. Advanced maternal age and adverse perinatal outcomes in an Asian population. Eur J Obstet Gynecol Reprod Biol. 2010; 148(1): 21-6. doi: 10.1016/j.ejogrb.2009.08.022.

12. Park JH, Lee BE, Park HS, Ha EH, Lee SW, Kim YJ. Association between pre-pregnancy body mass index and socioeconomic status and impact on pregnancy outcomes in Korea. J Obstet Gynaecol Res. 2011; 37(2): 138-45. doi: 10.1111/j.1447-0756.2010.01332.x.

13. Bansal R, Bedi M, Kaur J, Kaur K, Shergill HK, Khaira HK, et al. Prevalence and factors associated with anemia among pregnant women attending antenatal clinic. Adesh Univ J Med Sci Res. 2020; 2(1): 42-8. doi:10.25259/AUJMSR_8_2020.

14. Bhaware GM, Muneshwar SN, Pundkar RD. Anaemia in pregnancy: a cross-sectional study. Int J Comm Med Public Health. 2021;8(10):4876-9. doi: 10.18203/2394-6040.ijcmph20213786.

15. Mistry R, Jones AD, Pednekar MS, Dhumal G, Dasika A, Kulkarni U, et al. Antenatal tobacco use and iron deficiency anemia: integrating tobacco control into antenatal care in urban India. Reprod Health. 2018; 15(1): 1-8. doi: 10.1186/s12978-018-0516-5.

16. Adhikari J, Belbase M, Rijal S. Effects of maternal anemia on neonatal outcome. J Nepalgunj Med Coll. 2021; 19(1): 30-3. doi: https://doi.org/10.3126/jngmc.v19i1.40091.

17. Bakhtiar UJ, Khan Y, Nasar R. Relationship between maternal hemoglobin and perinatal outcome. RMJ. 2007; 32(2): 102-4.

18. Stangret A, Wnuk A, Szewczyk G, Pyzlak M, Szukiewicz D. Maternal hemoglobin concentration and hematocrit values may affect fetus development by influencing placental angiogenesis. J Matern Fetal Neonatal Med. 2017; 30(2): 199-204. doi: 10.3109/14767058.2016.1168395.

Correspondence to/Autor za korespondenciju
Lejla Dostović Hamidović
University Clinical Center of Tuzla, Pediatric Clinic
Prof. dr. Ibre Pašić bb 75000 Tuzla, BH
phone:+ 387 61 856 378
e-mail: lejladostovic@hotmail.com
ORCID ID:
Lejla Dostović Hamidović 0000-0002-3824-7522
Fahrija Skokić 0009-0008-8945-9016
Selma Muratović 0009-0000-5246-4534
Asja Muratović 0009-0002-1452-0464

How to cite this article: **Dostović Hamidović L**, Skokić F, Muratović S, Terzić A. Impact of maternal anaemia on neonatal outcomes: a single-centre experience. Sanamed. 2025; 20(2): 139-145. doi: 10.5937/sanamed0-58886.

SANAMED
2025; 20(2): 147–155
ISSN-1452-662X

DOI: 10.5937/sanamed0-58683
UDK: 616-001-083.98; 616-083
ID: 174766089
Original article

EARLY DETECTION OF TRAUMA PATIENTS REQUIRING INTENSIVE CARE IN THE EMERGENCY DEPARTMENT: A NEXT-GENERATION RISK SCORE MODEL

Boğa Erkan

Republic of Turkey, Ministry of Health, Esenyurt Necmi Kadıoğlu State Hospital, Istanbul, Turkey

Primljen/Received: 06. 05. 2025. Prihvaćen/Accepted: 12. 07. 2025. Published online first 16. 07. 2025.

Abstract: **Background:** Trauma remains a leading cause of death worldwide; therefore, it is important to identify patients who need intensive care unit (ICU) admission in the emergency department (ED). Current trauma scoring systems such as the Glasgow Coma Scale (GCS), Revised Trauma Score (RTS), and Injury Severity Score (ISS) are not very efficient at predicting ICU need. The application of machine learning (ML)-based predictive models is a novel approach to enhance the triage process.

Objective: The primary objective of this study was to develop and validate a risk scoring model based on machine learning for early identification of trauma patients requiring ICU admission from the emergency department. The study also aimed to assess the predictive ability of the ML model compared to traditional scoring systems such as the GCS, RTS, and ISS.

Methods: A retrospective, observational cohort study was conducted at Esenyurt Necmi Kadıoğlu State Hospital, collecting trauma patient data from January 1, 2024, to August 31, 2024. A total of 1,500 trauma patients aged ≥ 18 years with complete clinical, laboratory, and imaging data were included. Predictive variables consisted of demographics, trauma mechanism, vital signs, laboratory results, imaging findings, and existing trauma scores. The area under the curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were used to train and evaluate ML algorithms (Logistic Regression, Random Forest, Support Vector Machines, XGBoost, and LightGBM). The model was compared to traditional scoring systems using the DeLong test.

Results: Of the 1,500 patients, 50.73% (n = 761) required ICU admission. The developed ML model had an AUC of 0.999, with sensitivity of 99.22%, specificity of 99.69%, and accuracy of 99.56%, far outperforming traditional scoring systems. The strongest predictors of ICU admission were age, lactate level, RTS, systolic blood pressure, respiratory rate, and oxygen saturation. No significant difference in ICU admission rates was observed between blunt and penetrating trauma groups, indicating that trauma mechanism alone should not be used as a predictor.

Conclusion: The machine learning-based risk scoring model demonstrated better predictive performance than traditional trauma scoring systems in identifying trauma patients requiring ICU admission. Integration of this model into ED workflows may improve triage and patient care. However, validation in multicenter prospective studies is needed before clinical implementation.

Keywords: Machine Learning, Trauma Patients, ICU Admission, Risk Scoring Model, Emergency Medicine, Predictive Analytics.

INTRODUCTION

Trauma is one of the most common causes of morbidity and mortality worldwide. According to the 2023 World Health Organization (WHO) report, approximately 5 million people die annually due to trauma-related injuries (1). Early diagnosis and management of trauma patients are crucial for improving patient outcomes and enhancing the effectiveness of healthcare services.

It is vital that trauma patients are stabilized and managed appropriately in emergency departments (ED). However, early identification of patients who need intensive care is often based on clinical experience, and current scoring systems may be insufficient in this process. While the Glasgow Coma Scale (GCS), Revised Trauma Score (RTS), and Injury Severity Score (ISS) are commonly used to assess trauma severity, their performance varies across patient popu-

lations, and none reliably predict the need for intensive care unit (ICU) admission (2, 3). Studies have shown that existing triage systems produce high rates of false negatives and false positives, which can adversely affect patient outcomes (4, 5). Specifically, in the ED setting, the sensitivity and specificity of current scoring systems are not clinically strong enough, indicating a need for more advanced predictive models (6).

Over the past few years, machine learning (ML)-based predictive models have emerged as a promising approach for clinical decision support systems. ML has demonstrated significant potential in clinical medicine through predictive modeling and risk stratification in emergency and critical care settings (7, 8). These models do not rely on traditional scoring systems; instead, they incorporate big data analytics to analyze complex datasets and provide more accurate patient outcome predictions. ML-based models have been shown to outperform traditional scoring systems such as RTS, ISS, and GCS in predicting ICU admission among trauma patients (9, 10). Reported sensitivity and specificity values of ML models exceed those of traditional scores; however, their clinical integration remains challenging (11). Limitations include lack of external validation, difficulties integrating these models into clinical workflows, and inadequate performance comparisons with existing scoring systems (12, 13).

In this context, there is a clear need for an enhanced triage system that can rapidly and effectively identify trauma patients requiring intensive care while addressing the shortcomings of current scoring systems.

The main purpose of this study is to develop and assess a machine learning-based risk scoring model for early and accurate identification of trauma patients requiring intensive care in the ED. The predictive performance of the ML model for ICU admissions will be compared with traditional scoring systems (GCS, RTS, ISS), and key clinical and demographic predictors of ICU need will be identified. Additionally, the feasibility of implementing the developed model in real clinical practice will be explored.

This study is based on the hypothesis that machine learning algorithms provide better prediction of ICU admission than traditional trauma scoring systems. It is expected that the developed model will improve the triage process, serve as a superior decision support tool in patient management, and positively impact patient outcomes.

MATERIAL AND METHODS

This is an observational cohort study with a retrospective design. The goal was to create a machine learning model to help predict ICU admission for trauma patients and to compare its performance with existing scoring systems. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The research was carried out in the Emergency Department of Esenyurt Necmi Kadıoğlu State Hospital from January 1, 2024, to August 31, 2024. The hospital is a large urban facility, with an average of 500,000 emergency department visits per year. All data for this study were collected retrospectively from the Hospital Information Management System (HBYS). The data collection process was performed according to the guidelines of the American College of Surgeons (ACS) and the European Trauma Course (ETC). All variables were coded following standardized protocols to ensure consistency and reliability.

This study included patients aged 18 years and older who presented to the emergency department with trauma and had complete clinical, laboratory, and imaging data. Patients under 18 years, those with incomplete or missing data, and those transferred from other healthcare facilities were excluded. A total of 1500 trauma patients met these criteria and were included in the study.

The dependent variables were ICU admission (Yes/No), hospital length of stay in days, and 30-day mortality (Survived/Deceased). Independent variables included demographic data (age, sex, body mass index), trauma mechanism (blunt or penetrating trauma, traffic accident, fall, gunshot wound, etc.), vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, body temperature), laboratory values (hemoglobin, hematocrit, lactate, white blood cell count, blood gas parameters, electrolyte levels), imaging findings (Focused Assessment with Sonography for Trauma [FAST] ultrasound results), and trauma severity scores (Injury Severity Score [ISS], Revised Trauma Score [RTS], and New Injury Severity Score [NISS]).

All data were coded using predefined standardized clinical protocols, and accuracy was verified through double-checking processes. The main data source was the Hospital Information Management System (HBYS), where retrospective patient records were retrieved. Data on ICU admissions, hospital length of stay, and mortality were verified using the patient tracking system. Vital signs and laboratory values were based on the first measurements taken upon patient arrival at the emergency department. Imaging results were based on official reports interpreted by emergency physicians and radiologists.

To ensure adequate statistical power, a G*Power analysis was conducted with a 95% confidence interval, 80% power, and a 10% error margin. The calculated sample size of 1500 patients was determined to be statistically sufficient for the analyses performed.

To avoid bias, data collection was double-checked, and incorrect or missing data were minimized. Missing data were handled using regression-based imputation methods, rendering the dataset complete for statistical analysis. The Recursive Feature Elimination (RFE) method was used for feature selection, and only clinically important variables were included in the model.

Descriptive statistics were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). For data not normally distributed, the t-test or Mann-Whitney U test was used for group comparisons. The Chi-square test was applied for categorical variables.

To build the machine learning model, the following algorithms were used: Logistic Regression, Random Forest, Support Vector Machines (SVM), and Gradient Boosting algorithms (XGBoost and LightGBM). Model performance was evaluated by the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

To compare the new model's performance with existing trauma scoring systems (RTS, ISS, and NISS), the DeLong test was employed. Missing data were imputed by regression imputation, and the percentage of missing data was kept below 5%. As this was a retrospective study, there was no loss to follow-up.

To guarantee reproducibility of the analyses, the Python code used in model development will be posted on GitHub or another open-source platform. Moreover, feature selection and the algorithm employed in building the model will be provided as supplementary materials.

This structured methodology ensures that the study follows rigorous scientific standards and contributes to the development of a clinically applicable and validated machine learning model for predicting ICU admissions in trauma patients.

RESULTS

Initially, 1700 patients were potentially eligible for the study. However, 200 patients were excluded for the following reasons: 95 patients were under 18 years of age, 72 patients had incomplete data, and 33 patients were referred to another health facility. Thus, a total of 1500 trauma patients were included in the final analysis. Since this was a retrospective study, there was no loss to follow-up, and all data were analyzed completely (Table 1).

This table summarizes the baseline demographic and clinical characteristics of the trauma patients included in the study. These details help establish the overall profile of the study population in terms of age, gender, body mass index (BMI), and the types of traumatic injuries encountered.

Table 1. *Patient demographics and clinical characteristics*

Variable	Mean ± SD / n (%)
Age (years)	52.87 ± 20.86
Gender (Female)	776 (51.73%)
Body Mass Index	29.01 ± 6.35
Type of Trauma (Blunt)	1095 (73.0%)
Motor Vehicle Accident	723 (48.2%)
Falls	421 (28.1%)
Stab Injuries	187 (12.5%)
Other	67 (4.5%)

An analysis of the demographic, clinical, and laboratory characteristics of the first 1500 patients included in the cohort was performed. The mean age of the patients was 52.87 ± 20.86 years, with a median age of 53 years. Patient ages ranged from 18 to 89 years. In terms of gender distribution, 51.73% (n = 776) were female, and 48.27% (n = 724) were male. The mean body mass index (BMI) was 29.01 ± 6.35, with values ranging from 18.0 to 40.0 (Table 1).

Regarding trauma mechanisms, 73.0% of patients (n = 1095) suffered blunt trauma, and 27.0% (n = 405) penetrating trauma. Motor vehicle accidents were the most common trauma type (48.2%, n = 723), followed by falls (28.1%, n = 421), gunshot injuries (6.8%, n = 102), stab wounds (12.5%, n = 187), and other trauma types (4.5%, n = 67). There were no missing data; all patients had complete clinical and laboratory records.

In the analysis of ICU admissions and mortality rates, 50.73% of patients (n = 761) required ICU admission, while 49.27% (n = 739) did not require intensive care. The 30-day mortality was 50.2% (n = 753), while 49.8% of patients (n = 747) survived beyond the first 30 days of follow-up.

Comparing patients who required ICU admission with those who did not, there was a statistically significant difference in age (T-test $p = 3.58 \times 10^{-19}$; Mann-Whitney U test $p = 2.86 \times 10^{-100}$). Lactate levels were also significantly higher in patients admitted to the ICU (T-test $p = 1.22 \times 10^{-136}$; Mann-Whitney U test $p = 9.55 \times 10^{-110}$) (Table 2).

This table compares clinical and physiological variables between patients admitted to the ICU and those who were not. It highlights statistically significant differences in age, lactate levels, oxygen saturation, systolic blood pressure, and respiratory rate — variables most strongly associated with ICU admission. The p-values indicate the statistical significance of differences between the two groups.

Table 2. *Comparison of ICU and non-ICU trauma patients*

Variable	ICU Admission (n = 761)	No ICU Admission (n = 739)	p-Value
Age (years)	61.2 ± 17.4	44.1 ± 19.3	< 0.001
Lactate (mmol/L)	4.8 ± 2.1	1.7 ± 1.1	< 0.001
RTS Score	6.2 ± 1.3	7.1 ± 0.9	0.006
ISS Score	18.4 ± 5.9	18.3 ± 5.8	0.999
Oxygen Saturation (%)	88.7 ± 6.2	95.2 ± 3.1	< 0.001
Systolic BP (mmHg)	104.6 ± 18.3	119.8 ± 15.7	< 0.001
Respiratory Rate (breaths/min)	24.7 ± 4.6	20.2 ± 3.8	< 0.001

Table 3. *Variables correlated with ICU admission*

Variable	Pearson r	Spearman ρ	p-Value
Age	0.550	0.549	< 0.05
Lactate	0.582	0.575	< 0.05
RTS	0.071	0.072	< 0.05

However, there was no statistically significant difference in ISS (Injury Severity Score) between ICU and non-ICU patients (T-test p = 0.999; Mann-Whitney U test p = 0.980). In contrast, a statistically significant difference was observed in RTS (Revised Trauma Score) (T-test p = 0.006; Mann-Whitney U test p = 0.006). This indicates that patients with lower RTS values are more likely to require ICU admission (Figure 1).

In the comparison of gender and FAST ultrasound, no statistically significant differences were found between the groups (Gender, Chi-square test p = 0.376; FAST ultrasound, Chi-square test p = 0.515).

The relationship between ICU admission and clinical variables was also evaluated. A significant positive correlation was found between age and ICU admission (Spearman correlation coefficient: 0.549, Pearson correlation coefficient: 0.550, $p < 0.05$). Similarly, lactate levels showed a strong positive correlation with ICU admission (Spearman correlation coefficient: 0.575, Pearson correlation coefficient: 0.582, $p < 0.05$).

The RTS scores demonstrated a weak but statistically significant correlation with ICU admission (Spearman correlation coefficient: 0.072, Pearson correlation coefficient: 0.071, $p < 0.05$) (Table 3).

This table presents the strength of association between selected variables and ICU admission using both Pearson and Spearman correlation coefficients. Strong positive correlations were observed for age and lactate levels, suggesting these are key predictors of ICU necessity. The Revised Trauma Score (RTS) demonstrated a weaker, yet still statistically significant, correlation.

The subgroup analysis of blunt and penetrating trauma groups showed no statistically significant differences in ICU admission and mortality. The ICU

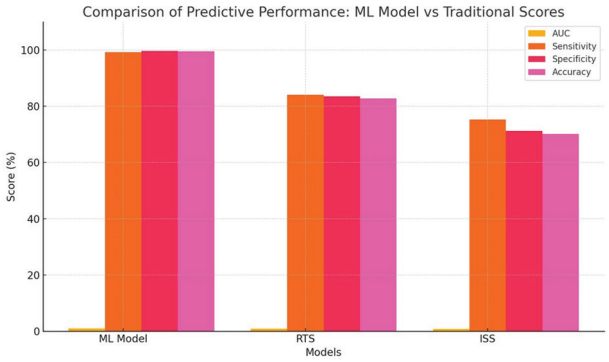


Figure 1. *Comparative performance metrics of ML model and traditional trauma scores*

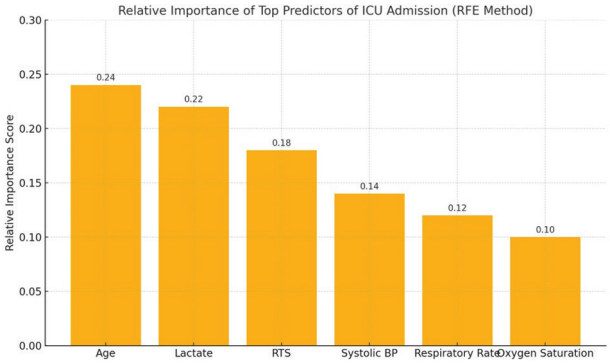


Figure 2. *Relative importance of top clinical predictors for ICU admission*

admission rate was 27.40% for patients with blunt trauma, with a 30-day mortality rate of 49.76%. For patients with penetrating trauma, the ICU admission rate was 27.62%, and the 30-day mortality rate was 51.22% (Figure 2).

These findings show that age, lactate level, and RTS are significant predictors of ICU admission in

trauma patients. On the other hand, ISS, gender, and FAST ultrasound findings were not significantly associated with ICU admission. Additionally, there was no difference in ICU admission rates between the blunt and penetrating trauma groups, indicating that trauma mechanism alone may not be a reliable predictor of ICU need.

DISCUSSION

In this study, a risk scoring model was developed and evaluated using machine learning to predict whether trauma patients require ICU admission. It was compared with traditional scoring systems such as RTS, ISS, and NISS, and found to be superior. The accuracy rate was 99.56%, and the AUC value was 0.99990, indicating a high predictive power of the model (14).

Key findings show that the new model is both sensitive (99.22%) and specific (99.69%) in identifying early ICU needs, while also avoiding unnecessary ICU admissions. Age, lactate, RTS, systolic blood pressure, respiratory rate, and oxygen saturation were identified as strong predictors of ICU admission using the Recursive Feature Elimination (RFE) method (15).

Compared to traditional scoring systems, the model demonstrated better predictive performance. The AUC value for RTS was 0.845, and for ISS it was 0.735, indicating that although these scores are useful for assessing trauma severity, they are less accurate at predicting ICU needs.

Subgroup analysis showed no significant differences in ICU admission rates or mortality between patients with blunt and penetrating trauma (16). This suggests that the model is generalizable across different trauma mechanisms, supporting its potential use in a broader patient population (17).

The study also demonstrates that machine learning–based models can be incorporated into decision support systems in emergency departments, potentially improving the efficiency and effectiveness of patient care. However, further work is required to determine how the model can be implemented practically in clinical settings and whether it can enhance clinicians' decision-making skills (18).

Limitations of this study include its single-center design, which limits generalizability. Further validation studies in other healthcare settings and patient populations are needed. Additionally, as a retrospective study, the model requires testing in real-time clinical decision-making environments for proper validation.

Because the data source was hospital records, the study may be subject to selection bias. Excluding patients due to missing or incomplete data may limit the applicability of the model to all trauma patients. The ICU admission prevalence of 50% in this study may reflect sampling bias or the specific patient population and does not match typical real-world distributions, where ICU admission rates are generally much lower. Future studies should evaluate model calibration under different ICU prevalence settings using methods such as recalibration plots, threshold adjustment, or prevalence-adjusted ROC analysis. These efforts would help determine whether the model maintains predictive performance and clinical usefulness across healthcare systems with differing ICU utilization patterns.

The model also faces challenges before clinical implementation. A main drawback of ML-based systems is their "black-box" nature, which can reduce clinical trust and adoption. The implementation of explainability techniques such as SHAP (Shapley Additive Explanations) values or decision tree visualizations would improve transparency by showing which features (e.g., lactate, RTS, age) influence individual predictions. These methods build user trust and enable clinicians to understand the rationale behind model decisions. Future versions of the model should include explainability tools to gain wider clinical acceptance. Integration of these models into clinical practice is further challenged by issues related to interpretation, ethical considerations, and real-time system integration in hospitals (12, 13).

For practical application, the model should be integrated into Hospital Information Management Systems (HBYS) and electronic health records to ensure seamless use in emergency department workflows. This integration would allow clinicians to test the model's real-world feasibility.

The results align with previous studies showing that machine learning models outperform traditional trauma scoring systems in predicting ICU need. The high AUC (0.99990) and accuracy (99.56%) demonstrate the potential of data-driven approaches to improve the reliability of clinical decision-making in trauma management.

Nonetheless, caution is warranted when applying these findings clinically. More studies are needed to assess how the model performs across different patient groups and in real-time practice.

Although conducted at a single center, the model shows potential for widespread use. Its stability across blunt and penetrating trauma cases suggests broad applicability. Future research should conduct multicenter prospective validation studies with diverse patient populations and clinical settings to establish external validity and generalizability. Such research should follow a structured framework including standardized data collection, local ICU admission criteria calibration, and performance comparison with current clinical tools at different sites. The model uses common

clinical variables (age, lactate, RTS, blood pressure, etc.), facilitating its deployment across various healthcare facilities (19).

Before recommending widespread adoption, multicenter validation is essential to increase external validity and reliability by testing the model across different healthcare systems and patient populations.

The machine learning–based risk scoring model developed in this study was more effective than conventional scoring systems in identifying trauma patients who require ICU admission. With an AUC of 0.99990, sensitivity of 99.22%, and specificity of 99.69%, the model appears to be a potentially useful decision support tool in trauma management.

Beyond high predictive accuracy, the RFE method also identified key ICU admission predictors such as age, lactate, RTS, blood pressure, respiratory rate, and oxygen saturation. Moreover, the absence of significant performance differences between blunt and penetrating trauma cases suggests the model's applicability across diverse trauma types.

This model is a promising tool for clinicians in emergency departments, where its speed and accuracy can enhance triage efficiency and improve patient outcomes. To ensure clinical implementation, the model should be integrated into real-time decision support systems and validated through multicenter studies.

Recommendations for Future Research

Multicenter prospective validation studies should be conducted to test the generalizability of the model. The model should be integrated into real-time clinical decision-support systems and evaluated in emergency departments. Optimization and refinement efforts should continue to improve its clinical usability. Once validated, this model may establish a new standard in trauma management by enabling early identification of critically ill patients and optimizing the utilization of ICU resources.

CONCLUSION

This paper aimed to evaluate the efficacy of a novel machine learning–based risk scoring model for early and accurate identification of trauma patients requiring ICU admission. The model was compared with traditional scoring systems such as the Revised Trauma Score (RTS), Injury Severity Score (ISS), and New Injury Severity Score (NISS) and was found to be significantly superior.

Key findings showed that the new model achieved high accuracy (99.56%), sensitivity (99.22%), and specificity (99.69%), making it a better tool for predicting ICU admission than existing scoring systems. The strongest predictors identified by the Recursive Feature Elimination (RFE) method included age, lactate level, RTS, systolic blood pressure, respiratory rate, and oxygen saturation.

Subgroup analysis demonstrated that the model performed similarly well for both blunt and penetrating trauma mechanisms. This supports the generalizability of the model across different types of trauma and suggests broad clinical applicability.

Clinically, the model's speed and accuracy could assist emergency departments in rapidly identifying critically ill patients, potentially improving clinical decision-making. Moreover, it could help optimize hospital resource utilization by outperforming traditional scoring systems.

The results indicate that machine learning–based models can be effectively used in trauma patient management. However, as this was a single-center retrospective study, its applicability remains somewhat limited. Therefore, the model requires further testing in multicenter prospective studies involving diverse patient populations.

Future research should focus on real-time implementation of the model in clinical decision-support systems and assess its generalizability across different healthcare settings. Machine learning–based risk scoring models have the potential not only to reduce healthcare costs but also to improve the quality of care provided to patients.

In conclusion, the model developed in this study shows promise as a decision-support tool for the early and specific identification of trauma patients requiring intensive care. Nonetheless, validation studies and integration into clinical workflows must be completed and proven effective in multicenter environments before widespread clinical use.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to privacy and ethical restrictions but can be provided by the corresponding author upon reasonable request. The dataset includes sensitive patient information and is stored securely in accordance with institutional and ethical guidelines. Researchers interested in accessing the data must submit a formal request to the corresponding author, and approval from the relevant ethics committee may be required. Data will only be shared for research purposes and in compliance with data protection regulations.

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study. There are no financial relationships, employment, consultancy, stock ownership,

honoraria, patents, or paid expert testimony that could influence the outcome of the research presented. Furthermore, there are no close relationships, competitive academic agendas, or philosophical biases that might have affected the conduct of the study. The study was carried out independently, and no agreements with sponsors limited access to data, analysis, interpretation, or publication. If any specific conflicts exist, they would be disclosed here. Since none exist, this statement confirms impartiality and scientific integrity.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was conducted as part of the author's employment at the Republic of Turkey, Ministry of Health, Esenyurt Necmi Kadıoğlu State Hospital. The funding organization had no role in the study design, data collection, analysis, manuscript writing, or the decision to publish this article.

Ethical Approval and Informed Consent

All subjects included in the study gave informed consent to participate. Participant information was kept anonymous and in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines for the protection of research participants. This research was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (Decision Number 1124, dated 28.11.2024). The study was conducted following the principles of the Declaration of Helsinki.

Authorship Statement

The author(s) have made substantial contributions to all phases of the study and are able to take public responsibility for the content and results presented in the manuscript. As the author of this study, I declare that I actively participated in the study design, data collection, analysis, interpretation, writing, and final approval of the manuscript. I take full responsibility for the accuracy and integrity of the content.

Author Contributions & Responsibilities

The author takes full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations.

Sažetak

RANO OTKRIVANJE PACIJENATA SA POVREDAMA KOJIMA JE POTREBNA INTENZIVNA NEGA U URGENTNOJ SLUŽBI: MODEL NOVE GENERACIJE ZA PROCENU RIZIKA

Boğa Erkan

Ministarstvo zdravlja Republike Turske, Državna bolnica Esenyurt Necmi Kadıoğlu, Istanbul, Turska

Uvod: Trauma ostaje vodeći uzrok smrti širom sveta; stoga je važno identifikovati pacijente kojima je potreban prijem u jedinicu intenzivne nege (JIN) u Urgentnoj službi (US). Trenutni sistemi bodovanja traume, kao što su Glasgow Coma Scale (GCS), Revised Trauma Score (RTS) i Injury Severity Score (ISS), nisu baš efikasni u predviđanju potreba za JIN. Primena prediktivnih modela zasnovanih na mašinskom učenju (ML) je novi pristup za poboljšanje procesa trijaže.

Cilj: Primarni cilj ove studije bio je razvoj i validacija modela bodovanja rizika zasnovanog na mašinskom učenju za ranu identifikaciju pacijenata sa traumom kojima je potreban prijem u JIN iz urgentne službe. Studija je takođe imala za cilj proceniti prediktivnu sposobnost ML modela u poređenju sa tradicionalnim sistemima bodovanja kao što su GCS, RTS i ISS.

Metode: U Državnoj bolnici Esenyurt Necmi Kadıoğlu sprovedena je retrospektivna, opservaciona kohortna studija, u kojoj su prikupljeni podaci o pacijentima s traumom od 1. januara 2024. do 31. augusta 2024. godine. U studiju je uključeno 1.500 pacijenata s traumom starosti ≥ 18 godina s kompletnim kliničkim, laboratorijskim i radiološkim dijagnostičkim podacima. Prediktivne varijable sastojale su se od demografskih podataka, mehanizma traume, vitalnih znakova, laboratorijskih rezultata, radioloških dijagnostičkih nalaza i postojećih trauma skorova. Površina ispod krive (AUC), osetljivost, specifičnost, tačnost, pozitivna prediktivna vrednost (PPV) i negativna prediktivna vrednost (NPV)

korišćene su za obuku i evaluaciju ML algoritama (Logistička regresija, Slučajna šuma, Mašine potpornih vektora, XGBoost i LightGBM). Model je upoređen s tradicionalnim skoring sistemima korištenjem DeLong testa.

Rezultati: Od 1500 pacijenata, 50,73% (n = 761) je zahtevalo prijem u Intenzivnu negu. Razvijeni ML model imao je AUC od 0,999, sa osetljivošću od 99,22%, specifičnošću od 99,69% i tačnošću od 99,56%, što daleko nadmašuje tradicionalne sisteme bodovanja. Najjači prediktori prijema u intenzivnu negu bili su dob, nivo laktata, RTS, sistolni krvni pritisak, frekvencija disanja i zasićenost kiseonikom. Nije uočena značajna razlika u stopama prijema u intenzivnu negu između grupa sa tupom i penetrirajućom traumom, što ukazuje na to da se sam mehanizam traume ne bi trebao koristiti kao prediktor.

Zaključak: Model bodovanja rizika zasnovan na mašinskom učenju pokazao je bolje prediktivne performanse od tradicionalnih sistema bodovanja traume u identifikaciji pacijenata sa traumom kojima je potreban prijem u intenzivnu negu. Integracija ovog modela u tokove rada Urgentnih službi može poboljšati trijažu i negu pacijenata. Međutim, pre kliničke implementacije potrebna je validacija u multicentričnim prospektivnim studijama.

Ključne reči: Mašinsko učenje, Pacijenti s traumom, Prijem u intenzivnu negu, Model bodovanja rizika, Urgentna medicina, Prediktivna analitika.

REFERENCES

1. World Health Organization. *Global status report on road safety 2023*. Geneva: WHO; 2023. Available from: https://www.who.int/publications/i/item/9789240086517.

2. Nathens AB, Cryer HG, Fildes J. The American College of Surgeons Trauma Quality Improvement Program. Surg Clin North Am. 2012; 92(2): 441-54, x-xi. doi: 10.1016/j.suc.2012.01.003.

3. Camilloni L, Giorgi Rossi P, Farchi S, Chini F, Borgia P, Guasticchi G. Triage and Injury Severity Scores as predictors of mortality and hospital admission for injuries: a validation study. Accid Anal Prev. 2010; 42(6): 1958-65. doi: 10.1016/j.aap.2010.05.019.

4. Galvagno SM Jr, Massey M, Bouzat P, Vesselinov R, Levy MJ, Millin MG, et al. Correlation between the Revised Trauma Score and Injury Severity Score: implications for prehospital trauma triage. Prehosp Emerg Care. 2019; 23(2): 263-70. doi: 10.1080/10903127.2018.1489019.

5. Fuller G, Pandor A, Essat M, Sabir L, Buckley-Woods H, Chatha H, et al. Diagnostic accuracy of prehospital triage tools for identifying major trauma in elderly injured patients: A systematic review. J Trauma Acute Care Surg. 2021; 90(2): 403-12. doi: 10.1097/TA.0000000000003039.

6. Sasser SM, Hunt RC, Faul M, Sugerman D, Pearson WS, Dulski T, et al. Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. MMWR Recomm Rep. 2012; 61(RR-1): 1-20.

7. Rajkomar A, Dean J, Kohane I. Machine Learning in medicine. N Engl J Med. 2019; 380(14): 1347-58. doi: 10.1056/NEJMra1814259.

8. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019; 25(1): 44-56. doi: 10.1038/s41591-018-0300-7.

9. Weidman AC, Malakouti S, Salcido DD, Zikmund C, Patel R, Weiss LS, et al. A machine learning trauma triage model for critical care transport. JAMA Netw Open. 2025; 8(6): e259639. doi: 10.1001/jamanetworkopen.2025.9639. Erratum in: JAMA Netw Open. 2025; 8(7): e2525559. doi: 10.1001/jamanetworkopen.2025.25559.

10. Shillan D, Sterne JAC, Champneys A, Gibbison B. Use of machine learning to analyse routinely collected intensive care unit data: a systematic review. Crit Care. 2019; 23(1): 284. doi: 10.1186/s13054-019-2564-9.

11. Johnson AE, Ghassemi MM, Nemati S, Niehaus KE, Clifton DA, Clifford GD. Machine learning and decision support in critical care. Proc IEEE Inst Electr Electron Eng. 2016; 104(2): 444-66. doi: 10.1109/JPROC.2015.2501978.

12. Stewart J, Freeman S, Eroglu E, Dumitrascu N, Lu J, Goudie A et al. Attitudes towards artificial intelligence in emergency medicine. Emergency medicine Australasia : EMA. 2024; 36(2): 252-65. doi: 10.1111/1742-6723.14345.

13. MacIntyre MR, Cockerill RG, Mirza OF, Appel JM. Ethical considerations for the use of artificial intelligence in medical decision-making capacity assessments. Psychiatry Res. 2023; 328: 115466. doi: 10.1016/j.psychres.2023.115466.

14. Andishgar A, Rismani M, Bazmi S, Mohammadi Z, Hooshmandi S, Kian B, et al. Developing practical machine learning survival models to identify high-risk patients for in-hospital mortality following traumatic brain injury. Sci Rep. 2025; 15(1): 5913. doi: 10.1038/s41598-025-89574-0.

15. Gonem S, Taylor A, Figueredo G, Forster S, Quinlan P, Garibaldi JM, et al. Dynamic early warning scores for predicting clinical deterioration in patients with respiratory disease. Respir Res. 2022; 23(1): 203. doi: 10.1186/s12931-022-02130-6.

16. Fernandes M, Mendes R, Vieira SM, Leite F, Palos C, Johnson A, et al. Predicting Intensive Care Unit admission among patients presenting to the emergency department using machine learning and natural language processing. PLoS One. 2020; 15(3): e0229331. doi: 10.1371/journal.pone.0229331.

17. Cobbe J, Lee MSA, Singh J. Reviewable automated decision-making: a framework for accountable algorithmic systems (December 17, 2020). ACM Conference on Fairness, Accountability, and Transparency (FAccT '21), March 1–10, 2021, Virtual Event, Canada, Available at SSRN: https://ssrn.com/abstract=3772964.

18. Kirubarajan A, Taher A, Khan S, Masood S. Artificial intelligence in emergency medicine: A scoping review. J Am Coll Emerg Physicians Open. 2020; 1(6): 1691-702. doi: 10.1002/emp2.12277.

19. Sendak MP, D'Arcy J, Kashyap S, Gao M, Nichols M, Corey K, et al. A path for translation of machine learning products into healthcare delivery. EMJ Innov. 2020; 10: 19-00172. doi: 10.33590/emjinnov/19-00172.

Correspondence to/Autor za korespondenciju
Erkan Boğa
Institutional Address: Fatih Mahallesi, 19 Mayıs Bulvarı, No:59, Esenyurt/İstanbul, Turkey
Institutional Email: erkan.boga@saglik.gov.tr
Personal Email: drerkanboga@gmail.com
ORCID ID: 0000-0001-6802-6301

***How to cite this article**:* Boga E. Early detection of trauma patients requiring intensive care in the emergency department: a next-generation risk score model. Sanamed. 2025; 20(2): 147-155. doi: 10.5937/sanamed0-58683.

SANAMED
2025; 20(2): 157–167
ISSN-1452-662X

DOI: 10.5937/sanamed0-57055
UDK: 616.8-009.832-053.2; 616.12-073-053.2
ID: 174824969
Original article

CARDIOLOGICAL DIAGNOSTIC APPROACH TO CHILDREN WITH CONSCIOUSNESS DISORDERS

Mišanović Verica,[1] Viteškić Selma,[2] Begić Nedim,[1] Mulać Ahmed,[1] Dizdar Selma,[1] Anić Duško,[1] Terzić Sabina,[1] Kovačević Prstojević Jelena,[3] Čengić Adisa,[1] Begić Zijo,[1] Užičanin Sajra,[1] Međedović Edin,[4] Selimović Amina[1]

[1] University Clinical Center Sarajevo, Pediatric Clinic, Sarajevo, Bosnia and Herzegovina
[2] Primary Health Care Center of Sarajevo Canton, Sarajevo, Bosnia and Herzegovina
[3] University Clinical Center Sarajevo, Clinic of Urology, Sarajevo, Bosnia and Herzegovina
[4] University Clinical Center Sarajevo, Clinic of Gynecology and Obstetrics, Sarajevo, Bosnia and Herzegovina

Primljen/Received: 25. 02. 2025. Prihvaćen/Accepted: 12. 07. 2025. Published online first 18. 07. 2025.

Abstract: Introduction: Syncope is one of the most common reasons for seeking medical attention in the pediatric population. The underlying etiology ranges from benign causes to potentially life-threatening conditions.

Objective: This cross-sectional retrospective study aimed to cardiologically evaluate children presenting with syncope and identify potential predictive parameters for cardiogenic syncope, the most dangerous type of syncope.

Patients and Methods: Data from 100 children aged 6 to 18 years who presented with syncope were retrospectively collected from medical records at the Pediatric Clinic of the Clinical Center of the University of Sarajevo between January 1, 2021, and December 31, 2022. Binary logistic regression was used to examine the predictive significance of the studied parameters.

Results: Of the 100 children with documented syncope, 71.0% were girls, with the peak incidence of syncope episodes occurring at age 15. There were no statistically significant differences in height, weight, or BMI between boys and girls. The most common cardiac diagnosis was sinus arrhythmia, while headache was the most frequent non-cardiac symptom. Seventy-three percent of patients experienced more than one syncope episode, with the highest percentage occurring at school. Prodromal symptoms were present in 87% of cases, whereas palpitations and chest pain prior to syncope were reported in 10% and 12% of cases, respectively. Among the 49 patients with abnormal ECG findings, 29% had sinus arrhythmia and 25% had incomplete right bundle branch block. The most common echocardiographic finding was mild pulmonary valve regurgitation, which is considered a physiological variant. Of all studied parameters, only EEG demonstrated significant predictive value for cardiogenic syncope ($p = 0.035$, $EXP(B) = 2.99$).

Conclusion: EEG findings have predictive significance for cardiogenic syncope in children. A borderline EEG increases the odds of cardiogenic syncope by approximately threefold.

Keywords: syncope, pediatric population, EEG, echocardiography, predictive parameters, clinical characteristics, electrocardiography.

INTRODUCTION

With the advancement of modern medicine, there has been significant progress in diagnosing and understanding the pathophysiological mechanisms underlying disorders of consciousness in adults. However, diagnosing and managing disorders of consciousness in children continue to pose challenges for clinicians and researchers (1, 2). This difficulty is partly due to the limited ability of the pediatric population to report on their consciousness (3 ,4).

Consciousness can be divided into two domains. The first domain is "wakefulness," referring to the level of consciousness or alertness. This component can be somewhat quantified using well-designed and universal methods that grade the level of consciousness. The second domain of consciousness, which is more resistant to quantification, is "awareness," referring to the content of consciousness. There is no objective way to quantify this component of consciousness. Disorders of

these two domains of consciousness are heterogeneous and numerous, with qualitative disorders falling more within the domain of psychology and psychiatry.

Syncope represents a transient loss of consciousness due to cerebral hypoperfusion, which can be benign but also indicative of more serious health problems. Syncope is a common problem in pediatrics. According to data from some hospitals, syncope is the most common paroxysmal non-epileptic event causing changes in consciousness in children (5).

The minimum duration of sudden cerebral blood flow reduction that causes syncope is 6 to 8 seconds. Syncope occurs when blood flow to the brain is compromised, resulting in symptoms such as nausea, dizziness, changes in visual fields, and ultimately loss of consciousness. Circulation does not necessarily need to be compromised for syncope to occur; sometimes the problem is a lack of oxygen or glucose in the blood.

Causes of inadequate blood flow to the brain can be different, and the most practical classification of syncope is based on etiology: neurological, orthostatic, and cardiovascular. In the diagnosis of syncope, it is essential to start with a well-constructed medical history, both personal and family. The physical examination that follows this initial step is perhaps the most important part of the diagnostic process as it can help exclude potentially life-threatening conditions. In addition, blood tests are necessary, paying attention to parameters related to red blood cells, electrolytes, and blood glucose levels (2).

An ECG (Electrocardiogram) is a necessary step in diagnostics and treating patients presenting with syncope, and in cases of suspected cardiac etiology of these syncope episodes, it is essential to continue with tests including echocardiography, continuous monitoring of cardiac rhythm, and possibly even cardiac enzymes. Ultimately, the tilt table test is indicated if patients present with recurrent episodes of syncope in the absence of a clear cardiac reason, in suspected vasovagal syncope, and orthostatic hypotensive syncope.

Although a wide range of diagnostic methods and tests are available for the diagnostic treatment of syncope, up to 45% of patients are discharged without a diagnosis. This speaks to the complexity of syncope, which requires multimodal approaches to treatment (6).

Neurological syncope is also known as neurocardiogenic or reflex syncope, and it includes vasovagal and situational syncope. Both occur due to inadequate cardiovascular reflexes that can lead to hypotension, bradycardia, or reduced cardiac output. The most common form of syncope in pediatric patients is vasovagal syncope. It is more common in children over 10 years old, with a predominance of females. It occurs after increased activation of the parasympathetic nervous system over the sympathetic nervous system, usually after exposure to a trigger. These triggers can be emotional stress, phobias, or trauma. Conditions that favor the occurrence of this response to a trigger are hunger and exhaustion. Before the onset of vasovagal syncope, children experience prodromal symptoms such as abdominal pain, dizziness, flushes of heat, or tunnel vision. Situational syncope occurs by a similar mechanism. The trigger is reduced preload, which causes stimulation of cardiac mechanoreceptors and subsequent activation of the parasympathetic nervous system. This happens in certain situations such as sneezing, coughing, micturition, defecation, after exercise, or lifting heavy weights. The diagnosis of neurological syncope is clinical and is based on the exclusion of other causes. Treatment is supportive, providing guidance and advice to prevent its occurrence. It is recommended to increase fluid and salt intake and assume a supine position in case of the onset of prodromal symptoms (2).

Orthostatic syncope occurs due to inadequate functioning of blood redistribution mechanisms and subsequent blood pressure drop upon changing from a sitting or supine position to a standing position. Normally, upon such a change in position, there is blood redistribution to the legs and splanchnic circulation. This causes decreased preload, and consequently, stroke volume, which activates a series of reflexes that increase sympathetic activity and normalize blood pressure. In cases where reflex mechanisms are compromised or hypovolemia is present, orthostatic syncope will occur. The diagnosis of orthostatic syncope is based on measuring orthostatic vital signs. There are discrepancies in defining abnormal vital signs that will be considered “positive.” However, the most accepted parameters for the diagnosis of orthostatic hypotension are a drop in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mm Hg, measured within 3 minutes of changing from supine to standing position. The most common cause of orthostatic syncope in children is hypovolemia. In children, changes in blood pressure do not have a significant impact because they are not as pronounced. Instead, an increase in heart rate of over 20 beats per minute upon changing from supine to standing position is sensitive enough to detect hypovolemia. The diagnosis is made through a series of tests aimed at excluding other causes. A complete blood count may be done (to detect anemia), thyroid hormone levels (to detect thyrotoxicosis), or an ECG (to exclude cardiac arrhythmias). Finally, the tilt-table test is performed to confirm intolerance to postural changes (7).

The treatment is supportive and largely overlaps with the treatment of neurologically induced syncope.

Sufficient hydration and salt intake, education, and regular physical activity represent first-line treatments.

Cardiac syncope can be divided into two groups: obstructive and arrhythmogenic. Obstructive syncope corresponds to structural causes, while arrhythmogenic syncope corresponds to non-structural causes, as described in two studies (8).

Obstructive or structural causes can arise from intrinsic and extrinsic reasons. Intrinsic causes involve congenital heart diseases, aortic stenosis, or hypertrophic cardiomyopathy. Extrinsic causes act on the heart and include pulmonary hypertension or embolism.

Arrhythmogenic or non-structural syncope arises from disturbances in cardiac rhythm.

The most common structural causes of cardiovascular syncope are ischemic cardiomyopathy due to congenital anomalies of the coronary arteries, aortic stenosis, non-ischemic dilated cardiomyopathy, and hypertrophic obstructive cardiomyopathy.

It is not necessary for the heart to be morphologically altered for syncope to occur. Arrhythmias, defined as deviations from the normal rhythm of cardiac activity, can be divided into tachyarrhythmias and bradyarrhythmias, as well as a separate group of congenital channelopathies (8, 9).

There are numerous studies investigating these phenomena in children, but this is not the case in Bosnia and Herzegovina. Careful assessment and diagnostic evaluation of children presenting with this type of consciousness disorder can reveal much and potentially provide answers to questions crucial for further treatment of these children.

Cardiological evaluation is an essential aspect of conducting diagnostic assessments of children with consciousness disorders. Cardiologically induced syncope represents the most dangerous type of syncope, indicating some form of cardiac issue. This study recognizes this fact and is designed to evaluate the presence of possible cardiac or other diseases and to investigate the presence of predictors that could aid in diagnosing cardiologically induced syncope. This study has general and specific objectives.

The general objective is to evaluate cardiac and other findings in children with consciousness disorders aged 6 to 18 years.

Aims of the paper:

1. To examine the sociodemographic characteristics of children aged 6 to 18 years with consciousness disorders.

2. To individually assess predictors for syncope in children who have experienced consciousness disorders.

3. To determine which predictor is most dominant in consciousness disorders among children.

PATIENTS AND METHODS

This is a cross-sectional retrospective study aimed at evaluating the medical histories, anamnesis, and other results of diagnostic tests of children presenting with syncope episodes. Data were collected from the medical records of patients hospitalized at the Pediatric Clinic of the University Clinical Center in Sarajevo from January 2021 to December 2022.

Among all hospitalized children, subjects younger than 6 years old and those without complete findings and measured parameters relevant to this study were excluded. One hundred patients who met all criteria were included in the analysis.

In this study, we evaluated the medical histories, anamnesis, and results of various diagnostic tests in children presenting with syncope episodes. We collected demographic information including age, gender, weight, height, and body mass index (BMI), as these factors may influence the incidence and underlying causes of syncope. The medical history of each participant was examined carefully, with particular attention to family history of consciousness disorders, heart diseases, and sudden death. Comorbidities such as epilepsy or neurological disorders, which could potentially contribute to syncope, were also recorded.

Clinical parameters included blood pressure measurements (both systolic and diastolic), heart rate, and cardiac auscultation to identify any abnormalities, such as innocent systolic murmurs commonly found in children.

We included a variety of diagnostic tests to help determine the cause of syncope. These tests included:

1. Anamnestic data.

2. Blood pressure.

3. Heart rate.

4. ECG (Electrocardiogram) – The ECG was used to assess for conditions like sinus arrhythmia, incomplete right bundle branch block, and other abnormal findings that could indicate arrhythmias or other cardiac abnormalities.

5. Echocardiography– Performed to evaluate pulmonary valve regurgitation, which is a normal finding in children, as well as to screen for any structural heart abnormalities that could contribute to syncope episodes.

6. Tilt Table Testing – Used to assess the presence of vasovagal syncope and evaluate whether the syncope episodes had a cardiac origin.

7. Holter Monitoring – Involved continuous monitoring of the heart's electrical activity to detect ar-

rhythmias or other abnormal heart rhythms that could be linked to syncope.

8. EEG (Electroencephalogram) – Used to detect signs of cerebral hypoperfusion, which may suggest that the syncope is related to a neurological origin. EEG results were also assessed for borderline readings, which were found to be predictive of syncope related to cardiac disorders.

9. Blood Tests – If applicable, blood tests were conducted to rule out any metabolic or electrolyte imbalances that could contribute to the occurrence of syncope.

10. Each of these parameters was carefully evaluated to determine the underlying cause of syncope in our sample. The data were collected and analyzed to help differentiate between **cardiac** and **non-cardiac** causes of syncope in children, with particular emphasis on factors such as arrhythmias, structural heart diseases, and neurological factors.

Statistical Analysis

Upon completion of the study, statistical data processing was conducted. The statistical analysis of the obtained data was performed using SPSS software for Windows (version 19.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, USA).

To determine the distribution of continuous variables, the Kolmogorov-Smirnov test was used (for samples larger than 50 subjects). For variables without statistically significant deviations from a normal distribution, mean values were presented as arithmetic means and standard deviations (SD). Parametric tests (one-sample t-test and paired t-test) were applied to compare these variables to reference values and repeated measurements, as well as to analyze trends in changes.

Variables showing statistically significant deviations from a normal distribution were presented using the median and interquartile range (25th–75th percentile). Non-parametric tests (Wilcoxon rank-sum test, Friedman test for repeated measurements) were used to compare these variables to reference values, repeated measurements, and trends in changes.

Logistic regression was employed to examine how independent predictor variables in the study influenced the outcome, specifically whether syncope was cardiologically induced or not.

A significance level of $\alpha = 0.05$ was used to determine statistical significance. Decisions regarding acceptance or rejection of hypotheses in the respective tests were based on the p-value (if $p \geq \alpha$, the hypothesis was accepted; if $p < \alpha$, the hypothesis was rejected).

RESULTS

In this sample, the girls had a mean age of 14.0 ± 2.7 years, while the boys had a mean age of 13.5 ± 2.9 years. There was no statistically significant difference in age between the groups ($p = 0.390$).

The average height of girls in this sample was 160.95 ± 11.8 cm, and the average height of boys was 161.24 ± 18.67 cm. There was no statistically significant difference in height between girls and boys ($p = 0.920$).The average weight of girls in this sample was 54.65 ± 14.78 kg, and the average weight of boys was 56.40 ± 19.15 kg. There was no statistically significant difference in weight between girls and boys ($p = 0.625$).The average BMI for girls in this sample was 20.76 ± 3.95 kg/m², and for boys, it was 21.01 ± 4.04 kg/m². There was no statistically significant dif-

Table 1. *Sexual structure of the sample*

	Frequency	Percentage	Cumulative Percentage
Female	71	71.0	71.0
Male	29	29.0	100.0
Total	100	100.0	

Table 2. *Average values of BMI, height and weight among the subjects*

	Sex	n	Mean value	Standard deviation (SD)	Standard error (SE)	p
Height (cm)	Female	71	160.95	11.786	1.399	0.920
	Male	29	161.24	18.671	3.467	
Weight (kg)	Female	71	54.65	14.786	1.755	0.625
	Male	29	56.40	19.158	3.557	
BMI (kg/m²)	Female	71	20.766	3.9583	0.4698	0.782
	Male	29	21.010	4.0480	0.7517	

Table 3. *Family history of consciousness disorders, heart diseases, and sudden death*

Family history	Outcome	Number (n)	Percentage (%)
Positive family history of the consciousness disorders	No	98	98.0
	Yes	2	2.0
Positive family history of heart disorders	No	83	83.0
	Yes	17	17.0
Positive family history of sudden death	No	98	98.0
	Yes	2	2.0

Table 4. *Age when the first syncope occurred*

	N	Min	Max	Mean value	Standard deviation (SD)
Age when the first syncope occurred	100	2	18	13.00	3.301

Table 5. *Blood pressure and heart rate values in the examined sample*

Variable		Systolic BP		Diastolic BP		Heart rate		
	Value	Number (n)	Percentage %	Number (n)	Percentage%	Value	Number (n)	Percentage %
	Low	25	25.0	23	23.0	Low	5	5.0
	Normal	73	73.0	64	64.0	Normal	67	67.0
	High	2	2.0	13	13.0	High	28	28.0

ference between the BMI values of girls and boys (p = 0.782).

A positive family history of consciousness disorders was present in 2.0% of the children, a positive family history of heart diseases in 17.0%, and a positive family history of sudden death in 2.0% (Table 3).

In addition to cardiological conditions, non-cardiological diseases were also examined. No non-cardiological disease was recorded in 45 children (45.0%), meaning that more than half (55.0%) of the children with documented syncope had at least one non-cardiological condition.

A total of 40 different non-cardiological diseases were recorded among the patients in this sample. The data show that the most common non-cardiological symptom among children with consciousness disorders was headache.

The earliest recorded age at which the first consciousness disorder occurred in these patients was 2 years, and the latest age was 18 years. The average age at which patients experienced a consciousness disorder was 13.0 ± 3.30 years (Table 4, Figure 1).

Normal systolic and diastolic blood pressure was observed in 73.0% and 64.0% of the subjects, respectively. Decreased systolic blood pressure was recorded

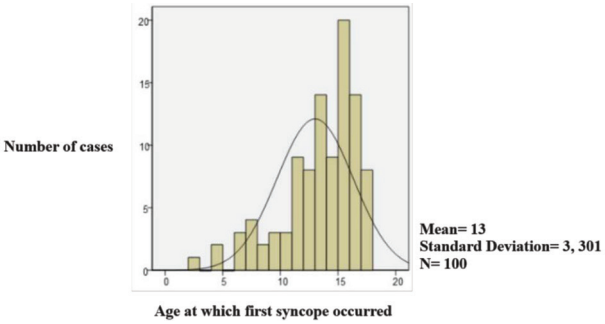


Figure 1. *Age distribution of subjects with consciousness disorders*

in 25.0% of the subjects, and decreased diastolic blood pressure in 23.0%. Elevated systolic blood pressure was noted in 2.0% of the children, while elevated diastolic blood pressure was seen in 13.0%.Normal heart rate was recorded in 67.0% of the subjects. Decreased heart rate was observed in 5.0%, and increased heart rate in 28.0% of the children (Table 5).

The average values of systolic blood pressure were 113.49 ± 13.42 mmHg (Figure 2).

The average values of diastolic blood pressure were 67.52 ± 10.18 mmHg.

The average heart rate was 94.66 ± 17.36 beats per minute (Figure 4).

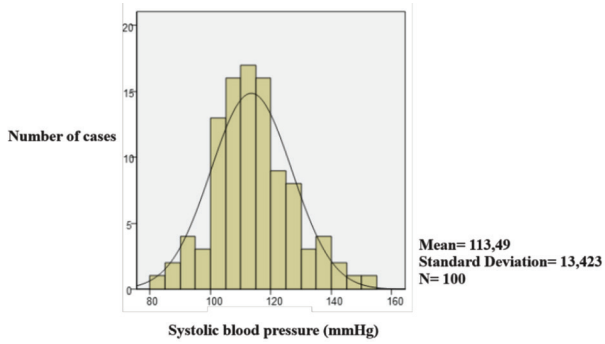


Figure 2. *Distribution of the systolic blood pressure value*

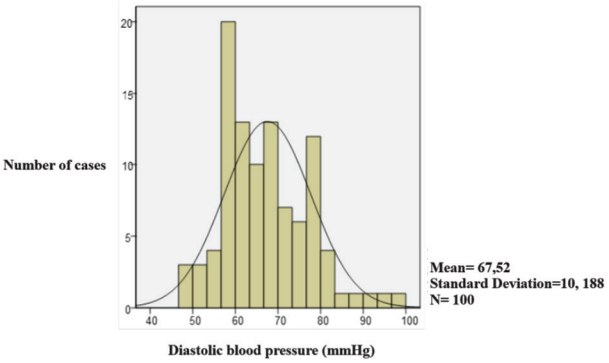


Figure 3. *Distribution of the diastolic blood pressure*

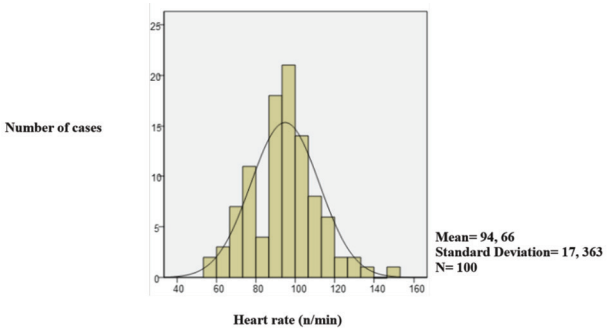


Figure 4. *Distribution of the heart rate*

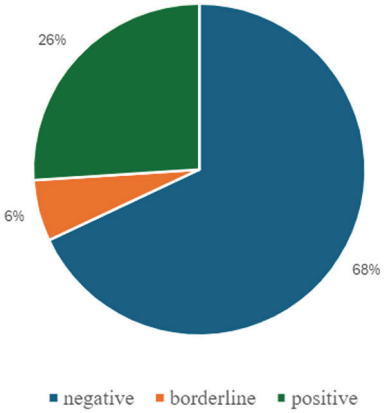


Figure 5. *Tilt table test*

Table 6. *The impact of sex, age, height, weight, and BMI on cardiologically caused syncope*

	B	S.E.	Wald	df	p.	Exp(B)
Sex	-0.378	0.474	0.638	1	0.425	0.685
Age	0.174	0.128	1.869	1	0.172	1.190
Height (cm)	-0.110	0.077	2.040	1	0.153	0.896
Weight (kg)	0.086	0.111	0.593	1	0.441	1.089
BMI (kg/m²)	-0.214	0.294	0.533	1	0.465	0.807
Constant	15.951	11.841	1.814	1	0.178	8459691.848

Table 7. *The impact of positive family history of consciousness disorders, heart diseases, and sudden death on cardiologically caused syncope*

		B	S.E.	Wald	df	p	Exp(B)
Step 1(a)	**Positive family history of consciousness disorders**	20.392	28420.722	0.000	1	0.999	718.511
	Positive family history of heart disorders	0.544	0.640	0.722	1	0.395	1.723
	Positive family history of sudden death	-0.811	1.537	0.279	1	0.598	0.444
	Constant	0.267	0.221	1.449	1	0.229	1.306

Out of 100 subjects, the tilt table test was normal in 68 (68.0%), borderline in 6 (6.0%), and positive in 26 (26.0%) (Figure 5).

Using binary logistic regression, we examined, in the following tables, the impact of independent predictors—variables in the study—on the outcome, specifically whether syncope was cardiologically caused or not.

The predictive significance of sex, age, height, weight, and BMI on whether syncope was cardio-

Table 8. *The impact of the presence of cardiological and non-cardiological diseases on cardiologically caused syncope*

		B	S.E.	Wald	df	p	Exp(B)
Step 1(a)	**Cardiac diseases**	0.517	0.520	0.988	1	0.320	1.676
	Non-Cardiac diseases	-0.764	0.422	3.275	1	0.070	0.466
	Constant	0.689	0.337	4.173	1	0.041	1.993

Table 9. *The Impact of the age of first syncope, number of syncopes, palpitations, chest pain, other prodromal symptoms, and the situation in which it occurred on cardiologically caused syncope*

	B	S.E.	Wald	df	p	Exp(B)
Age of the first syncope	-0.080	0.070	1.330	1	0.249	0.923
Number of syncopes	0.858	0.500	2.950	1	0.086	2.359
Palpitations before syncope	1.285	1.288	0.996	1	0.318	3.615
Pain chest before syncope	-1.699	1.193	2.029	1	0.154	0.183
Prodromal symptoms before syncope	-0.883	0.701	1.586	1	0.208	0.414
Situation in which syncope occurred	-0.059	0.057	1.046	1	0.306	0.943
Constant	1.954	1.242	2.473	1	0.116	7.055

Table 10. *The impact of systolic blood pressure, diastolic blood pressure, and heart rate on cardiologically caused syncope*

	B	S.E.	Wald	df	Sig.	Exp(B)
Systolic BP	-0.007	0.020	0.126	1	0.722	0.993
Diastolic BP	-0.032	0.027	1.430	1	0.232	0.968
Heart rate	-0.017	0.012	1.828	1	0.176	0.984
Constant	4.938	2.279	4.693	1	0.030	139.502

logically caused (yes/no) was examined using binary logistic regression. None of these predictors showed a significant impact, with $p > 0.05$ (Table 6).

The predictive significance of a positive family history of consciousness disorders, heart diseases, and sudden death on whether syncope was cardiologically caused (yes/no) was examined using binary logistic regression. None of these predictors showed a significant impact, with $p > 0.05$ (Table 7).

The predictive significance of the presence of cardiological and non-cardiological diseases on whether syncope is cardiologically caused (yes/no) was examined using binary logistic regression. None of these predictors showed a significant impact, with $p > 0.05$ (Table 8).

The predictive significance of the age of first syncope, number of syncopes, palpitations, chest pain, other prodromal symptoms, and the situation in which it occurred on whether syncope is cardiologically caused (yes/no) was examined using binary logistic regression. Ninety patients had palpitations before syncope, and eighty-seven patients had prodromal symptoms. None of the listed predictors had a significant impact, with $p > 0.05$ (Table 9).

The most prevalent cardiological condition was cardiac arrhythmia, observed in 11 children, accounting for 11.0% of the total number of children in the sample and 50.0% of those with any cardiological disease. The other causes were stenocardia in 2 patients and congenital heart diseases (after surgical corrections) in 5 patients.

Regarding echocardiography, 3 patients had trivial tricuspid regurgitation, 2 had trivial mitral regurgitation, and 12 patients had mild regurgitation of the pulmonary valve, which is considered a physiological finding. Additionally, 1 patient had a surgically corrected atrioventricularseptal defect (AVSD), 1 had a tumorous mass in the right ventricle, 1 had mitral valve prolapse, and 1 had an atrial septal defect (ASD).

The predictive significance of systolic blood pressure, diastolic blood pressure, and heart rate on whether syncope is cardiologically caused was examined using binary logistic regression. None of the listed predictors had a significant impact, with $p > 0.05$ (Table 10).

The predictive significance of the tilt table test and Holter ECG on whether syncope is cardiologically caused (yes/no) was examined using binary logistic regression. Neither of these predictors showed a significant impact, with $p > 0.05$ (Table 11).

Table 11. *The impact of Tilt table test and holter ECG on cardiologically caused syncope*

	B	S.E.	Wald	df	Sig.	Exp(B)
Tilt table test	0.108	0.238	0.204	1	0.651	1.114
Holter ECG	18.291	10524.227	0.000	1	0.999	990.929
Constant	0.232	0.247	0.879	1	0.348	1.261

Table 12. *The predictive significance of EEG findings on cardiologically caused syncope*

	B	S.E.	p	Exp(B)	95,0% C.I.forEXP(B)	
					Lower	Upper
EEG	1.096	0.520	0.035	2.991	1.079	8.297
Constant	0.108	0.233	0.642	1.114		

Table 13. *The relationship between EEG and cardiologically caused syncope*

			EEG		Total
			Normal	Borderline	
Cardiac syncope	**no**	Number	35	6	41
		%	85.4	14.6	100,0
	yes	Number	39	20	59
		%	66.1	33.9	100.0
Total		Number	74	26	100
		%	74.0	26.0	100.0

The significance of EEG findings (normal or borderline) on whether syncope is cardiologically caused (yes/no) was examined using binary logistic regression. EEG was found to be a significant predictor with $p = 0.035$ and $EXP(B) = 2.99$ (Table 12).

For each borderline EEG reading, the odds of syncope being cardiologically caused are approximately three times higher in our sample. In the broader population, this odds ratio ranges from 1 to 8 times.

A "borderline EEG" in children refers to an electroencephalogram (EEG) result that shows subtle, non-specific, or mildly abnormal findings.

The chi-square test of independence showed an association between EEG and syncope with $X^2 = 4.66$, $p = 0.031$. Among the 41 subjects who did not have cardiologically caused syncope, 35 (85%) had a negative EEG and 6 (14.6%) had a positive EEG. Among the 59 subjects with cardiologically caused syncope, 20 (33.9%) had a borderline EEG and 39 (66.1%) had a negative EEG.

DISCUSSION

Syncope is a common issue in pediatric populations and has been extensively studied over the years. According to data from several studies (10), approximately 20% of boys and 40% of girls experience syncope episodes by the age of 18. Our study supports these findings, with 71.0% of syncope patients being female and 29.0% male, showing a higher prevalence of syncope in females.

Two other studies (11, 12) also report a similar gender distribution in syncope prevalence. Another study (13) indicates a higher incidence of syncope among female adolescents compared to males (31.72% vs. 26.25%, $P < 0.05$). Our results align with these, with 71.0% of patients being female. The peak incidence at age 15 further corroborates previous research done by other authors (14).

Despite exploring potential predictors such as gender, age, weight, height, and BMI, our logistic regression analysis found no statistically significant impact on syncope of cardiac origin. However, BMI has been noted in other studies (15) as a potential risk factor for vasovagal syncope. Family history of cardiac diseases did not predict syncope in our study, contrasting with earlier research (16) which reported a positive correlation in 17% of cases. Most participants in our study did not have cardiac conditions (78.0%), with arrhythmias being the most common among those who did.

Our findings differ from previous studies (17, 18), which reported lower rates of cardiac involvement in pediatric syncope. Prodromal symptoms such as dizziness were common but were not predictive of cardiac syncope in our sample. Cardiac auscultation was mostly normal (71.0%), with innocent systolic murmurs widely observed. Blood pressure readings were normal in most cases (73.0% systolic, 64.0% diastolic), consistent with the known association of low blood pressure with vasovagal syncope. A large portion of our participants (78.0%) had no cardiac abnormali-

ties, with arrhythmias being the most frequent finding among those with cardiac conditions.

However, our results diverge from those of Nandini et al, who observed a higher rate of structural heart diseases as the main cause of syncope in children while arrhythmias were less prevalent. This discrepancy might be due to differences in study populations or diagnostic criteria (19).

Arrhythmias in children are increasingly recognized and differ significantly from those in adults (20, 21). In our study, ECG and echocardiogram abnormalities were found in 49.0% and 19.0% of cases, respectively, with sinus arrhythmia and incomplete right bundle branch block common on ECG (both normal pediatric findings), and mild pulmonary valve regurgitation, a normal echocardiographic finding. Tilt table testing and Holter ECG did not predict cardiac syncope in our sample, consistent with the low percentage of abnormal Holter results (4.0%).

Interestingly, EEG showed predictive value for cardiac-related syncope in our study, contrasting with its limited diagnostic value reported elsewhere. EEG findings consistent with cerebral hypoperfusion were seen across syncope types. Despite this, the diagnostic significance of EEG varies among syncope etiologies.

The peak incidence observed at age 15 in our study further aligns with findings by Park et al. which report syncope as being more frequent in adolescents, particularly between 12 and 16 years of age (22).

Among the 100 children studied, 78.0% had no cardiovascular disease, while 22.0% did. Arrhythmias were the most common heart disease in our cohort. A particularly noteworthy finding in our study is the significant predictive value of EEG in diagnosing cardiac syncope, a topic not widely explored previously. While EEG generally has limited value in diagnosing syncope without neurological symptoms, our data suggest that borderline EEG results are strongly associated with cardiac-origin syncope. This contrasts with Dantas et al. (2012), who found EEG useful mainly when neurological involvement was evident. In our population, the odds of cardiac syncope were approximately three times higher in children with borderline EEG findings (23).

CONCLUSION

The study identified syncope episodes peaking at age 15 among girls, with arrhythmia as the predominant cardiac condition. Despite non-cardiac ailments such as headaches being prevalent, most participants had normal cardiovascular parameters,including blood pressure and heart rate. The findings underscore the importance of considering both cardiac and non-cardiac factors in diagnosing and managing syncope in adolescents. Additionally, EEG emerged as a valuable predictor for identifying syncope related to cardiac disorders in children and adolescents aged 6 to 18. These insights highlight the complex nature of syncope etiology and the need for comprehensive diagnostic approaches in clinical practice.

This may reflect the developing brain's greater susceptibility to cerebral hypoperfusion, which can produce transient EEG changes such as generalized slowing or borderline abnormalities. Such findings highlight the importance of considering age-specific physiological responses when interpreting EEG in the context of syncope.

Abbreviations

BMI – Body Mass Index
ECG – Electrocardiogram
ECHO – Echocardiogram
EEG – Electroencephalogram
SD – Standard Deviation
SE – Standard Error
BP – Blood Pressure
AVSD – Atrioventricular septal defect
ASD – Atrial septal defect

Authors' contributions: MV – Supervision and conceptualization of study; **VS**- Writing - review and editing, data collection; Writing - original draft; **BN**-Writing - review and editing; **MA**- Writing - review and editing; **DS**–Conceptualisation; **AD**–Conceptualisation; **TS**–Conceptualisation; **KPJ**–Conceptualisation; **ČA**–Conceptualisation; **BZ** – Involvement in cardiological part of research; **US** – Involvement in neuropediatric pat of research; **ME**– Supervision; **SA** – Supervision.

The author takes full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations.

Authorship Statement

The authors have made substantial contributions to all phases of the study and are able to take public responsibility for the content and results presented in the manuscript.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: This research received no external funding.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

KARDIOLOŠKI DIJAGNOSTIĆKI PRISTUP DECI S POREMEĆAJIMA SVESTI

Mišanović Verica,[1] Viteškić Selma,[2] Begić Nedim,[1] Mulać Ahmed,[1] Dizdar Selma,[1] Anić Duško,[1] Terzić Sabina,[1] Kovačević Prstojević Jelena,[3] Čengić Adisa,[1] Begić Zijo,[1] Užičanin Sajra,[1] Međedović Edin,[4] Selimović Amina[1]

[1] Univerzitetski klinički centar Sarajevo, Pedijatrijska klinika, Sarajevo, Bosna i Hercegovina
[2] Dom zdravlja Kantona Sarajevo, Sarajevo, Bosna i Hercegovina
[3] Univerzitetski klinički centar Sarajevo, Klinika za urologiju, Sarajevo, Bosna i Hercegovina
[4] Univerzitetski klinički centar Sarajevo, Klinika za ginekologiju i akušerstvo, Sarajevo, Bosna i Hercegovina

Uvod: Sinkopa je jedan od najčešćih razloga traženja medicinske pomoći u pedijatrijskoj populaciji. Etiologija može varirati od benigne do potencijalno opasne po život.

Cilj: Cilj ove retrospektivne studije preseka bio je kardiološka evaluacija dece sa sinkopom i otkrivanje potencijalnih prediktornih parametara za kardiološki uzrokovanu sinkopu, koja je najopasniji oblik sinkope.

Učesnici i metode: Podaci o 100 dece uzrasta od 6 do 18 godina koji su se javili sa sinkopom prikupljeni su iz medicinske dokumentacije Pedijatrijske klinike Kliničkog centra Univerziteta u Sarajevu u periodu od 01. 01. 2021. do 31. 12. 2022. Binarnom logističkom regresijom ispitana je prediktivna značajnost parametara koje je ovo istraživanje obuhvatilo.

Rezultati: Od 100 dece sa zabeleženom sinkopom, 71,0% su bile devojčice, a najveći broj epizoda sinkope zabeležen je u dobi od 15 godina. Nije bilo statistički značajne razlike u visini, težini i BMI vrednostima između dečaka i devojčica. Najčešće kardiološko oboljenje bila je sinusna aritmija, dok je najčešći nekardiološki simptom bila glavobolja.Više od jedne epizode sinkope imalo je 73,0% dece, a najveći broj epizoda dogodio se u školi. Prodromalni simptomi su bili prisutni kod 87,0% ispitanika, dok su palpitacije i bol u prsima pre sinkope zabeležene kod 10,0% i 12,0% dece. Od 49 ispitanika koji nisu imali uredan EKG nalaz, 29,0% imalo je sinusnu aritmiju, a 25,0% nepotpuni blok desne grane. Najčešći EHO nalaz kod pacijenata bila je blaga regurgitacija pulmonalne valvule, što se smatra fiziološkim nalazom.Nijedan od ispitivanih parametara nije imao prediktivni značaj za kardiološki uzrokovanu sinkopu osim EEG-a, koji se pokazao kao značajan prediktor ($p = 0,035$, EXP(B) = 2,99).

Zaključak: EEG ima prediktivni značaj za kardiološki uzrokovanu sinkopu, pri čemu je verovatnoća da je sinkopa kardiološkog porekla otprilike tri puta veća kod deteta sa graničnim EEG nalazom.

Ključne reči: Sinkopa, pedijatrijska populacija, EEG, ehokardiografija, prediktivni parametri, kliničke karakteristike, elektrokardiografija.

REFERENCES

1. Zeman A. What in the world is consciousness? Prog Brain Res. 2005; 150: 1-10. doi: 10.1016/S0079-6123(05)50001-3.

2. Grossman SA, Badireddy M. Syncope. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442006/.

3. Singhi P, Saini AG. Syncope in pediatric practice. Indian J Pediatr. 2018; 85(8): 636-40. doi:10.1007/s12098-017-2488-9.

4. McLeod KA. Syncope in childhood. Arch Dis Child. 2003; 88(4): 350-3. doi: 10.1136/adc.88.4.350.

5. Lee M, Sanz LRD, Barra A, Wolff A, Nieminen JO, Boly M, et al. Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. Nat Commun. 2022; 13(1): 1064. doi: 10.1038/s41467-022-28451-0.

6. Ungar A, Sgobino P, Russo V, Vitale E, Sutton R, Melissano D, et al. Diagnosis of neurally mediated syncope at initial evaluation and with tilt table testing compared with that revealed by prolonged ECG monitoring. An analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3). Heart. 2013; 99(24): 1825-31. doi: 10.1136/heartjnl-2013-304399.

7. Jones PK, Shaw BH, Raj SR. Orthostatic hypotension: managing a difficult problem. Expert Rev Cardiovasc Ther. 2015; 13(11): 1263-76. doi: 10.1586/14779072.2015.1095090.

8. Smith PE. If it‘s not epilepsy.. J Neurol Neurosurg Psychiatry. 2001; 70(Suppl 2): II9-14. doi: 10.1136/jnnp.70.suppl_2.ii9.

9. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883-948. doi: 10.1093/eurheartj/ehy037.

10. DiMario FJ Jr, Wheeler Castillo CS. Clinical categorization of childhood syncope. J Child Neurol. 2011; 26(5): 548-51. doi: 10.1177/0883073810384864.

11. Deveau AP, Sheldon R, Maxey C, Ritchie D, Doucette S, Parkash R. Sex differences in vasovagal syncope: a post hoc analysis of the prevention of syncope trials (POST) I and II. Can J Cardiol. 2020; 36(1): 79-83. doi: 10.1016/j.cjca.2019.10.008.

12. Friedman KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac

disease. J Pediatr. 2013; 163(3): 896-901.e1-3. doi: 10.1016/j.jpeds.2013.05.001.

13. Hu E, Liu X, Chen Q, Wang C. Investigation on the incidence of syncope in children and adolescents aged 2-18 years in Changsha. Front Pediatr. 2021; 9: 638394. doi: 10.3389/fped.2021.638394.

14. Ganzeboom KS, Mairuhu G, Reitsma JB, Linzer M, Wieling W, van Dijk N. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. J Cardiovasc Electrophysiol. 2006; 17(11): 1172-6. doi: 10.1111/j.1540-8167.2006.00595.x.

15. Salari N, Karimi Z, Hemmati M, Mohammadi A, Shohaimi S, Mohammadi M. Global prevalence of vasovagal syncope: a systematic review and meta-analysis. Glob Epidemiol. 2024; 7: 100136. doi: 10.1016/j.gloepi.2024.100136.

16. Imes CC, Lewis FM. Family history of cardiovascular disease, perceived cardiovascular disease risk, and health-related behavior: a review of the literature. J Cardiovasc Nurs. 2014; 29(2): 108-29. doi: 10.1097/JCN.0b013e31827db5eb.

17. Yeom JS, Woo HO. Pediatric syncope: pearls and pitfalls in history taking. Clin Exp Pediatr. 2023; 66(3): 88-97. doi: 10.3345/cep.2022.00451.

18. Castro W, Skarin R, Roscelli JD. Orthostatic heart rate and arterial blood pressure changes in normovolemic children. Pediatr Emerg Care. 1985; 1(3): 123-7. doi: 10.1097/00006565-198509000-00004.

19. Madan N, Carvalho KS. Neurological complications of cardiac disease. Semin Pediatr Neurol. 2017; 24(1): 3-13. doi: 10.1016/j.spen.2017.01.001.

20. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015; 12(6): e41-63. doi: 10.1016/j.hrthm.2015.03.029.

21. Begic Z, Begic N, Granov N, Vila H, Berberovic-Hukeljic B, Begic E, et al. Pacemaker implantation in the pediatric population: Bosnian and Herzegovinian experience. Heart and Mind. 2025; 7(2): 111-4. doi: 10.4103/hm.hm_12_22.

22. Park J, Jang SY, Yim HR, On YK, Huh J, Shin DH, et al. Gender difference in patients with recurrent neurally mediated syncope. Yonsei Med J. 2010; 51(4): 499-503. doi: 10.3349/ymj.2010.51.4.499.

23. Dantas FG, Cavalcanti AP, Rodrigues Maciel BD, Ribeiro CD, NapyCharara GC, Lopes JM, et al. The role of EEG in patients with syncope. J Clin Neurophysiol. 2012; 29(1): 55-7. doi: 10.1097/WNP.0b013e318246b589.

Correspondence to/Autor za korespondenciju
Nedim Begić, MD, MA
Clinical Center University of Sarajevo, Pediatric Clinic, Department of Pediatric Gastroenterohepatology and Nutrition
Orcid ID: 0000-0001-5964-2305
e-mail: nedim_begic91@hotmail.com

ORCID ID:
Verica Mišanović – 0000-0002-8800-5003
Nedim Begić – 0000-0001-5964-2305
Ahmed Mulać – 0009-0002-7897-3999
DuškoAnić – 0009-0004-3803-6479
Sabina Terzić – 0000-0003-4917-0142
Zijo Begić – 0000-0002-1863-5755
Edin Međedović – 0000-0003-2357-9580
Amina Selimović – 0000-0002-4914-5468

***How to cite this article**:* Mišanović V, Viteškić S, Begić N, Mulać A, Dizdar S, Anić D,Terzić S, Kovačević Prstojević J, Čengić A, Begić Z, Užičanin S, Međedović E, Selimović A. Cardiological diagnostic approach to children with consciousness disorders. Sanamed. 2025; 20(2): 157-167. doi: 10.5937/sanamed0-57055.

SANAMED
2025; 20(2): 169–174
ISSN-1452-662X

DOI: 10.5937/sanamed0-59707
UDK: 616.89-008.454-08; 616.831-005.1-06
ID: 174832649
Original article

DEPRESSION IN PATIENTS WITH AND WITHOUT POST-STROKE EPILEPSY

Perovic Zlatana,[1] Rosandic Helena[2, 3]

[1] General Hospital Niksic, Neurology Department, Niksic, Montenegro
[2] General Hospital Niksic, Department of Psychiatry, Niksic, Montenegro
[3] Faculty of Philosophy, Department of Psychology, University of Montenegro, Niksic, Montenegro

Primljen/Received: 23. 06. 2025. Prihvaćen/Accepted: 09. 08. 2025. Published online first 19. 08. 2025.

Abstract: **Introduction:** Depression is the most common neuropsychological complication of stroke. It affects quality of life, prolongs hospitalization, and leads to more frequent doctor visits. The incidence of depression after stroke ranges from 18% to 33%. About 6–15% of patients develop epilepsy following stroke. Patients with post-stroke epilepsy tend to experience depression more frequently.

Objective: The aim of this study was to compare the incidence of depression during the first year after stroke in patients who developed epilepsy versus those who did not.

Patients and Method: We tested patients during the first year after stroke, treated at the Department of Neurology, General Hospital Nikšić, Montenegro. Two groups of 60 patients each were assessed: one group with post-stroke epilepsy and the other without epilepsy. Depression was measured using the Hamilton Depression Scale. Statistical analysis included mean values, t-test, and Chi-square test (χ^2). A significance level of $p < 0.05$ was used for all tests.

Results: The incidence of depression after stroke was high among our patients. Depression prevalence in the post-stroke epilepsy group was 55%, while it was 26.7% in the group without epilepsy.

Conclusion: Patients with epilepsy have almost twice the incidence of depression compared to those without epilepsy after stroke ($p < 0.05$). These patients require special monitoring and more frequent follow-ups. Early detection of epilepsy and timely initiation of treatment with appropriate antiepileptic drugs, along with early management of depression, are important to prevent suicide and mortality and to improve quality of life.

Keywords: post-stroke depression, post-stroke epilepsy.

INTRODUCTION

Depression is the most common neuropsychological complication of stroke (STS). Post-stroke depression (PSD) often remains undiagnosed and untreated, despite its significant impact on rehabilitation outcomes and quality of life (1). Patients with PSD have an increased risk of mortality compared to those who do not develop depression after STS. The incidence of PSD is estimated to range from 18% to 33%, with some authors reporting that it occurs in one in three people after STS (2, 3). Most stroke patients experience their first depressive episode within the first few years following the stroke (4). One of the most commonly used scales for assessing depression is the Hamilton Depression Rating Scale (HAM-D) (5).

The association between stroke location and the occurrence of PSD has not been consistently confirmed, but PSD is more frequently observed with lesions in the frontal regions, left hemisphere, and basal ganglia. Independent predictors of PSD development within the first year after stroke include a history of mental disorders, degree of physical disability, and level of social support (6).

Post-stroke epilepsy (PSE) occurs in 6% to 15% of patients. Risk factors for PSE include cortical lesion location, stroke severity, early symptomatic seizures, involvement of the anterior cerebral circulation, and hemorrhagic stroke (7). The highest risk for developing PSE is during the first year, with over 80% of patients developing epilepsy within two years after stroke. The choice of antiepileptic drugs in patients with depression presents a particular challenge, as does the selection of antidepressants in patients receiving antiepileptic treatment (8).

Although PSD and PSE are relatively well-studied individually, few studies have analyzed their as-

sociation, especially in the early post-acute period. The combination of these complications may worsen neurological outcomes, prolong recovery, and require a more complex therapeutic approach (9,10). This study aims to compare the incidence of depression in patients with and without post-stroke epilepsy during the first year after stroke.

PATIENTS AND METHODS

A total of 120 patients diagnosed with stroke and treated at the General Hospital Nikšić in Montenegro were included in the study. The research was conducted during the first year after stroke. The first group consisted of 60 patients who developed epilepsy following the stroke, while the control group consisted of 60 patients with MU who did not experience epileptic seizures.

The inclusion criterion was that at least 14 days had passed since the stroke. Patients with previously diagnosed and treated depression were excluded. In patients with post-stroke epilepsy (PSE), seizures first appeared at least 7 days after the stroke, thereby fulfilling the criteria for late post-stroke epilepsy.

Basic demographic data (age and gender), type of stroke—ischemic or hemorrhagic (intracerebral hemorrhage)—and lesion location (cortical or subcortical) were collected. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and classified as mild (≤ 6 points) or severe (7–21 points).

Depression was assessed using the Hamilton Depression Rating Scale (HAM-D). Based on the score, results were categorized as follows: no depression (0–7 points), mild (8–13 points), moderate (14–17 points), and severe depression (≥ 18 points).

Appropriate descriptive and inferential statistical tests, including mean, t-test, and chi-square test (χ^2-test), were used for data analysis. To compare differences between two independent groups, the nonparametric Mann-Whitney U test was applied. Statistical significance was determined at $p < 0.05$.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of the General Hospital Nikšić. All participants provided informed consent before participation, following oral and written explanations of the study's purpose, procedures, and possible risks.

RESULTS

The average age of patients with depression after MU in the PSE group was M = 69.00 (SD ± 8.97), while patients without PSE were slightly younger on average, M = 66.59 (SD ± 10.52). A t-test for large independent samples showed that this difference was not statistically significant (p = 0.212) (Table 1).

Among stroke patients who developed PSE, depression was more common in men (63.3% vs. 36.7%), whereas in stroke patients without epilepsy, depression was more common in women (56.7% vs. 43.3%) ($p < 0.05$).

PSD was significantly more frequent in patients with PSE compared to those without PSE ($p < 0.005$).

Patients with PSE had significantly higher rates of moderate depression compared to those without PSE (20.0% vs. 8.3%). Severe depression was also significantly more common among post-stroke patients who developed epilepsy compared to those without epilepsy (21.7% vs. 3.3%).

No significant difference was observed in the frequency of PSD between patients with and without PSE in relation to stroke type and lesion location (Table 2).

When analyzing individual items within the HAM-D scale, our results indicate that depressed mood**,** feelings of guilt, and agitation are significantly more frequent in patients with stroke and epilepsy compared to those with stroke without epilepsy (Table 3).

DISCUSSION

In our group of stroke patients who did not develop epilepsy, depression was registered in 26.7% of the subjects (16/60), which is consistent with other studies reporting depression in 20–50% of patients during the first year after stroke (1, 2). Studies with longer follow-up periods have shown that the rate of depression significantly increases (3, 4). However, in our study, patients were followed only for one year after stroke.

In the group of patients who developed post-stroke epilepsy (PSE) during the first year after stroke, the prevalence of depression was almost twice as high – 55% (33/60). Nearly half of these patients had a significant level of depression: 20% had moderate, and 21.7% had severe depression. These findings align with previous studies (10, 11).

Analysis of individual HAM-D items showed that patients with PSE more frequently exhibited depressed

Table 1. *Average age of patients with depression after stroke*

	M	SD	t	df	p
Stroke with EPI	69.00	8.97	1.257	107	0.212
Stroke ohne EPI	66.59	10.52			

Table 2. *Comparative analysis of the frequency of PSD in patients with and without PSE*

		Stroke with epilepsia		Stroke without epilepsia		χ^2	df	p
		N	%	N	%			
Gender	Male	38	63.3%	26	43.3%	4.821	1	***0.028*** *
	Female	22	36.7%	34	56.7%			
	Total	60	100.0%	60	100.0%			
Ischemic stroke	Cortical	25	78.1%	29	63.0%	2.015	1	0.156
	Subcortical	7	21.9%	17	36,9%			
	Total	32	100.0%	46	100.0%			
Hemorrhagic stroke	Cortical	21	75.0%	10	71.4%	0.062	1	0.803
	Subcortical	7	25.0%	4	44.0%			
	Total	28	100.0%	14	100.0%			
Hemisphere	Right	19	31.7%	23	38.3%	0.586	1	0.444
	Left	41	68.3%	37	61.7%			
	Total	60	100.0%	60	100.0%			
Stroke severity (NIHHS)	Severe	38	59.6%	32	62.9%	0.234	1	0.267
	Mild	22	40.4%	28	37.1%			
	Total	60	100.0%	60	100.0%			
HAM-D	Not depressed	27	45.0%	44	73.4%	15.078	3	***0.002*** *
	8-13 (mild)	8	13.3%	9	15.0%			
	14-17 (moderate)	12	20.0%	5	8.3%			
	> 17 (severe)	13	21.7%	2	3.3%			
	Total	60	100.0%	60	100.0%			

Legends: *Statistically Significant Difference; HAM-D – Hamilton Depression Rating Scale; NIHSS – National Institutes of Health Stroke Scale; PSD – post-stroke depression; PSE – post-stroke epilepsy.*

Table 3. *Intergroup comparison based on the Mean score of the HAM-D scale*

HAM-D scale	Mean score		U-value	Z-score	p
	Stroke with epilepsia	Stroke without epilepsia			
Depressed mood	2.6	2.0	5.5	-2.3	***0.019*** *
Feelings of guilt	3.0	1.0	2.5	1.9	***0.023*** *
Suicide	2.1	3.0	9.0	1.3	0.097
Insomnia: early in the night	1.9	2.0	17.0	0.0	0.500
Insomnia: middle of the night	1.2	1.4	10.0	-0.42	0.34
Insomnia: early hours of the morning	2.0	1.0	12.5	0.10	0.46
Work and activities	2.5	3.0	35.0	0.55	0.29
Retardation	1.2	1.4	10.0	-0.42	0.34
Agitation	3.0	1.2	7.5	1.93	***0.031*** *
Anxiety psychic	3.0	1.5	43.0	1.18	0.12
Anxiety somatic	2.3	3.0	42.0	0.36	0.36
Somatic symptoms gastro-intestinal	1.4	1.2	17.0	0.0	0.50
General somatic symptoms	2.0	2.0	26.0	0.11	0.46
Genital symptoms	1.5	2.0	12.5	0.10	0.46
Hypochondriasis	2.5	1.5	12.5	0.10	0.46
Loss of weight	1.7	1.0	5.5	1.36	0.09
Insight	1.5	1.0	5.0	1.46	0.07

Legends: *Statistically Significant Difference, HAM-D - Hamilton Depression Rating Scale

mood, feelings of guilt, and agitation compared to patients without epilepsy. The literature describes an atypical presentation of depressive disorders in individuals with epilepsy, which, alongside depressed mood, includes a pleomorphic pattern of symptoms such as affective disturbances, pronounced agitation, and irritability (10). Therefore, treatment of these patients is complex and requires not only appropriate selection of antidepressants but also mandatory psychotherapy (12).

Recognition and timely treatment of post-stroke depression (PSD) are crucial, given its association with increased risk of suicide, poorer quality of life, and higher treatment costs. Additionally, PSD is linked to an increased risk of recurrent cerebrovascular events, which may further affect mortality after stroke (8, 12).

PSD most commonly develops within the first few months post-stroke, with peak prevalence between 6 and 24 months. However, in some patients, symptoms may persist up to five years after the event (4–12).

Risk factors for depression in patients with epilepsy include older age, lower education level, irregular use of antiepileptic drugs, and presence of anxiety (13, 14). Thus, patients with PSE require increased clinical supervision.

PSD typically lasts from 6 to 24 months, with 5–10% of patients experiencing symptoms beyond two years. Although about half of patients show significant symptom reduction within the first eight weeks, the treatment goal remains complete remission. By six months, approximately 50% achieve remission, and about two-thirds within two years. However, 15–20% of patients do not respond to antidepressant therapy (15).

Diagnosing epileptic seizures in elderly patients can be challenging, as they often cannot clearly describe seizure symptoms. Early recognition of epilepsy is essential for timely initiation of antiepileptic treatment. Special attention is warranted for patients with severe neurological deficits, permanent disability, extensive cortical damage, and hemorrhagic stroke, as they represent a high-risk group for developing PSE (3, 13–19).

Early-onset PSD responds better to treatment within the first year, while remission is significantly less common with late onset (12). Some studies report higher PSD prevalence in women, especially during the first months after stroke, though gender differences tend to diminish over time (16). In our study, depression was more common in women without epilepsy (56.7%), while among patients with PSE, depression was more frequent in men (63.3%). A higher frequency of PSE in males has been confirmed in other studies (17, 18), consistent with our findings.

A meta-analysis by Yang et al. showed a strong association between epilepsy and increased risk of depression. Depression in epilepsy patients can hinder therapy response, worsen the condition, reduce quality of life, and increase suicide risk (19). Patients with stroke and epilepsy exhibit significantly higher rates of depressive mood. Other authors confirm that depression impacts epilepsy control, with more severe depression linked to more severe epilepsy forms. A Turkish study reported that about 30% of epilepsy patients develop moderate to severe depression, indicating high prevalence (20).

A lack of personalized treatment approaches often leads to failure to achieve remission with the first antidepressant. Emerging evidence supports developing decision-making tools to tailor treatment choices to individuals, potentially improving depression outcomes. Identifying depression subtypes, considering symptoms underrepresented in current diagnostic frameworks, is important. While depression severity guides treatment decisions, it is insufficient alone (21).

Individualized care planning that identifies factors contributing to depression, incorporates patient habits and needs, and actively involves patients in goal-setting and treatment planning improves treatment outcomes. Techniques such as problem-solving, motivational interviewing, and behavioral activation have proven effective (22). Psychological support methods encourage active patient participation in care development (8, 10, 22).

CONCLUSION

This study highlights the importance of early detection of depression after stroke. It is equally important to identify depression in all patients with post-stroke epilepsy (PSE) to ensure timely and appropriate treatment, thereby reducing mortality in this population. Early identification of patients at risk for developing post-stroke depression (PSD) may enable targeted preventive measures or prompt initiation of effective antidepressant therapy.

Abbreviations

EPI – Epilepsy
HAM-D – Hamilton Depression Rating Scale
PSD – Post-stroke Depression
PSE – Post-stroke Epilepsy

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study. There are no financial rela-

tionships, employment, consultancy, stock ownership, honoraria, patents, or paid expert testimony that could influence the outcome of the research presented. Furthermore, there are no close relationships, competitive academic agendas, or philosophical biases that might have affected the conduct of the study.

Funding: This study did not receive any external funding.

Ethical Approval and Informed Consent

All subjects included in the study gave informed consent to participate. Participant information was kept anonymous and in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines for the protection of research participants. The study was conducted in accordance with the Declaration of Helsinki. and approved by the Ethics Committee of the General Hospital Nikšić, Montenegro.

Author Contributions & Responsibilities

The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. **Author roles: PZ**: Conceptualisation, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review and editing, Supervision; **RH**: Validation, Formal analysis, Data curation, Writing - original draft, Writing - review and editing, Supervision

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

DEPRESIJA KOD PACIJENATA SA I BEZ EPILEPSIJE NAKON MOŽDANOG UDARA

Perović Zlatana,[1] Rosandić Helena[2, 3]

[1] Opšta bolnica Nikšić, Odeljenje za neurologiju, Nikšić, Crna Gora
[2] Opšta bolnica Nikšić, Odeljenje za psihijatriju, Nikšić, Crna Gora
[3] Filozofski fakultet, Odsek za psihologiju, Univerzitet Crne Gore, Nikšić, Crna Gora

Uvod: Depresija je najčešća neuropsihološka komplikacija moždanog udara. Ona utiče na kvalitet života, produžava dužinu hospitalizacije i zahteva češće posete lekaru. Incidenca depresije nakon moždanog udara kreće se od 18 do 33%. Oko 6–15% pacijenata nakon moždanog udara ima epilepsiju. Pacijenti koji razviju epilepsiju kao posledicu moždanog udara češće imaju depresiju.

Cilj: Cilj naše studije bio je da uporedimo učestalost depresije kod pacijenata tokom prve godine nakon moždanog udara, koji su razvili epilepsiju, sa onima koji nisu imali epilepsiju.

Pacijenti i Metode: Ispitivali smo pacijente tokom prve godine nakon moždanog udara, koji su lečeni na Odeljenju za neurologiju Opšte bolnice Nikšić u Crnoj Gori. Prisustvo depresije testirano je u dve grupe od po 60 pacijenata: jedna grupa je imala epilepsiju nakon moždanog udara, dok druga nije. Testiranje je obavljeno pomoću Hamiltonove skale za depresiju. Za statističku analizu korišćeni su standardni testovi: aritmetička sredina, t-test i hi-kvadrat test (χ^2-test). Statistički značajnim smatran je nivo od 95% ($p < 0,05$).

Rezultati:Učestalost depresije nakon moždanog udara je visoka kod naših pacijenata. Prevalenca depresije kod pacijenata koji su imali epilepsiju nakon moždanog udara iznosi 55%, dok je kod pacijenata bez epilepsije 26,7%.

Zaključak: Pacijenti sa epilepsijom imaju skoro dvostruko veću učestalost depresije u poređenju sa onima koji nemaju epilepsiju nakon moždanog udara ($p < 0,05$). Ovi pacijenti moraju biti pod posebnim nadzorom i češćim kontrolama. Rana detekcija epilepsije i rano započinjanje terapije uz pravilan izbor antiepileptika, kao i rano lečenje depresije, od suštinskog su značaja za prevenciju suicida i smrtnosti kod ovih pacijenata, kao i za poboljšanje kvaliteta života.

Ključne reči: depresija nakon moždanog udara, epilepsija nakon moždanog udara.

REFERENCES

1. Dafer RM, Rao M, Shareef A, Sharma A. Poststroke depression. Top Stroke Rehabil. 2008; 15(1): 13–21. doi: 10.1310/tsr1501-13.

2. Medeiros GC, Roy D, Kontos N, Beach SR. Post-stroke depression: A 2020 updated review. Gen Hosp Psychiatry. 2020; 66: 70–80. doi: 10.1016/j.genhosppsych.2020.06.011.

3. Guo J, Wang J, Sun W, Liu X. The advances of post-stroke depression: 2021 update. J Neurol. 2022; 269: 1236–49. doi: 10.1007/s00415-021-10597-4.

4. Liu L, Marshall IJ, Pei R, Bhalla A, Wolfe CD, O'Connell MD et al. Natural history of depression up to 18 years after stroke: a population-based South London stroke register study. Lancet Reg Health Eur. 2024; 40: 100882. doi: 10.1016/j.lanepe.2024.100882.

5. Hamilton M. A rating scale for depression. J NeurolNeurosurg Psychiatry. 1960; 23(1): 56–62. doi: 10.1136/jnnp.23.1.56.

6. Nickel A, Thomalla G. Post-stroke depression: impact of lesion location and methodological limitations—A topical review. Front Neurol. 2017; 8: 498. doi: 10.3389/fneur.2017.00498.

7. Ladwig S, Werheid K, Südmeyer M, Volz M. Predictors of post-stroke depression: validation of established risk factors and introduction of a dynamic perspective in two longitudinal studies. Front Psychiatry. 2023; 14: 1093918. doi: 10.3389/fpsyt.2023.1093918.

8. Phan J, Ramos M, Soares T, Parmar MS. Poststroke seizure and epilepsy: a review of incidence, risk factors, diagnosis, pathophysiology, and pharmacological therapies. Oxid Med Cell Longev. 2022; 2022: 7692215. doi: 10.1155/2022/7692215.

9. Zelano J, Holtkamp M, Agarwal N, Lattanzi S, Trinka E, Brigo F. How to diagnose and treat post-stroke seizures and epilepsy. Epileptic Disord. 2020; 22(3): 252–63. doi: 10.1684/epd.2020.1159.

10. Kanner AM. Depression and epilepsy: a new perspective on two closely related disorders. Epilepsy Curr. 2006; 6(5): 141–6. doi: 10.1111/j.1535-7511.2006.00125.x.

11. Jamil A, Csendes D, Gutlapalli SD, Prakash K, Swarnakari KM, Bai M, et al. Poststroke depression, an underrated clinical dilemma: 2022. Cureus. 2022; 14(12): e32948. doi: 10.7759/cureus.32948.

12. Elger CE, Johnston SA, Hoppe C. Diagnosing and treating depression in epilepsy. Seizure. 2017; 44: 184–93. doi: 10.1016/j.seizure.2016.10.018.

13. Myint PK, Staufenberg EFA, Sabanathan K. Post-stroke seizure and post-stroke epilepsy. Postgrad Med J. 2006; 82(971): 568–572. doi: 10.1136/pgmj.2005.041426.

14. Yang Y, Yang M, Shi Q, Wang T, Jiang M. Risk factors for depression in patients with epilepsy: a meta-analysis. Epilepsy Behav. 2020; 106: 107030. doi: 10.1016/j.yebeh.2020.107030.

15. Huang J, Zhou FC, Guan B, Zhang N, Wang A, Yu P, et al. Predictors of remission of early-onset poststroke depression and the interaction between depression and cognition during follow-up. Front Psychiatry. 2019; 9: 738. doi: 10.3389/fpsyt.2018.00738.

16. Volz M, Ladwig S, Werheid K. Gender differences in post-stroke depression: a longitudinal analysis of prevalence, persistence and predictive value of known risk factors. Neuropsychol Rehabil. 2021; 31(1): 1–17. doi: 10.1080/09602011.2019.1648301.

17. Kim HJ, Park KD, Choi KG, Lee HW. Clinical predictors of seizure recurrence after the first post-ischemic stroke seizure. BMC Neurol. 2016; 16(1): 212. doi: 10.1186/s12883-016-0729-6.

18. Wolf ME, Ebert AD, Chatzikonstantinou A. The use of routine EEG in acute ischemic stroke patients without seizures: generalized but not focal EEG pathology is associated with clinical deterioration. Int J Neurosci. 2017; 127(5): 421–6. doi: 10.1080/00207454.2016.1189913.

19. Qin SK, Yang ZX, Guan ZW, Zhang JH, Ping X, Lu Y, et al. Exploring the association between epilepsy and depression: a systematic review and meta-analysis. PLoS One. 2022; 17(12): e0278907. doi: 10.1371/journal.pone.0278907.

20. Eskut N, Tamer P, Delibas HD, Erdogan E. Evaluation of a group of patients with epilepsy regarding sleep quality, fatigue and depression. Sanamed. 2020; 15(3): 285–91. doi: 10.24125/sanamed.v15i3.452.

21. Maj M, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, et al. The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry. 2020; 19(3): 269–93. doi: 10.1002/wps.20771.

22. Guedes de Pinho L, Lopes MJ, Correia T, Sampaio F, Reis do Arco H, Mendes A, et al. Patient-centered care for patients with depression or anxiety disorder: an integrative review. J Pers Med. 2021 Aug 10; 11(8): 776. doi: 10.3390/jpm11080776.

Correspondence to/Autor za korespondenciju
Zlatana Perovic, Neurology specialist-epileptologist
Ul. Serdara **Šćepana S-70, Nikšić, Crna Gora**
phone: +382 69 351 378
email: zlataperovic@gmail.com
ORCID ID- 0000-0003-0800-1051

***How to cite this article**:* Perovic Z, Rosandic H. Depression in patients with and without post-stroke epilepsy. Sanamed. 2025; 20(2): 169-174. doi: 10.5937/sanamed0-59707.

SANAMED
2025; 20(2): 175–186
ISSN-1452-662X

DOI: 10.5937/sanamed0-58242
UDK: 616.155.194-053.2(669.1)
ID: 174844169
Original article

CLINICAL UTILITY OF RETICULOCYTE INDICES IN THE DIAGNOSIS AND MANAGEMENT OF PAEDIATRIC SICKLE CELL DISEASE PATIENTS IN PORT HARCOURT, NIGERIA

Jeremiah Zaccheaus,[1] Odozi Choice,[2] Jeremiah Bliss,[2] Okechukwu Chioma [2]

[1] Rivers State University, Faculty of Medical Laboratory Science,
Department of Haematology and Blood Transfusion Science, Port Harcourt, Nigeria
[2] Rivers State University teaching hospital,
Department of Paediatrics and Child Health,Port Harcourt, Nigeria

Primljen/Received: 15. 04. 2025. Prihvaćen/Accepted: 14. 08. 2025. Published online first 21. 08. 2025.

Abstract: **Introduction:**Sickle cell anemia (SCA) is a hereditary blood disorder resulting from a point mutation in the β-globin gene, leading to the production of abnormal hemoglobin S that distorts red blood cell morphology and impairs their function. Reticulocyte indices, which measure immature red blood cells in circulation, are key indicators of bone marrow response and erythropoietic activity in SCA patients.

Materials and Methods: This cross-sectional study examined reticulocyte indices in individuals with sickle cell anemia. It involved 45 children aged 2 to 19 at the Rivers State University Teaching Hospital. Blood samples were collected from each patient and placed in EDTA bottles. Reticulocyte counts were performed using the New Methylene Blue staining method and counted under a light microscope. Hemoglobin (Hb) and packed cell volume (PCV) were measured with a Veri-Q RED Hemoglobin meter. Reticulocyte indices, including absolute reticulocyte count (ARC), reticulocyte index (RI), and reticulocyte production index (RPI), were calculated using MDCalc.

Results: The mean reticulocyte count was 1.33 ± 0.22%, while the mean reticulocyte production index was 0.40 ± 0.09. Reticulocyte production index (RPI) showed a positive and significant correlation with Hb and PCV in both crisis and steady states ($r = 0.820$, $p = 0.02$). Additionally, RPI and RC were significantly correlated in patients on and off hydroxyurea ($p < 0.01$). Only 2 (4.4%) SCA patients demonstrated appropriate bone marrow response, while the remaining 43 (95.6%) SCA patients were hypoproliferative.

Conclusion: This study found derangements in the reticulocyte parameters indicating hypoproliferative anaemia. There is a need to monitor the patients closely by periodic reticulocyte counts for overall improved patient outcomes and quality of life in SCA patients.

Keywords: Sickle Cell Anaemia, hydroxyurea, reticulocyte count, reticulocyte production index, hypoproliferative anaemia, absolute reticulocyte count.

INTRODUCTION

Sickle cell disease (SCD) encompasses a spectrum of inherited hemoglobinopathies characterized by mutations in the HBB gene, which encodes the β-globin subunit of hemoglobin (1). Sickle cell disease (SCD) comprises a heterogeneous group of hemoglobinopathies, including sickle cell anemia (SCA), hemoglobin SC disease (HbSC), and hemoglobin S/β-thalassemia, which may present as either β^+ or β^0 thalassemia depending on the nature of the β-globin gene mutation. Several other minor variants exist within the group of SCDs, albeit not as common as the varieties mentioned above. It is essential to mention the sickle cell trait (HbAS), which carries a heterozygous mutation and seldom presents clinical signs or symptoms. Sickle cell anaemia is the most common form of SCD, with a lifelong affliction of haemolytic anaemia requiring blood transfusions, pain crises, and organ damage (2).

Sickle cell anaemia (SCA) involves mutations in haemoglobin (Hb), a protein in red blood cells (RBCs). Normal adult haemoglobin includes HbA1 (95%), HbA2 (less than 4%), and HbF (mostly in fetuses). The sickle cell mutation occurs when valine replaces glutamine at the beta-globin chain's sixth position (3). The sicklecell mutation follows an autosomal codominant inheritance pattern. Homozygosity for the

HbS allele (HbSS genotype) leads to the most severe form of sickle cell anemia, whereas heterozygosity (HbAS genotype) typically results in a carrier state with minimal or no clinical manifestations. Additional genotypic variants within the sickle cell disease spectrum include HbS/β^0-thalassemia and HbSC disease, which arise from compound heterozygosity involving the HbS allele and either β-thalassemia or hemoglobin C mutations (4, 5).

Sickle cell anaemia is characterized by haemolysis and vaso-occlusive crises (VOC). The mutation in the beta-globin gene causes haemoglobin S (HbS) to form rigid polymers when deoxygenated, leading to the cyclical sickling of red blood cells (RBCs). Over time, this sickling becomes irreversible, increasing the risk of haemolysis and VOC. Factors like the low oxygen affinity of HbS, high 2,3-diphosphoglycerate, and increased sphingokinase-1 activity contribute to HbS polymerization (6). Oxidative stress from auto-oxidation of HbS damages RBC membranes (7). Haemolyzed cells release free haemoglobin and arginase 1, reducing nitric oxide and increasing oxidative stress and vascular remodeling. Vaso-occlusion is further promoted by interactions between sickle RBCs, free haeme, reactive oxygen species, the endothelium, neutrophils, and platelets (8).

Globally, 20 to 25 million people are affected by SCD, with 12 to 15 million residing in Africa, while developed countries account for only 10% of cases (9). Sub-Saharan Africa accommodates 75% of all patients with SCD and 70% of all SCD births globally, with many affected children dying before the age of 5 (10).

Nigeria bears the highest burden of sickle cell disease (SCD) in Sub-Saharan Africa, with an estimated 2–3% of its population affected. Globally, approximately 300,000 infants are diagnosed with SCD each year, with Sub-Saharan Africa accounting for nearly 75% of these cases. Nigeria alone contributes between 100,000 and 150,000 newborns annually, representing roughly one-third of the global incidence (11). The prevalence of SCD within Nigerian states ranges from 1% to 3%, with HbSS being the predominant haemoglobin variant. A 2.4% prevalence of the HbSS genotype was reported in southwestern Nigeria (11, 12). In North Central Nigeria, a 5% prevalence rate of SCD among children was identified by Diwe et al. (13).

In patients with sickle cell anaemia (SCA), a peripheral blood smear shows elongated red blood cells (RBCs) with tapering ends (drepanocytes). Additional findings can include Howell-Jolly bodies (DNA remnants, indicating autosplenectomy), target cells (seen in thalassaemia and sickle-thalassaemia syndromes), polychromatic cells (reticulocytes, indicating a marrow response to haemolysis), and sometimes nucleated red blood cells (14). These findings are not confirmatory for SCA. Confirmation requires haemoglobin electrophoresis, high-performance liquid chromatography, or isoelectric focusing. DNA-based techniques are used for uncertain diagnoses and prenatal testing through amniocentesis, while foetal DNA capture from maternal blood remains investigational (15).

Treatment and management of sickle cell anaemia focus on alleviating symptoms, preventing complications, and improving the quality of life. This typically involves regular blood transfusions to manage anaemia, pain management strategies including medications and hydration, and the use of hydroxyurea to reduce the frequency of pain crises and the need for transfusions. Preventive measures include vaccinations and antibiotics to reduce infection risks. In severe cases, haematopoietic stem cell transplantation may be a potential cure (5).

Reticulocytes, the earliest form of erythrocytes released by the bone marrow into peripheral circulation, serve as a dependable indicator of recent erythropoietic activity. Under physiological conditions, nucleated erythroid precursors complete clonal maturation within the bone marrow over a period of 1–3 days (16). Following nuclear extrusion, reticulocytes—immature erythrocytes—are released into peripheral circulation, where they persist for approximately 1–2 days before maturation into fully developed erythrocytes. These cells can be detected using supravital staining techniques for manual reticulocyte enumeration or via automated methods that quantify residual ribonucleic acid (17).

The reticulocyte index (RI) is a calculated value employed in haematology to assess bone marrow function and erythropoiesis, the body's process of producing red blood cells (RBCs). Reticulocytes are immature RBCs recently released from the bone marrow into the peripheral blood. The reticulocyte count is a critical parameter that reflects the rate of RBC production. The RI is particularly significant in the evaluation of anaemia. It aids in differentiating between anaemias caused by decreased production of RBCs and those caused by increased destruction or loss of RBCs. By assessing the RI, healthcare professionals can determine whether the bone marrow responds appropriately to the body's demand for RBCs (18).

The reticulocyte index (RI) is calculated by multiplying the reticulocyte percentage by the patient's haematocrit, dividing this product by a normal haematocrit value of 45%, and then adjusting this result by a correction factor to account for early reticulocyte release in severe anaemia. This formula accounts for the fact that in severe anaemia, reticulocytes are released into the bloodstream earlier than usual and thus spend more time maturing in the peripheral circulation. The correc-

tion factor adjusts for this premature release, typically set at 1 for a haematocrit of 45% but varies depending on the actual haematocrit level (19).

Interpretation of the RI provides insights into bone marrow activity. An RI less than 2% suggests decreased RBC production, characteristic of conditions such as aplastic anaemia, iron deficiency anaemia, and chronic kidney disease. Conversely, an RI of 2% or higher indicates increased RBC production, seen in conditions involving accelerated RBC destruction, such as haemolytic anaemias, or following acute blood loss (19).

Sickle cell anemia (SCA) poses significant socio-economic challenges globally, including in Nigeria, deeply impacting individuals, families, and the healthcare system (20). The disease causes chronic anaemia, severe pain crises, and complications like acute chest syndrome, stroke, and organ damage, which frequently necessitate hospitalization and long-term medical care (5).

These health issues lead to substantial financial strain for families due to ongoing medical costs and lost income from missed work and school. The economic burden is particularly severe in rural areas, where access to healthcare is limited, resulting in long travel distances for treatment. Social stigma further exacerbates the challenges, leading to discrimination and mental health issues for those affected.

Nigeria's healthcare system is overwhelmed by the demand for SCA care, with resource limitations and a shortage of trained healthcare professionals resulting in suboptimal treatment. Monitoring the reticulocyte indices in SCA patients is crucial, as it helps assess bone marrow function and the body's response to anaemia, providing essential information for effective disease management.

The reticulocyte index (RI) measures the production of new red blood cells (reticulocytes) in the bone marrow. It provides valuable information about the bone marrow's response to anaemia and can help assess the effectiveness of treatments. However, the dynamics of reticulocyte production in SCA patients are complex and poorly understood. Sickle cell anemia patients often experience chronic haemolytic anaemia due to the rapid destruction of sickle cells (21). The bone marrow compensates by increasing reticulocyte production (22). Studying the RI in these patients can provide insights into the bone marrow's ability to respond to anaemia, which is critical for effective disease management.

Various treatments, such as hydroxyurea and blood transfusions, aim to reduce haemolysis and improve haemoglobin levels in SCA patients (23). Monitoring the response to intervention (RI) can help evaluate the efficacy of these treatments and inform therapeutic decisions. High or low RI levels in SCA patients can indicate different complications. For instance, a very high RI may suggest severe haemolysis, while a low RI could indicate bone marrow failure or aplastic crisis. Understanding these patterns can aid in the early detection and intervention of complications.

By establishing the significance of the RI in SCA patients, healthcare providers can develop better strategies for monitoring and managing the disease. This can lead to more personalized and effective treatment plans, ultimately improving patient outcomes and quality of life. Despite the importance of the RI, limited research specifically focuses on its role in SCA. This study aims to fill this gap by providing information on reticulocyte production in SCA patients, thereby contributing to the broader understanding of the disease.

MATERIALS AND METHODS

Study Area

This investigation was carried out at Rivers State University Teaching Hospital (RSUTH), formerly known as Braithwaite Memorial Specialist Hospital, located at 5–8 Harley Street, Old Government Reservation Area (GRA), Port Harcourt, Rivers State, Nigeria (coordinates: 4.7843°N, 7.0104°E). RSUTH is a government-owned tertiary healthcare facility and ranks among the largest in the Niger Delta region, with a bed capacity of 375 and accreditation across the majority of clinical departments. Port Harcourt, the capital and most populous city of Rivers State, lies along the Bonny River and has an estimated population of 1,148,665. As a major Nigerian city, it has experienced rapid urbanization driven by the country's social and economic history. Port Harcourt is a significant hub for various economic, social, and political activities, offering new opportunities across these sectors.

Study Population

The study population comprised 45 pediatric patients, aged 2 to 19, who attended the sickle cell clinic at Rivers State University Teaching Hospital (RSUTH). These individuals were referred to the haematology laboratory for diagnostic confirmation of sickle cell disease. Participants included both male and female children.

Study Design

This descriptive cross-sectional study evaluated the reticulocyte indices in sickle cell anaemia patients in a single-point measurement of reticulocyte indices in paediatric sickle cell disease patients attending the sickle cell disease clinic in a tertiary health institution in Port Harcourt, Nigeria.

Sample Size Calculation

To determine the minimum sample size of the subjects recruited in the study, the global prevalence of sickle cell disease, as reported by Naing et al. (11), was 3%. This value was used to calculate the minimum sample size as follows.

Using the formula:

$n = Z^2P(1-P)/d^2$

Where n is the minimum sample size

Z = Standard normal deviation corresponding to 95% confidence level set at 1.96

p = 3% = 0.03

1-P = 0.97

d = desired precision, 5% (0.05)

$n \approx 45$

According to the calculation, 45 samples were used in this study.

Ethical Considerations

Ethical clearance for the study was granted by the Research Ethics Committee of Rivers State University Teaching Hospital, Port Harcourt, Nigeria.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Children between the ages of 2 and 19 who are sickle cell clinic attendees of RSUTH.
- Individuals residing in Port Harcourt and its surrounding regions seeking medical attention at RSUTH sickle cell clinic.
- Those whose parents/guardians have given written informed consent for their children/ward to participate in the study.

Exclusion Criteria

- Individuals who are not within the age range of the study participants.
- Individuals who are not sickle cell clinic attendees of RSUTH.
- Those whose parents/guardians did not give written informed consent for their children/ward to participate in the study.

Sample Collection and Storage

Aseptic venipuncture of the cubital vein was performed using sterile, disposable Vacutainer® needles and tubes to collect 5 mL of blood from each patient. Samples were transferred into EDTA-containing tubes and analyzed for reticulocyte counts and haematological parameters within three hours of collection.

Procedures

Determination of Reticulocyte Count: New Methylene Blue Staining Method

Principle: An isotonic solution of a supravital stain (i.e., one that stains living material), such as new methylene blue, is incubated with a few drops of blood. The red blood cells must be stained while they are alive to detect ribosomal RNA in reticulocytes. A thin blood film preparation is made and stained, and the reticulocytes are counted microscopically. Reticulocytes are recognized by the violet-blue stained granules of ribosomal RNA (reticulin) they contain. The reticulocyte count is expressed as a percentage or preferably in absolute numbers when an electronic analyzer RBC count is available.

Procedure

Reticulocyte staining was performed using the supravital technique. Three drops of new methylene blue solution were combined with three drops of a well-mixed EDTA-anticoagulated blood sample in a test tube and thoroughly mixed. The mixture was incubated either at ambient temperature for 20 minutes or at 35–37 °C for 10–15 minutes. Following incubation, the red blood cells were gently resuspended, and a drop of the stained sample was applied to each of two microscope slides using a capillary or plastic bulb pipette. The blood was evenly spread to create thin films and air-dried by gentle waving. One of the slides was subsequently counterstained with Leishman stain and stored in a dust- and insect-free environment. Microscopic evaluation was carried out the following day. Initial assessment was conducted using the 10× objective lens with a partially closed condenser iris diaphragm to identify suitable areas of cell distribution. A drop of immersion oil was placed on the selected field, and detailed examination was performed with the oil immersion objective (100×), adjusting the diaphragm accordingly. Reticulocytes were enumerated by systematically scanning consecutive microscopic fields, counting 500 red blood cells—extended to 1,000 cells in cases of low reticulocyte prevalence. The reticulocyte percentage was calculated based on the total number of cells counted.

Determination of Haemoglobin and Packed Cell Volume: Veri-Q RED Haemoglobin Meter

Principle

Veri-Q test strips for Haemoglobin and Packed Cell Volume (PCV) are designed to quantify the concentration of red blood cells in whole blood through advanced biochemical and optical detection mechanisms. When a

blood sample is applied, capillary action draws it into the reaction zone, where reagents interact with haemoglobin or cellular components to generate a measurable signal. This signal may be electrochemical, based on changes in conductivity, or photometric, using light absorbance to determine red cell concentration. The paired device processes the signal using calibrated algorithms to calculate and display the PCV as a percentage and haemoglobin as g/dl.

Procedure

Whole blood samples, anticoagulated with EDTA, were gently mixed to ensure homogeneity before analysis. A precise volume of 20 µL of each sample was applied to the reaction zone of the test strip, ensuring complete coverage without overflow. The test strip was then inserted into the Veri-Q device, which quantified PCV by detecting electrochemical or photometric signals generated from the interaction of blood components with the strip's reagents. The device processed these signals using proprietary algorithms to calculate and display PCV as a percentage. Results were recorded for each sample, and quality control was conducted using standardized control samples to ensure accuracy.

Sickle SCAN RDT Test

Principle

The Sickle SCAN® test kit is a rapid, qualitative lateral flow immunoassay designed for the detection of haemoglobin variants A, S, and C associated with sickle cell disorders. A 5 µL blood sample is obtained via venipuncture using the provided capillary sampler and introduced into a buffer-loaded pretreatment module, facilitating erythrocyte lysis and haemoglobin release. Subsequently, four drops of the treated sample are dispensed into the sample inlet of the Sickle SCAN cartridge. The sample migrates through the cartridge via capillary action over a five-minute period, during which antibody-conjugated colorimetric nanoparticles interact with the haemoglobin variants. Capture zones yield up to four distinguishable lines, including a control (Ctrl) line that confirms successful fluid migration. The presence of blue indicator lines within the designated regions signifies detection of haemoglobin A, S, and C variants.

Procedures

Blood samples were obtained following standard laboratory procedures. A 5 µL sample was collected using a sterile capillary sampler and introduced into the buffer-loaded pretreatment module, which contains a premeasured volume of extraction buffer. Care was taken during module handling to avoid contamination. The module was inverted and gently mixed three times to ensure thorough haemoglobin extraction via erythrocyte lysis. The tip of the colored cap was broken off, and four drops of the treated sample were dispensed into the inlet port of the Sickle SCAN® cartridge, which was placed on a level surface at ambient temperature. The lateral flow assay was allowed to proceed for five minutes, after which results were interpreted via the cartridge's detection window. Any assays exceeding 10 minutes of run time were deemed invalid. This test served to confirm the sickle cell status of patients with a prior diagnosis of sickle cell anaemia.

Reticulocyte count was performed using light microscopy at 100× objective. A minimum of 500 red blood cells were counted, and the number of reticulocytes encountered was recorded and calculated as follows:(Number of reticulocytes seen / 500 cells) × 100%.

After obtaining the percentage of the reticulocyte count by microscopic examination of the reticulocyte film stained with New Methylene Blue and counterstained with Leishman stain, the reticulocyte indices—absolute reticulocyte count (ARC), corrected reticulocyte percentage/reticulocyte index (RI), and reticulocyte production index (RPI)—were calculated using MDCalc on the website www.mdcalc.com/calc/1667/absolute-reticulocyte-count-reticulocyte-index.

A reticulocyte production index of less than 2.0 defines a hypoproliferative bone marrow response.

Data Analysis

Data obtained from this study were analyzed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a p-value ≤ 0.05 at a 95% confidence interval.

RESULTS

This study was conducted on sickle cell anaemia (SCA) patients attending the sickle cell clinic of Riv-

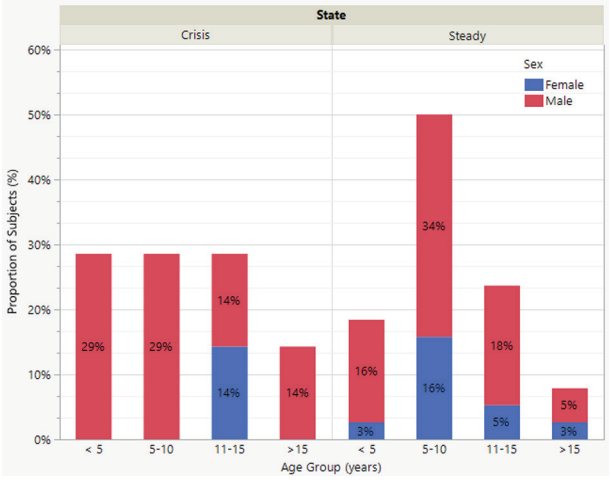


***Figure 1**. Distribution of Sickle Cell Anaemia patients by Age Group, Sex and the Disease States of the patients*

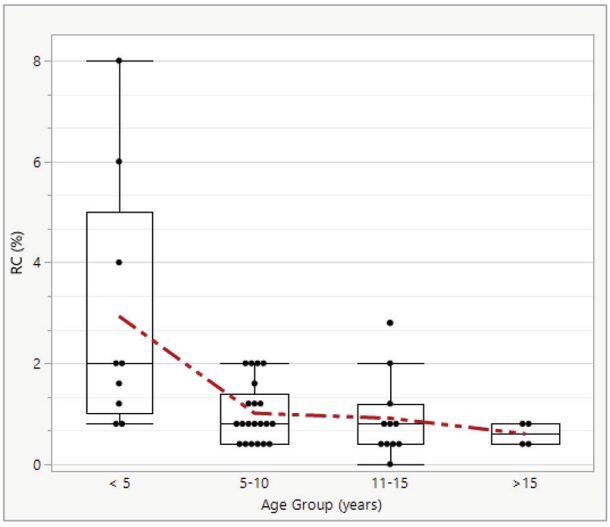


Figure 2. *Box Plot of Reticulocyte Count (RC) by Age Group of Sickle Cell Subjects*

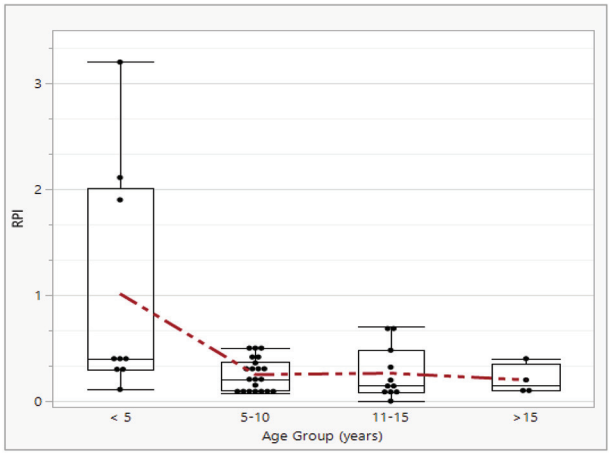


Figure 3. *Box Plot of Reticulocyte Production Index (RPI) by Age Group of Sickle Cell Subjects*

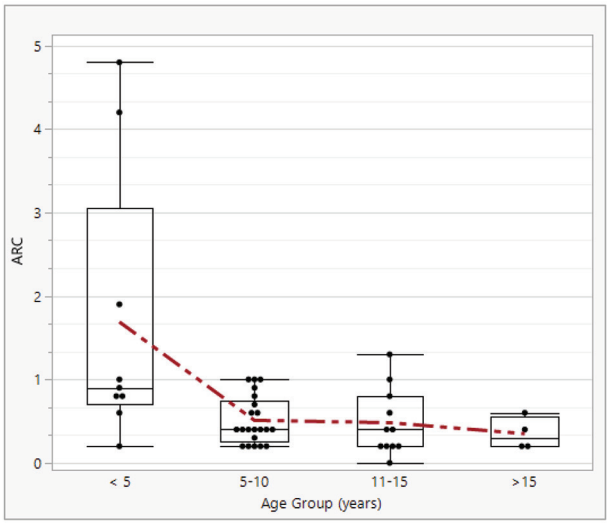


Figure 4. *Box Plot of Absolute Reticulocyte Count (ARC) by Age Group of Sickle Cell Subjects*

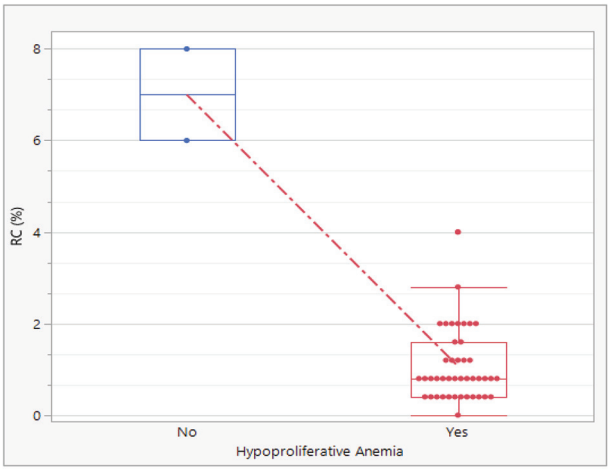


Figure 5. *Box Plot of Reticulocyte Count by Hypoproliferative Anemia Status Among Sickle Cell Subjects*

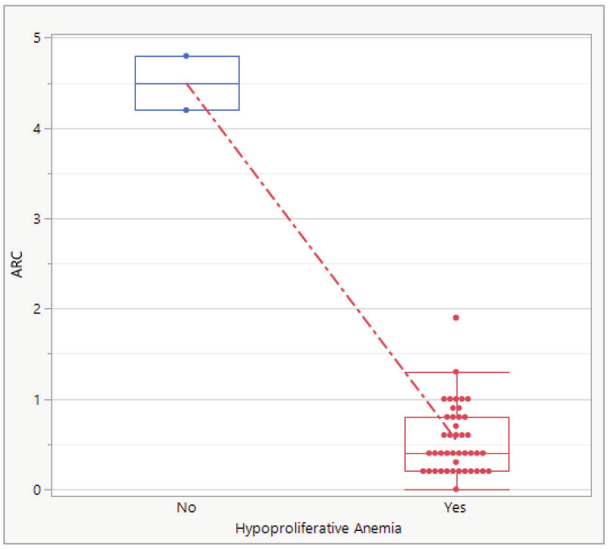
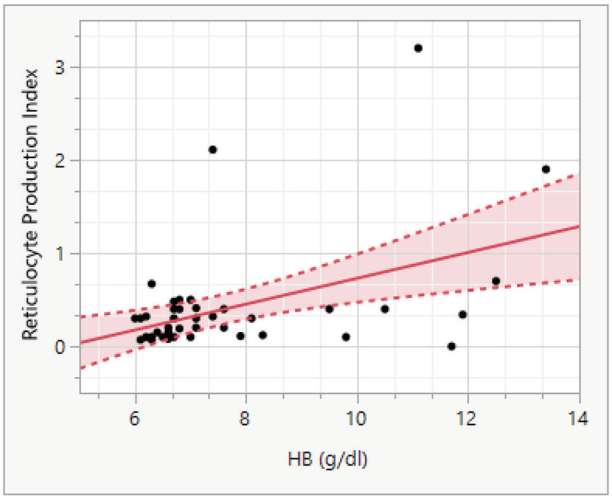


Figure 6. *Box Plot of Absolute Reticulocyte Count (ARC) by hypoproliferative Anemia Status Among Sickle Cell Subjects*

ers State University Teaching Hospital (RSUTH), Port Harcourt, to determine their reticulocyte indices.

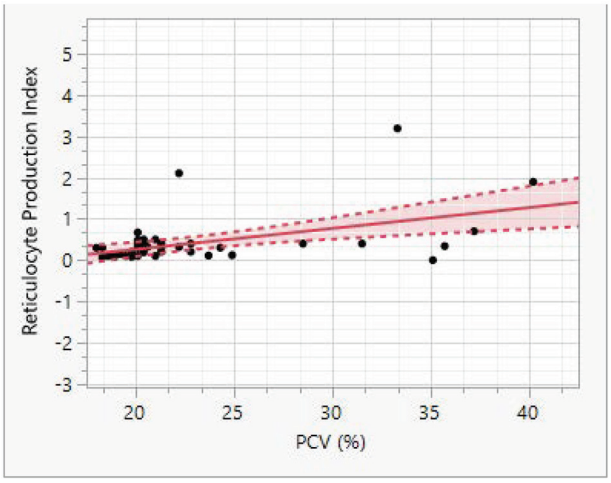
Figure 1 shows the distribution of SCA patients by age group, sex, and disease state. Most SCA patients in crisis were aged 11–15, while those in the steady state were aged 5–10. This is only referring to the age of the SCA patients who were in crisis and those in steady states as shown in the figures. It doesn't refer to the overall age of the SCA patients in the study.

Figure 2 presents a graphical representation of the reticulocyte count by age group for patients with sickle cell disease. The reticulocyte count was higher in children under 5 years old than in other age groups. The reticulocyte count was lowest among children 15 years and older. A similar pattern was observed with the Reticulocyte Production Index (RPI) and absolute Reticulocyte Count (ARC), as shown in Figures 3 and 4.



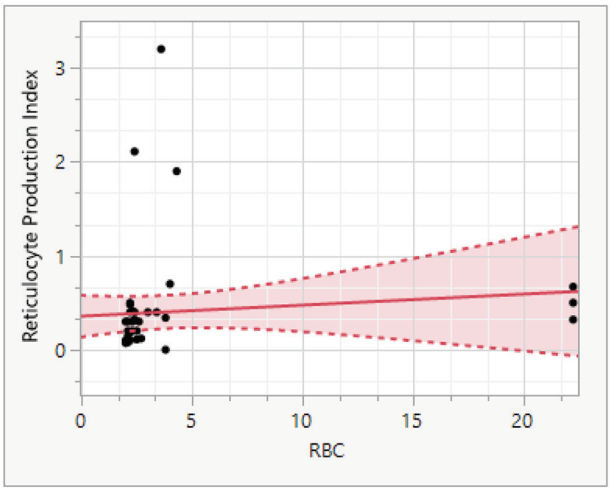
Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	-0.657066	0.334679	-1.96	0.0561
HB (g/dl)	0.1387649	0.042628	3.26	0.0022**
Equation	RPI = -0.657066 + 0.1387649*HB (g/dl)			
Correlation	0.4446, 95%CI: 0.174-0.653, p=0.0022			
R^2	0.1977			

Figure 7. *Relationship Between Hemoglobin and Reticulocyte Production Index*



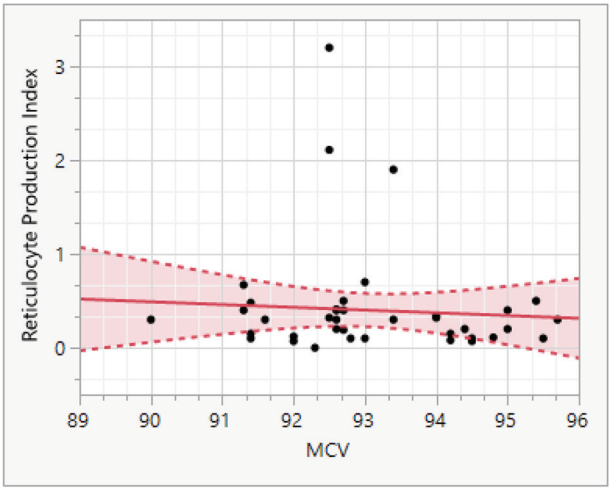
Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	-0.751659	0.334236	-2.25	0.0297*
PCV (%)	0.0507031	0.014293	3.55	0.0010***
Equation	RPI = -0.751659 + 0.0507031*PCV (%)			
Correlation	0.4758, 95%CI: 0.211-0.675, p=0.0010			
R^2	0.2264			

Figure 8. *Relationship Between Packed Cell Volume (PCV) and Reticulocyte Production Index*



Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	0.3571768	0.110437	3.23	0.0023**
RBC	0.0117404	0.017717	0.66	0.5111
Equation	RPI = 0.3571768 + 0.0117404*RBC			
Correlation	0.1005, 95%CI: -0.198-0.383, p=0.5111			
R^2	0.0101			

Figure 9. *Relationship Between Red Blood Cell (RBC) and Reticulocyte Production Index*

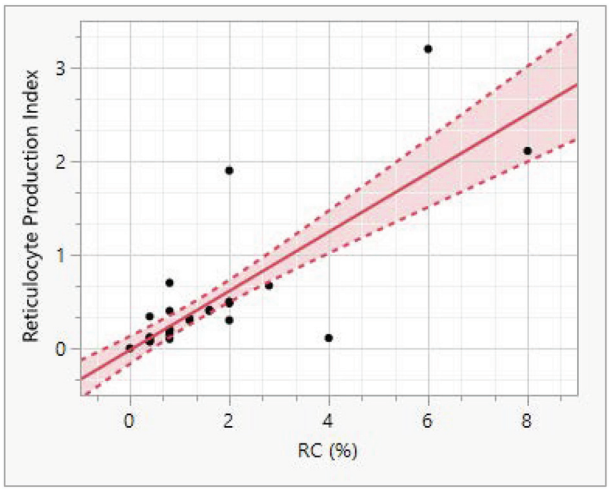


Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	3.1320241	5.990534	0.52	0.6038
MCV	-0.029351	0.064389	-0.46	0.6508
Equation	RPI = 3.1320241 - 0.0293515*MCV			
Correlation	-0.069, 95%CI: -0.356-0.229, *p=0.6508*			
R^2	0.005			

Figure 10*. Relationship Between Mean Cell Volume (MCV) and Reticulocyte Production Index*

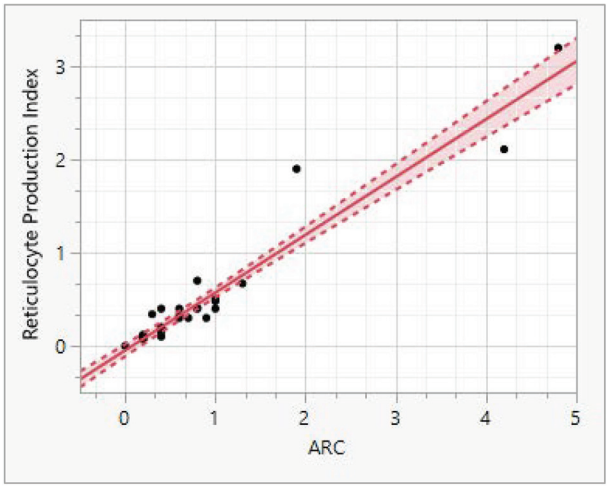
The Reticulocyte Production Index (RPI) measures the bone marrow response in patients with sickle cell disease. Patients with an RPI of less than 2.0 were interpreted as hypoproliferative. Only two of the SCA patients had an RPI of 2.0 or above, which is represented graphically in Figure 5. The same pattern follows with ARC in Figure 6.

Figure 7 graphically represents the relationship between haemoglobin (Hb) and RPI. There is a strong pos-



Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	-0.019077	0.073107	-0.26	0.7954
RC (%)	0.3154742	0.037068	8.51	<.0001****
Equation	RPI = -0.019077 + 0.3154742*RC (%)			
Correlation	0.792, 95%CI: 0.650-0.881, p<.0001****			
R^2	0.627			

Figure 11. *Relationship Between Reticulocyte Count (RC) and Reticulocyte Production Index*



Term	Estimate	Std Error	t Ratio	Prob > |t|
Intercept	-0.047929	0.032234	-1.49	0.1443
ARC	0.6204544	0.028004	22.16	<.0001****
Equation	RPI = -0.047929 + 0.6204544*ARC			
Correlation	0.959, 95%CI: 0.926-0.977, p<.0001****			
R^2	0.919			

Figure 12. *Relationship Between Absolute Reticulocyte Count (ARC) and Reticulocyte Production Index*

itive relationship between these variables (p = 0.002). A similar pattern existed between RPI and packed cell volume (PCV) (Figure 8) and RPI and red blood cell count (RBC) (Figure 9). No significant relationship

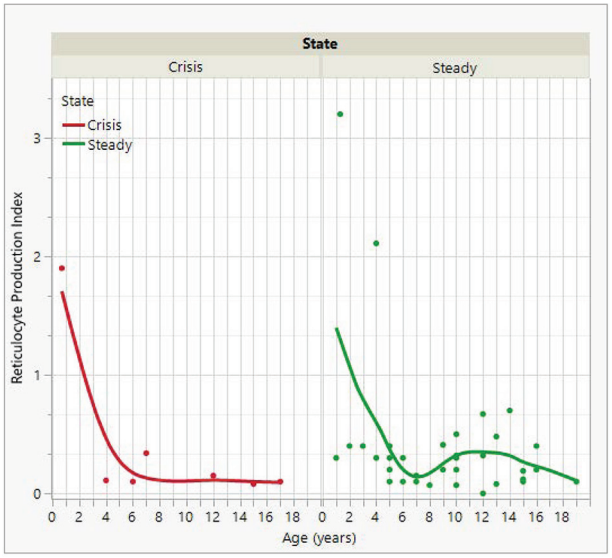


Figure 13. *Relationship Between Age and Reticulocyte Production Index for Sickle Cell Subjects in Crisis and Steady State*

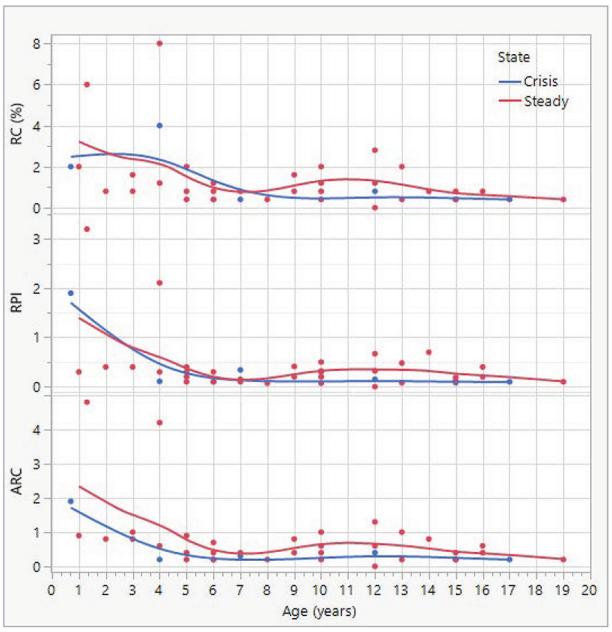


Figure 14. *Relationship Between ARC, RPI, and RC and Age by State of Sickle Cell Subjects*

existed between RPI and mean corpuscular volume (MCV), as shown in Figure 10 (p = 0.65).

Figure 11 graphically shows the relationship between reticulocyte count and reticulocyte production index. The relationship was highly significant and positive (p < 0.001). This suggests that an increase in reticulocytes leads to a corresponding increase in the production index, and vice versa. Similarly, the reticulocyte production index is significantly and positively related to the absolute reticulocyte count (p < 0.001). This relationship is graphically demonstrated in Figure 12.

Figure 13 shows the line graph of the RPI against the age of the SCA patients. The graph demonstrates

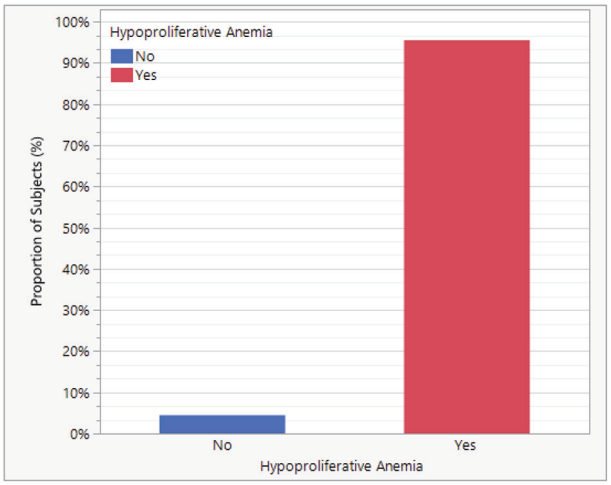


***Figure 15**. Distribution of Hypoproliferative Anemia Among Sickle Cell Subjects*

the trend of RPI across participants' ages. The RPI was higher in children aged 0–6 years in both crisis and steady states. The trend graphs of ARC, RPI, and reticulocyte count against the ages of SCA patients in different sickle cell states are represented together in Figure 14. The trend is consistent with that observed in Figure 13.

Figure 15 shows the proportion of SCA patients who demonstrate appropriate or hypoproliferative bone marrow response, as indicated by a cut-off RPI value of 2.0. SCA patients with an RPI less than 2.0 were classified as hypoproliferative, while those with RPI above 2.0 were classified as appropriate. Only 2 SCA patients demonstrated appropriate bone marrow response, while most were hypoproliferative.

DISCUSSION

Reticulocytes, the immature red blood cells produced by the bone marrow, play a crucial role in evaluating erythropoietic activity and bone marrow response in SCA patients. This study determined reticulocyte indices—including reticulocyte count, reticulocyte production index (RPI), and mean reticulocyte volume—to provide valuable insights into the dynamics of red blood cell production and destruction. These indices are vital for understanding the degree of haemolysis, compensatory erythropoiesis, and treatment response in SCA (24).

The mean reticulocyte count in children with sickle cell anaemia is typically around 12% of total red blood cells (RBCs), significantly higher than the normal range of approximately 0.5% to 2.5% in healthy children (25). In this study, the mean reticulocyte count of SCA patients was 1.33 ± 0.22%, while the mean RPI was 0.40 ± 0.09. The reticulocyte count observed here was lower than that reported by Sani et al. (26), who found 1.48 ± 1.46% in SCA patients. Similarly, the RPI in our study was lower than the 1.7/µL reported by Akingbola et al. (27). Our study's mean reticulocyte count and RPI fell within the normal reference range.

Sickle cell anaemia is known to cause reticulocytosis due to increased haemolysis of sickled red blood cells (28). However, our results showed a reduction in reticulocyte indices, likely due to hydroxyurea treatment received by some subjects, which is known to reduce erythropoiesis, as supported by the correlation analyses.

Although reticulocyte count, RPI, and absolute reticulocyte count were higher in males compared to females, these differences were not statistically significant. This finding aligns with Candar et al. (29), who reported no significant sex differences in platelet counts. Our study found a significant decrease in reticulocyte indices with increasing age, indicating age-related effects on erythropoiesis. Additionally, no significant differences were observed in reticulocyte indices between steady and crisis states, suggesting that disease state does not significantly affect these indices.

The haemoglobin levels, packed cell volume (PCV), red blood cell (RBC) counts, and mean corpuscular volume (MCV) in SCA subjects were 7.63 ± 0.28 g/dL, 22.74 ± 0.82%, 3.73 × 10^{12}/L, and 75.3 fL, respectively. These haemoglobin levels were higher than those reported by Jeremiah and Magnus (30), who found 5.68 ± 1.7 g/dL in SCA patients. Similarly, Akodu et al. (31) reported PCV, Hb, MCV, and RBC values of 20.9%, 6.9 g/dL, 75.3 fL, and 2.9 × 10^{12}/L, respectively, in SCA subjects.

Haemoglobin and PCV were significantly elevated in patients who did not receive hydroxyurea. According to study (32), hydroxyurea causes bone marrow suppression, which likely accounts for the reduced Hb and PCV observed in treated subjects due to delayed erythropoiesis.

Hydroxyurea (HU) is a widely used treatment for sickle cell anaemia, known to improve haemoglobin levels and reduce complications, thus decreasing the need for blood transfusions (33). HU increases foetal haemoglobin (HbF) levels, which reduces sickling of red blood cells and the frequency of vaso-occlusive crises (34, 35). Additionally, HU reduces leukocyte and platelet counts, potentially lowering inflammation and thrombotic risk (34).

In this study, an RPI of less than 2.0—indicative of a hypoproliferative bone marrow response—was observed in 95.5% of SCA patients on hydroxyurea, with only two patients showing an appropriate bone marrow response (RPI ≥ 2.0). This confirms that HU therapy can lead to hypoproliferative anaemia by in-

hibiting DNA precursor synthesis necessary for cell division (33, 36, 37).

While hydroxyurea effectively reduces sickle cell complications, it may exacerbate anaemia through bone marrow suppression. Therefore, careful monitoring and dose adjustments are essential to balance therapeutic benefits and side effects. Close collaboration between patients and healthcare providers is crucial for personalized management.

CONCLUSION

This study found derangements in reticulocyte parameters indicative of hypoproliferative anaemia in SCA patients. Regular monitoring of reticulocyte counts is necessary to improve patient outcomes and quality of life.

Abbreviations

EDTA - Ethylene diamine tetraacetic acid
RPI - Reticulocyte Production Index
SCA - Sickle Cell Anaemia
RC - Reticulocyte Count
RDT - Rapid Diagnostic Test
ARC - Absolute Reticulocyte Count
PCV - Packed Cell Volume
Hb - Haemoglobin

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study. There are no financial relationships, employment, consultancy, stock ownership, honoraria, patents, or paid expert testimony that could influence the outcome of the research presented. Furthermore, there are no close relationships, competitive academic agendas, or philosophical biases that might have affected the conduct of the study.

Funding: This study did not receive any external funding.

Ethical Approval and Informed Consent

All subjects included in the study gave informed consent to participate. Participant information was kept anonymous and in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines for the protection of research participants. The study was conducted in accordance with the Declaration of Helsinki. Ethical clearance for the study was granted by the Research Ethics Committee of Rivers State University Teaching Hospital, Port Harcourt, Nigeria.

Author Contributions & Responsibilities

The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. Author roles**:** ZAJ: Professor of Haematology and Blood Transfusion Science; designed and supervised the study; drafted the initial manuscript; CCO: Student researcher; collected samples and performed laboratory analysis; BNJ: Medical officer; assisted with sample collection; CO: Consultant paediatric haematologist; managed patients, obtained informed consent, and referred for blood sample collection.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

KLINIČKA PRIMENA RETIKULOCITNIH INDEKSA U DIJAGNOSTICI I LEČENJU PEDIJATRIJSKIH PACIJENATA SA SRPASTOM ANEMIJOM U PORT HARCORT-u U NIGERIJI

Jeremiah Zaccheaus,[1] Odozi Choice,[2] Jeremiah Bliss,[2] OkechukwuChioma [2]

[1] Rivers State Univerzitet, Fakultet medicinskih laboratorijskih nauka,
Odsek za hematologiju i transfuziju krvi, Port Harcourt, Nigerija
[2] Univerzitetska bolnica Rivers State univerziteta,
Odeljenje za pedijatriju i zdravlje djece, Port Harcourt, Nigerija

Uvod: Srpasta anemija (SA) je nasledni hematološki poremećaj izazvan tačkastom mutacijom u genu za β-globin, koja dovodi do stvaranja abnormalnog hemoglobina S, što menja oblik eritrocita i narušava njihovu funkciju. Indeksi retikulocita, koji kvantifikuju nezrele eritrocite u perifernoj krvi, predstavljaju ključne markere aktivnosti koštane srži i eritropoeze kod pacijenata sa SA.

Materijali i metode: U ovoj studiji preseka analizirani su indeksi retikulocita kod 45 dece uzrasta od 2 do 19 godina sa SA, lečene u Univerzitetskoj bolnici Rivers State. Uzorci krvi su prikupljeni u EDTA epruvetama. Brojanje retikulocita izvršeno je metodom bojenja novim metilen-plavim i mikroskopskim pregledom. Hemoglobin (Hb) i hematokrit (PCV) određeni su korišćenjem Veri-Q RED merača. Indeksi retikulocita — apsolutni broj retikulocita (ARC), indeks retikulocita (RI) i indeks produkcije retikulocita (RPI) — izračunati su primenom MDCalc alata.

Rezultati: Prosečan retikulocitni broj iznosio je 1,33 ± 0,22%, dok je prosečni indeks produkcije retikulocita bio 0,40 ± 0,09. Indeks produkcije retikulocita (RPI) značajno je pozitivno korelisan sa vrednostima hemoglobina i hematokrita u kriznim i stabilnim fazama bolesti ($r = 0,820$, $p = 0,02$). Takođe, kod pacijenata na terapiji i bez terapije hidroksiureom zabeležena je značajna korelacija između RPI i retikulocitnog broja ($p < 0,01$). Samo 2 pacijenta (4,4%) su pokazala adekvatan odgovor koštane srži, dok je kod preostalih 43 (95,6%) utvrđena hipoproliferacija.

Zaključak: Uočene su promene u retikulocitnim parametrima koje ukazuju na hipoproliferativnu anemiju. Neophodno je redovno praćenje retikulocitnog statusa radi poboljšanja ishoda lečenja i kvaliteta života kod pacijenata sa srpastom anemijom.

Ključne reči: Srpasta anemija, hidroksiurea, broj retikulocita, indeks produkcije retikulocita, hipoproliferativna anemija, apsolutni broj retikulocita.

REFERENCES

1. Elendu C, Amaechi DC, Alakwe-Ojimba CE, Elendu TC, Elendu RC, Ayabazu CP, et al. Understanding Sickle cell disease: causes, symptoms, and treatment options. Medicine (Baltimore). 2023; 102(38): e35237. doi: 10.1097/MD.0000000000035237.

2. Aygun B, Odame I. A global perspective on sickle cell disease. Pediatr Blood Cancer. 2022; 59(2): 386-90. doi: 10.1002/pbc.24175.

3. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017; 376(16): 1561-73. doi: 10.1056/NEJMra1510865.

4. Houwing ME, de Pagter PJ, van Beers EJ, Biemond BJ, Rettenbacher E, Rijneveld AW, et al. Sickle cell disease: Clinical presentation and management of a global health challenge. Blood Rev. 2019; 37: 100580. doi: 10.1016/j.blre.2019.05.004.

5. Mangla A, Agarwal N, Maruvada S. Sickle Cell Anemia. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.

6. Tebbi CK. Sickle cell disease, a review. Haematology. 2022; 3(2): 341-66. doi: 10.3390/hemato3020024.

7. Inusa BPD, Hsu LL, Kohli N, Patel A, Ominu-Evbota K, Anie KA, et al. Sickle cell disease—Genetics, pathophysiology, clinical presentation and treatment. Int J Neonatal Screen. 2019; 5(2): 20-31. doi: 10.3390/ijns5020020.

8. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018; 4: 18010. doi: 10.1038/nrdp.2018.10.

9. Adigwe OP, Onavbavba G, Onoja SO. Impact of sickle cell disease on affected individuals in Nigeria: A critical review. Int J Gen Med. 2023; 16: 3503-15. doi: 10.2147/IJGM.S410015.

10. Stephen N, Nden N, Gusen NJ, Kumzhi P, Gaknung BK, Auta D, et al. Prevalence of sickle cell disease among children attending Plateau Specialist Hospital, Jos, Nigeria. Acta Med Int. 2018; 5: 20-3. doi: 10.4103/ami.ami_60_17.

11. Naing L, Nordin RB, Abdul Rahman H, Naing YT. Sample size calculation for prevalence studies using Scalex and ScalaR calculators. BMC Med Res Methodol. 2022; 22(1): 209. doi: 10.1186/s12874-022-01694-7.

12. Taiwo IA, Oloyede OA, Dosumu AO. Frequency of sickle cell genotype among the Yorubas in Lagos: Implications for the level of awareness and genetic counseling for sickle cell disease in Nigeria. J Community Genet. 2011; 2(1): 13-8. doi: 10.1007/s12687-010-0033-x.

13. Diwe K, Iwu AC, Uwakwe K, Duru C, Merenu I, Ogunniyan T, et al. Prevalence and patterns of sickle cell disease among children attending tertiary and non-tertiary health care institutions in a South Eastern State, Nigeria: A 10-year survey. J Res Med Dent Sci. 2016; 4(3): 183-9. doi: 10.5455/jrmds.2016432.

14. Hockham C, Bhatt S, Colah R, Mukherjee MB, Penman BS, Gupta S, et al. The spatial epidemiology of sickle-cell anemia in India. Sci Rep. 2018; 8(1): 17685. doi: 10.1038/s41598-018-36077-w.

15. Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. J Hematol Oncol. 2022; 15(1): 20. doi: 10.1186/s13045-022-01237-z.

16. Gaur M, Sehgal T. Reticulocyte count: a simple test but tricky interpretation! Pan Afr Med J. 2021; 40: 3. doi: 10.11604/pamj.2021.40.3.31316.

17. Rai D, Wilson AM, Moosavi L. Histology, reticulocytes. Florida, USA: StatPearls Publishing; 2023.

18. Das J, Khonglah Y, Tiewsoh I, Chowdhury Z, Barman H. Utility of reticulocyte indices in the diagnosis of pancytopenia. J Fam Med Prim Care. 2022; 11(4): 1335-40. doi: 10.4103/jfmpc.jfmpc_1121_21.

19. Piva E, Brugnara C, Spolaore F, Plebani M. Clinical utility of reticulocyte parameters. Clin Lab Med. 2015; 35(1): 133-63. doi: 10.1016/j.cll.2014.10.004.

20. Nwabuko ON, Onwuchekwa U, Iheji O. An overview of sickle cell disease from the socio-demographic triangle: A Nigerian single-institution retrospective study. Pan Afr Med J. 2022; 41: 161. doi: 10.11604/pamj.2022.41.161.27117.

21. Odièvre MH, Verger E, Silva-Pinto AC, Elion J. Pathophysiological insights in sickle cell disease. Indian J Med Res. 2011; 134(4): 532-7.

22. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010; 376(9757): 2018-31. doi: 10.1016/S0140-6736(10)61029-X.

23. Santos FK, Maia CN. Patients with sickle cell disease taking hydroxyurea in the Hemocentro Regional de Montes Claros. Rev Bras Hematol Hemoter. 2011; 33(2): 105-9. doi: 10.5581/1516-8484.20110029.

24. Carden MA, Fasano RM, Meier ER. Not all red cells sickle the same: Contributions of the reticulocyte to disease pathology in sickle cell anemia. Blood Rev. 2020; 40: 100637. doi: 10.1016/j.blre.2019.100637.

25. Janus J, Moerschel SK. Evaluation of anemia in children. Am Fam Physician. 2010; 81(12): 1462-71.

26. Sani MA, Adewuyi JO, Babatunde AS, Olawumi HO, Shittu RO. The iron status of sickle cell anaemia patients in Ilorin, North Central Nigeria. Adv Hematol. 2015: 2015: 386451. doi: 10.1155/2015/386451.

27. Akingbola TS, Ezekekwu CA, Yaria J, Saraf SL, Hsu LL, Cooper R, et al. Assessment of bone marrow function in sickle cell anaemia patients using corrected reticulocyte counts. Blood. 2015; 126(23): 4581. doi: 10.1182/blood.V126.23.4581.4581.

28. Kaushal M, Byrnes C, Khademian Z, Duncan N, Luban NL, Miller JL et al. Examination of reticulocytosis among chronically transfused children with sickle cell anemia. PLoS One. 2016; 11(4): e0153244. doi: 10.1371/journal.pone.0153244.

29. Candar Ö, Ekinci Ö, Doğan A, Ebinç S. Do mean platelet volume and platelet count vary on a daily or gender basis? J Curr Hematol Oncol Res. 2024; 2(1): 6-9. doi: 10.51271/JCHOR-0027.

30. Jeremiah Z, Magnus A. Elevated mean cell volume in sickle cell anaemia: One story, too many? Sanamed. 2024; 19(1): 51–7. doi: 10.5937/sanamed19-49277.

31. Akodu SO, Njokanma OF, Adeolu-Kehinde O. Erythrocyte indices in preschool Nigerian children with sickle cell anaemia in steady state. Int J Hematol Oncol Stem Cell Res. 2015; 9(1): 5-9.

32. Kabuyi PL, Mbayabo G, Ngole M, Zola AL, Race V, Matthijs G, et al. Hydroxyurea treatment for adult sickle cell anemia patients in Kinshasa. EJHaem. 2023; 4(3): 595-601. doi: 10.1002/jha2.735.

33. Ofakunrin AO, Oguche S, Adekola K, Okpe ES, Afolaranmi TO, Diaku-Akinwumi IN, et al. Effectiveness and Safety of Hydroxyurea in the Treatment of Sickle Cell Anaemia Children in Jos, North Central Nigeria. J Trop Pediatr. 2020; 66(3): 290-8. doi: 10.1093/tropej/fmz070.

34. Amarendar S, Chandra S, Karedla S, Jyothi AK, Gupta D, Jagadale KA. Optimizing hematological profiles and reducing vaso-occlusive crises: hydroxyurea therapy's impact on complete blood count parameters in sickle cell disease patients. Journal of Population Therapeutics and Clinical Pharmacology. 2024; 31(6): 2041-57. doi: 10.53555/jptcp.v31i6.6768.

35. Parodi E, Romano F, Ramenghi U. How we use reticulocyte parameters in workup and management of pediatric hematologic diseases. Front Pediatr. 2020; 8: 588617. doi: 10.3389/fped.2020.588617.

36. López Rubio M, Argüello Marina M. The current role of hydroxyurea in the treatment of Sickle Cell Anemia. J Clin Med. 2024; 13(21): 6404. doi: 10.3390/jcm13216404.

37. Khargekar N, Banerjee A, Athalye S, Mahajan N, Kargutkar N, Tapase P, et al. Role of hydroxyurea therapy in the prevention of organ damage in Sickle Cell Disease: a systematic review and meta-analysis. Syst Rev. 2024; 13(1): 60. doi: 10.1186/s13643-024-02461-z.

Correspondence to/Autor za korespondenciju
Professor Zaccheaus Jeremiah
Department of Haematology and Blood Transfusion Science
Faculty of Medical Laboratory Science
Rivers State University
Port Harcourt, Nigeria
Email: zaccheaus.jeremiah@ust.edu.ng
Phone: +234 803 404 5636

ORCID iD
Prof Z.A. Jeremiah – 0000-0003-4994-9826
Dr Bliss Nsan Jeremiah – 0009-0007-4309-9441
Dr Chioma Okechukwu – 0000-0001-8616-8047

***How to cite this article**:* Jeremiah Z, Odozi C, Jeremiah B, Okechukwu C. Clinical utlity of reticulocyte indices in the diagnosis and management of paediatric sickle cell disease patients in Port Harcourt, Nigeria. Sanamed. 2025; 20(2): 175-186. doi: 10.5937/sanamed0-58242.

SANAMED
2025; 20(2): 187–193
ISSN-1452-662X

DOI: 10.5937/sanamed0-58968
UDK: 616.284-002-06-053.2; 616.833.17-009.11-053.2
ID: 174861833
Case report

FACIAL NERVE PARALYSIS AS A COMPLICATION OF ACUTE OTITIS MEDIA IN CHILDREN: A CASE REPORT AND LITERATURE REVIEW

Zdravković Đorđe,[1] Zlatković Slađan[2]

[1] General Hospital "Sveti Luka", Department of Otorhinolaryngology, Smederevo, Serbia
[2] General Hospital "Sveti Luka", Department of Neurology, Smederevo, Serbia

Primljen/Received: 19. 05. 2025. Prihvaćen/Accepted: 15. 07. 2025. Published online first 11. 08. 2025.

Abstract: **Introduction**: The facial nerve controls facial expression, and its dysfunction causes facial asymmetry and reduced mimic function. Facial nerve paralysis is significantly less common in children compared to adults. Children under the age of 10 are estimated to have an incidence rate of approximately 3 per 100,000 per year. The leading cause of facial paralysis in the pediatric population is idiopathic (Bell's palsy), similar to that in adults. In cases where the cause is not idiopathic, infections accompanied by trauma and congenital anomalies are the most frequent etiological factors of facial nerve paralysis in children. This condition is most often attributed to nerve edema and subsequent compression within the bony fallopian canal.

Case Report: This report presents a case of peripheral facial nerve paralysis as an extracranial complication of acute otitis media in a 2-year-old child. It also includes a literature review focusing on recent diagnostic protocols, evaluation, and therapeutic approaches.

Conclusion: As demonstrated in our case, the prognosis for facial nerve paralysis associated with acute otitis media (AOM) was generally good after appropriate therapy. Recovery from facial paralysis usually occurs within three months. This report delineates a rare complication of AOM in children. Timely recognition and appropriate therapy are crucial to achieve good outcomes.

Keywords: facial nerve paralysis, acute otitis media, complications.

INTRODUCTION

Acute otitis media (AOM) is an inflammation of the middle ear mucosa, characterized by the presence of effusion and symptoms that develop within a period of up to 48 hours (1). It is one of the most common infectious diseases affecting children worldwide. AOM usually develops as a viral upper respiratory tract infection caused by respiratory viruses, followed by a bacterial superinfection in the presence of a weakened immune response or inadequate treatment. The infection typically spreads through the rhinogenic route, that is, from the nasopharynx via the eustachian tube (2).

In most children older than one year, the condition resolves spontaneously within several days, even without the use of antibiotic therapy. However, in approximately 20% of cases, the disease progresses, and serial superinfections may lead to serious complications. The most common extracranial complication is acute mastoiditis, which typically occurs in the third week after disease onset, either in a latent or manifested form. Facial nerve paralysis, an extracranial complication of AOM, is also possible, although it is extremely rare and occurs in approximately 0.005% of affected children (3). The primary reason for the low incidence, particularly in developed countries, is mandatory immunization and the use of broad-spectrum antibiotics for the treatment of acute otitis media (AOM) (4). Severe intracranial complications, such as meningitis or brain abscesses, fortunately occur only rarely (Figure 1).

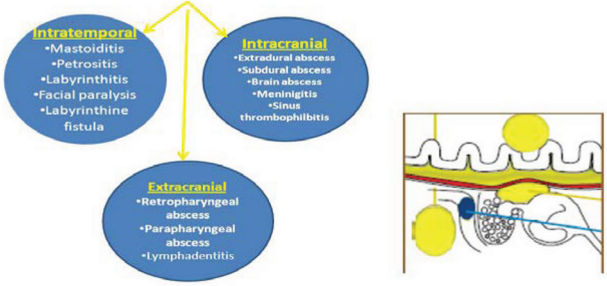


Figure 1. *Complications of otitis media (Wikipedia. Available at: https://en.wikipedia.org/wiki/Otitis_media)*

Considering the still not fully defined etiopathogenetic mechanisms of AOM and the rarity of peripheral FNP as a complication of this condition, there is an ongoing debate regarding diagnostic and therapeutic approaches. In this context, particular attention should be paid to the indications for surgical treatment of this complication (5).

Case Report

A two-year-old boy was brought to the otorhinolaryngology outpatient clinic by his parents due to an acute onset of paralysis on the left side of his face. The symptoms began four days before the examination and initially presented as occasional coughing and clear nasal discharge. The child did not have a fever. Before referral to an otorhinolaryngology specialist, the attending pediatrician initiated symptomatic therapy.

The patient was the first child, born from an uncomplicated pregnancy and delivered vaginally three weeks before term. The APGAR score was 9/10, and the birth weight was 2,900 g. He had received all vaccinations appropriate for his age. He had previously experienced one episode of bronchitis. There was no known history of allergies to food or medications. Family history revealed that the mother had experienced hearing impairment requiring hearing aids since the age of four, due to recurrent ear infections.

Upon admission to the pediatric department, the child was conscious, afebrile, eupneic, and hemodynamically stable, with the following vital signs: body weight, 12 kg; body temperature, 36.8°C; oxygen saturation, 99%; and heart rate, 90 beats/min. There was no rash, and the skin had normal coloration and turgor. Lung auscultation revealed normal breath sounds, with no additional findings. The heart rhythm was regular and the tone was clear, with no murmurs.

Neurological examination revealed weakness and asymmetry of the left facial muscles, sparing the forehead muscles. There was loss of the left nasolabial and frontal folds, a lag in the left corner of the mouth when crying, and a drooping of the left corner of the mouth at rest, accompanied by difficulty closing the left eye and infrequent blinking (Figure 2). The clinical presentation corresponded to grade IV peripheral facial nerve paralysis based on the House–Brackmann scale (6) (Table 1).

Figure 2. *Left-sided peripheral facial nerve palsy in a child at the time of initial examination (The image is from the authors' personal archive)*

Otorhinolaryngological examination revealed bilateral hyperemia of the tympanic membranes on otomicroscopy, with a visible fluid level in the middle ear and a deformed light reflex. There was no swelling or hyperemia in the retroauricular or mastoid regions, and no tenderness on palpation. Oropharyngoscopy showed mild hyperemia of the pharyngeal mucosa. Endonasally, there was a serous discharge in the nasal passages, whereas palpation of the neck revealed no enlarged lymph nodes.

Laboratory tests performed after admission indicated an elevated leukocyte count of 12.87/mm³, with

Table 1. *House-Brackmann facial nerve grading system. (Adapted from: House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg. 1985; 93(2): 146–7. (6))*

Grade	Description	Eye Closure	Forehead Movement	Mouth Movement	Synkinesis
I	Normal facial function in all areas.	Complete	Normal	Symmetrical	None
II	Slight weakness; normal tone & symmetry at rest.	Complete, slight effort	Normal	Slight asymmetry	Mild
III	Moderate dysfunction, no noticeable weakness at rest.	Complete, with effort	Slightly reduced	Asymmetry present	Noticeable
IV	Severe dysfunction, obvious facial weakness.	Incomplete	No movement	Asymmetry with effort	Present
V	Severe dysfunction, minimal facial motion.	Incomplete	No movement	Very asymmetrical	Present
VI	Total facial paralysis; no motion.	None	No movement	No movement	None

a predominance of 67% lymphocytes. The C-reactive protein (CRP) level was 0.9 mg/L, whereas all other biochemical parameters and urinalysis with sediment were within the reference ranges.

Tympanometry showed a flat Type B tympanogram, indicating immobility of the tympanic membrane and the presence of fluid in the middle ear. Head and temporal bone computed tomography (CT) was planned as an emergency procedure but was not performed due to the parents' refusal to consent to this diagnostic procedure.

After establishing the diagnosis of acute paralysis nervi Facialis (FNP) associated with AOM, the child was promptly started on intravenous antibiotic therapy (Ceftriaxone 500 mg i.v. every 12 hours), along with probiotic syrup, tapering corticosteroids (Methylprednisolone 20 mg i.v.), vitamin B infusion (every 24 hours), and an analgesic–antipyretic (Paracetamol syrup 5 ml every 6–8 hours).

On the second day of hospitalization, an ophthalmology consultation was performed to prevent the most serious complications of facial nerve paralysis, such as corneal damage due to reduced secretion and lagophthalmos. The on-call ophthalmologist noted that mydriasis was appropriate for the child's age, and all other ophthalmological findings were normal. Artificial tears were prescribed to keep the eye moisturized, and the mother was advised to monitor the child and ensure that the affected eye was closed during sleep. A follow-up ophthalmology appointment was scheduled for seven days later, at which point the findings remained normal.

For the purpose of further etiological diagnostics of peripheral facial nerve paralysis and identification of potential infectious agents, serological tests were performed for herpes simplex virus, varicella virus, coxsackievirus, and adenovirus, all of which returned negative results. The urine culture results were also negative.

On the same day, left-sided paracentesis was performed for both diagnostic and therapeutic purposes. Microbiological analysis of the purulent drainage yielded negative results. Follow-up laboratory tests conducted the following day revealed inflammatory marker levels within the reference range.

During hospitalization, the patient remained afebrile and hemodynamically stable. Intravenous antibiotics, corticosteroids, and symptomatic therapy were administered for several days. On the seventh day of hospitalization, the child was discharged in good general condition, with a recommendation to continue oral antibiotic therapy (Cefixime oral suspension, 5 ml once daily) for the next seven days. Additionally, facial muscle exercises were advised under the supervision of a physiotherapist and a speech therapist at the local health center. A follow-up examination was scheduled seven days later, with instructions to immediately contact an otorhinolaryngologist through the emergency service in case of any new symptoms.

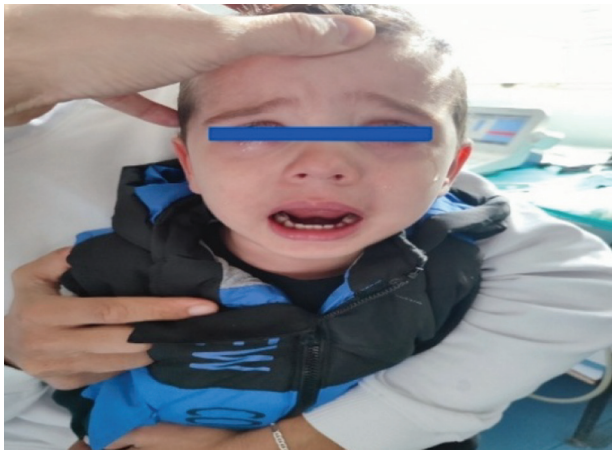


Figure 3. *Follow-up examination.Significant improvement in local findings*
(The image is from the authors' personal archive)

Figure 4. *One-month follow-up.*
Complete recovery of facial function
(The image is from the authors' personal archive)

At the follow-up visit, a significant improvement in local findings was observed. Inspection revealed only slight facial asymmetry, with normal closure of the left eye and forehead wrinkling (Figure 3). Otoscopic examination showed no hyperemia of the tympanic membranes; pink oropharyngeal mucosa was noted during oropharyngoscopy, and clear nasal passages were observed during anterior rhinoscopy. Palpation of the neck revealed no enlarged lymph nodes. The parents reported that the child remained afebrile throughout, with normal sleep and a preserved appetite.

At the next follow-up examination one month later, paralysis of the left side of the face had undergone complete regression (Figure 4).

The child was subsequently monitored over a six-month period with monthly check-ups, during which findings related to the seventh cranial nerve remained normal. Throughout this period, the child was in good general health and showed appropriate developmental progress for his age.

Two months later, the child developed a new episode of bilateral otitis media accompanied by low-grade fever, but without any cranial nerve deficits or other signs of intra- or extratemporal complications. The condition was treated conservatively following a ten-day course of antibiotic therapy according to protocol. At the follow-up examination, the tympanic membranes appeared normal, and the child was in good general condition.

A consultative examination by an otologic surgeon was also conducted at that time. The clinical findings were normal, and bilateral Type A tympanograms were recorded. Recommendations were made to maintain nasal patency, support the child's immune system, and schedule follow-up visits as needed.

Since then, there have been no recurrent ear infections or related complications, and the child, accompanied by his parents, has not returned to the otorhinolaryngology outpatient clinic or emergency pediatric services.

DISCUSSION

The facial nerve is the seventh cranial nerve, and its most prominent function is the innervation of the muscles involved in facial expression. Additionally, it has secretory and sensory functions. The nerve can be divided into six segments: intracranial, intrameatal, labyrinthine, tympanic, mastoid, and extracranial. In the final segment, after exiting the facial canal, it enters the parotid gland and divides into two main branches, which further split into the "pes anserinus" — five terminal branches. The ramus marginalis is particularly important in the facial musculature because it is the only branch that does not form anastomoses with neighboring branches (7).

Etiology

The possible etiological factors of FNP in children can be classified as congenital or acquired, with acquired causes further divided into infectious, traumatic, neoplastic, hypertension-related, and idiopathic causes (Bell's palsy).

If there is no definitive cause for acute unilateral facial paralysis (onset <72 h), the diagnosis is Bell's palsy. In children, the incidence of Bell's palsy is estimated at 6.1 cases per 100,000 children annually between the ages of 1 and 15 (8).

Acute otitis media remains the most common infectious cause of facial nerve paralysis in children (9). Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), among others, can also lead to facial paralysis.

Iatrogenic facial nerve paralysis may occur because of oromaxillofacial, parotid, or otologic surgery. In a case series of 35 pediatric patients with facial nerve paralysis, only three cases were iatrogenic, and all patients achieved full recovery. However, if a child does not show relatively rapid improvement, less common causes, such as malignancies and metabolic disorders, must be considered. Hypertension is a rare cause of facial nerve paralysis in children. FNP in children may, in very rare instances, be associated with systemic diseases such as granulomatosis with polyangiitis (GPA), sarcoidosis, and systemic lupus erythematosus. Due to the scarcity of pediatric cases, evidence is mostly restricted to individual case reports (9).

In the pre-antibiotic era, the incidence of facial nerve paralysis in acute otitis media (AOM) was 0.5%. In the era of antimicrobial therapy, the frequency of AOM dropped sharply. The etiology of facial nerve paralysis in patients with AOM remains unknown (10, 11). Nerve paralysis typically develops gradually in children, within 2–3 days of the onset of acute otitis media.

Diagnostic approaches in previous studies

The assessment of peripheral FNP is twofold: the cause and degree of the lesion must be examined, and the location of the lesion must be topographically assessed. The investigation of the cause, in addition to a thorough medical history (which must include details on prior ear treatments, injuries, or diagnosed systemic diseases), should include a detailed clinical examination (otorhinolaryngological, neurological, assessment of the degree of the lesion, internal medicine, and ophthalmological examinations), radiological investigations (CT of the temporal bones and MRI of the temporal region and pontocerebellar angle, ultrasound of the parotid glands), and electrodiagnostic tests such as electromyography.

During physical examination, a patient with FNP cannot raise the eyebrow or close the eyelid on the affected side. The nasolabial fold is typically absent, and the affected side of the mouth droops with possible drooling (12). During clinical examination, special attention should be given to examining the external auditory canal, auricle, and mastoid. Infections of the middle ear leading to facial nerve paralysis are commonly associated with middle ear effusion, redness of

the tympanic membrane, purulent ear discharge, and tenderness over the mastoid region. These symptoms typically precede the onset of facial weakness by approximately 5 to 8 days (13). Topographical assessment of the lesion site is performed using multiple tests, including the Schirmer test, stapedius reflex, gustometry, and sialography.

If other inflammatory etiologies are considered, studies on C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) should be ordered.

A tympanogram should be performed for all children with acute FNP. As part of the diagnostic protocol, in patients with facial nerve paralysis caused by AOM, computed tomography (CT) of the head should be performed to exclude a radiological diagnosis of otomastoiditis and document the presence of associated intracerebral or extracerebral complications (14).

Therapeutic modalities in previous studies

After diagnosis, facial nerve paralysis associated with AOM should be treated appropriately according to the prescribed protocol, with eradication of the purulent process as the primary goal (15). The therapy should include a third-generation broad-spectrum cephalosporin (e.g., Ceftriaxone, as in the case of our patient) as the initial antibiotic therapy, which may be modified based on microbiological susceptibility. The actual efficacy of antiviral medications in cases of facial nerve paralysis is still not fully understood (16). Corticosteroids appear to reduce recovery time, especially when applied in the early stages of the disease (17). Eye care is extremely important to prevent corneal abrasion and vision loss. If incomplete eyelid closure is present, it is essential to use saline eye drops during the day and ophthalmic ointments during sleep.

Surgical approaches for the treatment of this condition remain unclear. Several authors have reached a consensus on the need for myringotomy with or without the placement of ventilation tubes in cases of otomastoiditis without tympanic membrane perforation, suggesting that mastoidectomy should be performed, or less commonly, decompression of the facial nerve should be considered if no improvement occurs within a few days (18).

Prognosis

Children with facial paralysis typically have a favorable prognosis. Complete recovery of facial function occurs in about 90% of Bell's palsy cases in children aged 14 or younger, whereas only around one-third of patients over the age of 60 experience full recovery (19).

As demonstrated in our case, the outcome for facial nerve paralysis associated with AOM was generally good after appropriate therapy, although the incidence of residual dysfunction was 6% (20). While functional recovery is common, a study by Biebl and colleagues showed that in 175 children with facial paralysis, although most had complete functional recovery, residual facial asymmetry persisted in up to half of the cases (21).

CONCLUSION

This case highlights the intricacy of peripheral facial nerve paralysis as an extracranial complication of acute otitis media in children. Recovery from facial paralysis usually occurs within three months. This integration of data contributes to a deeper understanding of the clinical course of peripheral facial nerve paralysis during AOM in children and reinforces the necessity for vigilant monitoring and proactive intervention to improve the quality of life of our patients.

Abbreviations

AOM – Acute Otitis Media
PNF – Paralysis Nervi Facialis

Conflict of Interest Statement: The authors declare that there is no conflict of interest related to this study.

Authorship Statement: The author(s) have made substantial contributions to all phases of the study and are able to take public responsibility for the content and results presented in the manuscript.

Author Contributions & Responsibilities: The author takes full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. Both authors contributed equally to the preparation of this manuscript. The publisher remains neutral regarding jurisdictional claims in institutional affiliations.

Funding: This research received no external funding.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

PARALIZA FACIJALNOG NERVA KAO KOMPLIKACIJA AKUTNOG ZAPALJENJA SREDNJEG UVA KOD DECE: PRIKAZ SLUČAJA I PREGLED LITERATURE

Zdravković Đorđe,[1] Zlatković Slađan[2]

[1] Opšta Bolnica "Sveti Luka", Odeljenje za otorinolaringologiju, Smederevo, Srbija
[2] Opšta Bolnica "Sveti Luka", Odeljenje za neurologiju, Smederevo, Srbija

Uvod: Facijalni nerv je živac čije oštećenje dovodi do poremećaja mimike i pojave asimetrije lica. Paraliza facijalnog nerva je značajno ređa kod dece u poređenju sa odraslima. Procenjuje se da deca mlađa od 10 godina imaju učestalostod približno 3 na 100.000 godišnje. Vodeći uzrok facijalne paralize u pedijatrijskoj populaciji je idiopatski (Bell-ova paraliza), slično kao i kod odraslih. U slučajevima kada uzrok nije idiopatski, infekcije praćene traumom i urođene anomalije su najčešći etiološki faktori paralize facijalnog nerva kod dece. Javlja se kao posledica edematozne reakcije živca i sledstvene kompresije u Falopijevom koštanom kanalu.

Prikaz slučaja: Prikazujemo slučaj periferne paralize facijalisa kao egzokranijalne komplikacije akutnog otitisa kod deteta uzrasta dve godine. Zatim će biti načinjen pregled literature sa fokusom na savremene dijagnostičke protokole, evaluaciju i terapijske pristupe.

Zaključak: Kao što je prikazano u našem slučaju, prognoza paralize facijalnog nerva povezane sa akutnim zapaljenjem srednjeg uva (AOM) je generalno dobra nakon odgovarajuće terapije. Oporavak od facijalne paralize obično se dešava u roku od tri meseca. Ovaj prikaz prikazuje retku komplikaciju AOM-a kod dece. Pravovremeno prepoznavanje i adekvatna terapija su ključni za postizanje dobrih ishoda.

Ključne reči: paraliza facijalnog nerva, akutni otitis medijalis, komplikacije.

REFERENCES

1. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013; 131(3): e964-e99. doi: 10.1542/peds.2012-3488.

2. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: Otitis media with effusion (update). Otolaryngol Head Neck Surg. 2016; 154(1 Suppl): S1–S41. doi: 10.1177/0194599815623467.

3. Ellefsen B, Bonding P. Facial palsy in acute otitis media. Clin Otolaryngol Allied Sci. 1996; 21(5): 393–5. doi: 10.1046/j.1365-2273.1996.00810.x.

4. Dissanayake G, Zergaw M, Elgendy M, Billey A, Saleem A, Zeeshan B, et al. Effectiveness of pneumococcal conjugate vaccines over antibiotic resistant acute otitis media in children: a systematic review. Cureus. 2024; 16(8): e67771. doi: 10.7759/cureus.67771.

5. Popovtzer A, Raveh E, Bahar G, Oestreicher-Kedem Y, Feinmesser R, Nageris BI. Facial palsy associated with acute otitis media. Otolaryngol Head Neck Surg. 2005; 132(2): 327–9. doi: 10.1016/j.otohns.2004.09.013.

6. House JW, Brackmann DE. Facial nerve grading system. Otolaryngol Head Neck Surg. 1985; 93(2): 146-7. doi: 10.1177/019459988509300202.

7. Lorch M, Teach SJ. Facial nerve palsy: etiology and approach to diagnosis and treatment. Pediatr Emerg Care. 2010; 26(10): 763–9. doi: 10.1097/PEC.0b013e3181f3bd4a.

8. Ozkale Y, Erol I, Saygi S, Yilmaz I. Overview of pediatric peripheral facial nerve paralysis: analysis of 40 patients. J Child Neurol. 2015; 30(2): 193–9. doi: 10.1177/0883073814530497.

9. Evans AK, Licameli G, Brietzke S, Whittemore K, Kenna M. Pediatric facial nerve paralysis: patients, management and outcomes. Int J Pediatr Otorhinolaryngol. 2005; 69(11): 1521–8. doi: 10.1016/j.ijporl.2005.04.025.

10. Gupta DK, Atam V, Chaudhary SC. Recurrent lower motor neuron type facial palsy: an unusual manifestation of SLE. BMJ Case Rep. 2011; 2011: bcr1220103564. doi: 10.1136/bcr.12.2010.3564.

11. D'Anna C, Diplomatico M, Tipo V. Facial palsy in a baby with acute otitis media. Arch Dis Child Educ Pract Ed. 2018; 103(3): 155–7. doi: 10.1136/archdischild2017312743.

12. Ciorba A, Corazzi V, Conz V, Bianchini C, Aimoni C. Facial nerve paralysis in children. World J Clin Cases. 2015; 3(12): 973–9. doi: 10.12998/wjcc.v3.i12.973.

13. Shargorodsky J, Lin HW, Gopen Q. Facial nerve palsy in the pediatric population. Clin Pediatr (Phila). 2010; 49(5): 411–7. doi: 10.1177/0009922809347798.

14. Chen XC, Lu CW, Liu CH, Wei CC. Facial palsy complicated by masked otomastoiditis in a 3 month old infant. J Emerg Med. 2014; 46(2): e47–50. doi: 10.1016/j.jemermed.2013.08.029.

15. Gaio E, Marioni G, de Filippis C, Tregnaghi A, Caltran S, Staffieri A. Facial nerve paralysis secondary to acute otitis media in infants and children. J Paediatr Child Health. 2004; 40(8): 483–6. doi: 10.1111/j.1440-1754.2004.00436.x.

16. Wohrer D, Moulding T, Titomanlio L, Lenglart L. Acute facial nerve palsy in children: gold standard management. Children (Basel). 2022; 9(2): 273. doi: 10.3390/children9020273.

17. Malik M, Cubitt JJ. Paediatric facial paralysis: An overview and insights into management. J Paediatr Child Health. 2021; 57(6): 786–90. doi: 10.1111/jpc.15310.

18. Helms D, Roberge RJ, Kovalick M. Otomastoiditis related facial nerve palsy. J Emerg Med. 2003; 25(1): 45–9. doi: 10.1016/S07364679(03)00132X.

19. Peitersen E. Bell's palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl. 2002; (549): 4–30. doi: 10.1080/000164802320401694.

20. White N, McCans KM. Facial paralysis secondary to acute otitis media. Pediatr Emerg Care. 2000; 16(5): 343–5. doi: 10.1097/00006565200010000000010.

21. Biebl A, Lechner E, Hroncek K, Preisinger A, Eisenkölbl A, Schmitt K, et al. Facial nerve paralysis in children: is it as benign as supposed. Pediatr Neurol. 2013; 49(3): 178–81. doi: 10.1016/j.pediatrneurol.2013.03.013.

Correspondence to/Autor za korespondenciju
Đorđe Zdravković
Department of Otorhinolaryngology, General Hospital "Sveti Luka" Smederevo
Email: drzdravkovic@hotmail.com
Phone number: +381 65 636 476
Adress: Mome Ardelića, 7/21, Smederevo, Serbia
ORCID: 0009-0005-0757-6795

How to cite this article: **Zdravković Đ**, Zlatković S. Facial Nerve Paralysis as a Complication of Acute Otitis Media in Children: A Case Report and Literature Review**.** Sanamed. 2025; 20(2): 187-193. doi: 10.5937/sanamed0-58968.

SANAMED
2025; 20(2): 195–200
ISSN-1452-662X

DOI: 10.5937/sanamed0-59888
UDK: 616.5-006.81-033.2
ID: 174865161
Case report

A CHALLENGING "SILENT DEPTH" CLINICAL SCENARIO IN NORTH MACEDONIA: UNMASKING A RARE CASE OF AMELANOTIC MELANOMA WITH TRAPEZIUS MUSCLE INVASION AND METASTATIC DISEASE

Peneva Margarita,[1] Gjorgjeska Andrijana,[1] Zhogovska Elizabeta,[1] Ivanova Maja,[2] Aleksovski Darko,[1] Baneva Evgenija,[2] Breshkovska Hristina[3]

[1] Ss. Cyril and Methodius University, Faculty of Medicine, University Clinic for Plastic and Reconstructive Surgery, Skopje, North Macedonia
[2] Ss. Cyril and Methodius University, Faculty of Medicine, University Clinic for Oncology and Radiotherapy, Skopje, North Macedonia
[3] Ss. Cyril and Methodius University, Faculty of Medicine, University Clinic for Dermatology, Skopje, North Macedonia

Primljen/Received: 01. 07. 2025. Prihvaćen/Accepted: 14. 08. 2025. Published online first 26. 08. 2025.

Abstract: **Introduction:** Amelanotic melanoma is a subtype of melanoma that exhibits little or no pigment on visual or histological examination. Approximately 1–8% of all melanomas are amelanotic. It can mimic various benign or malignant melanocytic and non-melanocytic skin tumors, thereby presenting a significant diagnostic challenge. Primary amelanotic melanoma with muscle involvement is an extremely rare entity. A review of the literature revealed no series or case reports.

Case Report: We present the case of a 62-year-old female patient with primary amelanotic melanoma infiltrating the trapezius muscle. The tumor was excised together with a clinically positive lymph node on the right side of the neck. Computed tomography (CT) angiography of the lungs, abdomen, and pelvis demonstrated bilateral diffuse nodular changes, a mediastinal pretracheal lymph node, and multiple diffuse liver lesions, consistent with secondary deposits. Molecular pathology revealed positivity for the BRAF V600E2/K/R/D mutation, and the patient began first-line targeted therapy with BRAF/MEK inhibition in accordance with protocols for BRAF-positive metastatic melanoma. Three months later, a follow-up CT scan demonstrated complete remission of the previously observed metastatic changes.

Conclusion: Primary amelanotic melanoma with muscle involvement is exceptionally rare, with no published series or case reports identified. This case highlights the importance of early detection and treatment in suspected melanoma and underscores the need to consider melanoma in all clinically unclear cases.

Keywords: amelanotic melanoma, muscle invasion, trapezius muscle, metastatic disease.

INTRODUCTION

Melanoma is a malignant tumor arising from melanocytes in the skin, mucosa, and various internal organs. Amelanotic melanoma (AM) is a subtype that shows little or no pigment on visual or histological examination (1, 2). It is classified into three groups according to the presence and amount of melanin: amelanotic, partially pigmented, and lightly colored melanoma (3). Although completely amelanotic melanomas are rare, hypomelanotic melanomas with slight pigmentation are more common. Approximately 1–8% of all melanomas are amelanotic; however, the true incidence is difficult to determine due to frequent misdiagnosis (4, 5).

Amelanotic melanoma typically appears as a pink, red, or flesh-colored lesion and may mimic both benign and malignant melanocytic and non-melanocytic skin tumors, as well as inflammatory skin diseases, thereby posing a diagnostic challenge. Therefore, any erosive tumor should raise suspicion for amelanotic melanoma, particularly when located on the palms or soles (6, 7).

Dermoscopy is an essential diagnostic tool for pigment evaluation and for identifying characteristic

vascular structures that are not visible to the naked eye. A polymorphous vascular pattern, especially with irregular dot vessels or a combination of dotted and linear irregular vessels, is the most frequent dermoscopic finding (8, 9). In some cases, a full-thickness biopsy is required for definitive diagnosis.

Surgical excision remains the gold standard for primary melanoma treatment. The National Comprehensive Cancer Network (NCCN) recommends surgical margins based on Breslow depth. For tumors thicker than 2 mm, wide local excision with a 2-cm negative margin is advised, with the deep margin extending to, but not including, the fascia—the first lymphovascular barrier (10, 11).

Targeted therapy with BRAF/MEK inhibitors has emerged as a critical treatment strategy for patients with metastatic BRAF-positive melanoma. This approach specifically targets aberrant signaling pathways driven by BRAF mutations, leading to enhanced therapeutic efficacy and improved clinical outcomes (12–15).

Primary amelanotic melanoma with muscle involvement is exceedingly rare. A review of the literature revealed no series or case reports. Here, we present a case of amelanotic melanoma with invasion of the trapezius muscle.

CASE REPORT

A 62-year-old female patient with a large lump in the right scapular region extending to the supraclavicular fossa was referred to the University Clinic for Plastic and Reconstructive Surgery in Skopje, North Macedonia, from a smaller hospital in the country (Figure 1). The patient's history revealed progressive tumor growth over several years. Two years prior, at the hospital from which she was referred, the lesion had been

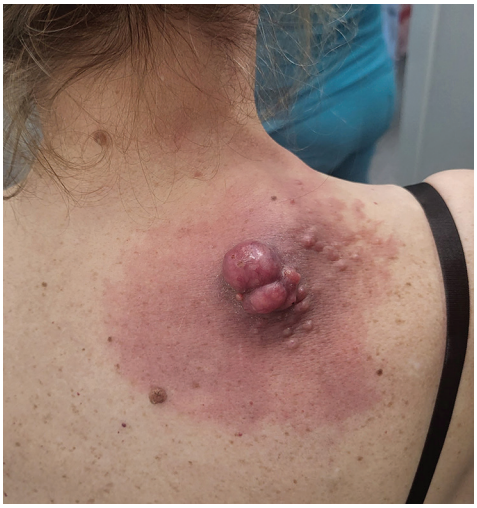


***Figure 1**. A large, pink-grey, multinodular dermal tumor measuring 7 × 8 cm, with the largest nodule protruding 2 cm above the surrounding skin*
(The image is from the authors' personal archive)

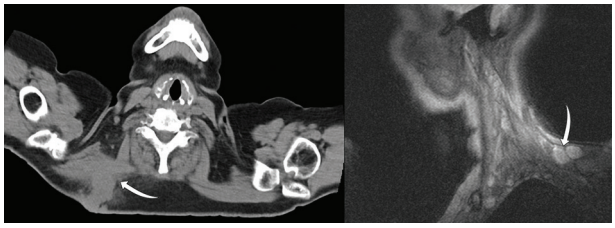


***Figure 2**. (Left Image) The arrow shows the tumor infiltrating the trapezius muscle (CT scan)*
(Right image) The arrow points the 2 subcutaneous nodules at the posterolateral site of the neck on the MRI
(The image is from the authors' personal archive)

followed with a differential diagnosis of a lipoma. The patient was advised to have it removed for pathological examination but declined the recommendation.

At presentation, clinical examination revealed a large, pink-grey, multinodular dermal tumor in the right scapular region extending toward the right supraclavicular fossa. The tumor measured 7 × 8 cm, with the largest nodule protruding 2 cm above the surrounding skin. On physical examination, the tumor was firm and relatively immobile to the underlying tissues. Additionally, two subcutaneous palpable masses were noted at the back of the neck, along with an enlarged lymph node on the right side of the neck. Clinically, it was an unclear case, which prompted further examinations.

Therefore, the patient underwent computed tomography (CT) angiography, magnetic resonance imaging (MRI), and fine-needle aspiration (FNA) biopsy. The CT and MRI revealed a tumor infiltrating the trapezius muscle (Figure 2), and the FNA biopsy categorized the tumor in the V classification group for malignancy, strongly suggesting melanoma. Owing to the tumor's aggressiveness and muscle involvement, sarcoma was also considered in the differential diagnosis.

Surgical removal of the tumor and the positive cervical lymph node was planned. Under general anesthesia, with the patient positioned in lateral decubitus, the tumor was excised with a 2-cm free lateral margin, and the deep

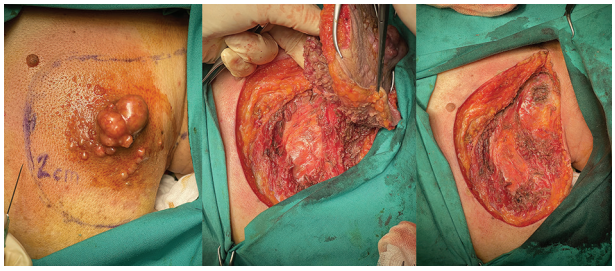


***Figure 3**. Intraoperative view: the tumor was excised with a 2-cm healthy lateral margin, and the deep margin included part of the trapezius muscle*
(The image is from the authors' personal archive)

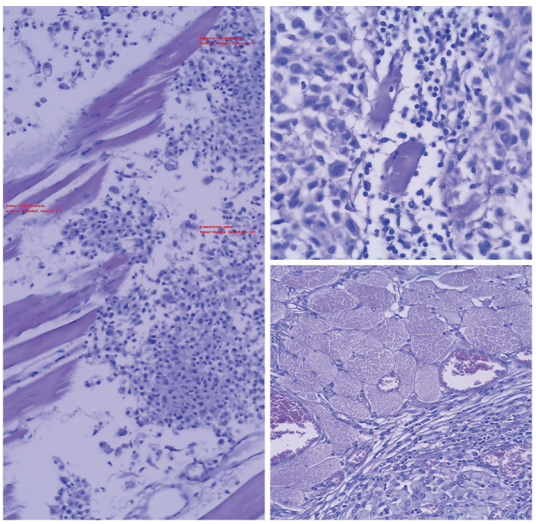


***Figure 4**. Histopathological Features of Amelanotic Melanoma with Muscle Invasion (H&E)*

(*) Tumor infiltration within skeletal muscle: The left panel demonstrates extensive infiltration of atypical amelanotic melanocytes between and around skeletal muscle fibers.

(→) Atypical melanocytes between muscle fibers: High magnification shows pleomorphic, non-pigmented tumor cells infiltrating the muscle tissue.

(#) Transition zone: tumor-muscle interface: The bottom right highlights the border between invaded tumor areas and relatively preserved skeletal muscle bundles.

(The image is from the authors' personal archive)

margin included part of the trapezius muscle (Figure 3). The clinically positive lymph node on the right side of the neck was also removed. After achieving hemostasis, the wound was left open to heal by secondary intention pending the pathohistological results. One week later, the pathology report confirmed primary amelanotic nodular melanoma involving the skin, subcutaneous tissue, and infiltrating the trapezius muscle, along with satellitosis and amelanotic metastases to the cervical lymph node (pT4a, pN3, pMX, R0, stage IIIC according to the AJCC staging system) (Figure 4). Both the lateral and deep margins were tumor-free. Additional molecular pathology findings confirmed positivity for the BRAF V600E2/K/R/D mutation. At that time, the wound was closed using a split-thickness skin graft (STSG), and a second subcutaneous metastatic deposit was removed.

Laboratory findings supported the diagnosis, with an increased S-100 protein level of 0.432 µg/L (reference < 0.12 µg/L). The postoperative course was uneventful, and one week after the second operation, the patient was discharged and referred to the University Clinic for Oncology and Radiotherapy for further evaluation and treatment.

CT angiography of the lungs, abdomen, and pelvis showed bilateral diffuse nodular changes predominantly in the basal lung regions, with the largest lesion in the right basal lung measuring up to 11 mm, consistent with secondary deposits. A mediastinal pretracheal lymph node measured up to 1.25 cm. Additionally, the liver exhibited multiple (approximately seven) diffuse hypodense lesions that were poorly demarcated in the venous phase; the largest lesion in segment 6 measured up to 1.2 cm, suggestive of secondary deposits.

The patient began first-line targeted therapy with BRAF/MEK inhibitors following National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) protocols for BRAF-positive metastatic melanoma (Vemurafenib 1920 mg daily and Cobimetinib 60 mg daily) (12–15).

Three months later, a follow-up CT angiography of the lungs, abdomen, and pelvis demonstrated complete remission of the previously observed metastatic changes in the lungs, mediastinum, and liver. The patient continues targeted therapy with BRAF/MEK inhibitors, with no reported adverse effects.

The patient was last evaluated at the University Clinic for Oncology and Radiotherapy on April 22, 2025, after 8 months of therapy. At that time, it was decided to transition melanoma treatment from targeted therapy (Vemurafenib/Cobimetinib) to immunotherapy (Pembrolizumab). This change in therapeutic approach was prompted by the diagnosis of a second, independent malignancy—stage IIB squamous cell carcinoma of the cervix—for which concurrent radiochemotherapy was indicated and will also be administered at the Clinic for Oncology and Radiotherapy. The second tumor was diagnosed eight months after the initial diagnosis of amelanotic melanoma.

DISCUSSION

Amelanotic melanoma is a variant characterized by the absence of melanin production, which complicates early detection, identification, and pathological diagnosis. The absence of ulceration may mislead clinicians, although it can be associated with a better prognosis; however, it does not mitigate the risks of deep infiltration and metastasis.

In this case, the clinical examination showed no tumor ulceration, while MRI confirmed muscle involvement—a rarity in melanoma cases. Although the fine-needle biopsy suggested melanoma, its limited sensitivity contributed to the initial exclusion of dermoscopy from the diagnostic workup. As supported by the literature, the absence of melanin combined with the lack of ulceration and the presence of muscle involvement initially obscured the diagnosis of melanoma.

According to the American Joint Committee on Cancer (AJCC), amelanotic melanoma carries a poor-

er prognosis than other melanoma types due to deeper infiltration from delayed diagnosis and its inherently aggressive nature.

The aggressive tumor behavior in this case is exemplified by the muscle involvement. It remains a subject of discussion whether muscle involvement was solely a function of tumor aggressiveness in the absence of ulceration. Skeletal muscle is generally resistant to primary and metastatic cancer; however, primary malignant tumors—including melanomas—can involve skeletal muscle more commonly than metastases. This muscle resistance to cancer may be related to the inherent resistance of muscle tissue to tumor growth, its variable blood flow, and metabolism (15). The rich vasculature of skeletal muscle, regulated by beta-adrenergic receptors, results in highly variable blood flow (16). Some studies suggest that lactic acid production by muscles may inhibit tumor cell growth (17), and that cancer cell survival is enhanced in denervated muscle compared to electrically stimulated muscle (18).

The pathology report confirmed the presence of satellitosis and amelanotic metastases to the cervical lymph node in this case of primary amelanotic nodular melanoma.

A meta-analysis on nodular melanoma indicated that lymph node involvement is associated with a reduced 5-year survival rate—estimated at around 40–60%, depending on tumor characteristics and treatment options. Furthermore, amelanotic metastases in amelanotic melanoma are linked to a poorer prognosis, as documented in the literature (5).

The anatomical distribution of amelanotic melanoma varies by gender. In males, these lesions are typically located on the trunk, whereas in females they are more commonly found on the limbs. In contrast to these trends, the present case involves a female patient with an amelanotic melanoma located on the trunk (19).

Systemic therapy is recommended for stage III cutaneous melanoma following wide local excision, with or without sentinel lymph node biopsy and lymph node dissection (12–15). Evaluation for potential hereditary syndromes and appropriate genetic referral should also be considered.

CONCLUSION

Primary amelanotic melanoma with muscle involvement is exceptionally rare. A review of the literature revealed no series or case reports.

This case underscores the importance of early detection and treatment in suspected melanoma and highlights the need to consider melanoma in all clinically unclear cases. Due to the aggressive nature of the disease, timely surgical management and careful monitoring are essential to address potential metastases and ensure comprehensive care.

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study.

Funding: None.

Author Contributions & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. All authors contributed equally to the preparation of this manuscript.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

IZAZOVAN KLINIČKI SLUČAJ U SEVERNOJ MAKEDONIJI: REDAK SLUČAJ AMELANOTIČNOG MELANOMA SA INVAZIJOM TRAPEZASTOG MIŠIĆA I METASTATSKOM BOLEŠĆU

Peneva Margarita,[1] Gjorgjeska Andrijana,[1] Zhogovska Elizabeta,[1] Ivanova Maja,[2] Aleksovski Darko,[1] Baneva Evgenija,[2] Breshkovska Hristina[3]

[1] Univerzitet Svetog Ćirila i Metodija, Medicinski fakultet, Univerzitetska klinika za plastičnu i rekonstruktivnu hirurgiju, Skoplje, Severna Makedonija

[2] Univerzitet Svetog Ćirila i Metodija, Medicinski fakultet, Univerzitetska klinika za onkologiju i radioterapiju, Skoplje, Severna Makedonija

[3] Univerzitet Svetog Ćirila i Metodija, Medicinski fakultet, Univerzitetska klinika za dermatologiju, Skoplje, Severna Makedonija

Uvod: Amelanotični melanom je podtip melanoma koji pri vizuelnom ili histološkom pregledu pokazuje malo ili nimalo pigmenta. Čini 1–8% svih melanoma. Može imitirati različite benigne i maligne tumore kože, kako melanocitne tako i nemelanocitne, što često predstavlja dijagnostički izazov. Primarni

amelanotični melanom sa zahvatanjem mišića je izuzetno redak, a u literaturi nisu opisane serije slučajeva ili pojedinačni izveštaji.

Prikaz slučaja: Predstavljamo slučaj 62-godišnje pacijentkinje sa primarnim amelanotičnim melanomom koji infiltriše trapezasti mišić. Tumor je hirurški odstranjen zajedno sa klinički pozitivnim limfnim čvorom sa desne strane vrata. CT pluća, abdomena i karlice pokazao je bilateralne difuzne nodularne promene, pretrahealni mediastinalni limfni čvor i više difuznih lezija u jetri, u skladu sa sekundarnim promenama. Molekularna analiza otkrila je BRAF V600E2/K/R/D mutaciju, te je pacijentkinja započela ciljanu terapiju BRAF/MEK inhibitorima po protokolu za BRAF-pozitivni metastatski melanom. Tri meseca kasnije kontrolni CT je pokazao potpunu remisiju prethodno registrovanih metastatskih promena.

Zaključak: Primarni amelanotični melanom sa zahvatanjem mišića je izuzetno redak, bez ranije objavljenih slučajeva. Ovaj slučaj ističe značaj ranog otkrivanja i pravovremenog lečenja sumnjivih melanoma i podseća da melanom treba razmatrati u svim klinički nejasnim slučajevima.

Ključne reči: amelanotični melanom, infiltracija mišića, trapezasti mišić, metastatska bolest.

REFERENCES

1. Osama MA, Rao S, Bakshi N, Badwal S, Aggarwal S. Amelanotic melanoma: a great masquerader. J Lab Physicians. 2022; 15(2): 300–5. doi: 10.1055/s-0042-1757236.

2. Peneva M, Zhogovska E, Noveski L, Dzonov B, Trenchev V, Breshkovska H, et al. Multiple primary melanomas. a case report. Mac. Med. Preview. 2022; 76(2): 89–94.

3. Stojkovic-Filipovic J, Kittler H. Dermatoscopy of amelanotic and hypomelanotic melanoma. J Dtsch Dermatol Ges. 2014; 12(6): 467–72. doi: 10.1111/ddg.12368.

4. Pizzichetta MA, Talamini R, Stanganelli I, Puddu P, Bono R, Argenziano G, et al. Amelanotic/hypomelanotic melanoma: clinical and dermoscopic features. Br J Dermatol. 150(6): 1117–24. doi: 10.1111/j.1365-2133.2004.05928.x.

5. Okobi OE, Abreo E, Sams NP, Chukwuebuni OH, Tweneboa Amoako LA, Wiredu B, et al. Trends in melanoma incidence, prevalence, stage at diagnosis, and survival: an analysis of the United States Cancer Statistics (USCS) database. Cureus. 2024; 16(10): e70697. doi: 10.7759/cureus.70697.

6. Stanec S, Stanec Z, et al. Melanom. Zagreb: Medicinska naklada, 2006.

7. Kaizer-Salk KA, Herten RJ, Ragsdale BD, Sengelmann RD. Amelanotic melanoma: a unique case study and review of the literature. BMJ Case Rep. 2018; 2018: bcr2017222751. doi: 10.1136/bcr-2017-222751.

8. Steglich RB, Meotti CD, Ferreira MS, Lovatto L, de Carvalho AV, de Castro CG. Dermoscopy clues in the diagnosis of amelanotic and hypomelanotic malignant melanoma. An Bras Dermatol. 2012; 87(6): 920–3. doi:10.1590/s0365-05962012000600019.

9. Kreusch J, Koch F. Auflichtmikroskopische Charakterisierung von Gefässmustern in Hauttumoren [Incident light microscopic characterization of vascular patterns in skin tumors]. Hautarzt. 1996; 47(4): 264-72. German. doi: 10.1007/s001050050412.

10. Chung KC. Grabb and Smith's Plastic Surgery. 8th ed. Philadelphia: Wolters Kluwer; 2020.

11. Pathak S, Zito PM. Clinical guidelines for the staging, diagnosis, and management of cutaneous malignant melanoma. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2025.

12. Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. J Transl Med. 2012; 10: 85. doi: 10.1186/1479-5876-10-85.

13. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010; 363(9): 809-19. doi: 10.1056/NEJMoa1002011.

14. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014; 371(20): 1877-88. doi: 10.1056/NEJMoa1406037.

15. Viswanathan N, Khanna A. Skeletal muscle metastasis from malignant melanoma. Br J Plast Surg. 2005; 58(6): 855-8. doi: 10.1016/j.bjps.2004.12.001.

16. Fidler IJ, Hart IR. Principles of cancer biology: biology of cancer metastasis. In: De Vita VT, Hellman S, Rosenberg SA, eds. Cancer, principles and practice in oncology. Philadelphia: JB Lippincott; 1982: 80–92.

17. Seely S. Possible reasons for the high resistance of muscle to cancer. Med Hypotheses. 1980; 6(2): 133–7. doi: 10.1016/0306-9877(80)90079-1.

18. Weiss L. Biomechanical destruction of cancer cells in skeletal muscle: a rate-regulator for hematogenous metastasis. Clin Exp Metastasis. 1989; 7(5): 483–91. doi: 10.1007/BF01753809.

19. Butrimas G, Cibulskaitė R, Janonytė U, Silickytė R. Associations Between Cutaneous Melanoma Traits and the Likelihood of Metastasis. Cureus. 2024; 16(7): e65754. doi: 10.7759/cureus.65754.

Correspondence to/Autor za korespondenciju
Assoc. Prof. Margarita Peneva
University Clinic for Plastic and Reconstructive Surgery, Ss Cyril and Methodius University,
Skopje, North Macedonia
Address: Blvd. Partizanski odredi 117-3/8 1000 Skopje, North Macedonia
Mobile: +389 70 255 303
Email: mapeneva@yahoo.com; margarita.peneva@plasticsurgery.com.mk

ORCID iDs
Margarita Peneva: 0000-0002-7434-2439
Andrijana Gjorgjeska: 0009-0003-5985-6452
Elizabeta Zhogovska: 0009-0009-8747-0200
Maja Ivanova: 0009-0008-1698-1938
Darko Aleksovski: 0009-0002-8075-1586
Evgenija Baneva: 0009-0008-9458-302X
Hristina Breshkovska: 0009-0005-2072-2160

***How to cite this article**:* Peneva M, Gjorgjeska A, Zhogovska E, Ivanova M, Aleksovski D, Baneva E, Breshkovska H. A challenging "silent depth" clinical scenario in North Macedonia: unmasking a rare case of amelanotic melanoma with trapezius muscle invasion and metastatic disease. Sanamed. 2025; 20(2): 195-200. doi: 10.5937/sanamed0-59888.

SANAMED
2025; 20(2): 201–205
ISSN-1452-662X

DOI: 10.5937/sanamed0-59880
UDK: 616.348/.35-006.6-085; 61:004.8
ID: 174897417
Review article

THE ROLE OF THE MUCINOUS COMPONENT AS AN INDEPENDENT PREDICTIVE FACTOR IN COLORECTAL ADENOCARCINOMA THERAPY - THE POTENTIAL OF ARTIFICIAL INTELLIGENCE AS AN ADJUNCT TOOL TO IMPROVE TREATMENT OUTCOMES

Milina Srđan,[1] **Nikolić Marija**,[1] Trifunović Nemanja,[1] Trifunović Jovana,[2] Surla Dimitrije[1]

[1] Clinical Hospital Center Zemun, Department of General Surgery, Belgrade, Serbia
[2] Clinical Hospital Center Zemun, Oncology Hospital, Belgrade, Serbia

Primljen/Received: 01. 07. 2025. Prihvaćen/Accepted: 09. 08. 2025. Published online first 19. 08. 2025.

Abstract: Mucinous adenocarcinoma of the colon (MAC) is a distinct histological subtype of colorectal cancer (CRC), defined by the presence of ≥ 50% extracellular mucin. This CRC subtype exhibits unique clinical and molecular characteristics, including more frequent localization in the right colon, higher prevalence among younger patients, and associations with microsatellite instability-high (MSI-H) and BRAF gene mutations. Evidence suggests that MAC demonstrates a poorer response to conventional therapies; however, the independent prognostic value of the mucinous component remains unclear.

This narrative review aims to evaluate the prognostic significance of the mucinous component in CRC. Twenty relevant studies published between 2018 and 2025 were analyzed. Results indicate that MAC is more often detected at advanced stages and shows a weaker response to fluorouracil-based regimens and neoadjuvant chemoradiotherapy in rectal tumors. Nonetheless, several studies reported no significant difference in overall survival between mucinous and non-mucinous carcinomas. Additionally, immune-related factors such as tumor-infiltrating lymphocytes (TILs) and desmoplasia are gaining importance and may have greater prognostic value than mucinous differentiation itself.

MAC also frequently exhibits marked molecular heterogeneity, complicating prognosis and treatment decisions. Consequently, careful patient monitoring and timely molecular profiling are essential for optimizing therapy. Novel artificial intelligence–based models that integrate histological images, molecular biomarkers, and clinical data show promise for personalizing treatment in MAC.

In conclusion, although MAC is currently treated according to standard CRC guidelines, its distinct features underscore the need for individualized therapeutic approaches and further clinical research.

Keywords: mucinous adenocarcinoma, colorectal cancer, prognosis, MSI-H, treatment response.

INTRODUCTION

Colorectal cancer (CRC) is among the leading causes of cancer incidence and mortality worldwide, particularly in countries with medium to high socioeconomic status. Mucinous adenocarcinoma of the colon (MAC) is a distinct histological subtype of CRC, defined by the presence of ≥ 50% extracellular mucin within the tumor. This subtype is characterized by specific features, including preferential localization in the right colon, higher prevalence among younger patients, high microsatellite instability (MSI-H), BRAF gene mutations, and a generally poorer response to therapy, especially fluorouracil-based chemotherapy (1).

In contrast to non-mucinous adenocarcinomas, which often show different biological behavior and clinical outcomes, mucinous adenocarcinomas exhibit notable heterogeneity and distinct patterns of invasion and metastasis. However, the independent prognostic significance of the mucinous component remains a subject of ongoing debate.

The aim of this paper is to explore the prognostic potential of the mucinous component in colon adenocarcinoma through a narrative review of recent literature and to evaluate its clinical relevance.

Histopathological and Molecular Characteristics of Mucinous Adenocarcinoma

Mucinous adenocarcinoma of the colon (MAC) represents a histologically distinct and biologically unique subgroup of colorectal cancer (CRC), with its presence significantly influencing clinical presentation, therapeutic response, and disease outcomes. Defined by the presence of ≥ 50% extracellular mucin in tumor tissue, MAC encompasses a complex biological background beyond its histological classification.

Numerous studies suggest that MAC is not simply a histological variant but a tumor type marked by a distinct molecular profile and immune microenvironment, which poses challenges for standard treatment protocols and raises important questions about its independent prognostic value.

Epidemiological data indicate that MAC occurs more frequently in the right colon and among younger patients, often diagnosed at advanced stages (2–5). Analyses of the SEER database confirm that mucinous tumors are more commonly identified at stages III and IV, reflecting their aggressive clinical behavior (3, 5). Additionally, MAC is more frequently associated with high microsatellite instability (MSI-H) and BRAF mutations, which contribute to its biological uniqueness and have important therapeutic implications (1, 6).

However, the molecular heterogeneity within MAC raises the question of whether all mucinous adenocarcinomas should be regarded as a single homogeneous group.

Immune Microenvironment and Prognostic Indicators

Beyond molecular factors, the immune landscape of MAC has attracted increasing attention. Tumor-infiltrating lymphocytes (TILs) hold particular prognostic significance as strong predictors of survival. Fadel et al. emphasize that the density of lymphocytic infiltration and the presence of desmoplasia have greater predictive value for survival than mucinous differentiation alone (3). High lymphocyte density correlates with a more robust immune response and better prognosis, whereas desmoplasia — reactive fibrous proliferation surrounding the tumor — is linked to a more aggressive disease phenotype and poorer outcome.

Kepil et al. thoroughly characterized the immune phenotype of mucinous tumors, highlighting significant differences in the expression of immune markers (PD-L1, CD8+ T-cells, macrophages CD68 and CD163) compared to non-mucinous tumors (7). These alterations suggest distinct immune evasion mechanisms and potentially differential responses to immunotherapy. Methodologically, the study employed immunohistochemistry to precisely localize and quantify these markers, contributing to the reliability of findings and advancing understanding of the mucinous tumor microenvironment.

Controversies in Prognosis and Therapeutic Implications

Prognostic data for MAC remain heterogeneous. Kim et al. reported poorer prognosis and diminished response to adjuvant chemotherapy in stages II and III compared to non-mucinous tumors (4). Conversely, Huang et al. and Dai et al. found no significant differences in outcomes at earlier disease stages (8, 9). These findings suggest that mucinous histology alone is insufficient as an independent prognostic factor, underscoring the need to integrate molecular, histological, and immune parameters.

Chemotherapy Resistance and Limitations of Standard Treatment

Therapeutic response in MAC further complicates clinical management. Standard CRC regimens include FOLFOX, CAPOX, and FOLFIRI; however, MAC tumors often exhibit resistance to fluorouracil-based therapies, especially those with MSI-H and BRAF mutations (1, 6–11). A meta-analysis by McCawley et al. demonstrated that mucinous rectal adenocarcinoma responds significantly worse to neoadjuvant chemoradiotherapy, evidenced by lower pathological regression, higher rates of positive surgical margins, and inferior overall prognosis compared to non-mucinous tumors (10). These differences are attributed to the unique biological properties and microenvironment of mucinous tumors, highlighting the necessity for individualized therapeutic approaches.

While RAS wild-type status remains a key criterion for selecting patients for anti-EGFR therapy, Moretto et al. showed that the presence of a mucinous component may substantially reduce the efficacy of this treatment even in patients with molecular markers of sensitivity (11). This suggests that tumor histological subtype independently influences therapeutic response, advocating for an integrated approach that incorporates both molecular and histopathological tumor characteristics.

Secondary Tumor Risk and Surveillance Considerations

Wu et al. analyzed the risk of secondary malignancies in patients with various CRC histological subtypes, including MAC, and identified specific patterns of new tumor development with elevated risks for certain secondary primary tumors (12). These findings emphasize the need for vigilant long-term follow-up and consideration of histological subtype in secondary prevention strategies.

Emerging Role of Immunotherapy in MSI-H Mucinous CRC

Immunotherapy, particularly anti-PD-1 blockade, shows significant promise in MSI-H mucinous carcinomas, offering novel treatment options for this subgroup characterized by poor chemotherapy response. Interest in applying artificial intelligence (AI) and radiomics for personalized therapy is rapidly increasing, as these approaches enable integration of multidimensional data and more precise prediction of therapeutic outcomes.

Radiomics and Artificial Intelligence in Precision Oncology

Radiomics—the quantitative analysis of medical imaging data (CT, MRI)—combined with AI facilitates prediction of tumor molecular features (KRAS, NRAS, BRAF mutations) and assessment of treatment response. Yang et al. successfully predicted these mutations using CT-based radiomics (13). Shaish et al. demonstrated that MRI-radiomics can predict response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer (14). Li et al. developed machine learning models to preoperatively predict perineural invasion and KRAS mutation, with direct clinical applications (15). Within the ATTRACT study, Caruso et al. applied radiogenomics to identify high-risk colorectal tumors, paving the way for integrated strategies to detect biologically aggressive MACs (16, 17). Golia Pernicka et al. showed that MSI status can be predicted using radiomics from baseline CT scans (18), while Abbaspour et al. successfully predicted lymph node metastasis preoperatively with radiomics (19).

Although these data confirm the considerable potential of radiomics and AI in optimizing MAC therapy, widespread clinical implementation requires further research, methodological standardization, and validation through prospective multicenter studies.

CONCLUSION

Mucinous adenocarcinoma of the colon represents a biologically and clinically distinct subgroup of colorectal cancer, characterized by unique molecular, histological, and immunological features that significantly influence therapeutic response and potentially impact patient survival. Although multiple studies have reported a poorer prognosis associated with MAC, especially in advanced disease stages, the prognostic value of the mucinous component alone remains controversial and appears to be modulated by additional factors such as molecular alterations and the tumor immune microenvironment.

The integration of molecular biomarkers—including MSI status, BRAF and RAS mutations—with immune indicators like tumor-infiltrating lymphocytes and immune checkpoint expression offers a promising avenue for personalizing therapeutic strategies in this subgroup. Moreover, emerging technologies such as radiomics and artificial intelligence hold considerable potential to enhance preoperative tumor characterization, predict treatment response, and refine risk stratification.

To translate these advances into clinical practice, further prospective, multicenter studies are required to validate stratification models and optimize tailored treatment protocols specifically for patients with mucinous adenocarcinoma. Such efforts are essential to improve clinical outcomes and advance precision oncology for this challenging CRC subtype.

Abbreviations

AI – Artificial Intelligence
CAPOX – Capecitabine and Oxaliplatin
CRC – Colorectal Cancer
CT – Computed Tomography
EGFR – Epidermal Growth Factor Receptor
FOLFIRI – 5-Fluorouracil, Leucovorin, and Irinotecan
FOLFOX – 5-Fluorouracil, Leucovorin, and Oxaliplatin
MAC – Mucinous Adenocarcinoma of the Colon
MRI – Magnetic Resonance Imaging
MSI-H – Microsatellite Instability-High
PD-1 – Programmed Cell Death Protein 1
PD-L1 – Programmed Death-Ligand 1
RAS – Rat Sarcoma Viral Oncogene Homolog
SEER – Surveillance, Epidemiology, and End Results (database)
TILs – Tumor-Infiltrating Lymphocytes

Conflict of Interest Statement

The authors declare that there is no conflict of interest related to this study.

Funding: None.

Author Contributions & Responsibilities: The authors take full responsibility for the accuracy and integrity of the content, as well as the validity of institutional affiliations. The publisher remains neutral regarding jurisdictional claims in institutional affiliations. All authors have read and agreed to the published version of the manuscript. All authors contributed equally to the preparation of this manuscript.

Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

ULOGA MUCINOZNE KOMPONENTE KAO NEZAVISNOG PREDIKTIVNOG FAKTORA U TERAPIJI ADENOKARCINOMA KOLONA-POTENCIJAL VEŠTAČKE INTELIGENCIJE KAO POMOĆNOG ALATA ZA UNAPREĐENJE ISHODA LEČENJA

Milina Srđan,[1] **Nikolić Marija**,[1] Trifunović Nemanja,[1] Trifunović Jovana,[2] Surla Dimitrije[1]

[1] Kliničko-bolnički centar Zemun, Služba opšte hirurgije, Beograd, Srbija
[2] Kliničko-bolnički centar Zemun, Bolnica za onkologiju, Beograd, Srbija

Mucinozni adenokarcinom kolona (MAC) je posebna histološka varijanta kolorektalnog karcinoma (CRC), definisana prisustvom ≥ 50% ekstracelularnog mucina. Ovaj podtip CRC-a ima različite kliničke i molekularne karakteristike, kao što su češća lokalizacija u desnom kolonu, viša prevalence kod mlađih pacijenata, prisustvo mikrosatelitske nestabilnosti (MSI-H), kao i mutacije u BRAF genu. Postoje indicije da MAC pokazuje slabiji odgovor na konvencionalne terapije, ali ostaje pitanje da li mucinozna komponenta ima nezavisan prognostički značaj.

U ovom radu prikazan je narativni pregled literature sa ciljem procene prognostičke vrednosti mucinozne komponente kod CRC. U analizu je uključeno 20 relevantnih studija objavljenih u periodu od 2018. do 2025. godine. Rezultati ukazuju da MAC češće biva otkriven u uznapredovalim stadijumima bolesti i pokazuje slabiji odgovor na fluorouracil-bazirane protokole i neoadjuvantnu radiohemoterapiju kod rektalnih tumora. Ipak, nekoliko studija nije pronašlo značajnu razliku u ukupnom preživljavanju između mucinoznih i nemucinoznih karcinoma. Pored toga, sve veći značaj imaju imunološki faktori kao što su prisustvo TILs i desmoplazije, koji mogu nadmašiti prognostički uticaj same mucinozne diferencijacije.

Zapaženo je i da MAC često pokazuje izraženiju molekularnu heterogenost, što dodatno komplikuje prognozu i terapijski pristup. U tom kontekstu, pažljivo praćenje bolesnika i pravovremena molekularna karakterizacija postaju od ključnog značaja za optimalno lečenje. Novi modeli zasnovani na veštačkoj inteligenciji, koji integrišu histološke slike, molekularne biomarkere i kliničke podatke, ukazuju na potencijal u personalizaciji terapije za MAC. U zaključku, iako se MAC leči prema važećim CRC smernicama, njegove specifičnosti ukazuju na potrebu za individualizovanim terapijskim pristupom i daljim kliničkim istraživanjima.

***Ključne reči**:* mucinozni adenokarcinom, kolorektalni karcinom, prognoza, MSI-H, terapijski odgovor.

REFERENCES

1. Reynolds IS, O'Connell E, Fichtner M, McNamara DA, Kay EW, Prehn JHM, et al. Mucinous adenocarcinoma of the colon and rectum: a genomic analysis. J Surg Oncol. 2019; 120(8): 1427–35. doi: 10.1002/jso.25764.

2. Eunus MF, Saleh FM, Karim SN, Tanzim MA, Hossain MI. Clinicopathological characteristics of mucinous and non-mucinous adenocarcinoma of the colon and rectum. Mymensingh Med J. 2023; 32(2): 480–6.

3. Fadel MG, Malietzis G, Constantinides V, Pellino G, Tekkis P, Kontovounisios C. Clinicopathological factors and survival outcomes of signet-ring cell and mucinous carcinoma versus adenocarcinoma of the colon and rectum: a systematic review and meta-analysis. Discov Oncol. 2021; 12(1): 5. doi: 10.1007/s12672-021-00398-6.

4. Kim S, Huh JW, Lee WY, Yun SH, Kim HC, Cho YB, et al. Prognostic impact of mucinous adenocarcinoma in stage II and III colon cancer. Dis Colon Rectum. 2023; 66(11): 1473–80. doi: 10.1097/DCR.0000000000002733.

5. Zhu L, Ling C, Xu T, Zhang J, Zhang Y, Liu Y, et al. Clinicopathological features and survival of signet-ring cell carcinoma and mucinous adenocarcinoma of right colon, left colon, and rectum. Pathol Oncol Res. 2021; 27: 1609800. doi: 10.3389/pore.2021.1609800.

6. Reynolds IS, O'Connell E, Fichtner M, Blümel A, Mason SE, Kinross J, et al. An insight into the driver mutations and molecular mechanisms underlying mucinous adenocarcinoma of the rectum. Dis Colon Rectum. 2021; 64(6): 677–88. doi: 10.1097/DCR.0000000000001825.

7. Kepil N, Batur S, Goksel S. Immunohistochemical and genetic features of mucinous and signet-ring cell carcinomas of the stomach, colon and rectum: a comparative study. Int J Clin Exp Pathol. 2019; 12(9): 3483–91.

8. Huang L, Luo S, Lai S, Liu Z, Hu H, Chen M, et al. Survival after curative resection for stage I colorectal mucinous adenocarcinoma. BMC Gastroenterol. 2022; 22(1): 192. doi: 10.1186/s12876-022-02276-z.

9. Dai D, Zhou B, Zhong Y, Jin H, Wang X. Survival of patients with resected primary colorectal mucinous adenocarcinoma: A competing risk nomogram analysis. Oncol Lett. 2019; 18(6): 6594–604. doi: 10.3892/ol.2019.11024.

10. McCawley N, Clancy C, O'Neill BD, Deasy J, McNamara DA, Burke JP. Mucinous rectal adenocarcinoma is associated with a poor response to neoadjuvant chemoradiotherapy: a systematic review and meta-analysis. Dis Colon Rectum. 2016; 59(12): 1200–8. doi: 10.1097/DCR.0000000000000635.

11. Moretto R, Morano F, Ongaro E, Rossini D, Pietrantonio F, Casagrande M, et al. Lack of benefit from anti-EGFR treatment in RAS and BRAF wild-type metastatic colorec-

tal cancer with mucinous histology or mucinous component. Clin Colorectal Cancer. 2019; 18(2): 116–24. doi: 10.1016/j.clcc.2019.02.007.

12. Wu M, Huang M, He C, Chen C, Li H, Wang J, et al. Risk of second primary malignancies based on the histological subtypes of colorectal cancer. Front Oncol. 2021; 11: 650937. doi: 10.3389/fonc.2021.650937.

13. Yang L, Dong D, Fang M, Zhu Y, Zang Y, Liu Z, et al. Can CT-based radiomics signature predict KRAS/NRAS/BRAF mutations in colorectal cancer? EurRadiol. 2018; 28(5): 2058–67. doi: 10.1007/s00330-017-5146-8.

14. Shaish H, Aukerman A, Vanguri R, Spinelli A, Armenta P, Jambawalikar S, et al. Radiomics of MRI for pretreatment prediction of pathologic complete response, tumor regression grade, and neoadjuvant rectal score in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation: an international multicenter study. Eur Radiol. 2020; 30(11): 6263–73. doi: 10.1007/s00330-020-06968-6.

15. Li Y, Eresen A, Shangguan J, Yang J, Benson AB 3rd, Yaghmai V, et al. Preoperative prediction of perineural invasion and KRAS mutation in colon cancer using machine learning. J Cancer Res Clin Oncol. 2020; 146(12): 3165–74. doi: 10.1007/s00432-020-03354-z.

16. Caruso D, Polici M, Zerunian M, Monterubbiano A, Tarallo M, Pilozzi E, et al. CT-based radiogenomic analysis to predict high-risk colon cancer (ATTRACT): a multicentric trial. Eur Radiol. 2025 Jun 5. doi: 10.1007/s00330-025-11728-5. Online ahead of print.

17. Mei WJ, Mi M, Qian J, Xiao N, Yuan Y, Ding PR. Clinicopathological characteristics of high microsatellite instability/mismatch repair-deficient colorectal cancer: a narrative review. Front Immunol. 2022; 13: 1019582. doi:10.3389/fimmu.2022.1019582.

18. Golia Pernicka JS, Gagniere J, Chakraborty J, Yamashita R, Nardo L, Creasy JM, et al. Radiomic-based prediction of microsatellite instability in colorectal cancer at initial computed tomography evaluation. Abdom Radiol (NY). 2019; 44(11): 3755–63. doi: 10.1007/s00261-019-02117-w.

19. Abbaspour E, Karimzadhagh S, Monsef A, Joukar F, Mansour Ghanaei F, Hassanipour S. Application of radiomics for preoperative prediction of lymph node metastasis in colorectal cancer: a systematic review and meta-analysis. Int J Surg. 2024; 110(6): 3795–813. doi: 10.1097/JS9.0000000000001239.

Correspondence to/Autor za korespondenciju
Marija Nikolić,
Vukova 9, CHC Zemun, Belgrade, Serbia
Email: marija.nikolic80@gmail.com
phone: +381 64 4139268

ORCID iD:
Marija Nikolić: 0009-0004-3415-1277
Nemanja Trifunović: 0009-0001-1085-9500
Jovana Trifunović: 0009-0005-1373-6521

***How to cite this article**:* Milina S, Nikolić M, Trifunović N, Trifunović J, Surla D. The role of the mucinous component as an independent predictive factor in colorectal adenocarcinoma therapy – the potential of artificial intelligence as an adjunct tool to improve treatment outcomes. Sanamed. 2025; 20(2): 201-205. doi: 10.5937/sanamed0-59880.

SANAMED
2025; 20(2): 207–212
ISSN-1452-662X

DOI: 10.5937/sanamed0-56752
UDK: 616.379-008.64-085.37
ID: 174899977
Review article

DIABETES MELLITUS TYPE 2 - THE IMPORTANCE OF HEALTH EDUCATION OF PATIENTS: A REVIEW

Pelicic Damir,[1, 2] Djukic Vukica[1]

[1] Clinical Center of Montenegro, Podgorica, Montenegro
[2] University of Montenegro, Faculty of Medicine Podgorica, Berane College of Nursing, Montenegro

Primljen/Received: 13. 02. 2025. Prihvaćen/Accepted: 29. 04. 2025. Published online first 05. 05. 2025.

Abstract: Diabetes mellitus (DM) represents a significant public health problem, and Type 2 Diabetes Mellitus (DM2) is the most common form of this disease, accounting for about 90% of all DM cases worldwide. The prevalence of DM2 has reached pandemic proportions, especially in developed countries. Studies have shown that a low level of health literacy among patients with DM2 can be a significant predictor of premature death, disability, and increased healthcare costs. It is important to emphasize patient education to reduce mortality and improve the quality of life for DM2 patients. This review is based on a search of scientific literature, focusing on original research articles and meta-analyses found in scientific databases such as PubMed, SCOPUS, MEDLINE, and SCI Index, all published within the last ten years. The search focused on topics related to the public health issue of DM2 and the health literacy of affected individuals. Key terms used in the search included diabetes mellitus, Type 2 diabetes mellitus, prevention, health education, public health, risk factors, and others. Studies have shown that a low level of health literacy among DM2 patients can significantly increase the risk of premature death and disability, as well as healthcare costs. It is crucial to emphasize patient education to reduce mortality and improve the quality of life for DM2 patients.

Keywords: Diabetes mellitus, risk factors, obesity, cardiovascular disease, prevention, education.

INTRODUCTION

DM is a significant public health problem, leading to severe complications due to inadequate glucose regulation and control, which causes considerable disability, mortality, and economic consequences for both individuals and countries (1, 2). DM is a metabolic disorder characterized by persistent hyperglycemia (3). Today, DM is one of the leading causes of death from chronic non-communicable diseases (3). The importance of this disease lies in its potential to cause numerous complications, leading to increased morbidity and mortality (3, 4). DM2 is the most common form of this disease, making up about 90% of all DM cases globally (5). The prevalence of DM2 has reached pandemic levels, especially in developed countries (6). DM2 results from mutations in multiple genetic loci and the involvement of about 250 polymorphic genes. Genetic predisposition does not always lead to disease development, but favorable conditions, such as reduced physical activity, obesity, and aging, can accelerate the onset of the disease (7, 8). In terms of complications, DM2 has become a significant cause of morbidity and mortality in European countries, leading to persistent economic and individual burdens of diabetes (9, 10). The World Health Organization (WHO) and the International Diabetes Federation estimate that in 2019, 463 million people globally were affected by DM, and that number is expected to rise to 700 million by 2045 (11). Studies suggest that in 2015, the global prevalence of DM2 was 8.8%, with an anticipated increase to 10.4% by 2040 (12, 13). This paper aims to provide an overview of the significance of DM and its threat to public health, as well as the importance of health literacy for DM2 patients. It is evident that in recent years, a younger population has been increasingly affected by this disease. This highlights the importance of early preventive measures and the need for information dissemination, particularly for healthcare professionals like nurses, who play a crucial role in patient education, prevention, diagnosis, treatment, and care, especially in preventing disease and educating patients with DM2.

METHODOLOGY

This review is based on a search of scientific literature, with a particular focus on original research

articles and meta-analyses available in scientific databases such as PubMed, SCOPUS, MEDLINE, and SCI Index, published within the last ten years. The search focused on topics related to the public health issue of DM2 and health literacy among patients. Key search terms included diabetes mellitus, Type 2 diabetes mellitus, prevention, health education, public health, and risk factors.

Type 2 diabetes mellitus as a public health problem

Globally, the WHO DIAMOND project registers show that in high-income countries, the prevalence of Type 2 diabetes is highest among the poorest individuals, though some data indicate a reversal of this trend in middle-income countries (14, 15). A significant point to highlight is the variation in undiagnosed Type 2 diabetes from region to region. Data from seven countries have shown that diabetes is undiagnosed and untreated in 24% to 62% of individuals (14, 15). The literature suggests that complications of DM are significantly more common than other chronic non-communicable diseases if not recognized in time, and people with lower health literacy are more prone to complications (14, 15). DM2 is a chronic health condition that is reaching alarming global rates, and a healthy population is an important indicator of health culture (15-17). Persistently high blood sugar levels over time can cause significant damage to individual organs (15, 16).DM has become one of the leading public health problems of the 21st century, and WHO projects that by 2025, 200–300 million people worldwide will be affected by the disease, leading to around 6 million new cases annually (according to the Centers for Disease Control and Prevention – CDC) (18). The highest prevalence of DM2 is found in Southeast Asia. In the United States, DM2 is the sixth leading cause of death among all diseases, and third in some ethnic populations (18). The emergence of DM2 is linked to changes in lifestyle and the increasing standard of living in many Western European countries and the United States. Key risk factors include genetic predisposition and environmental factors. Among the main causes of this disease are obesity (particularly visceral obesity), lack of or reduced physical activity, sedentary lifestyle, poor diet and food preparation, and perinatal factors (19). Globally, approximately 540 million adults (one in 11) live with diabetes, and by 2045, this number is expected to rise to 783 million (one in eight adults) (20, 21). Incidence of DM2 increases with age, with the highest rates occurring between 55 and 59 years, slightly earlier in men than in women (16). Over the past three decades, there have been no major changes in the age distribution of DM2 incidence or prevalence, but with the rising obesity epidemic, there is an expectation that younger age groups with risk factors will increasingly be affected by DM2 (22-24). DM2 is a leading risk factor for ischemic cerebrovascular disease or stroke. Studies have shown that the pathophysiology of strokes and transient ischemic attacks in people with DM2 complications is due to cerebral hemodynamic and vascular disturbances, hyperglycemia, and other associated risk factors. One of the most common complications of DM2 is diabetic polyneuropathy, which can exist with or without neuropathic pain. Its incidence increases with the duration of diabetes. About 50% of patients with DM2 suffer from this condition, compared to around 30% with Type 1 diabetes (DM1). These complications significantly reduce quality of life, shorten life expectancy, and further increase the already rising cost of diabetes treatment (25). It has been proven that the etiopathogenic mechanism of strokes and transient ischemic attacks in individuals with complications from DM2 is a consequence of cerebral hemodynamic and vascular disorders, hyperglycemia, and other associated risk factors in the older population with DM2 (26).

The importance of health literacy in people with type 2 diabetes mellitus

Health literacy is a crucial determinant of health in a population and serves as a foundation for responsible individual and family behavior in managing chronic conditions. The European Union (EU) recognizes the importance of health literacy for improving healthcare across the EU. According to WHO, health literacy is an indicator of a country's health status. Literature suggests that individuals with lower health literacy are more prone to complications from diabetes and more likely to use healthcare services than informed and health-literate patients (14, 15). As DM2 is a chronic health condition reaching alarming global rates, health literacy serves as an important indicator of population health (15-17). Persistent high blood sugar over time can cause damage, dysfunction, or loss of function in various organs, most commonly the heart and blood vessels, kidneys, and nervous system. The complications of DM2 are inevitable, but early disease recognition, self-monitoring, balanced diet, and physical activity can significantly help delay complications (15, 16). The study by Poulimeneas D and colleagues showed that knowledge about DM2 improves blood sugar control and is associated with several demographic parameters. Greece is a country with a high obesity rate, and knowledge about the disease had never been evaluated in diabetics before this study. The aim of this

study was to assess knowledge about DM2. The questionnaire on disease knowledge was correlated with blood glucose levels and sociodemographic characteristics of the participants, showing poor knowledge of the disease (mean DKT score 8.3 ± 2.2/14.0 and mean DKT as a percentage of correct answers 59.6 ± 15.8%). This study showed the urgent need for training and education for patients with DM2 in Greece to improve disease outcomes (27). In the study by Bains SS and colleagues, who assessed knowledge among patients in primary healthcare, participants filled out survey questionnaires related to their knowledge of their own disease, health literacy, diabetes knowledge, and self-care (28). The majority of the sample in this study was younger than 65 years, and it was found that health literacy influences the course of the disease and complications through diabetes knowledge (28). The meta-analysis by Marciano L and colleagues focused on quantitative findings about the relationship between health literacy and diabetes knowledge, self-management activities, and blood glucose control outcomes related to the disease and the assessment of health literacy. Key studies included patients with type 1 (DM1) and/or type 2 diabetes aged 18 or older and provided an estimated effect size for functional health literacy and diabetes knowledge, self-management activities, or HbA1C. This meta-analysis included a total of 61 studies with 18,905 patients. Most of these studies were conducted in the United States on patients with type 2 diabetes, using S-TOFHLA as a measure of functional health literacy based on performance or BHLS as a measure based on perception. The results showed that all three outcomes were associated with health literacy. This study concluded that the health literacy of patients with DM2 plays a significant role in diabetes knowledge (29). As for DM2, a large number of studies assessing the relationship between health literacy and diabetes knowledge concluded that the connection between health literacy and diabetes is crucial for the prevention of complications (30-32). The study by Santa Cruz-Álvarez P and colleagues suggests that developing educational programs for adolescents with DM2 transitioning from pediatric to adult care is important for maintaining blood glucose control and emotional well-being, which are key predictors for the prevention and delay of complications from hyperglycemia in individuals with DM2 (33). The study by Fernández-Duque MV and colleagues suggests that patient education for DM2 should be included in primary healthcare institutions, where there are five pillars of DM2 treatment, and patients need to be educated about nutrition, exercise, self-monitoring of blood glucose, medications, and controlling vascular risk factors for DM2 complications (34). Studies suggest that health literacy in patients with DM2 has a small but significant impact on better blood glucose control, measured by HbA1C (35-37). The fundamental role in developing appropriate educational and health programs about diabetes primarily falls to nurses based on the analysis of learning needs and patient characteristics. These health literacy education programs for DM2 patients could reduce or prevent complications associated with this widespread chronic disease. One of the leading aspects that should be considered is that patients with diabetes mellitus should be committed to proper nutrition, which should exclude foods containing simple sugars. This is because the progression of DM2 leads to certain acute or chronic complications, most often in the blood vessels and nerves. Unfortunately, due to the unpredictable nature of this disease, many patients remain undiagnosed until serious complications appear, which significantly impact premature mortality and disability in individuals with DM2. This also represents a major public health issue (38-42). In Table 1, we present a brief overview of some of the relevant studies that we analyzed in review paper.

Table 1. *Systematic reviews of papers published in 8 journals in the last 10 years*

Reference	Publication Year	Journal
Marciano LYesilbas [29]	2019	J Gen Intern Med
Ogurtsova Ket al[30]	2017	Diabetes Res ClinPract
Santa Cruz-Álvarez Pet al[33]	2024	Endocrinol Diabetes Nutr
Gomes MB[35]	2018	Patient Prefer Adherence
Kueh YC[36]	2017	Psychol Health Med
Kueh YC[37]	2015	Health Qual Life Outcomes
Alhaik S[38]	2019	Diabetes MetabSyndr.
Zowgar AM[39]	2018	Saudi Med J.

CONCLUSION

As the number of diabetes cases continues to grow rapidly and patients live longer, healthcare systems will face increasing challenges inmeeting their needs. Therefore, new and less resource-intensive care models for diabetes are necessary to address this rising demand. Given that nearly half of the adult population is expected to develop diabetes during their lifetime, advances in diabetes outcomes will soon be outpaced by the sheer number of people requiring care. Primary prevention strategies are urgently needed. Strong evidence has shown that diabetes can be prevented through lifestyle changes, and the role of healthcare professionals, particularly nurses, in educating the population and providing health education at all levels of healthcare, with an emphasis on primary care, is crucial to detect this disease early and prevent complications. Only a population-based prevention approach can address this scale of the problem. Prevention strategies should include optimizing urban planning, food marketing policies, and creating work and school environments that allow individuals to adopt healthier lifestyles. Studies have shown that a low level of health literacy among DM2 patients is a significant predictor of premature death, disability, and increased healthcare costs. Therefore, it is important to focus on patient education to reduce mortality and improve the quality of life for DM2 patients.

Abbreviations

CDC - Centers for Disease Control
DM - Diabetes mellitus
DM1 - Diabetes mellitus type 1.
DM2 - Diabetes mellitus type 2.
EU- European Union
WHO - The World Health Organization

Contribution of Authors: All authors contributed equally in the development of this paper.

Conflict of Interest: The authors declare no conflicts of interest related to this article.

NOTE: Artificial intelligence was not used as a tool in this study.

Funding: None.

Sažetak

DIJABETES MELITUS TIP 2 - ZNAČAJ ZDRAVSTVENOG PROSVEĆIVANJA OBOLELIH: PREGLED

Peličić Damir,[1, 2] Đukić Vukica[1]

[1] Klinički centar Crne Gore, Podgorica, Crna Gora
[2] Univerzitet Crne Gore, Medicinski fakultet, Visoka medicinska škola Berane, Crna Gora

Dijabetes melitus (lat. Diabetes mellitus, DM) predstavlja značajan javnozdravstveni problem, a Dijabetes melitus tip dva (DM2), je najčešći oblik ove bolesti koji čini oko 90% svih obolelih od DM u svetu. Učestalost DM2 ima pandemijske razmere, posebno u razvijenim zemljama. Studije u svetu su pokazale da je nizak stepen zdravstvene pismenosti bolesnika sa DM2 što može biti značajan prediktor za prerano umiranje i invaliditet i povećane troškove za negu i lečenje ovih bolesnika. Značajno je staviti akcenat na edukaciju bolesnika kako bi se smanjio mortalitet i poboljšao kvalitet života bolesnika sa DM2. Ovaj pregledni rad se temelji na pretraživanju naučne literature, sa posebnim fokusom na originalne naučne članke i metaanalize koje se nalaze u naučnim bazama podataka: PubMed, SCOPUS, MEDLINE i SCI index i druge, koje nisu starije od deset godina. Pretraživanje publikacija se odnosilo na temu vezano za javnozdravstveni problem DM2 i zdravstvenu pismenost obolelih. Za potrebe ovog članka koristili smo ključne reči: Dijabetes melitus, dijabetes melitus tip 2, prevencija, zdravstveno prosvećivanje, javno zdravlje, faktori rizika i druge. Studije u svetu su pokazale da je nizak stepen zdravstvene pismenosti bolesnika sa DM2 što može biti značajan prediktor za prerano umiranje i invaliditet i povećane troškove za negu i lečenje ovih bolesnika. Značajno je staviti akcenat na edukaciju bolesnika kako bi se smanjio mortalitet i poboljšao kvalitet života bolesnika sa DM2.

Ključne reči: Dijabetes Melitus, faktori rizika, gojaznost, kardiovaskularne bolesti, prevencija, edukacija.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Alas. 10th ed. Brussels: International Diabetes Federation; 2021.

2. Saeedi P, Salpea P, Karuranga S, Petersohn I, Malanda B, Gregg EW, et al. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2020; 162: 108086. doi: 10.1016/j.diabres.2020.108086.

3. Yan Ping W, Lu Yao P, Xian Ming Y, Ting Ting C, Lin L, Kai Qin D. A multidisciplinary collaborative care model involving family members in the treatment of type 2 diabetes mellitus and associated diabetes distress in young and middle-aged patients. Vojnosanitetski pregled. 2024; 81(12): 747-59. doi: 10.2298/VSP240206084W.

4. Ruszkiewicz K, Jagielski P, Traczyk I. Glycemic control and awareness among diabetic patients of nutrition recommendations in diabetes. Rocz Panstw Zakl Hig. 2020; 71(2): 191-6. doi: 10.32394/rpzh.2020.0116.

5. Kishi A, Fukuma S. Implementation status of prediction models for type 2 diabetes. Prim Care Diabetes. 2023; 17(6): 655-7. doi: 10.1016/j.pcd.2023.09.002.

6. Katanić D, Gučev Z, Vlaški J, Dautović S, Vorgućin I. Definicija, klasifikacija, dijagnoza i etiopatogeneza dijabetesa. in: Vlaški J., Katanić D. [ed.] Klinička pedijatrijska dijabetologija, Novi Sad: Symbol. 2007: 22-55.

7. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR et al. American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care. 2010; 33(12): 2692-6. doi: 10.2337/dc10-1548.

8. van Tilburg J, van Haeften TW, Pearson P, Wijmenga C. Defining the genetic contribution of type 2 diabetes mellitus. J Med Genet. 2001; 38(9): 569-78. doi: 10.1136/jmg.38.9.569.

9. SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration. SCORE2-Diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. Eur Heart J. 2023; 44(28): 2544-56. doi: 10.1093/eurheartj/ehad260.

10. Agyemang C, van der Linden EL, Bennet L. Type 2 diabetes burden among migrants in Europe: unravelling the causal pathways. Diabetologia. 2021; 64(12): 2665-75. doi: 10.1007/s00125-021-05586-1.

11. International Diabetes Federation. IDF Diabetes Atlas, 9th ed.; International Diabetes Federation: Brussels, Belgium, 2019; Available online: https://www.diabetesatlas.org (accessed on 20 January 2025).

12. Kim SH, Lee A. Health-Literacy-Sensitive Diabetes Self-Management Interventions: A Systematic Review and Meta-Analysis. Worldviews Evid Based Nurs. 2016; 13(4): 324-33. doi: 10.1111/wvn.12157.

13. Frisch AL, Camerini L, Diviani N, Schulz PJ. Defining and measuring health literacy: how can we profit from other literacy domains? Health Promot Int. 2012; 27(1): 117-26. doi: 10.1093/heapro/dar043.

14. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2017; 40(Suppl 1): S11-S24. doi: 10.2337/dc17-S005.

15. Ling W, Huang Y, Huang YM, Fan RR, Sui Y, Zhao HL. Global trend of diabetes mortality attributed to vascular complications, 2000-2016. Cardiovasc Diabetol. 2020; 19(1): 182. doi: 10.1186/s12933-020-01159-5.

16. Jandrić Kočić M. Is knowledge of diabetes mellitus a prerequisite for optimal self-care and control of this disease?. Zdravstvena zaštita. 2024; 53(4): 78-91. doi: 10.5937/zdravzast53-53040.

17. Isiklar A, OcakSerin S. Fasting blood glucose level in patients presenting with erectile dysfunction. Sanamed. 2021; 16(2): 139-42. doi: 10.24125/sanamed.v16i2.512.

18. Dar MS, Bég SA. TNM cancer staging: can it help develop a novel staging system for type 2 diabetes? Diabetes Metab Syndr Obes. 2018; 11: 845-53. doi: 10.2147/DMSO.S179963.

19. Romadlon DS, Hasan F, Wiratama BS, Chiu HY. Prevalence and risk factors of fatigue in type 1 and type 2 diabetes: A systematic review and meta-analysis. J Nurs Scholarsh. 2022; 54(5): 546-53. doi: 10.1111/jnu.12763.

20. Hussain A, Claussen B, Ramachandran A, Williams R. Prevention of type 2 diabetes: a review. Diabetes Res Clin Pract. 2007; 76(3): 317-26. doi: 10.1016/j.diabres.2006.09.020.

21. Diabetes: Kidney disease (nephropathy). Available on: https://diabetes.org/diabetes/chronic-kidney-disease.

22. International Diabetes Federation: Type 2 diabetes. Available on: https://idf.org/about-diabetes/type-2-diabetes/.

23. Konatar R, Pelicic D, Maras B, Music K. Chronic non-communicable diseases caused by adolescent eating disorders. Sanamed. 2024; 19(3): 357-65. doi: 10.5937/sanamed0-52856.

24, Konatar R, Peličić D, Maraš B, Musić K, Miljanović G. Specificities and challenges in adolescent nutrition. Zdravstvena zaštita. 2024; 53(3): 86-99. doi: 10.5937/zdravzast53-52806.

25. Peličić D. Prevention of atherosclerosis with reference to obesity and inadequate nutrition as risk factors for cardiovascular diseases. Zdravstvena zaštita. 2022; 51(1): 101-8. doi: 10.5937/zdravzast51-35681.

26. Dzhambov AM, Dikova K, Georgieva T, Panev TI, Mukhtarov P, Dimitrova R. Short-term effects of air pollution on hospital admissions for cardiovascular diseases and diabetes mellitus in Sofia, Bulgaria (2009-2018). Arh Hig Rada Toksikol. 2023; 74(1): 48-60. doi: 10.2478/aiht-2023-74-3704.

27. Poulimeneas D, Grammatikopoulou MG, Bougioukli V, Iosifidou P, Vasiloglou MF, Gerama MA, et al. Diabetes knowledge among Greek Type 2 Diabetes Mellitus patients. Endocrinol Nutr. 2016; 63(7): 320-6. [Article in English, Spanish]. doi: 10.1016/j.endonu.2016.04.008.

28. Bains SS, Egede LE. Associations between health literacy, diabetes knowledge, self-care behaviors, and glycemic control in a low income population with type 2 diabetes. Diabetes Technol Ther. 2011r; 13(3): 335-41. doi: 10.1089/dia.2010.0160.

29. Marciano L, Camerini AL, Schulz PJ. The role of health literacy in diabetes knowledge, self-care, and glycemic control: a meta-analysis. J Gen Intern Med. 2019; 34(6): 1007-17. doi: 10.1007/s11606-019-04832-y.

30. Ogurtsova K, Fernandes JD da R, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128: 40–50. doi: 10.1016/j.diabres.2017.03.024.

31. Institute of Medicine (US) Committee on Health Literacy; Nielsen-Bohlman L, Panzer AM, Kindig DA, editors.

Health Literacy: A Prescription to End Confusion. Washington (DC): National Academies Press (US); 2004. Available from: https://www.ncbi.nlm.nih.gov/books/NBK216033/.

32. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med 2011; 155(2): 97–107. doi: 10.7326/0003-4819-155-2-201107190-00005.

33. Santa Cruz-Álvarez P, Ruiz-Trillo CA, Pérez-Morales A, Cortés-Lerena A, Gamero-Dorado C, Garrido-Bueno M. Nurse-led therapeutic patient education program on glycemic control and emotional wellbeing in adolescents with type 1 diabetes mellitus during hospital transition. Endocrinol Diabetes Nutr (Engl Ed). 2025; 72(1): 14-25. doi: 10.1016/j.endien.2024.07.004.

34. Fernández-Duque MV, Maciá-Bobes C, Prida-Villa E, Ronzón-Fernández A. Revisión integral del tratamiento de la diabetes tipo 2 en atención primaria. Aspectos higienicodietéticos, educacionales y farmacológicos [Comprehensive review of type 2 diabetes treatment in primary health care. Hygienic, dietetic, educational and pharmacological aspects]. Enferm Clin. 2008; 18(1): 41-5. [Article in Spanish]. doi: 10.1016/s1130-8621(08)70692-2.

35. Gomes MB, Santos DC, Pizarro MH, Barros BSV, de Melo LGN, Negrato CA. Does knowledge on diabetes management influence glycemic control? A nationwide study in patients with type 1 diabetes in Brazil. Patient Prefer Adherence. 2018; 12: 53-62. doi: 10.2147/PPA.S146268.

36. Kueh YC, Morris T, Ismail AA. The effect of diabetes knowledge and attitudes on self-management and quality of life among people with type 2 diabetes. Psychol Health Med. 2017; 22(2): 138-44. doi: 10.1080/13548506.2016.1147055.

37. Kueh YC, Morris T, Borkoles E, Shee H. Modelling of diabetes knowledge, attitudes, self-management, and quality of life: a cross-sectional study with an Australian sample. Health Qual Life Outcomes. 2015; 13: 129. doi: 10.1186/s12955-015-0303-8.

38. Alhaik S, Anshasi HA, Alkhawaldeh J, Soh KL, Naji AM. An assessment of self-care knowledge among patients with diabetes mellitus. Diabetes Metab Syndr. 2019; 13(1): 390-4. doi: 10.1016/j.dsx.2018.10.010.

39. Zowgar AM, Siddiqui MI, Alattas KM. Level of diabetes knowledge among adult patients with diabetes using diabetes knowledge test. Saudi Med J. 2018; 39(2): 161-8. doi: 10.15537/smj.2017.2.21343.

40. Rahaman KS, Majdzadeh R, Holakouie Naieni K, Raza O. Knowledge, Attitude and Practices (KAP) regarding chronic complications of diabetes among patients with type 2 diabetes in Dhaka. Int J Endocrinol Metab. 2017; 15(3): e12555. doi: 10.5812/ijem.12555.

41. Asghar S, Asghar S, Mahmood T, Bukhari SMH, Mumtaz MH, Rasheed A. Microalbuminuria as the Tip of Iceberg in type 2 diabetes mellitus: prevalence, risk factors, and associated diabetic complications. Cureus. 2023; 15(8): e43190. doi: 10.7759/cureus.43190.

42. Kazeminia M, Salari N, Mohammadi M. Prevalence of cardiovascular disease in patients with type 2 diabetes mellitus in Iran: a systematic review and meta-analysis. J Diabetes Res. 2020;2020:3069867. doi: 10.1155/2020/3069867.

Correspondence to/Autor za korespondenciju
Dr sc. med. Damir Peličić, PhD
Scientific Center, Clinical Center of Montenegro, Podgorica, Montenegro
Ljubljanska bb, Podgorica 81000
e-mail: damir.pelicic@t-com.me
phone +382 69 302 924
ORCID No
Damir Peličić 0000-0002-0544-9638
Vukica Đukić 0009-0003-8722-5885

***How to cite this article**:* Pelicic D, Djukic V. Diabetes mellitus type 2-the importance of health education of patients: a review. Sanamed. 2025; 20(2): 207-212. doi: 10.5937/sanamed0-56752.

UPUTSTVO AUTORIMA

Časopis **SANAMED** je međunarodni, recenzirani, multidisciplinarni medicinski časopis otvorenog pristupa, osnovan 2006. godine, a izdaje ga Udruženje lekara Sanamed, neprofitna organizacija lekara i naučnika. Časopis objavljuje: originalne članke, prikaze slučajeva, preglede literature, članke o istoriji medicine, članke za praktičare, prikaze knjiga, komentare i pisma uredniku i druge medicinske informacije posvećene unapređenju medicinskih istraživanja, praksi i obrazovanju, iz oblasti medicine i srodnih oblasti.

Časopis izlazi u elektronskom i štampanom formatu, tri puta godišnje. Odmah nakon objavljivanja, svi radovi su besplatno dostupni online, na web stranici časopisa i drugim bazama podataka.

Molimo autore da dostave, potpisane od svih autora, formulare Author statement, Patient consent, and Conflict of interests prilikom prilaganja članka (https://new.sanamed.rs/).

Od februara 2022. časopis Sanamed počeo je sa korišćenjem ASSISTANT sistema za elektronsko uređivanje časopisa. Svi korisnici sistema: autori, recenzenti i urednici moraju biti registrovani sa jedinstvenom email adresom. Za registraciju idite na https://aseestant.ceon.rs/index.php/sanamed/about/submissions.

Rukopisi se dostavljaju u elektronskoj formi putem ASSISTANT sistema.

Radovi se uvek dostavljaju sa sažetkom na engleskom i srpskom jeziku. Strani autori podnose radove samo na engleskom jeziku. Za nazive lekova isključivo se koriste generički nazivi. Uređaji (aparati, instrumenti) se nazivaju trgovačkim nazivima, a njihov naziv i mesto proizvodnje treba navesti u zagradama. Ako se koristi kombinacija slovo-broj, broj treba precizno označiti superskriptom ili indeksom (tj. 99Tc, IL-6, O2, B12, CD8). Ako se nešto obično piše kurzivom, kao što su geni (npr. BRCA1), to bi trebalo na ovaj način pisati i u radu.

Ako je rad deo magistarske ili doktorske teze, ili istraživačkog projekta, to treba navesti u posebnoj napomeni na kraju teksta. Takođe, ako je članak prethodno predstavljen na nekom naučnom skupu, potrebno je navesti naziv, mesto i vreme održavanja skupa, kao i način na koji je rad objavljen (npr. promenjen naslov ili sažetak).

IZJAVA O SUKOBU INTERESA. Rukopis mora biti propraćen izjavom o sukobu interesa svih autora u kojoj se izjašnjava o potencijalnom interesu ili navodi da autori nemaju sukob interesa. Obrazac izjave o sukobu interesa mora biti potpisan od strane svih autora i dostavljen uz rukopis.

AUTORSTVO. Svi pojedinci navedeni kao autori trebaju biti kvalifikovani za autorstvo. Svaki autor je trebao dovoljno sudelovati u pisanju članka kako bi preuzeo odgovornost za celi članak i rezultate prikazane u tekstu. Autori trebaju priložiti opis doprinosa svakog koautora pojedinačno (na kraju teksta).

PLAGIJAT. Svi rukopisi se proveravaju na plagijarizam (softver iThenticate).

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 400 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

Propratno pismo. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži: izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu, te izjavu da su rukopis pročitali i odobrili svi autori koji ispunjavaju merila autorstva. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprineli izradi rada.

Troškovi pripreme rada

Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

Napomena. Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pisanje rada za SANAMED znatno će se skratiti vreme celokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet i redovnost izlaženja svezaka.

INSTRUCTIONS TO AUTHORS

SANAMED journal is international, peer-reviewed, multidisciplinary open-access medical journal, founded in 2006 and is published by the Association of medical doctors Sanamed, a nonprofit organization of physicians and scientists. The journal publishes: original articles, case reports, literature reviews, Systematic review, articles on history of medicine, articles for practitioners, book reviews, comments and letters to editor, and other medical information dedicated to the advancement of medical research, practice, and education, in the field of medicine and related fields.

The journal is published both in electronic and print format, three times a year. Immediately after publication, all papers are available online for free, on the journal's website and other databases.

IMPORTANT. Authors please fill out Author statement, Patient consent, and Conflict of interests forms when submitting your article (https://new.sanamed.rs/).

From February 2022, Sanamed journal started using electronic journal management editing via the ASSISTANT system. All users of the system: authors, reviewers and editors must be registered with a unique email address. To register go to https://aseestant.ceon.rs/index.php/sanamed/about/submissions.

Manuscripts are submitted in electronic form via ASSISTANT system.

The papers are always submitted with Abstract in both English and Serbian, included in the manuscript file. Foreign authors submit papers only in English Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors declaring any potential interest or stating that the authors have no conflict of interest. Conflict of interest statement form must be signed by all authors and submitted with manuscript.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text..The authors should enclose the description of contribution to the article of every co-author individually (at the end of the manuscript).

PLAGIARISM. All manuscripts have been submitted to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings),

title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 400 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

Photographs of identifiable patients are accompanied by written permission from the patient.

For figures published previously, the original source is acknowledged, and written permission from the copyright holder to reproduce it is submitted.

Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about publicly known persons or naming the people who contributed to the creation of the work.

Costs of paper preparation

All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

CIP — Каталогизација у публикацији
Народна библиотека Србије, Београд

61

SANAMED : medical journal / glavni i odgovorni urednici Džemail Detanac, Massimo Sartelli, Demet Sengul. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara „Sanamed“, 2006– (Kraljevo : Ofset). — 30 cm

Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X