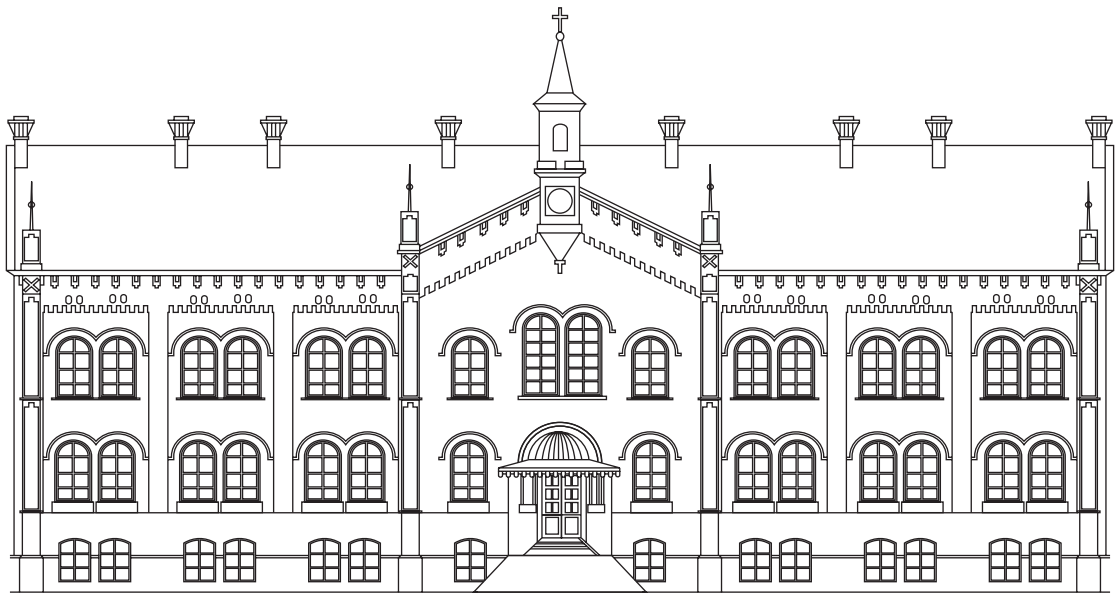
SRP ARH CELOK LEK

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

COBISS.SR-ID 3378434
UDC 61(497.11)

СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО

ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

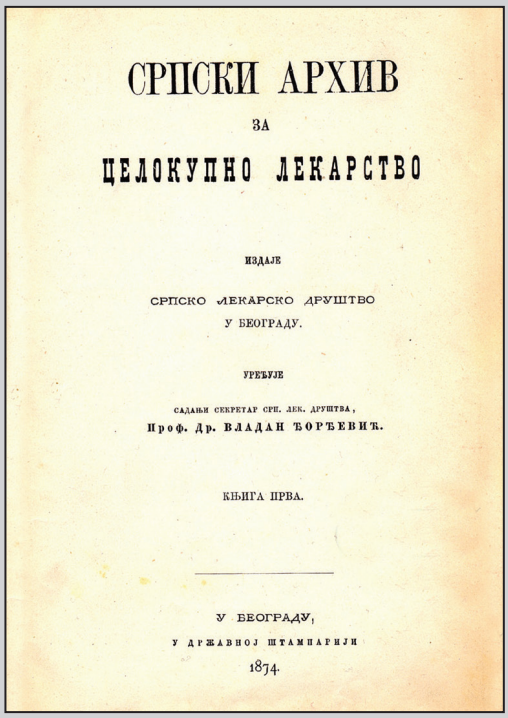


SERBIANARCHIVES
OF MEDICINE

JOURNAL OF THE SERBIAN MEDICAL SOCIETY

VOLUME 153 · MAY–JUNE 2025 · ISSUE 5–6

www.srpskiarhiv.rs



СРПСКИ АРХИВ

ЗА

ЦЕЛОКУПНО ЛЕКАРСТВО

ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

САДАШЊИ СЕКРЕТАР СРП. ЛЕК. ДРУШТВА,

Проф. Др. ВЛАДАН ЂОРЂЕВИЋ.

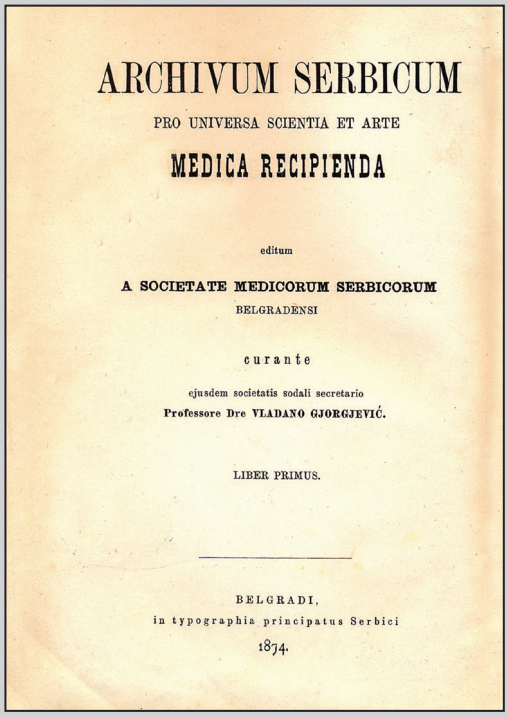
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



ARCHIVUM SERBICUM

PRO UNIVERSA SCIENTIA ET ARTE

MEDICA RECIPIENDA

editum

A SOCIETATE MEDICORUM SERBICORUM

BELGRADENSI

curante

ejusdem societatis sodali secretario

Professore Dre VLADANO GJORGJEVIĆ.

LIBER PRIMUS.

BELGRADI,

in typographia principatus Serbici

1874.

The title page of the first journal volume in Latin

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ГОДИШТЕ 153 МАЈ–ЈУН 2025. СВЕСКА 5–6

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

ОСНИВАЧ, ВЛАСНИК И ИЗДАВАЧ
Српско лекарско друштво
Џорџа Вашингтона 19, 11000 Београд, Србија
Председник
Проф. др Милан А. Недељковић
Интернет страна: http://www.sld.org.rs

ИЗДАВАЧКИ САВЕТ
Проф. др Павле Миленковић, председник
Академик Владимир Бумбаширевић
Проф. др Љубица Ђукановић
Академик Небојша Лалић
Проф. др Милица Чоловић

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

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

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

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

Штампање „Српског архива за целокупно лекарство" током 2025. године помогло је Министарство науке, технолошког развоја и иновација Републике Србије.

ISSN 0370-8179; ISSN Suppl 0354-2793

eISSN 2406-0895
Отворен приступ

Штампано у Србији

Штампа: ЈП „Службени гласник", Београд

Тираж: 850 примерака

Serbian Archives of Medicine

VOLUME 153 MAY–JUNE 2025 ISSUE 5–6

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

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

Printed by: JP "Službeni glasnik", Belgrade

Circulation: 850 copies

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

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

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

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

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

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

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

The publishing of the Serbian Archives of Medicine during 2025 is supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

ISSN 0370-8179; ISSN Suppl 0354-2793

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

Printed in Serbia

САДРЖАЈ • CONTENTS

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

CASE REPORTS • ПРИКАЗИ БОЛЕСНИКА

REVIEW ARTICLES • ПРЕГЛЕДНИ РАДОВИ

CURENT TOPIC • АКТУЕЛНА ТЕМА

DOI: https://doi.org/10.2298/SARH241122043X
UDC: 616.831-005.1:616.32-008.1

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Multidisciplinary approach to patients with post-stroke dysphagia to improve swallowing and quality of life

Bu Xu[1], Xiangxia Rong[1], Yan Gan[1], Tao Wei[1], Xiufang Zhang[1], Jingjing Liu[1], Jing Zhang[1], Zilin Wang[2]

[1]Anhui University of Science and Technology, The First Affiliated Hospital Department of Nursing, Huainan City, China
[2]Huainan Xinhua Medical Group, Xinhua Hospital, Department of Medical Psychology, Huainan City, China

SUMMARY

Introduction/Objective This study aimed to investigate the impact of multidisciplinary management led by brain–heart health experts on the quality of life (QoL) of patients suffering from post-stroke dysphagia.

Methods A total of 194 patients with post-stroke dysphagia, treated between January 2021 and June 2024, were selected and randomly assigned to a control group (99 cases, standard care) and an observation group (95 cases, multidisciplinary management by brain–heart health experts). Both groups received intervention for three months. The swallowing function, clinical efficacy, nutritional risk and QoL were compared between the two groups before and after the intervention using the water-swallowing test (WST), the Gugging Swallowing Screen (GUSS), Nutritional risk screening 2002 (NRS2002) and stroke-specific QoL scale (SS-QOL).

Results Compared to the pre-intervention period, both the observation group and the control group exhibited reduced WST grades, GUSS scores and NRS2002 screening risks post-intervention ($p < 0.05$), with a significant increase in the SS-QOL scores ($p < 0.05$). Compared with the control group, the observation group demonstrated lower WST grades, GUSS scores and NRS2002 screening risks post-intervention ($p < 0.05$). The clinical efficacy of the observation group was superior to that of the control group ($p < 0.05$), and the SS-QOL scores in the observation group were significantly higher than those in the control group ($p < 0.05$).

Conclusion Multidisciplinary management led by brain–heart health experts significantly improved swallowing functions, reduced malnutrition risk and enhanced QoL in patients with post-stroke dysphagia.

Keywords: dysphagia; stroke; brain–heart health experts; multidisciplinary care; quality of life

INTRODUCTION

Stroke is a prevalent detrimental condition that often leads to long-term complications. Subnuclear damage to the swallowing, hypoglossal and vagus nerves due to stroke can lead to true bulbar palsy, while bilateral corticobulbar tract damage can result in pseudobulbar palsy. These conditions impair voluntary tongue movements, reduce muscular coordination and contribute to dysphagia [1]. Surveys suggest a complication incidence rate oscillating between 28% and 67% [2]. This range is influenced by differences in study populations, assessment methods, and dysphagia screening times. Nonetheless, it highlights the significant burden of dysphagia after stroke and highlights the importance of early identification and targeted management to prevent associated complications such as aspiration pneumonia, malnutrition, and prolonged hospitalization. Dysfunctional swallowing predisposes patients to malnutrition, electrolyte imbalances, psychological disorders and other health issues, thereby impeding recovery from cerebral injury and diminishing quality of life (QOL). Moreover, the risk of aspiration during mealtimes can lead to life-threatening conditions such as aspiration pneumonia and choking [3]. Consequently, in clinical practice, expedited restoration of swallowing functionality constitutes a cornerstone of rehabilitative care. Predominant therapeutic modalities include respiratory function training, electrical stimulation, central stimulation, swallowing function training and acupuncture therapy. However, these singular rehabilitation treatments are susceptible to external factors, potentially leading to suboptimal patient compliance and outcomes. To meet these challenges, there is an increasing shift to a multidisciplinary management model, moving away from the traditional, experience-guided, personalized approach. The model emphasizes collaborative decision-making between professionals from different disciplines who integrate their expertise to design individualized and evidence-based intervention plans based on each patient's clinical situation [4]. Recent studies highlighted the pivotal role of multidisciplinary collaboration (involving a multidisciplinary diagnosis and treatment pattern) in the rehabilitation process of patients who experienced stroke [5, 6]. Consensus among experts advocates for a multidisciplinary team approach to

Received • Примљено: November 22, 2024
Revised • Ревизија: May 28, 2025
Accepted • Прихваћено: May 30, 2025
Online first: June 3, 2025

Correspondence to:
Zilin WANG
Huainan Xinhua Medical Group
Xinhua Hospital
Department of Medical Psychology
Health Road
Xiejiaji District
Anhui Province
232052Huainan City
China
wangzl2024zl@163.com

dysphagia management, with brain–heart health experts emerging as pivotal figures responsible for comprehensive patient evaluations, health management and professional follow-ups [7]. They are professionally trained and evaluated in multidisciplinary theoretical knowledge and communication skills, possessing extensive medical knowledge and practical experience [8]. Numerous studies have shown that the involvement of brain–heart health experts in the rehabilitation process can effectively enhance patient recovery outcomes [9, 10]. This study endeavors to investigate the effects of multidisciplinary management involving brain–heart health experts on the rehabilitation of patients with post-stroke dysphagia. The aim of this examination was to identify an effective management model to provide a reference for guiding the clinical practice of rehabilitation treatment for patients with post-stroke dysphagia.

METHODS

Study participants

A cohort of 213 newly diagnosed patients with stroke-dysphagia, treated in the Department of Neurology at the First Affiliated Hospital of Anhui University of Science and Technology between January 2021 and June 2024, were selected as the study participants. They were divided into an observation group (103 cases) and a control group (110 cases). After accounting for dropouts (five cases) and deaths (three cases) in the observation group, and dropouts (three cases) and deaths (eight cases) in the control group, 95 cases in the observation group and 99 cases in the control group were ultimately included in the statistical analysis. The inclusion criteria were as follows:

(1) patients experiencing their first stroke episode, with diagnoses corroborated by head magnetic resonance imaging or computed tomography scans, aligning with established stroke diagnostic criteria [11];

(2) patients with the manifestation of dysphagia, as evidenced by a water-swallowing test (WST) grade of III or higher [12];

(3) patients who demonstrated an ability to cooperate well;

(4) patients who voluntarily consented to participate in the study.

The exclusion criteria were as follows:

(1) patients with severe cardiac, renal, or hepatic dysfunction;

(2) patients with moderate to severe cognitive impairments or psychiatric conditions that precluded cooperative;

(3) patients in a comatose state.

All participants were randomly divided into an observation group and a control group using a random number table method. Based on their admission sequence number, each participant was assigned a three-digit number from a pre-set random number table. Patients with an odd number were placed in the observation group, while those with an even number were placed in the control group. The control group followed the rehabilitation management methods outlined in the Chinese Guidelines for Dysphagia Rehabilitation Management (2023) [13]. Conversely, the observation group received multidisciplinary management led by brain–heart health experts, who collaborated to develop treatment and care plans.

Specific strategies: team formation

The multidisciplinary team included: a deputy director of the nursing department with extensive clinical nursing experience as the team leader; the head of the neurology department and the head nurse from the neurology ward as deputy leaders; and members comprising a neurologist, a charge nurse, a rehabilitation therapist, a dietitian, a psychological counsellor, and a brain–heart health expert.

Division of labor

(1) The team leader managed the multidisciplinary team and coordinated communication between specialities.

(2) The deputy leaders were responsible for establishing team working protocols to ensure the adoption of optimal rehabilitation measures for patients.

(3) The neurologist was tasked with interpreting the Chinese Guidelines for Early Rehabilitation Treatment of Stroke, conducting examinations and providing guidance for nursing care.

(4) The charge nurse was responsible for recognizing aspiration risk, monitoring patient progress and psychological state and implementing health education.

(5) The rehabilitation therapist conducted swallowing function screenings, assessed patients' swallowing functions, established swallowing function training programs, and initiated rehabilitation interventions.

(6) The dietitian conducted comprehensive nutritional assessments of patients and developed and adjusted nutritional plans based on individual nutritional needs to ensure adequate nutrient intake.

(7) The psychological counsellor was responsible for assessing and intervening in patients' psychological states.

(8) The brain–heart health expert was tasked with the comprehensive assessment, health management, and professional follow-up of inpatients and outpatients.

Implementation of multidisciplinary management interventions led by brain–heart health experts

A multidisciplinary management communication platform was established and spearheaded by the team leader through the creation of a "Multidisciplinary management team" WeChat group. Specific intervention measures based on the information platform included:

1) Nutritional risk screening: Brain–heart health experts assisted dietitians in conducting nutritional risk screenings using the Nutritional risk screening 2002 (NRS2002) tool [14] to assess patients' nutritional status.

2) Swallowing function training [15]: included exercises for lip, cheek, and tongue movements. Pharyngeal stimulation involved using an ice cotton swab to stimulate the

palatoglossal arch, the base of the tongue and the posterior pharyngeal wall, and instructing patients to perform dry swallowing actions to help stimulate pharyngeal muscles. Each session lasted five minutes and was conducted three times daily.

3) Health education: Focused health education sessions were held weekly, with brain–heart health experts responsible for notifying team members to prepare PowerPoint presentations in advance. The multidisciplinary team organized and ensured active participation by patients with stroke-dysphagia and their families.

4) Psychological care: Psychological counsellors dynamically assessed patients' psychological states and promptly communicated any psychological issues to psychiatrists.

5) Rehabilitation follow-up: a follow-up database for discharged patients was established and a follow-up WeChat group was created; weekly phone calls were conducted with patients for continuous rehabilitation guidance and ensured via the implementation of a three-month in-person follow-up process.

Evaluation indicators

The patients in both groups were assessed before the intervention and three months after discharge using the following indicators. Follow-up at three months was conducted via on-site outpatient visits, where members of the multidisciplinary management team evaluated clinical efficacy, swallowing function, nutritional status, and QoL using questionnaires or on-site examinations. The findings were subsequently reviewed and validated by the team leader and deputy leader.

WST: utilizing the WST for grading, patients initially consumed 1–3 tablespoons of water [12]. If no abnormalities were observed, they proceeded to drink 30 mL of water, with the duration of drinking being recorded to observe the condition of drinking and the presence of coughing or choking. The test consisted of five grades, Grade I: normal, i.e., drinking in one gulp within five seconds without coughing or choking; Grade II: suspected swallowing disorder, i.e., taking more than five seconds to drink in one gulp or needing more than two attempts without coughing or choking; Grade III: able to drink in one gulp but with coughing or choking; Grade IV: needing more than two attempts with coughing or choking; Grade V: frequent coughing or choking, unable to finish drinking. Grades III to V were considered to include swallowing disorders.

Clinical efficacy: markedly effective – a two-grade improvement in the WST compared to before the intervention; improved – a one-grade improvement compared to before the intervention; ineffective – no improvement in the WST results. The overall response rate (ORR) was calculated by comparing the efficacy between the two groups as ORR = (significant effect + improved) / total number of cases × 100%.

Swallowing function: the Standardized Swallowing Assessment [16] was utilized to evaluate patients' swallowing function before and after the intervention and included a clinical examination, water drinking test and normal eating assessment, with a total score of 18–46 points. The score was inversely related to swallowing function.

Nutritional status of patients: The NRS2002 tool [17] was employed to screen patients for nutritional risk and covered nutritional status, disease severity and age. A score of 3 or above indicated a risk of malnutrition.

QoL: The stroke-specific QoL scale (SS-QOL) [18] was used for the assessment of 12 dimensions including family roles, cognition, mobility, and self-care, with 49 items and a total score of 49–245 points. A higher score indicated a better QoL.

Statistical analysis

All data were statistically analyzed using the IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp., Armonk, NY, USA). Quantitative data were described as mean ± standard deviation ($\bar{x} \pm s$), and differences between the two groups were compared using a t-test. Categorical data were described as rates (%), and between-group comparisons were made using the χ^2 test with a significance level of $\alpha = 0.05$.

Ethics approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of The First Affiliated Hospital of Anhui University of Science and Technology.

RESULTS

Comparison of baseline data between the two groups

A cohort of 213 patients was recruited according to the inclusion criteria and randomly divided into an observation group (103 cases) and a control group (110 cases). After a three-month follow-up, 95 cases in the observation group and 99 cases in the control group were included. The comparison of baseline data between the two groups showed no significant differences in demographic characteristics, stroke type, and average hospital stay ($p > 0.05$), indicating comparability between the groups (Table 1).

Comparison of WST grades between the two groups

WST scores were significantly improved in both groups after the intervention ($p < 0.05$), and greater improvements were observed in the observation group, particularly in terms of a reduction in severe dysphagia (Grade V) and an increase in normal swallowing function (Grade I) (Table 2).

Comparison of clinical efficacy between the two groups

The ORR in the observation group (92.63%) was significantly higher than in the control group (66.67%), with a statistically significant difference ($p < 0.05$).

Table 1. Comparison of baseline data between the two groups

Parameters	Observation Group (n = 95)	Control Group (n = 99)	p
Age*	71.11 ± 11.56	73.21 ± 11.08	0.196
Gender∞			
Male	56 (58.95)	61 (61.62)	0.704
Female	39 (41.05)	38 (38.38)	
Stroke Type∞			
Ischemic Stroke	80 (84.21)	80 (80.81)	0.533
Hemorrhagic Stroke	15 (15.79)	19 (19.19)	
Average Hospital Stay[a]	14.16 ± 6.37	14.62 ± 7	0.634

*data are presented in years with mean value and standard deviation;
∞data are presented as u number of patients with percentage in brackets;
[a]data are presented in days with mean value and standard deviation

Table 2. Comparison of water-swallowing test grades before and after intervention

Parameters	Cases	Grade I	Grade II	Grade III	Grade IV	Grade V	p
Observation Group							
Before	95	1	11	27	27	29	< 0.001
After	95	36	28	25	3	3	
Control Group							
Before	99	2	10	27	29	31	< 0.001
After	99	25	30	21	12	11	

Table 3. Comparison of Swallowing Function Scores (SFS) before and after intervention

Parameters	Number of Cases	SFS	p
Observation Group			
Before	95	31.53 ± 6.31	< 0.001
After	95	23.33 ± 4.60	
Control group			
Before	99	29.49 ± 7.06	< 0.001
After	99	20.83 ± 3.78	

Table 4. Comparison of Nutritional Risk Screening 2002 before and after treatment

Group	Cases	Risk of malnutrition	Without the risk of malnutrition	p
Observation Group				
Before	95	82	13	< 0.001
After	95	47	48	
Control Group				
Before	99	84	15	< 0.001
After	99	55	44	

Table 5. Comparison of stroke-specific quality of life scale (SS-QOL) scores before and after treatment

Group	Cases	SS-QOL Scores	p
Observation Group			
Before	95	128.75 ± 38.17	< 0.001
After	95	170.83 ± 35.61	
Control Group			
Before	99	124.96 ± 38.83	< 0.001
After	99	159.77 ± 26.09	

Comparison of swallowing function between the two groups

The swallowing function score showed a significant improvement in both groups after the intervention ($p < 0.001$), and a greater reduction was observed in the observation group, suggesting that swallowing function enhancement was more effective (Table 3).

Comparison of NRS2002 results between the two groups

NRS2002 risk screening showed a significant reduction in the risk of malnutrition in both groups after the intervention ($p < 0.05$), with a more significant improvement in the observation group compared to the control group. (Table 4).

Comparison of QoL between the two groups

SS-QOL scores showed a significant improvement ($p < 0.001$) in both groups after the intervention, with a greater increase in the observation group compared to the control group, indicating an improved QoL after the intervention (Table 5).

DISCUSSION

The *Chinese Stroke Dysphagia and Nutritional Management Manual* (2019) underscores that the management of post-stroke dysphagia is a clinical management process involving multidisciplinary collaboration [19]. Management teams involving brain–heart health experts conduct comprehensive assessments primarily based on patient needs and risk factors and provide patients with high-quality, professional, and comprehensive management, thereby improving patient outcomes. Furthermore, these teams significantly contribute to enhancing the compliance of patients with stroke concerning medical advice and health education [20, 21].

The results of the present study indicate that multidisciplinary management involving brain–heart health experts significantly improved the clinical efficacy, swallowing function, nutritional status and QoL of patients with post-stroke dysphagia compared to the control group. Stroke and its complications require a lengthy rehabilitation process. Brain–heart health experts play an active and affirmative role in improving the awareness of patients with stroke and high-risk populations' awareness of the disease and treatment compliance through effective health management and follow-up [22]. Within the team, they are instrumental in conducting comprehensive assessments, health management and professional follow-ups for both in-hospital and out-hospital patients with stroke. Implementing multidisciplinary management for dysphagia ensures the continuous professional management of patients and timely assessment and adjustment of rehabilitation treatment plans, where it acts as a bridge

between in-hospital and out-hospital care to ensure effective rehabilitation treatment for patients.

The results of this study are consistent with multiple studies and demonstrate unique advantages. Chen et al. [6] proposed that the multidisciplinary collaboration model could effectively improve the recovery rate of swallowing function, however, their model lacked a clearly defined core coordinator, which may have limited team collaboration efficiency. In contrast, the present study introduced a management model led by brain–heart health experts, which improved the communication efficiency between various disciplines and realized continuous management from hospitalization to discharge and significantly improved clinical efficacy. Wang et al. [9] showed that the intervention of brain–heart health experts through mobile health platforms could improve patient treatment compliance. In our study, the model was further applied to the field of swallowing function rehabilitation, combined with nutritional support, psychological care and family participation, and the results for the observation group were better than the control group in terms of swallowing function score, nutritional status and QoL, indicating that this management model has high promotional value. In addition, the community-based group rehabilitation program of Yang et al. [16] demonstrated that structured rehabilitation could help improve patients' QoL. Accordingly, a digital follow-up system (via the WeChat platform) was included in this study to enhance the continuity and operability of the intervention, thereby enabling patients to still receive professional guidance after discharge and ensure the stability of rehabilitation effects. In summary, this study followed a more systematic and practical approach than previous studies in terms of integrating multidisciplinary resources, strengthening the role of experts and optimizing the use of assessment tools, which provides new ideas and a practical path for the standardized management and rehabilitation of post-stroke dysphagia.

Patients with stroke, hindered by partial brain tissue damage, encounter restrictions in self-care, language capabilities, and social participation. The condition's slow and prolonged rehabilitation process and sequelae can easily trigger mental afflictions. Patients with stroke-induced dysphagia experience swallowing dysfunction, leading to aspiration, coughing, and even pulmonary infection under adverse psychological and physiological states, which can lead to malnutrition. Brain–heart health experts can implement systematic, standardized, and stratified follow-up management, covering physical, psychological, and medication-related aspects to tailor the timing and content of follow-up according to each patient's condition [21, 23]. By establishing a robust communication relationship with patients that focuses on their psychological frame of mind and providing necessary socio-psychological support, brain–heart health experts can significantly alleviate adverse psychological emotions such as anxiety and depression among patients with stroke and improve outcomes while also addressing nutritional issues and enhancing patients' QoL [20].

CONCLUSION

In conclusion, multidisciplinary management involving brain–heart health experts integrate multidisciplinary resources, personnel, and professional knowledge and applies them to the clinical care of patients with stroke and dysphagia. This enhances the accuracy and specificity of rehabilitation measures, ensuring timely and effective treatment of the condition, and providing social and psychological support. This approach exerts a more pronounced ameliorative effect on patients' dysphagia, enhances clinical efficacy, diminishes the risk of nutritional malnutrition, and improves patients' QoL, demonstrating substantial value for clinical implementation.

This study is not without its limitations. Being a single-centre study with a relatively small cohort size, the findings are susceptible to bias, potentially curtailing the universality and applicability of the conclusions. Moreover, the short follow-up time and the small number of follow-up visits preclude a comprehensive evaluation of patients' recovery process and long-term outcomes, including an absence of statistical analysis on the recurrence rates of stroke. To address these shortcomings, future studies should aim to conduct more rigorous multi-centre, large-sample studies and provide references for the rehabilitation treatment of patients with stroke-induced dysphagia through extended follow-up periods.

Availability of data and materials

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Funding

The research is supported by 2023 Wannan Medical College-level Scientific Research Project (WK2023JXYY002).

Conflict of interest: None declared.

REFERENCES

1. Labeit B, Michou E, Hamdy S, Trapl-Grundschober M, Suntrup-Krueger S, Muhle P, et al. The assessment of dysphagia after stroke: state of the art and future directions. Lancet Neurol. 2023; 22(9):858–70. [DOI: 10.1016/S1474-4422(23)00153-9] [PMID: 37596008]
2. Wong SM, Kamarunas E, Ludlow CL. Impaired Movement Scaling and Reduced Synchrony with Vestibule Closure Characterize Swallowing in Severe Dysphagia. Dysphagia. 2020; 35(4):643–56. [DOI: 10.1007/s00455-019-10067-0] [PMID: 31630250]
3. Cheng H, Deng X, Li J, Tang Y, Yuan S, Huang X, et al. Associations Between Dysphagia and Adverse Health Outcomes in Older Adults with Dementia in Intensive Care Units: A Retrospective Cohort Study. Clin Interv Aging. 2023; 3(18):1233–48. [DOI: 10.2147/CIA.S409828] [PMID: 37554511]
4. Deng Y, Sang Y, Shang Y, Wu C, Xu X. To explore the application value of nursing staff involved multidisciplinary continuous nursing in stroke patients with limb dysfunction. BMC Health Serv Res. 2024;24(1):1051. [DOI: 10.1186/s12913-024-11511-0] [PMID: 39261901]
5. Serber SL, Wachtel N, Fox M, Petrushonis C. A Multidisciplinary Approach to Increase Dysphagia Compliance in Stroke Patients. J Neurosci Nurs. 2024;56(5):180–5. [DOI: 10.1097/JNN.0000000000000778] [PMID: 38968388]
6. Dysphagia Research Team; Chen J, Dai L, Guo M, Huang H, He R, Jin H, et al; Japan NCGM Cooperation Team; Fujitani J, Sugiura Y, Hinohara C, Tang W. A multidisciplinary collaborative diagnosis and rehabilitation program for dysphagia in general hospitals. Biosci Trends. 2024;18(2):108–15. [DOI: 10.5582/bst.2024.01076] [PMID: 38599879]
7. Liu M, Chen X, Ma P, Deng M. Summary of the best evidence for the management of dysphagia in elderly patients. Eur Arch Otorhinolaryngol. 2024;281(8):3893–901. [DOI: 10.1007/s00405-024-08530-2] [PMID: 38459985]
8. Fontaine G, Cossette S, Maheu-Cadotte MA, Deschênes MF, Rouleau G, Lavallée A, et al. Effect of implementation interventions on nurses' behaviour in clinical practice: a systematic review, meta-analysis and meta-regression protocol. Syst Rev. 2019;8(1):305. [DOI: 10.1186/s13643-019-1227-x] [PMID: 31806051]
9. Wang S, Li Y, Tian J, Peng X, Yi L, Du C, et al. A randomized controlled trial of brain and heart health manager-led mHealth secondary stroke prevention. Cardiovasc Diagn Ther. 2020;10(5):1192–9. [DOI: 10.21037/cdt-20-423] [PMID: 33224743]
10. Yan X, Liu Z, Guo ZN, Sun Y, Jin H, Sun X, et al. Positive Influence of Stroke Health Manager on Risk Factors Control and Medication Adherence After Ischemic Stroke. Front Neurol. 2020;11:168. [DOI: 10.3389/fneur.2020.00168] [PMID: 32218766]
11. Wang G, Fang B, Yu X, Li Z. [Interpretation of 2018 guidelines for the early management of patients with acute ischemic stroke]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2018;30(4):289–95. [DOI: 10.3760/cma.j.issn.2095-4352.2018.04.001] [PMID: 29663986]
12. Sella-Weiss O. The Test of Mastication and Swallowing Solids and the Timed Water Swallow Test: Reliability, associations, age and gender effects, and normative data. Int J Lang Commun Disord. 2023;58(1):67–81. [DOI: 10.1111/1460-6984.12768] [PMID: 36036753]
13. Chinese Expert Consensus Group of Dysphagia and Nutrition Management. Chinese expert consensus on food and nutrition management for dysphagia (2019 version). Asia Pac J Clin Nutr. 2020;29(2):434–44. [DOI: 10.6133/apjcn.202007_29(2).0026] [PMID: 32674251]
14. Trollebø MA, Skeie E, Revheim I, Stangeland H, Erstein MH, Grønning MK, et al. Comparison of nutritional risk screening with NRS2002 and the GLIM diagnostic criteria for malnutrition in hospitalized patients. Sci Rep. 2022;12(1):19743. [DOI: 10.1038/s41598-022-23878-3] [PMID: 36396666]
15. Zhang W, Pan H, Zong Y, Wang J, Xie Q. Respiratory Muscle Training Reduces Respiratory Complications and Improves Swallowing Function After Stroke: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2022;103(6):1179–91. [DOI: 10.1016/j.apmr.2021.10.020] [PMID: 34780729]
16. Yang C, Zhao F, Xie C, Zhang Y, Dou Z, Wei X. Community-based group rehabilitation program for stroke patients with dysphagia on quality of life, depression symptoms, and swallowing function: a randomized controlled trial. BMC Geriatr. 2023;23(1):876. [DOI: 10.1186/s12877-023-04555-0] [PMID: 38124046]
17. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321–36. [DOI: 10.1016/s0261-5614(02)00214-5] [PMID: 12765673]
18. Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. Stroke. 1999;30(7):1362–9. [DOI: 10.1161/01.str.30.7.1362] [PMID: 10390308]
19. Wang Z, Shi R, Moreira P. Post-stroke dysphagia: identifying the evidence missing. Front Med (Lausanne). 2025;12:1494645. [DOI: 10.3389/fmed.2025.1494645] [PMID: 40078394]
20. Vu S, Mahmoud N, Sivakumar S, Yazdanian F, Fisher M. Dilemmas in Secondary Stroke Prevention. Stroke. 2025. [DOI: 10.1161/STROKEAHA.124.050403] [PMID: 40255157]
21. Bogenschutz KM, Fisher DS, Wright GW. Acute ischemic stroke: A guideline-based overview of evaluation and management. JAAPA. 2025;38(5):13–20. [DOI: 10.1097/01.JAA.0000000000000203] [PMID: 40197996]
22. Dusenbury W, Barnason S, Vaughn S, Leclaire A, Jaarsma T, Camicia M. Sexual Health After a Stroke: A Topical Review and Recommendations for Health Care Professionals. Stroke. 2025;56(5):1312–22. [DOI: 10.1161/STROKEAHA.124.044723] [PMID: 40116003]
23. Eustace I, Buckley BJR, Kaya I, Hoad KL, France-Ratcliffe M, Hill AR, et al, Higginbotham K. Integrated care management for patients following acute stroke: a systematic review. QJM. 2025:hcaf029. [DOI: 10.1093/qjmed/hcaf029] [PMID: 39854272]

Мултидисциплинарни приступ болесницима са дисфагијом после можданог удара ради побољшања гутања и квалитета живота

Бу Сју[1], Сјангсја Ронг[1], Јен Ган[1], Тао Вej[1], Сјуфанг Џанг[1], Ђингђинг Љу[1], Ђинг Џанг[1], Цилин Ванг[2]

[1]Универзитет науке и технологије Анхуја, Прва придружена болница, Одељење за негу, Хуајнан, Кина;
[2]Медицинска група Синхуа у Хуајнану, Болница Синхуа, Одељење медицинске психологије, Хуајнан, Кина

САЖЕТАК

Увод/Циљ Ова студија имала је за циљ да истражи утицај мултидисциплинарног приступа којим руководе стручњаци за здравље мозга и срца на квалитет живота болесника који пате од дисфагије после можданог удара.

Методе Укупно 194 болесника са дисфагијом после можданог удара, лечених од јануара 2021. до јуна 2024. године, насумично су распоређена у контролну групу (99 случајева, стандардна нега) и групу за посматрање (95 случајева, мултидисциплинарни приступ стручњака за здравље мозга и срца). Обе групе биле су подвргнуте тромесечној интервенцији. Функција гутања, клиничка ефикасност, нутритивни ризик и квалитет живота упоређени су између група пре и после интервенције коришћењем теста гутања воде (*WST*), Гугинг скрининга за процену гутања (*GUSS*), скрининга нутритивног ризика 2002 (*HPC*2002) и скале квалитета живота специфичне за мождани удар (*SS-QOL*).

Резултати У поређењу са периодом пре интервенције, и посматрачка и контролна група показале су смањење вредности у тестовима *WST*, *GUSS* и *HPC*2002 после интервенције ($p < 0,05$), уз значајно повећање резултата на скали *SS-QOL* ($p < 0,05$). У поређењу са контролном групом, посматрана група је показала ниже вредности резултата тестова *WST*, *GUSS* и *HPC*2002 после интервенције ($p < 0,05$). Клиничка ефикасност посматране групе била је значајно већа у односу на контролну групу ($p < 0,05$), а резултати *SS-QOL* у посматраној групи били су значајно виши од оних у контролној групи ($p < 0,05$).

Закључак Мултидисциплинарни приступ под вођством стручњака за здравље мозга и срца значајно је побољшао функцију гутања, смањио ризик од неухрањености и унапредио квалитет живота код болесника са дисфагијом после можданог удара.

Кључне речи: дисфагија; мождани удар; стручњаци за здравље мозга и срца; мултидисциплинарна нега; квалитет живота

DOI: https://doi.org/10.2298/SARH240611045K
UDC: 613.883:[616.34-056.24

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Sexual dysfunction in patients with inflammatory bowel disease

Delyadil Karakaş Kılıç[1], Feyzullah Uçmak[2], Jehat Kılıç[3]

[1]Dicle University, Department of Internal Medicine, Diyarbakir, Turkey;
[2]Dicle University, Department of Gastroenterology, Diyarbakir, Turkey;
[3]Gazi Yaşargil Research and Training Hospital, Department of Internal Medicine, Diyarbakir, Turkey

SUMMARY

Introduction/Objective Inflammatory bowel disease (IBD) is often diagnosed during patients' sexually active years, and factors like disease severity, treatment, and surgery may impact sexual function. This study aimed to assess the sexual quality of life in IBD patients.

Methods Patients with IBD and control groups (n = 45) were prospectively included in this study. Demographic data of patients and duration of illness, laboratory and endoscopic data, and treatment information were recorded. Participants completed the Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Activity Index.

Results In total, 103 patients were included (41 patients with ulcerative colitis and 17 patients with Crohn's disease). The mean age of patients with IBD was 34.26 ± 10.1 years, while the control group had a mean age of 32.93 ± 10.5 years (p = 0.518). The mean total PROMIS was found to be lower in the patient group (men: 29.8 ± 7.4; women: 28.1 ± 7.7) than in the control group (men: 38.5 ± 5.4; women: 34.8 ± 11.6), but the difference was statistically significant only in men (p < 0.001). The median value of the Sexual Life Quality Index was found to be lower in the patient group [men: 3 (1–5); women: 3 (1–4)] than in the control group [men: 5 (3–5); women: 4 (1–5)]. The low Sexual Life Quality Index difference was significant in both men (p < 0.001) and women (p = 0.042).

Conclusion IBD patients showed lower sexual quality of life compared to the general population. Assessing sexual well-being alongside disease activity may positively impact disease management.

Keywords: inflammatory bowel disease; PROMIS; sexual dysfunction

INTRODUCTION

The term "sexual function" refers to the ability to complete the sexual cycle – sexual interest, arousal, orgasm, resolution, and satisfaction – after a sexual stimulus (tactile, visual, olfactory, etc.) without any limitations (e.g., physical, psychological, or psychosocial). Many physiological, psychosocial, and sociocultural factors influence sexual function. A problem in any of these factors limits sexual function in the person [1].

Inflammatory bowel disease (IBD) predominantly affects individuals of young and reproductive age. Consequently, factors such as disease type, disease activity, and medications administered may negatively impact sexual quality of life. Therefore, treatment should be personalized based on disease activity and individual clinical conditions, in consultation with physicians [2–5].

IBD can alter patients' physical appearance — and their perception of it — through fistulae, ostomies, and surgical scars [6]. Distorted body image is present in seventy percent of patients with IBD and has been shown to affect women more than men (75% *vs*. 51%) [7, 8]. Female patients with Crohn's disease (CD) state that they avoid sexual activity owing to fear of abdominal pain, diarrhea, and fecal incontinence [9]. Although sexual dysfunction and distorted body perception are common in patients with IBD, these issues are rarely discussed by clinicians and patients [10].

Given the sociocultural characteristics of the region, this study aimed to evaluate sexual dysfunction among patients with IBD – a topic often overlooked because it is seldom addressed. The purpose of this study is to enhance patient support, improve disease management, raise physician awareness, and contribute meaningfully to the medical literature.

METHODS

Fifty-eight patients diagnosed with IBD in the Gastroenterology Clinic of the Dicle University Faculty of Medicine between 2009 and 2020 and 45 healthy controls with matching demographic characteristics were included.

Sexually active patients aged 18 – 65 years with an endoscopic and histopathological diagnosis of IBD were included. Exclusion criteria were as follows:

- receipt of medications other than standard IBD therapy that could affect sexual life;
- prior surgical intervention for IBD; and

Received • Примљено: June 11, 2024
Revised • Ревизија: May 19, 2025
Accepted • Прихваћено: May 26, 2025
Online first: June 6, 2025

Correspondence to:
Jehat KILIÇ
Gazi Yaşargil Training and Research Hospital
Qadya Street
Kuçukkadi district
Azel Villas No:47 Sur/Diyarbakir
Diyarbakir 21010, Turkey
jehat_kilic@outlook.com

• current treatment for sexual dysfunction.

Remission in IBD, including CD and ulcerative colitis (UC), was evaluated using the following criteria:

- **Clinical remission:** CD = Crohn's Disease Activity Index (CDAI) < 150; UC = Mayo score ≤ 2 with no sub-score > 1.
- **Biochemical remission:** normalization of inflammatory biomarkers, such as C-reactive protein (CRP) and fecal calprotectin.
- **Endoscopic remission:** absence of visible inflammation on endoscopy, indicating mucosal healing.
- **Histologic remission:** lack of microscopic inflammation in biopsies, indicating deep-tissue healing [11].

Demographic and clinical data were recorded, including age, socio-economic status, education level, marital status, disease duration, total protein, albumin, white-blood-cell count, hemoglobin, CRP, site of endoscopic involvement, clinical activity status, medications used, and type of treatment (local or systemic). The Turkish version of the internationally validated Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire was administered to patients and controls (Tables 1 and 2). Lower scores indicate dissatisfaction with sexual life, whereas higher scores reflect greater satisfaction.

For men, the score range is 8 – 45: 8–13 very low, 14–20 low, 21–33 medium, 34–39 high, 40–45 very high.

For women, the score range is 10 – 53: 10–17 very low, 18–25 low, 26–36 medium, 37–44 high, 45–53 very high. In questions 3–7, the more sexual complaints patients have, the fewer points they receive.

Table 1. PROMIS survey questions and scoring addressed to male participants

Question number	Questions	Points
1	To what extent is your desire for sexual activity present?	1–4
2	How often do you want to have sex?	1–5
3	Difficulty getting an erection [hardening] when you want during sexual activity?	1–6
4	How difficult is it for you to maintain an erection [hardening] whenever you want during sexual activity?	1–6
5	How would you describe your ability/grade to be erect?	1–5
6	How would you rate your ability to have a satisfying orgasm?	1–6
7	How much pleasure do you get during sexual activity?	1–6
8	How would you describe your degree of satisfaction during sexual activity?	1–6

Table 2. PROMIS survey questions and scoring addressed to female participants

Question number	Questions	Points
1	To what extent is your desire for sexual activity present?	1–5
2	How often do you want to have sex?	1–5
3	How often have you been lubricated during sexual intercourse in the last 4 weeks?	1–6
4	When you want to be lubricated [wet]; How often do you experience difficulties?	1–5
5	How would you describe your vaginal discomfort during sexual activity? [1: high –5: low]	1–5
6	How often do you have problems with sexual activity due to vaginal pain and/or discomfort?	1–5
7	How often do you have to stop your sexual activity due to vaginal pain and discomfort?	1–5
8	How would you rate your ability to have a satisfying orgasm?	1–5
9	How much pleasure do you get during sexual activity?	1–6
10	How would you describe your degree of satisfaction during sexual activity?	1–6

Statistics

The research was conducted prospectively, and the data obtained were cross-sectional in two groups. The survey was administered, and survey scores – total score and sexual-life indices – were evaluated with the one-sample Kolmogorov–Smirnov test, Student's t-test, and Mann–Whitney U test. Normality of the data was tested with the one-sample Kolmogorov–Smirnov test. Values with non-normal distribution were evaluated with the Mann–Whitney U test, and those with normal distribution were evaluated with the Student's t-test. Parametric values were expressed as mean ± SD, and non-parametric values were expressed as median (min–max). Yates' correction and Pearson's χ^2 test were used to analyze cross-tabulations. Student's t-test was used to compare normally distributed data of the patient and control groups, and the Mann–Whitney U test was used to compare non-normally distributed data. A value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using PASW for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics: The protocol was approved by the Dicle University Faculty of Medicine Clinical Research Ethics Committee (16 July 2020; No. 132, Annex 4).

RESULTS

A total of 58 patients, 41 with UC and 17 with CD, were included in this study. Forty-two (63.4%) of these patients were male and 16 (27.6%) were female. In the control group, 25 (55.6%) were male and 20 (44.4%) were female. The mean age of patients with IBD was 34.26 ± 10.1 years, while the control group had a mean age of 32.93 ± 10.5 years. There was no statistically significant difference between the patient and control groups for either sex distribution ($p = 0.075$) or mean age ($p = 0.518$).

The duration of disease in patients with UC was 70.6 ± 42.5 months, and in patients with CD it was 52 ± 33.5 months ($p = 0.112$). When the patients were examined in terms of clinical and endoscopic activity/remission, 37 were in remission, 63.8% (UC = 23, 39.7%; CD = 14, 24.1%), 20 were active, 34.5% (UC = 18; CD = 2), and one patient (1.7%) had newly diagnosed CD.

Table 3. Data of patients with ulcerative colitis and Crohn's disease

Patient data	Ulcerative colitis		Crohn's disease		p
Number of patients	41		17		> 0.05
Sex	Female	13	Female	3	
	Male	28	Male	14	
Diagnosis time (mean + SD)	70.6 ± 42.5		52 ± 33.5		0.112
Localization	Proctitis (E1)	8 (13.8%)	Ileal (L1) İleo-colonic (L2)	9 (15%) 2 (3.4%)	
	Left colon (E2)	22 (37.9%)	Isolated colonic (L3)	2 (3.4%)	
	Extensive	11 (19%)	Fistulized (p)	4 (29.3%)	
Disease activity	Active	N: 18 (31%)	Active	N : 3 (5.2%)	0.026
	Remission	N: 23 (39.7%)	Remission	N: 14 (24.1%)	

Table 4. Male PROMIS survey scores and sexual life quality index results

Question number	Patients	Control	p
1*	4 [1–5]	5 [3–5]	< 0.05
2*	3 [2–5]	4 [3–5]	< 0.05
3*	4 [1–5]	6 [1–6]	< 0.001
4*	4 [1–5]	6 [1–6]	< 0.001
5*	3 [2–5]	4 [4–6]	0.067
6*	4 [1–6]	5 [4–6]	0.009
7	5 [1–6]	6 [4–6]	< 0.001
8*	3 [1–5]	5 [4–6]	< 0.001
Total scores**	29.8 ± 7.4	38.5 ± 5.4	< 0.001
Sexual Life Quality Index*	3 [1–5]	5 [3–5]	< 0.001

*Mann–Whitney test;
**Student's t-test

Table 5. Women's PROMIS survey scores and sexual life quality index results

Question number	Patients	Control	p
1*	2.5 [1–4]	4 [1–5]	< 0.05
2*	2 [1–3]	3 [1–5]	< 0.05
3*	3 [1–6]	4 [1–6]	0.727
4**	3.4 ± 0.3	3.5 ± 0.3	0.892
5**	2.3 ± 0.2	3.3 ± 0.3	< 0.05
6*	3.5 [1–5]	4 [1–5]	0.912
7**	3.4 ± 0.3	3.3 ± 0.3	0.794
8*	3 [2–4]	4 [2–5]	< 0.001
9*	3 [1–4]	4.5 [1–6]	< 0.001
10**	3.1 ± 0.3	3.8 ± 0.3	0.191
Total scores**	28.1 ± 7.7	34.8 ± 11.6	0.060
Sexual Life Quality Index*	3 [1–4]	4 [1–5]	< 0.05

*Mann–Whitney test;
**Student's t-test

Disease-activity rates were significantly higher in patients with ulcerative colitis (p = 0.026) (Table 3).

The individual scores, total scores, and Sexual-Life-Quality Index (SLQI) values for the male patient and control groups are shown in Table 4. The PROMIS total score was statistically significantly lower in male patients (29.8 ± 7.4) than in male controls (38.5 ± 5.4) (p < 0.001). In addition, the SLQI based on this total score was 3 (1–5) in male patients and 5 (3–5) in male controls, which was also statistically significantly lower (p < 0.001).

Individual scores, total scores, and SLQI values for the female patient and control groups are shown in Table 5. Although the PROMIS total score was lower in female patients (28.1 ± 7.7) than in female controls (34.8 ± 11.6), the difference was not statistically significant (p > 0.05). The SLQI based on the total score was 3 (1–4) in female patients and 4 (1–5) in female controls, and this difference was statistically significant (p = 0.042).

DISCUSSION

Our aim in this study was to investigate regional epidemiological data on the SLQI in male and female patients with IBD. The relationship and frequency of IBD-related SLQI, male erectile dysfunction, and female sexual dysfunction, which have a wide place in the medical literature, were investigated in individuals with IBD followed in our clinic. IBD is a disease that generally affects both sexes equally and has serious negative effects on quality of life [12]. It generally has a negative impact on physical appearance and self-perception owing to fistulae, surgical scars, and ostomy operations. However, symptoms such as abdominal pain, diarrhea, and fecal incontinence also have negative effects on sexuality and body image.

IBD is a disease that is generally more common in young adults, and sexual dysfunction may negatively affect this group more than expected [13, 14]. To our knowledge, there is no study investigating the quality of sexual life in patients with IBD in our region. The main aim of this study was to assess the sexual-life quality of patients using a validated survey and contribute to the literature.

Sexual dysfunction is a complex biological, psychological, and social process. Physiologically, it involves many body systems, especially the neurological, vascular, and endocrine systems [15]. Sexual dysfunction seen in IBD has both psychological and physiological dimensions and these dimensions are closely intertwined. For example, physiological conditions such as fatigue, joint pain, abdominal pain, and dyspareunia can cause psychological diseases such as depression and anxiety, and these symptoms can decrease with the correction of the disease by a gastroenterologist [6]. Women with IBD are at greater risk for vaginal infection and decreased lubrication than the normal population. Men with IBD experience decreased sexual function and erectile dysfunction more than those without IBD or those with IBD in remission [16–20].

In a study conducted by Rivière et al. [21] on 358 patients with inflammatory bowel disease, 238 had CD and 120 had UC. These patient groups were compared with normal control groups, and the rate of sexual dysfunction in female patients with IBD was found to be higher than in the normal population. This rate was 53.6% (women with IBD) and 28% (control group). Male patients with IBD were evaluated for erectile dysfunction, and the rate

of erectile dysfunction was found to be higher than the healthy control group. In patients with IBD, sexual dysfunction was detected in 54% of women and erectile dysfunction in 43% of men. These rates were quite high compared to healthy control groups. The result of our study is consistent with the result found by Rivière et al. [21], and the sexual-life quality index in both groups of men and women is lower than the control group.

In a study conducted by Marin et al. [22] on 555 patients, 355 of whom had inflammatory bowel disease and 200 of whom were healthy controls, they showed that one-half of the women and one-third of the men had a decrease in sexual desire and satisfaction after the diagnosis of IBD. These patients have significantly lower sexual-function-index scores compared to the control group. Corticosteroids and biological agents used in the treatment of the disease, depression, and diabetes mellitus have been identified as independent predictors of sexual dysfunction in patients with IBD [23–26]. According to the results we obtained in our study, when the quality of sexual life was evaluated statistically, the quality of sexual life of the patient group was found to be significantly lower in women and men compared to the control group, more prominently in men [22]. The survey we applied was more comprehensive and included questioning erectile dysfunction in men, and according to the results of our study, when evaluated based on the total survey score in male and female patients, the scores of the patient group were statistically significantly lower than the control group.

In the multicenter study conducted by Bel et al. [27] on 168 female and 119 male inflammatory-bowel patients, no significant difference was found in terms of sexual dysfunction compared to the normal control group. In this study, sexual dysfunction was 54% in female patients with IBD and 44% in the normal group. It was 25% in both male patients and the control group. IBD patients with active disease had impaired sexual function compared to patients in remission and the control group. There was a significant relationship between sexual dysfunction and disease activity, fatigue, depressive state, and quality of life in both male and female patients. The main characteristic of the relationship between disease activity and sexual dysfunction was depression. Patients with active IBD had more sexual dysfunction than patients in remission and the control group, and depression was found to be the strongest determinant. In our study, the patients' relationship with depression was not questioned. The fact that Bel et al. [27] did not find a significant relationship between sexual dysfunction and IBD may be because they focused on its relationship with depression. Again, the larger number of patients in the study by Bel et al. [27] may have produced different results than our study, since it was multicentric.

As a result of this study, we showed that the total score of the PROMIS survey was lower in the patient group of both sexes than in the control group, although statistical significance was reached only in men. Again, we found that the sexual-life quality index was statistically significantly lower in both male and female patient groups compared to the control group. These results revealed that the quality of sexual life was low in both male and female patients with inflammatory bowel disease.

Although our study is the first to investigate sexual dysfunction in patients with inflammatory bowel disease in our region, it has some limiting factors. The first is that the number of our patients, especially women, is relatively low. The main reason for this is that it was a study conducted during the COVID-19 pandemic, the lower literacy rate of women, and the fear of sexual evaluations due to the cultural structure of the region. Defining and finalizing the survey form for patients on the internet increases patient participation, even if it is not at the level we want. Secondly, the quality of sexual life of the patients could not be correlated with disease activation, medication used, and socioeconomic level because responses were anonymous. This situation is related to the fact that it is not possible to see which patient filled out which survey because the study must comply with ethical rules. Another limiting factor was that, although a small number of our patients were illiterate, the questionnaires were answered with the help of the patients' relatives, which may have caused incorrect scoring in this group. One of the primary limitations of this study is the relatively small sample size. Additionally, some patients were reluctant to share detailed information on this sensitive topic, which may have affected the depth of the data collected. It is evident that future studies with larger patient cohorts and well-defined control groups will provide more comprehensive insights and contribute significantly to the literature.

CONCLUSION

Inflammatory bowel disease is usually diagnosed at sexually active age; it is a chronic inflammatory disease with relapses and remissions. Considering the sociocultural structure of our region, during routine follow-up of IBD patients the quality of sexual life – which seriously affects overall quality of life – should be assessed proactively, without waiting for the patient to raise the issue, and the necessary support should be provided to maintain both psychological and physiological well-being.

Conflict of interest: None declared.

REFERENCES

1. Potki R, Ziaei T, Faramarzi M, Moosazadeh M, Shahhosseini Z. Bio-psycho-social factors affecting sexual self-concept: a systematic review. Electron Physician. 2017;9(9):5172–8. [DOI: 10.19082/5172] [PMID: 29038693]
2. Allocca M, Gilardi D, Fiorino G, Furfaro F, Peyrin-Biroulet L, Danese S, et al. Sexual and reproductive issues and inflammatory bowel disease: a neglected topic in men. Eur J Gastroenterol Hepatol. 2018;30(3):316–22. [DOI: 10.1097/MEG.0000000000001074] [PMID: 29351114]
3. Peppercorn MA, Cheifetz AS, Lamont JT, Robson KM. Definitions, epidemiology, and risk factors for inflammatory bowel disease in adults. UpToDate [Internet]. Waltham (MA): UpToDate; 2025 Feb 2.
4. Peppercorn MA, Kane SV, Lamont JT, Robson KM. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. UpToDate [Internet]. Waltham (MA): UpToDate; 2024 Sep 16.
5. Romano L, Fonticelli M, Miranda A, Priadko K, Napolitano L, Crocetto F, et al. Sexual dysfunctions in inflammatory bowel disease: role of Mediterranean diet and quality of life. Andrology. 2024. Online ahead of print. [DOI: 10.1111/andr.13791] [PMID: 39492590]
6. Elias S, Nandi N, Fourie S, Grover L, Newman KL. Addressing factors that impact sexual well-being and intimacy in IBD patients. Curr Gastroenterol Rep. 2025;27(1):10. [DOI: 10.1007/s11894-024-00956-2] [PMID: 39779620]
7. Inns S, Su H, Chen A, Ovenden C, Alcantara J, Lilic P, et al. Body image dissatisfaction is increased in inflammatory bowel disease compared with healthy matched controls but not diseased controls: a case-control study from New Zealand. Nutrients. 2024;17(1):15. [DOI: 10.3390/nu17010015] [PMID: 39796452]
8. Schulz F, Foldenauer AC, Weidmann L, Thomann AK, Tal AO, Plachta-Danielzik S, et al. Women with IBD show higher psychophysiological burden in comparison to men with IBD. J Clin Med. 2024;13:7806. [DOI: 10.3390/jcm13247806] [PMID: 39768729]
9. Mercuri C, Bosco V, Juárez-Vela R, Guillari A, Simeone S, Doldo P. Sexual health in women with inflammatory bowel diseases: a narrative review. Healthcare. 2025;13:716. [DOI: 10.3390/healthcare13070716] [PMID: 40218014]
10. Zhang J, Nie J, Zou M, Zeng Q, Feng Y, Luo Z, et al. Prevalence and associated factors of sexual dysfunction in patients with inflammatory bowel disease. Front Endocrinol (Lausanne). 2022;13:881485. [DOI: 10.3389/fendo.2022.881485] [PMID: 35573991]
11. Kishi M, Hirai F, Takatsu N, Hisabe T, Takada Y, Beppu T, et al. A review on the current status and definitions of activity indices in inflammatory bowel disease: how to use indices for precise evaluation. J Gastroenterol. 2022;57(4):246–66. [DOI: 10.1007/s00535-022-01862-y] [PMID: 35235037]
12. Lungaro L, Costanzini A, Manza F, Barbalinardo M, Gentili D, Guarino M, et al. Impact of female gender in inflammatory bowel diseases: a narrative review. J Pers Med. 2023;13(2):165. [DOI: 10.3390/jpm13020165] [PMID: 36836400]
13. Mancheron A, Dumas A, Martinez-Vinson C, Bourmaud A. Impact of inflammatory bowel diseases on the intimate lives of youths: creating a brief screening questionnaire. J Pediatr Gastroenterol Nutr. 2024;79(6):1142–52. [DOI: 10.1002/jpn3.12379] [PMID: 39370815]
14. Aydamirov M, Erbayrak M, Karkin K, Vuruskan E, Tunckıran MA. Effects of inflammatory bowel diseases on sexual function in women. Ir J Med Sci. 2025;194(2):497–502. [DOI: 10.1007/s11845-025-03890-y] [PMID: 39873965]
15. Tandon A. Psychosexual health and sexuality: multidisciplinary considerations in clinical practice. J Psychosex Health. 2023;5(2):106–13. [DOI: 10.1177/26318318231158246]
16. Pereira H. Psychosexual health and sexuality: multi-disciplinary considerations in clinical practice. Front Psychiatry. 2023;14:1244139. [DOI: 10.3389/fpsyt.2023.1244139] [PMID: 37564240]
17. Mules TC, Swaminathan A, Hirschfeld E, Borichevsky GM, Frampton CM, Day AS, et al. Impact of disease activity on sexual and erectile dysfunction in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2023;29(8):1244–54. [DOI: 10.1093/ibd/izac258] [PMID: 36166573]
18. Timmer A, Bauer A, Dignass A, Rogler G. Sexual function in persons with inflammatory bowel disease: a survey with matched controls. Clin Gastroenterol Hepatol. 2007;5(1):87–94. [DOI: 10.1016/j.cgh.2006.10.018] [PMID: 17234557]
19. Wang JY, Hart SL, Wilkowski KS, Lee JW, Delmotte EC, Del Rosario KM, et al. Gender-specific differences in pelvic organ function after proctectomy for inflammatory bowel disease. Dis Colon Rectum. 2011;54(1):66–76. [DOI: 10.1007/DCR.0b013e3181fd48d2] [PMID: 21160316]
20. Boyd T, de Silva PS, Friedman S. Sexual dysfunction in female patients with inflammatory bowel disease: an overview. Clin Exp Gastroenterol. 2022;15:213–24. [DOI: 10.2147/CEG.S359367] [PMID: 36540885]
21. Rivière P, Zallot C, Desobry P, Sabaté JM, Vergniol J, Zerbib F, et al. Frequency of and factors associated with sexual dysfunction in patients with inflammatory bowel disease. J Crohns Colitis. 2017;11(11):1347–52. [DOI: 10.1093/ecco-jcc/jjx100] [PMID: 28981625]
22. Marín L, Mañosa M, Garcia-Planella E, Gordillo J, Zabana Y, Cabré E, et al. Sexual function and patients' perceptions in inflammatory bowel disease: a case-control survey. J Gastroenterol. 2013;48(6):713–20. [DOI: 10.1007/s00535-012-0700-2] [PMID: 23124604]
23. McCulloch DK, Campbell IW, Wu FC, Prescott RJ, Clarke BF. The prevalence of diabetic impotence. Diabetologia. 1980;18(4):279–83. [DOI: 10.1007/BF00251005] [PMID: 7418954]
24. Perelman MA. Erectile dysfunction and depression: screening and treatment. Urol Clin North Am. 2011;38(2):125–39. [DOI: 10.1016/j.ucl.2011.03.004] [PMID: 21621079]
25. Shin T, Okada H. Infertility in men with inflammatory bowel disease. World J Gastrointest Pharmacol Ther. 2016;7(3):361–9. [DOI: 10.4292/wjgpt.v7.i3.361] [PMID: 27602237]
26. Hwang JM, Varma MG. Surgery for inflammatory bowel disease. World J Gastroenterol. 2008;14(17):2678–90. [DOI: 10.3748/wjg.14.2678] [PMID: 18461653]
27. Bel LG, Vollebregt AM, Van der Meulen-de Jong AE, Fidder HH, Ten Hove WR, Vliet-Vlieland CW, et al. Sexual dysfunctions in men and women with inflammatory bowel disease: the influence of IBD-related clinical factors and depression on sexual function. J Sex Med. 2015;12(7):1557–67. [DOI: 10.1111/jsm.12913] [PMID: 26054013]

Сексуална дисфункција код болесника са запаљенском болешћу црева

Дељадил Каракаш Килич[1], Фејзулах Учмак[2], Џехат Килич[3]

[1]Универзитет „Диџле", Катедра за интерну медицину, Дијарбакир, Турска;
[2]Универзитет „Диџле", Катедра за гастроентерологију, Дијарбакир, Турска;
[3]Истраживачко-наставна болница „Гази Јашаргил", Катедра за интерну медицину, Дијарбакир, Турска

САЖЕТАК

Увод/Циљ Запаљенска болест црева (ЗБЦ) често се дијагностикује током сексуално активних година, а тежина болести, начин лечења и хируршки захвати могу утицати на сексуалну функцију.

Циљ ове студије био је да процени квалитет сексуалног живота код болесника са ЗБЦ.

Методе У студију су проспективно укључени болесници са ЗБЦ и контролна група ($n = 45$). Забележени су демографски подаци, трајање болести, лабораторијски и ендоскопски налази и подаци о терапији. Сви испитаници попунили су *PROMIS* индекс сексуалне активности.

Резултати Укупно је укључено 103 испитаника (41 са улцерозним колитисом и 17 са Кроновом болешћу). Просечна старост болесника са ЗБЦ износила је 34,26 ± 10,1 година, а контролне групе 32,93 ± 10,5 година ($p = 0,518$). Средњи укупни скор *PROMIS*-а био је нижи у групи болесника (29,8 ± 7,4 код мушкараца; 28,1 ± 7,7 код жена) него у контролној групи (38,5 ± 5,4 код мушкараца; 34,8 ± 11,6 код жена), а статистички значајна разлика утврђена је само код мушкараца ($p < 0,001$). Медијана Индекса квалитета сексуалног живота такође је била нижа у групи болесника [3 (1–5) код мушкараца; 3 (1–4) код жена] у поређењу са контролном групом [5 (3–5) код мушкараца; 4 (1–5) код жена]. Разлика је била статистички значајна и код мушкараца ($p < 0,001$) и код жена ($p < 0,042$).

Закључак Болесници са ЗБЦ су показали нижи сексуални квалитет живота у односу на општу популацију. Процена сексуалног благостања уз активност болести може позитивно утицати на управљање болестима.

Кључне речи: запаљенска болест црева; *PROMIS*; сексуална дисфункција

DOI: https://doi.org/10.2298/SARH250515041C
UDC: 612.432.018

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Immunohistomorphometric response of pituitary growth hormone-producing cells in rats to prolonged exposure to moderately elevated ambient temperature

Jovana Čukuranović Kokoris[1], Monika Dovenska[2], Biljana Parapid[3], Lazo Pendovski[2], Martin Nikolovski[2], Braca Kundalić[1], Ivana Graovac[1], Rade Čukuranović[1], Verica Milošević[1], Florina Popovska Perčinić[2]

[1]University of Niš, Faculty of Medicine, Department of Anatomy, Niš, Serbia;
[2]Ss. Cyril and Methodius University in Skopje, Faculty of Veterinary Medicine, Department of Functional Morphology, Skopje, Republic of North Macedonia;
[3]University of Belgrade, Faculty of Medicine, University Clinical Center of Serbia, Division of Cardiology, Belgrade, Serbia

SUMMARY
Introduction/Objective The main objective of this study was to investigate the effect of prolonged exposure (4, 7, 14, 21, 60 days) of rats to moderately high ambient temperature (35 ± 1°C) on the immunohistomorphometric parameters of pituitary somatotrophic (GH) cells.
Methods The experiment was conducted on 42 adult Wistar rats, equally divided into six experimental groups (n = 7). Five were continuously exposed to a temperature of 35 ± 1°C, while the control group was kept at 20 ± 2°C. GH cells were visualized using the peroxidase–antiperoxidase immunohistochemical method. The morphometric analysis was conducted using the M_{42} multipurpose test system.
Results Rats from all experimental groups had significantly ($p < 0.05$) reduced body mass compared with the control. After four and 14 days of exposure to moderate heat, the absolute pituitary weight was significantly ($p < 0.05$) increased by 23.1% and 27.7%, respectively, in comparison with the control. GH cells in all groups were oval and located near capillaries with numerous dark granules. Morphometric analysis of cellular and nuclear volumes of GH cells in the experimental group significantly decreased ($p < 0.05$) compared with the control group.
Conclusion It can be concluded that chronic exposure of adult male rats to moderately high ambient temperatures reduced the immunohistomorphometric parameters of GH cells.
Keywords: moderately high ambient temperature; immunohistomorphometry; somatotrophic cells; rats

INTRODUCTION

High ambient temperatures have become a significant environmental factor in recent decades, directly affecting all biological processes in the body and causing numerous consequences for the functioning of living organisms [1, 2, 3]. Due to climate change and global warming, the impact of high temperatures on body growth, food consumption, muscle mass growth [1], bone mineralization, energy metabolism, and reproduction has become an important aspect of thermophysiology [4].

Exposure to high or low environmental temperatures and continuous exposure to light or darkness are considered environmental stressors for the body [5–8]. In such conditions, a stressogenic reaction occurs, causing the neuroendocrine system response and particularly affecting the hypothalamic–pituitary axis [6, 9, 10]. Earlier studies showed that adrenocorticotropic [6, 11], somatotropic (GH), and mammotropic [7] cells of the pituitary gland are most sensitive to this kind of stress reaction.

GH cells synthesize and secrete growth hormone into the bloodstream; its release is regulated by several circulating hormones and metabolites [12]. The pulsatile control of GH secretion and release into the pituitary portal system is regulated by hypothalamic neurons through the release of stimulatory (GHRH) [12], or GH-inhibitory hormone, somatostatin (SRIH) [13]. GH regulates numerous physiological functions, including protein synthesis, cellular proliferation, body growth [2, 14], neuroendocrine responses, behavior, and metabolism through specific populations of neurons [15].

Current climate changes and global warming have also affected the Western Balkans and Southeastern Europe. It is expected that by 2035 the average annual temperature in this region will increase by 0.5–1°C, especially during the summer period [11]. Having in mind that during summer all animals and humans are subjected to longer or shorter periods of warm climate, we hypothesized that their exposure to high ambient temperatures might have a significant impact on the morphofunctional

Received • Примљено: May 14, 2025
Accepted • Прихваћено: May 28, 2025
Online first: May 30, 2025

Correspondence to:
Jovana ČUKURANOVIĆ KOKORIS
University of Niš
Faculty of Medicine
81 Dr Zorana Đinđića Blvd.
Niš 18000, Serbia
jovana.cukuranovic.kokoris@medfak.ni.ac.rs

characteristics of GH cells. Therefore, this study aimed to elucidate the potential changes in the immunohistomorphometric characteristics of GH cells after short-term and prolonged exposures of animals to moderately elevated ambient temperature.

METHODS

Experimental animals and experimental design

The experiment was conducted on 2.5-month-old adult Wistar male rats. A detailed description of the experimental protocol can be found in our previous study [11]. Briefly, the experimental animals (n = 7 per group) were continuously exposed (4, 7, 14, 21, 60 days) to moderately high ambient temperature in a special heated chamber with controlled air temperature (35 ± 1°C) and air humidity of 30–40%, while the control group (n = 7) was kept at room temperature (20 ± 2°C). Food and water were given *ad libitum* to all animals throughout the whole experiment. After the sacrifice, the pituitary gland was removed, weighed, and subjected to immunohistochemical staining for GH cell visualization.

Immunohistochemical staining

The rat pituitary glands were fixed in 4% paraformaldehyde, dehydrated in ethanol, cleared in xylol, and embedded in paraffin. The distal part of the glands was cut in a series of seven horizontal 5 μm-thick sections through three levels (superior, middle, and inferior) [11]. The immunohistochemical localization of pituitary GH cells was performed using the peroxidase–antiperoxidase method. The procedure is described in detail elsewhere [5, 9, 11].

All animal procedures were compliant with EU Directive 2010/63/EU and approved by the Local Animal Care Committee of the Faculty of Veterinary Medicine – Skopje (No. 0201-4506/2 from 7.11.2011).

Stereological measurements

The cellular volume (Vc_{GH}; μm³), nuclear volume (Vn_{GH}; μm³), and volume density of immunopositive GH cells (Vv_{GH}; %) were determined on 5 μm-thick sections. Measurements were made with the multipurpose test system M_{42} on 50 test fields at × 1000 magnification, previously described in detail by Popovska-Perčinić et al. [5]. Digital recordings were made on a DM RB photomicroscope (Leica, Wetzlar, Germany).

Statistical analysis

The morphometric data obtained for each rat were averaged per experimental group, and the standard deviation (SD) was calculated. One-way analysis of variance (ANOVA) followed by a Tukey test was used to compare differences between the groups. A probability value of 5% or less was considered statistically significant.

Ethics: All animal procedures were approved by the Animal Care Committee of the Faculty of Veterinary Medicine, University in Skopje (No. 0201-4506/2) and followed the instructions provided in the EU Directive 2010/63/EU.

RESULTS

Body mass, absolute and relative pituitary weights

The body mass and the absolute and relative pituitary weights are given in Table 1 and Figure 1. It was found that the body mass in rats exposed to moderate heat for 4, 7, 14, 21, and 60 consecutive days was significantly ($p < 0.05$) reduced by 19.8%, 22.6%, 16.4%, 22.6%, and 37.6%, respectively, compared with the controls. After 4 and 14 days of exposure to moderate heat, the absolute pituitary weight was significantly ($p < 0.05$) increased by 23.1% and 27.7%, respectively, in comparison with the control group. The relative weight of the pituitary gland was significantly ($p < 0.05$) increased by 36% only in rats exposed to moderate ambient temperature for four days.

Immunohistochemical characteristics of GH cells

The GH cells of the control group were intensely stained, with an oval shape and a prominent spherical nucleus located centrally within the cell cytoplasm (Figure 2A). The

Table 1. Absolute and relative pituitary weight in animals exposed to moderately high ambient temperature

Group	Absolute pituitary weight (mg)	Relative pituitary weight (mg%)
Control	6.5 ± 0.6	2.5 ± 0.1
4 days	8.0 ± 0.4* (+23.1%)	3.4 ± 0.3* (+36.5)
7 days	6.3 ± 0.5 (-3.1%)	2.4 ± 0.2 (-4.0%)
14 days	8.3 ± 0.6* (+27.7%)	2.9 ± 0.2 (+16%)
21 days	6.4 ± 0.5 (-1.5%)	2.5 ± 0.1 (0.0%)
60 days	5.8 ± 0.5 (-10.1%)	2.6 ± 0.2 (+4%)

The values are expressed as means ± SD;
*p < 0.05 *vs.* control

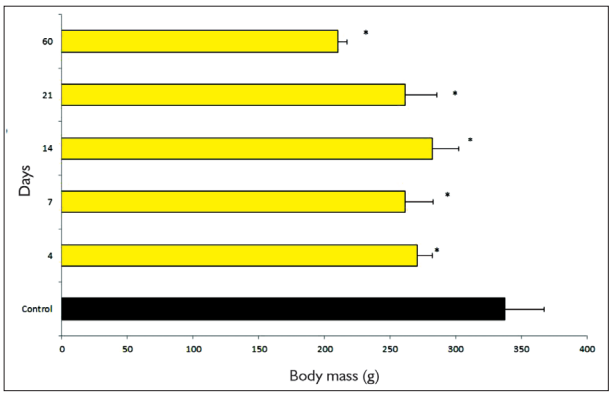


Figure 1. Body mass in animals exposed to moderately high ambient temperature 4, 7, 14, 21, and 60 days; the values are expressed as means ± SD;
*p < 0.05 vs. control

location of GH cells was not significantly changed in the experimental groups. The shape of most cells was oval (Figure 2B–F). However, there were also some stellate cells with noticeable cytoplasmic processes (Figure 2D). Generally, rats exposed for a prolonged time to moderately elevated ambient temperature had smaller GH cells containing darker cytoplasmic areas throughout their cytoplasm. They were found mostly arranged in groups (Figure 2B).

Stereological parameters

In rats exposed to moderate heat for 4, 7, 14, 21, and 60 days, the morphometric analysis of pituitary GH cells showed a significant decrease in their volume ($p < 0.05$) by 18.4%, 25.8%, 14.1%, 24.4%, and 19.1%, respectively (Figure 3A), compared to the control. The nuclear volume of these cells was significantly reduced by 9.5%, 5.3%, 7.4%, 3.2%, and 10.6%, respectively, in comparison with the control group (Figure 3B). The volume density of GH cells was significantly reduced ($p < 0.05$) after 4, 7, and 60 days by 23.7%, 13.2%, and 15.9%, respectively, compared with the control (Figure 3C).

DISCUSSION

Global warming is characterized by an increase in the average annual temperatures. The Western Balkans and Southeastern Europe have experienced prolonged periods of high ambient temperatures during the summer months [11, 16].

In this research, a significant decrease in body weight was found in all groups compared with the control. The largest decrease (-37.6%) was recorded in animals that were exposed to moderately high environmental temperatures for 60 days. Similar results were obtained after exposure of rats to a temperature of 35 ± 1°C for 30 days [5], as well as after acute exposure of mice to temperatures between 34–38.5°C [17]. Increased water intake and reduced food intake are most probably the causes of body weight reduction, which was observed in rats [18] and broilers [1].

The increased absolute weight of the pituitary gland was observed after the fourth and 14th day of exposure to elevated ambient temperature, whereas increased values of the relative weight were registered only after the 4th day. A similar result was reported in earlier studies after acute [19] and chronic [5] (30 days) exposure of rats to high environmental temperature.

Literature data on the effects of temperature on GH cells are very scarce. Most of them concern acute exposure, such as studies from Vigas et al. [20], which describe the stimulatory effect of high temperature on GH release for several

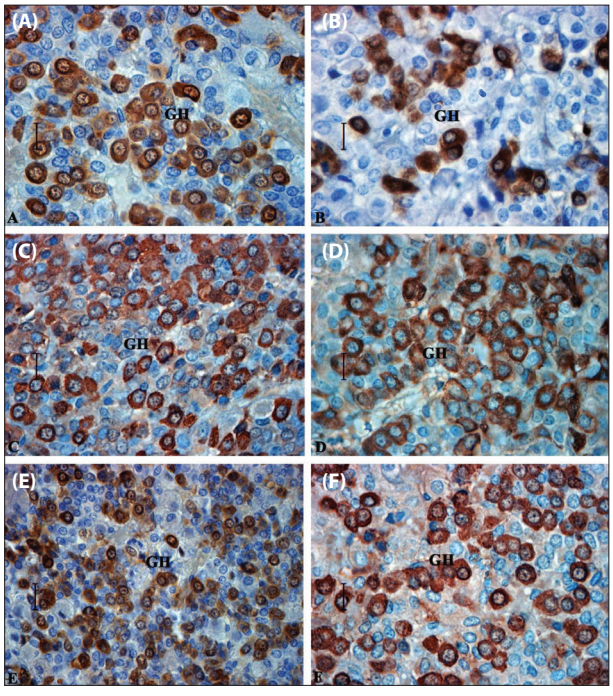


Figure 2. Representative micrographs of immunopositive GH cells in controls (**A**), in animals exposed to moderately high ambient temperature 4 days (**B**); 7 days (**C**); 14 days (**D**); 21 days (**E**); and 60 days (**F**); peroxidase–antiperoxidase method; bar: 16 µm

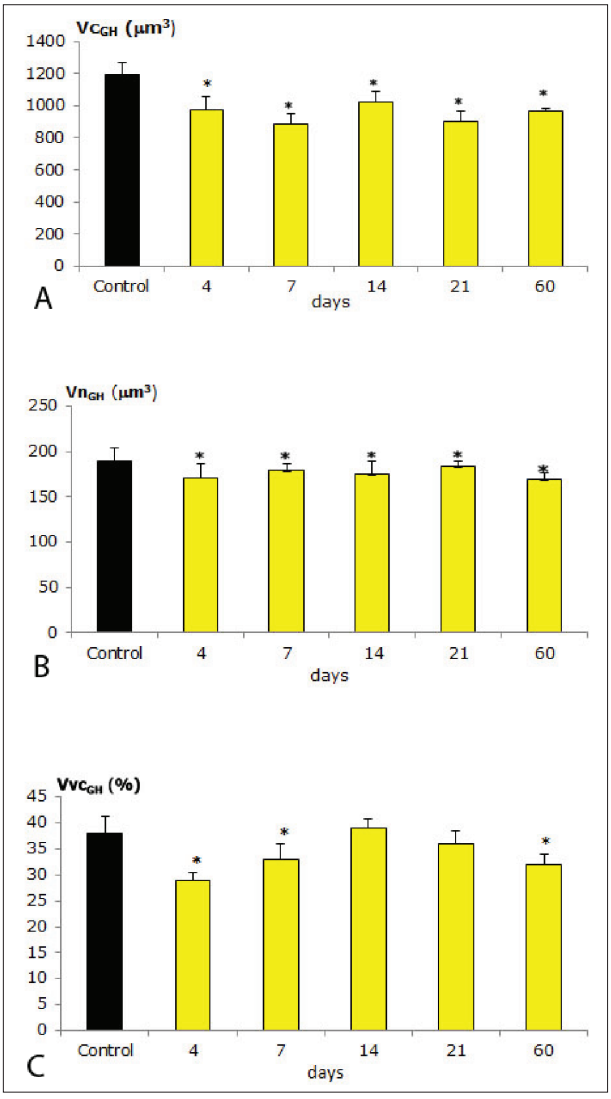


Figure 3. Stereological parameters of immunopositive GH cells in adult male rats after exposure to moderately high ambient temperatures; **A**) Vc-volume of cells (µm3); **B)** Vn-volume of nuclei (µm3); and **C)** Vvc-volume of density (%); the values are expressed as means ± SD; *$p < 0.05$ *vs.* control

minutes to an hour. The current study aimed to expand the information on the properties of GH cells after prolonged exposure to moderately high temperatures.

The stereological analysis in this study showed that the cellular and nuclear volumes of GH cells were significantly reduced compared with the control. These results indicate a decreased activity of somatotropic cells during the entire heat exposure period. A decrease in the stereological parameters of GH cells was also observed after 30 days of exposure to moderately high temperatures [5], which is in agreement with our results. The inhibitory effect of GH secretion and reduced blood GH concentration were noticed after acute and chronic stress [21], as well as during short-term acclimation to high temperatures [22]. This can be explained by the increased secretion of SRIH from the hypothalamus, which serves as a suppressor of GH hormone release [21].

Trifunović et al. [22] and Nestorović et al. [7] reported similar findings after chronic exposure of adult rats to other types of stressors (immobilization, sound, constant light). The decreased somatotropes' activity might be due to the increased SRIH blood concentration, known to exhibit an inhibitory effect on the secretion of GH from the pituitary somatotropic cells [23]. Similar results after exposure to a moderately warm ambient environment were also obtained in birds [24]. Studies in rats reported that increased SRIH synthesis and storage and decreased GH-releasing hormone mRNA synthesis play a major role in the GH inhibitory effects on glucocorticoids [25]. In addition, it was shown that glucocorticoids are directly involved in the increase of pituitary GHS-R mRNA levels by stimulating GHS-R gene transcription [26]. This might be a possible explanation for the decreased activity of GH cells found in this study since reduced serum corticosterone concentration was found in our previous research in rats subjected to moderately high temperatures for 7–60 days [11].

CONCLUSION

Prolonged exposure of adult male rats to moderately high ambient temperature has an inhibitory effect on the immunohistochemical and stereological parameters of GH cells.

ACKNOWLEDGEMENTS

This research was supported by the Ministry of Science, Technological Development, and Innovation of the Republic of Serbia (grant No. 451-03-137/2025-03/200113).

Conflict of interest: None declared.

REFERENCES

1. Ružić Z, Kanački Z, Jokanović M, Vidakovic S, Knežević S, Jović S, et al. The influence of vitamin C and early-age thermal conditioning on the quality of meat and specific production characteristics of broilers during heat stress. Turk J Vet Anim Sci. 2020;44(2):314–22. [DOI: 10.3906/vet-1905-95]
2. Ružić Z, Kanački Z, Stojanović S, Kovačević Z, Knežević S, Todorović S, et al. Rectal temperature and respiration rate as indicators of heat stress in broiler chickens subjected to early-age thermal conditioning and vitamin C supplementation. Turk J Vet Anim Sci. 2023;47(2):160–6. [DOI: 10.55730/1300-0128.4281]
3. Sejian V, Silpa MV, Reshma Nair MR, Devaraj C, Krishnan G, Bagath M, et al. Heat stress and goat welfare: adaptation and production considerations. Animals (Basel). 2021;11(4):1021. [DOI: 10.3390/ani11041021] [PMID: 33916619]
4. Huang Q, Li N, Li Y. Long-term trend of heat waves and potential effects on phytoplankton blooms in Lake Qiandaohu, a key drinking-water reservoir. Environ Sci Pollut Res Int. 2021;28(48): 68448–59. [DOI: 10.1007/s11356-021-15414-z] [PMID: 34272668]
5. Popovska-Perčinić F, Ajdžanović V, Pendovski L, Živanović J, Ilieski V, Dovenska M, et al. Immunohistomorphometric and fluorescent characteristics of rat GH cells after chronic exposure to moderate heat. Mac Vet Rev. 2012;35(2):65–72.
6. Čukuranović-Kokoris J, Ružić Z, Kanački Z, Stojanović S, Paraš S, Milošević V, et al. Effects of vitamin C and early-age thermal conditioning on pituitary ACTH cells in broilers chronically exposed to heat stress: an immunohistomorphometric and hormonal study. Vet Res Forum. 2024;15(3):125–30. [DOI: 10.30466/vrf.2023.2009320.3981] [PMID: 38770378]
7. Nestorović N, Ristić N, Ajdžanović V, Trifunović S, Milošević V. Morphological and functional changes of pituitary GH and PRL cells following prolonged exposure of female rats to constant light. Exp Appl Biomed Res. 2023;24(3):2019–25. [DOI: 10.2478/sjecr-2019-0063]
8. Jasnić N, Dakić T, Bataveljić D, Vujović P, Lakić I, Jevdjović T, et al. Distinct vasopressin content in the hypothalamic supraoptic and paraventricular nucleus of rats exposed to low and high ambient temperature. J Therm Biol. 2015;52:1–7. [DOI: 10.1016/j.jtherbio.2015.04.004] [PMID: 26267492]
9. Popovska-Perčinić F, Jarić I, Pendovski L, Ristić N, Trifunović S, Milošević V, et al. The effect of moderate heat on rat pituitary ACTH cells: histomorphometric, immunofluorescent and hormonal study. Acta Vet. 2017;67(4):495–507. [DOI: 10.1515/acve-2017-0040]
10. Popovska-Perčinić F, Manojlović-Stojanoski M, Pendovski L, Dinevska-Kjovkarovska S, Miova B, Grubin J, et al. A moderate increase in ambient temperature influences the structure and hormonal secretion of adrenal glands in rats. Cell J. 2021;22(4):415–24. [DOI: 10.22074/cellj.2021.6827] [PMID: 32347034]
11. Čukuranović-Kokoris J, Ajdžanović V, Pendovski L, Ristić N, Milošević V, Dovenska M, et al. The effects of long-term exposure to moderate heat on rat pituitary ACTH cells: histological and hormonal study. Acta Vet. 2022;72(1):1–15. [DOI: 10.2478/acve-2022-0001]
12. Rampersaud A, Connerney J, Waxman DJ. Plasma growth hormone pulses induce male-biased pulsatile chromatin opening and epigenetic regulation in adult mouse liver. Elife. 2023;12:RP91367. [DOI: 10.7554/eLife.91367] [PMID: 38091606]
13. Liguz-Lecznar M, Dobrzanski G, Kossut M. Somatostatin and somatostatin-containing interneurons—from plasticity to pathology. Biomolecules. 2022;12(2):312. [DOI: 10.3390/biom12020312] [PMID: 35204812]
14. Martínez-Moreno CG, Arámburo C. Growth hormone (GH) and synaptogenesis. Vitam Horm. 2020;114:91–123. [DOI: 10.1016/bs.vh.2020.04.001] [PMID: 32723552]
15. Wasinski F, Tavares MR, Gusmao DO, List EO, Kopchick JJ, Alves GA, et al. Central growth hormone action regulates neuroglial and pro-inflammatory markers in the hypothalamus of male mice. Neurosci Lett. 2023;806:137236. [DOI: 10.1016/j.neulet.2023.137236] [PMID: 37030549]
16. Perkins-Kirkpatrick SE, Gibson PB. Changes in regional heatwave characteristics as a function of increasing global temperature. Sci Rep. 2017;7(1):12256. [DOI: 10.1038/s41598-017-12520-2] [PMID: 28947762]
17. Harikai N, Tomogane K, Miyamoto M, Shimada K, Onodera S, Tashiro S. Dynamic responses to acute heat stress between 34 °C and 38.5 °C, and characteristics of heat-stress response in mice. Biol Pharm Bull. 2003;26(5):701–8. [DOI: 10.1248/bpb.26.701] [PMID: 12736516]

18. Kim MG, Oh JS, Kim HK, Leem KH. Effects of exogenous growth hormone administration on dexamethasone-induced growth impairment in adolescent male rats. Exp Ther Med. 2017;14(4):3455–62. [DOI: 10.3892/etm.2017.5017] [PMID: 29042933]
19. Koko V, Djordjevic J, Cvijic G, et al. Effect of acute heat stress on the rat pituitary gland: morphological and stereological study. J Therm Biol. 2006;31(5):394–9. [DOI: 10.1016/j.jtherbio.2006.01.009]
20. Vigas M, Celko J, Koska J. Role of body temperature in exercise-induced growth hormone and prolactin release in untrained and physically fit subjects. Endocr Regul. 2000;34(4):175–80. [PMID: 11137977]
21. Pedroso JAB, Dos Santos LBP, Furigo IC, Spagnol AR, Wasinski F, List EO, et al. Deletion of growth-hormone receptor in hypothalamic neurons affects the adaptation capacity to aerobic exercise. Peptides. 2021;135:170426. [DOI: 10.1016/j.peptides.2020.170426] [PMID: 33069692]
22. Trifunović S, Lakić I, Vujović P, Jevdjović T, Šošić-Jurjević B, Milošević V, et al. Morphofunctional parameters of rat somatotrophes after acute and repeated immobilization or restraint stress. Acta Histochem. 2019;121(1):29–34. [DOI: 10.1016/j.acthis.2018.10.003] [PMID: 30342863]
23. Čukuranović-Kokoris J, Kundalić B, Pavlović M, Ugrenović S. Pituitary cells in humans during ageing: an immunohistological and morphometric study. J Med Biochem. 2025;44(2):203–10. [DOI: 10.5937/jomb0-54605]
24. Bohler MW, Chowdhury VS, Cline MA, Gilbert ER. Heat-stress responses in birds: a review of the neural components. Biology (Basel). 2021;10(11):1095. [DOI: 10.3390/biology10111095] [PMID: 34827087]
25. Fife SK, Brogan RS, Giustina A, Wehrenberg WB. Immunocytochemical and molecular analysis of the effects of glucocorticoid treatment on the hypothalamic-somatotropic axis in the rat. Neuroendocrinology. 1996;64(2):131–8. [DOI: 10.1159/000127109] [PMID: 8857607]
26. Tamura H, Kamegai J, Sugihara H, Kineman RD, Frohman LA, Wakabayashi I. Glucocorticoids regulate pituitary growth-hormone secretagogue-receptor gene expression. J Neuroendocrinol. 2000;12(6):481–5. [DOI: 10.1046/j.1365-2826.2000.00446.x] [PMID: 10844575]

Имунохистоморфометријски одговор ћелија хипофизе које производе хормон раста код пацова на продужено излагање умерено повишеној температури околине

Јована Чукурановић Кокорис[1], Моника Довенска[2], Биљана Парапид[3], Лазо Пендовски[2], Мартин Николовски[2], Браца Кундалић[1], Ивана Граовац[1], Раде Чукурановић[1], Верица Милошевић[1], Флорина Поповска Перчинић[2]

[1]Универзитет у Нишу, Медицински факултет, Катедра за анатомију, Ниш, Србија;
[2]Универзитет Светог Ћирила и Методија у Скопљу, Факултет ветеринарске медицине, Катедра за функционалну морфологију, Скопље, Република Северна Македонија;
[3]Универзитет у Београду, Медицински факултет, Универзитетски клинички центар Србије, Одељење за кардиологију, Београд, Србија

САЖЕТАК

Увод/Циљ Основни циљ овог истраживања био је да се испита ефекат продужене изложености (4, 7, 14, 21, 60 дана) пацова умерено високој температури околине (35 ± 1° *C*) на имунохистоморфометријске параметре соматропних (ГХ) ћелија хипофизе.

Методе Експеримент је спроведен на 42 одрасла Вистар пацова, подељена у шест експерименталних група ($n = 7$), од којих је пет непрекидно изложено температури од 35 ± 1° *C*, док је контролна група држана на 20 ± 2° *C*. ГХ ћелије су имунохистохемијски визуелизоване методом пероксидаза–антипероксидаза. Морфометријска анализа је спроведена коришћењем вишенаменског тест-система M_{42}.

Резултати Пацови из свих експерименталних група имали су значајно ($p < 0,05$) смањену телесну масу у односу на контролну групу. После четири и 14 дана излагања умереној топлоти, апсолутна тежина хипофизе је значајно ($p < 0,05$) повећана за 23,1% односно 27,7%, у поређењу са контролном групом. ГХ ћелије у свим групама биле су овалног облика и смештене у близини капилара са бројним тамним гранулама. Морфометријска анализа ћелијских и нуклеарних запремина ГХ ћелија у експерименталној групи значајно је смањена ($p < 0,05$) у односу на контролну групу.

Закључак Може се закључити да је хронична изложеност одраслих мужјака пацова умерено високим температурама околине смањила имунохистоморфометријске параметре ГХ ћелија.

Кључне речи: умерено висока температура околине; имунохистоморфометрија; соматотропне ћелије; пацови

DOI: https://doi.org/10.2298/SARH250328032G
UDC: 616.441-006-089.85(497.6)"2022/2024"

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Complications after total thyroidectomy in correlation with histopathological and hormonal findings

Mirjana Gnjatić[1,2], Dalibor Vranješ[1,2], Vanja Nežić[2], Branko Jurišić[1,2], Irma Ovčina[3]

[1]University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[2]University Clinical Center of Republic of Srpska, ENT Clinic, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;
[3]University Clinical Center of Republic of Srpska, Clinic for Internal Diseases, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

SUMMARY

Introduction/Objective Total thyroidectomy (TT) is frequently performed in head and neck surgery and is considered a relatively straightforward procedure, yet it is still associated with a number of complications. This study aimed to examine the role and significance of TT in the occurrence of postoperative complications in correlation with histopathological (HP) and endocrinological findings.

Methods A cross-sectional study was conducted involving 90 patients in the University Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina who underwent the thyroid gland surgery 2022–2024. Preoperatively, hormonal analyses, thyroid ultrasound examination, and endovideolaryngoscopy were performed. TT was performed in all patients. Postoperatively, HP diagnostics, control hormonal tests, and endovideolaryngoscopy were performed.

Results Vocal fold paralysis (VFP) was reported by 11 (12.2%) patients. HP analysis showed that goiter was the leading cause in 37 (41.1%) patients, followed by follicular adenoma in 25 (27.8%) and papillary carcinoma in 18 (20%); other causes were present in the remaining 10 (11%). Regarding endocrinological complications, hypocalcemia was present in 67 (74.4%) patients, and elevated parathyroid hormone levels in four (4.4%) patients.

Conclusion VFP and hypocalcemia represented the most common postoperative complications after TT, particularly in patients with HP-diagnosed goiter, follicular adenoma, or papillary thyroid carcinoma. These findings may help identify older patients who are at increased risk of TT-related complications that could significantly impair their quality of life.

Keywords: hypocalcemia; thyroid gland diseases; vocal fold paralysis

INTRODUCTION

Thyroid disorders are among the most common endocrine-system diseases, and thyroidectomy is the therapy of choice for benign lesions, and is a surgical intervention routinely used in cases of suspected malignancy after ultrasound examination and fine-needle aspiration [1]. Other reasons for thyroid surgery include enlargement of the thyroid gland in the form of nodular or colloid goiter that interferes with breathing or swallowing [2]. Even with recent adjustments to total thyroidectomy (TT) meant to reduce the financial strain on hospitals, expenses are still growing by 4.3% annually [3]. Currently, this surgical intervention is very common and is among the safest surgical procedures [4]. Ultrasound is a mandatory diagnostic procedure for thyroid disease due to its reliability, non-invasiveness among diagnostic procedures, and its reliability and non-invasiveness, whereas computed tomography and magnetic resonance imaging are reserved for complex cases [5].

However, thyroid surgery still carries a number of complications, regardless of whether it is performed using the classic open technique or micro-invasive surgery, and even includes a certain degree of mortality risk [6]. The most common complications include hypoparathyroidism (HPT), damage to the external branch of the superior laryngeal nerve, the recurrent laryngeal nerve, postoperative hemorrhage, laryngeal edema, and tracheospasm with dyspnea [6]. Post-thyroidectomy hypocalcemia occurs due to HPT, which can result from the devascularization or unintentional removal of the parathyroid glands [7]. A frequent and dangerous complication after TT is hypocalcemia [8]. Its incidence is about 1.2%, and it is transient in approximately 40% of cases and permanent in only 3% [7, 8]. Another common complication is damage to the recurrent laryngeal nerve.

The incidence of transient recurrent vocal-fold paralysis (VFP) ranges 5–8%, while the rate of permanent recurrent VFP is 0.3–3% [9]. The increase in the number of TT is associated with more postoperative complications. Surgeon experience, or lack thereof, accounts for 46–56% of cases of unilateral and bilateral VFP, which can ultimately lead to dysphonia, dysphagia, and dyspnea [10]. Postoperative dysphonia can

Received • Примљено: February 24, 2025
Revised • Ревизија: April 17, 2025
Accepted • Прихваћено: April 25, 2025
Online first: April 29, 2025

Correspondence to:
Mirjana GNJATIĆ
ENT Clinic
University Clinical Center of Republic of Srpska
12 beba bb
78000 Banja Luka
Republic of Srpska
Bosnia and Hercegovina
mgnjatic@gmail.com

have significant implications for patients, so it is crucial to take all necessary measures to minimize this complication [11]. Postoperative hypocalcemia has a variety of causes. Since many of these characteristics may be changed, it is critical to identify them after surgery so that high-risk population groups can be identified and early preventive measures can be put in place [12].

For patients who are experiencing changes in their voice, a multidimensional voice assessment and a postoperative laryngeal examination are advised [13]. After thyroid surgery, 80% of patients have voice disorders, meaning that roughly 10% of patients have recurrent laryngeal nerve damage [10]. Dysphonia after TT can significantly affect a patient's quality of life and interfere with their ability to perform work and daily activities [11]. Preoperative voice education, managing anticipated voice changes during surgery, and thorough voice care after TT are all recommended by the guidelines [13]. This study aimed to examine the role and significance of TT in the occurrence of postoperative complications in correlation with histopathological (HP) and endocrinological findings.

METHODS

A cross-sectional study was conducted involving 90 patients with thyroid diseases who underwent TT at the University Clinical Center of the Republic of Srpska (UCC RS) in Banja Luka 2022–2024. Inclusion criteria were that the patients had s thyroid disease not surgically treated until arrival at the center. Patients under 18 years of age and those without a history of fine-needle aspiration were excluded.

The patients underwent an initial examination. Demographic characteristics and medical history were recorded at the Clinic for Endocrine Diseases. Indications for surgery were determined by endocrinologists who, based on anamnestic data, clinical examination, ultrasonography of the thyroid gland, laboratory findings in the form of hormonal status and basic laboratory tests, diagnosed one of the thyroid diseases. Following TT, which involved removing all thyroid tissue, calcium, parathyroid hormone (PTH) and FT4 levels were measured at the Clinic for Endocrinology. After 48 h, the patients were examined in the phoniatrics office to assess the condition of the vocal folds, and endovideolaryngoscopy was performed to diagnose whether there was proper mobility of both vocal folds or unilateral or bilateral damage to the *n. laryngeus recurrens*.

Data analysis was conducted using SPSS v22.0 (IBM, USA). Descriptive statistics are presented as the mean, median and standard deviation. Quantitative values are expressed as absolute numbers (n) and percentages (%). For analysis of categorical variables, we used the чI test and Fisher's exact test. Depending on the normality of the data distribution, we used the Student's t-test for independent samples or the Mann–Whitney test. For dependent variables, we used the t-test for dependent samples or the Wilcoxon test. For numerical variables, either Spearman's or Pearson's correlation was used. Results were considered significant if $p < 0.05$.

Ethics: The study was approved by the Ethics Committee of UCCRS (approval no. 01-19-439-2/24) and complied with the revised ethical guidelines of the Declaration of Helsinki.

RESULTS

This cross-sectional study included 90 patients of both sexes. Demographic data, indications for surgery, symptoms before and after surgery, thyroid-stimulating hormone (TSH) before and after surgery, postoperative serum calcium level, PTH and occurrence of unilateral or bilateral vocal-fold paralysis were collected. Of the total number of patients, 81 (90%) were female, with a mean age of 54.18 ± 11.8 years. The most common indication for TT was the isolated presence of goiter in 51 (56.7%), followed by Hashimoto's thyroiditis in 11 (12.2%) (Figure 1).

Five (5.6%) patients had preoperative symptoms, all of whom were women, while 85 (94.4%) patients had no preoperative symptoms. The most common postoperative symptoms were dyspnea on exertion, dizziness, neck pain, dysphagia, and cough. Laryngeal symptoms after TT were present in 13 (14.4%) patients and were reported as: hoarseness; hoarseness and difficulty swallowing; difficulty swallowing and cough (Figure 2). HP findings showed the highest presence of goiter in 37 (41.1%) patients, followed by follicular adenoma in 25 (27.8%) and papillary carcinoma in 18 (20%). VFP occurred in 11 patients (12.2%). The highest incidence of VFP occurred in patients with an HP diagnosis of goiter in 4 (4.4%) patients and papillary carcinoma in 4 (4.4%) patients, but it was not statistically

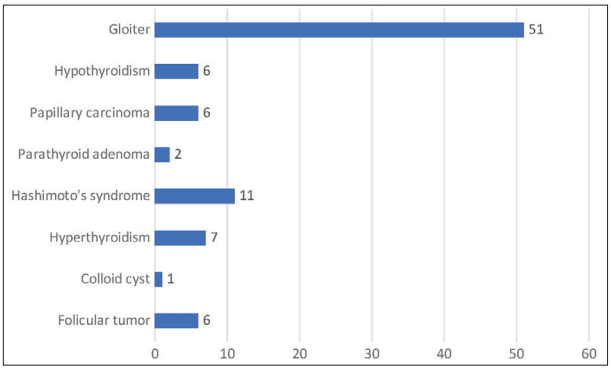


Figure 1. Frequency of preoperative thyroid disease diagnosis

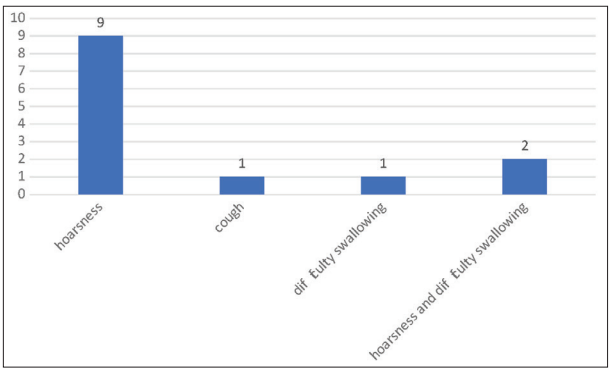


Figure 2. Presentation of laryngeal symptoms after surgery

significant (чI = 3.88, df = 3, p = 0.27) (Table 1). In the total sample, 11 (12.2%) had unilateral VFP, while no cases of bilateral VFP were detected.

Table 1. Correlation of pathohistological findings and paralysis

Paresis	HP				p
	Goiter	Papillary carcinoma	Follicular adenoma	Other	
Yes	4 (4.4)	4 (4.4)	1 (1.1)	2 (2.2)	> 0.05
No	33 (36.7)	14 (15.6)	24 (26.7)	8 (8.9)	

$\chi^2 = 3.88$, df = 3, p = 0.27; HP – histopathological

In the total sample, 12 (13.3%) patients had clinical endocrinological symptoms postoperatively. Among the symptoms reported were calf pain, leg cramps, tingling sensations, and a general feeling of weakness. Sixty-seven (74.4%) patients had hypocalcemia, of which 51 (56.7%) had mild (1.9–2.2 mmol L^{-1}) and 16 (17.8%) severe hypocalcemia (< 1.9 mmol L^{-1}). Four (4.4%) patients had elevated PTH levels. A statistically significant correlation was found between age and postoperative calcium levels ($r_s = 0.2$, p = 0.05). However, no statistically significant associations were observed between age and postoperative TSH ($r_s = -0.09$, p = 0.37), age and preoperative TSH ($r_s = 0.004$, p = 0.97) or postoperative PTH ($r_s = 0.02$, p = 0.84) (Table 2).

Table 2. Correlation of endocrinological complications with laboratory parameters

Laboratory parameters	N	Min.	Max.	Mean	SD
TSH preoperatively	90	0	4.33	1.55	1.14
TSH postoperatively	90	0.01	45	13.84	10.56
PTH postoperatively	90	1	75	32.7	16.28
Hypocalcemia postoperatively	90	1.06	2.56	2.02	0.32

TSH – thyroid-stimulating hormone; PTH – parathyroid hormone

Table 3. Correlation of the occurrence of postoperative symptomatology overall with age and laboratory parameters

	Age	PTH postoperatively	TSH preoperatively	TSH postoperatively
p	0.35	0.005	0.35	0.31

U = 470, p = 0.005; PTH – parathyroid hormone; TSH – thyroid-stimulating hormone

There is a statistically significant correlation between postoperative PTH levels and the onset of postoperative symptoms overall (U = 470, p = 0.005). Age does not show a statistically significant correlation with postoperative symptoms (U = 671.5, p = 0.35), nor do preoperative TSH (U = 670, p = 0.35), postoperative TSH (U = 662, p = 0.31) or postoperative pH (Table 3).

Logistic-regression analysis was conducted to evaluate the influence of age, HPT presence, preoperative TSH levels, pH, and sex on the total incidence of postoperative symptoms. The overall model did not show a statistically significant difference when compared with the null model ($\chi^2 = 5.013$, p = 0.658), accounting for 8% of the variation in postoperative symptoms (Nagelkerke R^2). There was no statistically significant effect of individual factors on the occurrence of postoperative symptoms: age (p = 0.45), hyperthyroidism (p = 0.68), preoperative TSH (p = 0.88), pH (p = 0.57), and sex (p = 0.20) (Table 4).

DISCUSSION

The analysis of post-thyroidectomy complications reveals that, while these procedures are typically routine and relatively safe, they do carry some risks. The most common complications, including VFP and HPT, can significantly affect patients' quality of life [14]. TT still has an overall complication rate of up to 54.4% [1]. Our study reveals several key findings regarding laryngeal complications after TT, highlighting their association with HP findings and the patient's hormonal status [9]. The findings also align with earlier research on complications following thyroid surgery, particularly highlighting hypocalcemia and recurrent laryngeal-nerve dysfunction as the most frequently encountered negative outcomes. We demonstrated that the rate of recurrent laryngeal-nerve dysfunction is 12.2%, with symptoms observed in 14.4% of individuals. Our results align with previous studies that have reported comparable complications [15].

Excessive use of alcohol, due to its toxic effect, can be one of the risk factors for thyroid cancer [16]. We found that VFP occurred in 11 (12.2%) patients after TT, with no statistically significant association with sex, age, presence of goiter, or hyperthyroidism. However, goiter and papillary carcinoma were present in the majority of patients with VFP [17]. EVLS offers insights into the anatomical structures and functional changes of the vocal folds, including their appearance and vibratory patterns, without any complications [18]. These results align with research conducted by other authors, which found that a notable proportion of patients experienced VFP, with its occurrence being influenced by

Table 4. Correlation of demographic laboratory and endocrinological and PH factors with postoperative complications

Variable		Coef. (B)	SE	Odds ratio (Exp B)	95% confidence interval		p
					Lower	Upper	
Age		0.016	0.022	0.984	0.943	1.026	0.45
Hyperthyroidism	No			1			
	Yes	0.476	1.159	1.610	0.166	15.592	0.68
TSH before		0.033	0.222	1.034	0.669	1.598	0.88
HP							0.57
1		-0.952	0.794	0.389	0.081	1.828	0.23
2		-0.210	0.846	0.476	0.154	4.257	0.80

χ^2-test = 5.013, p = 0.658, TSH – thyroid-stimulating hormone; HP – histopathological

the surgeon's level of expertise and the scope of the operation [19]. In this regard, the importance of standardizing recurrent laryngeal-nerve identification activities was emphasized to prevent nerve damage during surgery [20].

Regardless of changes in laryngeal mobility, individuals may experience swallowing issues following thyroidectomy. Although they are more frequently noticed in the late postoperative phase, these problems, characterized by delayed triggering and stasis of food, may be seen in the early postoperative period [21]. A study assessing a tool designed to calculate the likelihood of hypocalcemia following TT discovered that the decline in PTH levels 1 h and 8 h after surgery, in addition to magnesium levels on the second postoperative day, were reliable indicators of more severe hypocalcemia [22].

These results are in line with research showing that hypocalcemia is the most frequent side effect following thyroidectomy, with a frequency as high as 54.4%. Postoperative endocrinological symptoms, such as tingling, muscle cramps and fatigue, were reported in 12 (13.3%) patients. The most important factor influencing the occurrence of these symptoms was the degree of hypocalcemia ($p = 0.001$), while other factors such as the presence of goiter, hyperthyroidism and histopathological findings did not show a significant association. This confirms previous findings linking hypoparathyroidism with postoperative hypocalcemia [23]. Increased surgeon operative volume has been linked to better outcomes across various procedures, including thyroidectomy. A study showed that thyroidectomies on elderly persons were less common among high-volume thyroid surgeons, who had fewer complications [24]. Risk-factor analysis showed that the presence of goiter alone significantly influences the occurrence of postoperative symptoms, which is consistent with the results of our study [25].

The decision regarding which surgical approach to take should be guided by the patient's risk factors, tumor characteristics and overall clinical context [26]. Thoracoscopy is considered the technique of choice for large retrosternal goiters descending into the mediastinum [27]. The treatment of autoimmune diseases of the thyroid gland such as Hashimoto's thyroiditis also requires surgical therapy. The solution would be improvement of diagnostics, good preoperative preparation, adequate intraoperative monitoring of the *n. laryngeus recurrens* and preoperative use of corticosteroids. Adequate and good results are directly related to precise surgical techniques, good operator experience and early voice rehabilitation [28].

CONCLUSION

Patients with VFP and hypocalcemia show the highest incidence of postoperative complications after TT due to HP-diagnosed goiter, follicular adenoma, and papillary thyroid carcinoma. These findings may be useful in identifying elderly patients at increased risk of complications after TT that can significantly affect their quality of life.

Conflict of interest: None declared.

REFERENCES

1. Chahardahmasumi E, Salehidoost R, Amini M, Aminorroaya A, Rezvanian H, Kachooei A, et al. Assessment of the early and late complication after thyroidectomy. Adv Biomed Res. 2019;8:14. [DOI: 10.4103/abr.abr_3_19] [PMID: 30993084]
2. El-Sebai Ali M, Atef Ebada H, El-Shaheed MA, Musaad AbdElFattah A, Kamal ES. Routine thyroidectomy with total laryngectomy: is it really indicated? A randomised controlled trial. Ann Med Surg (Lond). 2022;74:103309. [DOI: 10.1016/j.amsu.2022.103309] [PMID: 35145675]
3. Sahli ZT, Zhou S, Sharma AK, Segev DL, Massie A, Zeiger MA, et al. Rising cost of thyroid surgery in adult patients. J Surg Res. 2021;260:28–37. [DOI: 10.1016/j.jss.2020.11.049] [PMID: 33316757]
4. Bobanga ID, McHenry CR. Treatment of patients with Graves' disease and the appropriate extent of thyroidectomy. Best Pract Res Clin Endocrinol Metab. 2019;33(4):101319. [DOI: 10.1016/j.beem.2019.101319] [PMID: 31530446]
5. Ћahin E, Elbopa U, Kalender E. Regional reference values of thyroid gland volume in Turkish adults. Srp Arh Celok Lek. 2015;143(3–4):141–5. [DOI: 10.2298/SARH1504141S] [PMID: 26012121]
6. Scerrino G, Melfa G, Raspanti C, Rotolo G, Salamone G, Licari L, et al. Minimally invasive video-assisted thyroidectomy: analysis of complications from a systematic review. Surg Innov. 2019;26(3):381–7. [DOI: 10.1177/1553350618823425] [PMID: 30632464]
7. Metere A, Biancucci A, Natili A, Intini G, Graves CE. PTH after thyroidectomy as a predictor of post-operative hypocalcemia. Diagnostics (Basel). 2021;11(9):1733. [DOI: 10.3390/diagnostics11091733] [PMID: 34574074]
8. Prduraru DN, Ion D, Carsote M, Andronic O, Bolocan A. Post-thyroidectomy hypocalcemia – risk factors and management. Chirurgia (Bucur). 2019;114(5):564–70. [DOI: 10.21614/chirurgia.114.5.564] [PMID: 31670631]
9. Jin S, Sugitani I. Narrative review of management of thyroid surgery complications. Gland Surg. 2021;10(3):1135–46. [DOI: 10.21037/gs-20-859] [PMID: 33842257]
10. Francis DO, Pearce EC, Ni S, Garrett CG, Penson DF. Epidemiology of vocal-fold paralyses after total thyroidectomy for well-differentiated thyroid cancer in a Medicare population. Otolaryngol Head Neck Surg. 2014;150(4):548–57. [DOI: 10.1177/0194599814521381] [PMID: 24482349]
11. Pace-Asciak P, Russell JO, Tufano RP. Improving voice outcomes after thyroid surgery and ultrasound-guided ablation procedures. Front Surg. 2022;9:882594. [DOI: 10.3389/fsurg.2022.882594] [PMID: 35599805]
12. Jan BS, Alamri AH, Alkaff HH, Almuqati WQ, Sayed SI, Abdelmonim SK, et al. Risk factors for postoperative hypocalcemia following total thyroidectomy: a retrospective study. Ann Saudi Med. 2024;44(1):39–47. [DOI: 10.5144/0256-4947.2024.39] [PMID: 38311865]
13. Ryu CH, Lee SJ, Cho JG, Choi IJ, Choi YS, Hong YT, et al. Care and management of voice change in thyroid surgery: Korean Society of Laryngology, Phoniatrics and Logopedics clinical practice guideline. Clin Exp Otorhinolaryngol. 2022;15(1):24–48. [DOI: 10.21053/ceo.2021.00633] [PMID: 34098629]
14. Gerardi I, Verro B, Amodei R, Richiusa P, Saraniti C. Thyroidectomy and its complications: a comprehensive analysis. Biomedicines. 2025;13(2):433. [DOI: 10.3390/biomedicines13020433] [PMID: 40002845]
15. Chen HC, Pei YC, Fang TJ. Risk factors for thyroid surgery-related unilateral vocal-fold paralysis. Laryngoscope. 2019;129(1):275–83. [DOI: 10.1002/lary.27336] [PMID: 30284255]
16. Kalezic N, Karadzic-Kocica M, Dimic N, Kocica M, Tољkovic A, Jovanovic M, et al. Alcohol abuse as a risk factor for developing thyroid cancer. Srp Arh Celok Lek. 2021;149(3–4):185–8. [DOI: 10.2298/SARH201123113K]

17. Brown RL, de Souza JA, Cohen EE. Thyroid cancer: burden of illness and management of disease. J Cancer. 2011;2:193–9. [DOI: 10.7150/jca.2.193] [PMID: 21509149]
18. Stojanovic J, Milovanovic D, Mitrovic S, Jevtovic A, Bozovic N, Jovanovic M, et al. Videolaryngostroboscopy in early vocal-fold carcinoma diagnosis. Srp Arh Celok Lek. 2021;149(11–12):691–5. [DOI: 10.2298/SARH200529077S]
19. Huang CF, Jeng Y, Chen KD, Yu JK, Shih CM, Huang SM, et al. The preoperative evaluation prevents postoperative complications of thyroidectomy. Ann Med Surg (Lond). 2014;4(1):5–10. [DOI: 10.1016/j.amsu.2014.11.005] [PMID: 25685337]
20. Gualniera P, Scurria S, Mondello C, Asmundo A, Sapienza D, Gianlorenzo D. Narrative review of proving the causal link of recurrent laryngeal-nerve injury and thyroidectomy: a medico-legal appraisal. Gland Surg. 2020;9(5):1564–72. [DOI: 10.21037/gs-20-203] [PMID: 33224832]
21. Elbeltagy YM, Bassiouny SE, Sobhy TS, Ismail AE, Teaima AA. Swallowing problems after thyroidectomy. Int Arch Otorhinolaryngol. 2021;26(3):e327–33. [DOI: 10.1055/s-0041-1730302] [PMID: 35846825]
22. Soares CSP, Koga KH, Moriguchi SM, Terra SA, Tagliarini JV, de Vasconcelos Affonso PHD, et al. Development of a tool to calculate the probability of hypocalcemia after total thyroidectomy: a prospective study. Langenbecks Arch Surg. 2024;409(1):33. [DOI: 10.1007/s00423-024-03229-8] [PMID: 38195723]
23. Suwannasarn M, Jongjaroenprasert W, Chayangsu P, Suvikapakornkul R, Sriphrapradang C. Single measurement of intact parathyroid hormone after thyroidectomy can predict transient and permanent hypoparathyroidism: a prospective study. Asian J Surg. 2017;40(5):350–6. [DOI: 10.1016/j.asjsur.2015.11.005] [PMID: 26780986]
24. Kim J, Seib CD. Operative management of thyroid disease in older adults. J Endocr Soc. 2023;7(7):bvad070. [DOI: 10.1210/jendso/bvad070] [PMID: 37324534]
25. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical practice guidelines we can trust. Washington (DC): National Academies Press; 2011. [DOI: 10.17226/13058]
26. Javidi S, Sadrizadeh S, Sadrizadeh A, Bonakdaran S, Jarahi L. Postoperative complications and long-term outcomes after total and subtotal thyroidectomy: a retrospective study. Sci Rep. 2025;15:3705. [DOI: 10.1038/s41598-024-79860-8] [PMID: 39881145]
27. Jokic R, Antic J, Vorgucin I, Stajevic M, Nikin Z, Zeravica R, et al. Video-assisted thoracoscopic surgery for primary hyperparathyroidism with ectopic parathyroid adenoma in thymus. Srp Arh Celok Lek. 2021;149(5–6):365–9. [DOI: 10.2298/SARH200529042J]
28. Diklic A, Zivaljevic V, Paunovic I, Kalezic N, Tatic S. Surgical procedures in patients with thyroid autoimmune disease. Srp Arh Celok Lek. 2005;133(1):77–83. [DOI: 10.2298/SARH05S1077D] [PMID: 16405262]

Компликације после тоталне тиреоидектомије у корелацији са хистопатолошким и хормоналним налазима

Мирјана Гњатић[1,2], Далибор Врањеш[1,2], Вања Нежић[2], Бранко Јуришић[1,2], Ирма Овчина[3]

[1]Универзитет у Бањој Луци, Медицински факултет, Бања Лука, Република Српска, Босна и Херцеговина;
[2]Универзитетски клинички центар Републике Српске, Клиника за болести уха, грла и носа, Бања Лука, Република Српска, Босна и Херцеговина;
[3]Универзитетски клинички центар Републике Српске, Клиника за унутрашње болести, Бања Лука, Република Српска, Босна и Херцеговина

САЖЕТАК

Увод/Циљ Тотална тиреоидектомија (ТТ) често се изводи у хирургији главе и врата и сматра се релативно једноставном процедуром, али је још увек праћена бројним компликацијама. Циљ ове студије био је да се испита улога и значај ТТ у настанку постоперативних компликација у корелацији са хистопатолошким (ХП) и ендокринолошким налазима.

Методе Студија пресека обухватила је 90 болесника који су били подвргнути операцији штитасте жлезде у Универзитетском клиничком центру Републике Српске у Бањој Луци, у Босни и Херцеговини, у периоду од 2022. до 2024. године. Преоперативно су урађене хормонске анализе, ултразвучни преглед штитасте жлезде и ендовидеоларингоскопија. Код свих болесника урађена је ТТ. Постоперативно су урађене ХП дијагностика, контролне хормонске анализе и ендовидеоларингоскопија.

Резултати Парализу гласница имало је 11 (12,2%) болесника. ХП анализа показала је да је у већини случајева узрок био струма – код 37 (41,1%) болесника, затим фоликуларни аденом – код 25 (27,8%), папиларни карцином код 18 (20%) и остали узроци код 10 (11%) болесника. Од ендокринолошких компликација, хипокалцемија је била присутна код 67 (74,4%) болесника, а повишен ниво паратироидног хормона код четири (4,4%) болесника.

Закључак Највећи број постоперативних компликација након ТТ јавља се код болесника са парализом гласница и хипокалцемијом због ХП дијагностиковане струме, фоликуларног аденома и папиларног карцинома штитасте жлезде. Ови налази могу бити корисни у идентификацији болесника старије животне доби с повећаним ризиком од компликација након ТТ, што може значајно утицати на квалитет њиховог живота.

Кључне речи: хипокалцемија; болести штитасте жлезде; парализа гласница

DOI: https://doi.org/10.2298/SARH240318034M
UDC: 616.65-006-089.85

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Unfavorable low-risk factors predict pathologic upstaging and upgrading following radical prostatectomy: evidence for further subclassification of low-risk prostate cancer?

Aleksandar Magdelinić[1], Aleksandar Spasić[2], Marko Vuković[1]

[1]Clinical Center of Montenegro, Urology Clinic, Podgorica, Montenegro;
[2]Military Medical Academy, Urology Clinic, Belgrade, Serbia

SUMMARY

Introduction/Objective We aimed to validate the stratification of low-risk prostate cancer (PCa) into "favorable" and "unfavorable" subgroups of patients undergoing radical prostatectomy (RP), based on the correlation of various biopsy features with high-risk characteristics at final pathology.

Methods The research involved 173 patients who were selected as low-risk PCa. The planned stratification categorized patients into favorable and unfavorable low-risk PCa subgroups, based on their Gleason upgrading (GU) and tumor upstaging (TU) status at final pathology. Unfavorable low-risk PCa was defined by the presence of biopsy results correlating with high-risk characteristics at final pathology, pathological Gleason score (pGS ≥ 4 + 3, or ≥ pT3a, or pN1). Patients were divided into two groups according to the presence of high-risk pathology features: Group 1 (n = 84, favorable) and Group 2 (n = 89, unfavorable).

Results In total, 18 patients from the second group (20.2%) experienced Gleason score upgrading (GS ≥ 4 + 3), and in 94.4% of these cases, their biopsy reports indicated the presence of both perineural invasion (PNI) and lymphovascular invasion (LVI). Furthermore, among patients with upstaging to pT3a or pT3b, both PNI and LVI were observed in 60% and 85.7% of cases, respectively. Multivariate analysis demonstrated that PNI (OR = 3.35; 95% CI: 1.16–7.56; p < 0.001) and LVI (OR = 5.34; 95% CI: 2.02–11.2; p < 0.001) were independently associated with both GU and TU.

Conclusion The presence of PNI and LVI in prostate biopsy samples is associated with both clinically significant GU score and TU following pathologic prostate examination. Therefore, these features represent unfavorable characteristics in biopsy results.

Keywords: prostate cancer; low-risk; unfavorable low-risk; Gleason upgrading; tumor upstaging

INTRODUCTION

Low-risk prostate cancer (PCa) is defined as clinical stage T1/T2a biopsy with a Gleason score (GS) ≤ 6 and a prostate-specific antigen (PSA) level < 10. This is a broad category encompassing a range of pathological characteristics and clinical behaviors [1], within which a small percentage of low-grade cancers progress to high-grade disease [2]. It is well-established that a high incidence of understaging and undergrading on the initial biopsy can occur in this patient group, potentially delaying the initiation of curative treatment [3–6]. Moreover, cancer upgrading is a negative prognostic factor, making the early identification of high-grade cancer in men diagnosed with low-risk disease a priority [2].

The challenge in managing low-risk PCa lies in distinguishing patients with clinically significant cancers who may benefit from radical treatment from the remainder who do not require any intervention [1]. A significant unmet need remains for further stratification of this often-heterogeneous cohort to optimize treatment decisions among the various options available for these patients. It is well-established that low-risk PCa can be classified as very low-risk or low-risk disease based on biopsy and clinical criteria [7]. Nevertheless, this stratification system does not include information regarding several biopsy variables, including perineural (PNI) and lymphovascular invasion (LVI) [5, 6]. Consequently, a more comprehensive clinical model is desirable to identify unfavorable low-risk PCa, which may necessitate a more complex surveillance protocol or early active treatment.

Therefore, our study aims to define the unfavorable biopsy factors that predict a clinically significant form of low-risk PCa, thereby helping to determine which patients may require active, curative interventions rather than deferred treatment.

METHODS

Following approval from the Institutional Review Board, 700 patients underwent radical prostatectomy (RP) between 1995 and 2014. Utilizing databases from two university centers, only those patients meeting the following criteria were included in the analysis: preoperative localized disease, classification as low-risk PCa or International Society of Urological Pathology

Received • Примљено: March 18, 2024
Revised • Ревизија: April 27, 2025
Accepted • Прихваћено: April 29, 2025
Online first: April 30, 2025

Correspondence to:
Aleksandar MAGDELINIĆ
Clinical Center of Montenegro
Department of Urology
Ljubljanska bb
81000 Podgorica
Montenegro
acomgd@yahoo.com

grade I (PSA ≤ 10; cT1–T2a, GS ≤ 6), normal total serum testosterone levels, and no clinical signs of hypogonadism. Each patient had previously declined active surveillance (AS) as an initial treatment option. Exclusion criteria were: intermediate or high-risk grade PCa determined by the initial biopsy (n = 490), unknown surgical margin status, or total serum testosterone level below 12.1 nmol/l (n = 17) [8]. Finally, patients with unknown PSA levels at six weeks post-RP were also excluded (n = 20). Applying these selection criteria resulted in a cohort of 173 patients, who constitute the focus of this analysis.

The clinical variables [age, preoperative PSA, PSA density, and clinical stage (CT)] and all histopathological findings were recorded. All prostate biopsies were performed under transrectal ultrasound [9], and PSA density was calculated based on prostate volume records. The biopsy pathology report included the following variables: (I) PCa grade, (II) percentage of biopsy core involved by PCa (P+), (III) tumor volume (TV), (IV) LVI, (V) perineural invasion (PNI), and (VI) multifocal high-grade intraepithelial neoplasia (hg PIN). The proportion of positive cores (P+) was calculated as the ratio of P+ to the total number [10]. Additionally, PNI was identified according to the previously described principle using the same immunohistochemistry assay [11].

RP was performed using an open retropubic approach, and the entire prostate specimen was subsequently evaluated [12]. In addition, limited lymph node dissection was performed in each patient for the purposes of the study; lymph node specimens were reported as negative (pN0) or positive for cancer (pN1). Seminal vesicle invasion was defined as tumor involvement of the vesicle muscle wall (pT3b). Surgical margins (R) were reported as negative (Ro) or positive for cancer (R1). The pathological GS (pGS) was calculated by summing the two most prevalent tumor patterns [5, 13]. Tumor upstaging (TU) was defined as the detection of pT3 in the final post-prostatectomy pathology or the presence of tumor cell invasion in lymph nodes (pN1). Adverse pathologic features included extraprostatic extension (EPE), ≥ pT3a, R1, GS ≥ 4 + 3, multifocal high-grade PIN, and pN1.

The planned stratification for this study categorized patients with low-risk PCa as either favorable or unfavorable, based on their Gleason upgrading (GU) and TU status at final pathology. Unfavorable low-risk PCa was defined by the presence of biopsy or clinical variables correlating with any of the following high-risk (unfavorable) characteristics at final pathology: pGS ≥ 4 + 3, EPE, ≥ pT3a, or pN1 [14]. This categorization was chosen based on the widely accepted principle that deferred treatment is inappropriate for patients harboring

Table 1. Demographic and clinical characteristics between groups

Parameters	Overall	Group I (favorable)	Group II (unfavorable)	p
Patients, n (%)	173 (100)	84 (49.6)	89 (51.4)	0.32
Mean age, years (SD)	65.4 (6.1)	65 (5.9)	65.9 (4.9)	0.51
Preoperative PSA, ng/ml (SD)	6.7 (3)	6.34 (2.54)	*7.03 (1.7)**	0.03
PSA density, ng/ml/gr (IQR)	0.09 (0.03–0.46)	0.07 (0.02–0.18)	*0.14 (0.03–0.46)**	*0.01*
[a]Clinical T stage, n (%)				
T1	81 (46.8)	*70 (83.3)**	11 (12.3)	*0.04*
T2a	92 (53.2)	14 (16.7)	*78 (87.7)**	*0.007*
[a]Patients with PNI, n (%)	66 (38.1)	6 (7.1)	*60 (67.4)**	*0.001*
[a]Patients with LVI, n (%)	54 (31.2)	1 (1.2)	*53 (59.5)**	*0.001*
[a]Mean percentage of cores involved with PC (P+), %, SD	47.4 (5.2)	40.3 (4.6)	*52.3 (7.2)**	*0.02*
[a]Tumor volume (%), IQR	15 (10–25)	10 (10–20)	*50 (60–10)**	*0.01*
[b]Gleason upgrading, n (%)	104 (60.1)			
GS 3 + 4 (ISUP 2)	86 (49.7)	*61 (72.6)**	25 (27.4)	0.03
GS 4 + 3 (ISUP 3)	9 (5.2)	-	9 (10.1)	-
GS 4 + 4 (ISUP 4)	3 (1.7)	-	3 (3.3)	-
GS 3 + 5 (ISUP 4)	1 (0.5)	-	1 (1.1)	-
GS 4 + 5 (ISUP 5)	5 (2.8)	-	5 (5.6)	-
[b]Tumor upstaging, n (%)	94 (54.3)			
pT2	50 (28.9)	50 (59.5)	-	-
pT3a	30 (17.3)	-	30 (33.7)	-
pT3b	14 (8.1)	-	14 (15.7)	-
[b]Surgical margin positivity, n (%)				
unifocal (R1)	45 (26)	*30 (35.7)**	15 (16.8)	*0.03*
multifocal (R1)	25 (14.4)	8 (9.5)	*17 (19.1)**	*0.04*
[b]Apical involvement, n (%)	34 (19.6)	16 (19)	18 (20.2)	0.6
[b]EPE, n (%)				
Unifocal EPE	14 (8)	-	14 (15.7)	-
Multifocal EPE	17 (9.8)	-	17 (19.1)	-
[b]Positive lymph nodes, n (%)	7 (4)	-	7 (7.8)	-
[b]Multifocal hg PIN, n (%)	70 (40.6)	11 (13)	*59 (66.2)**	*0.02*

PSA – prostate-specific antigen; PNI – perineural invasion; P+ – percentage of positive cores; PC – prostate cancer; GS – Gleason score; ISUP – the International Society of Urological Pathology; EPE – extraprostatic extension; LVI – lymphovascular invasion; R1 – positive surgical margin; hg PIN – high-grade intraepithelial neoplasia; IQR – interquartile range
*statistically significant difference between two groups ($p < 0.05$);
[a]pathologic data on initial biopsy specimen;
[b]pathologic data on prostatectomy specimen

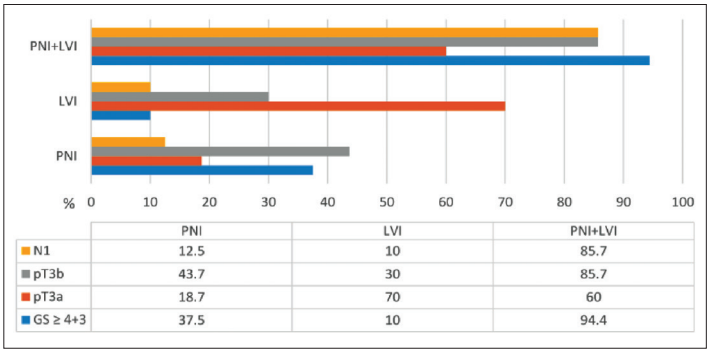


Figure 1. Association between individual and combined biopsy features (predictors of both, Gleason upgrading and tumor upstaging) and high-risk characteristics at final pathology

PNI – perineural invasion; LVI – lymphovascular invasion; GS – Gleason score; pT3a – pathological tumor stage 3a; pT3b – pathological tumor stage 3b

such features [15]. Group 1 (favorable) consisted of patients without high-risk characteristics on final histology, while Group 2 (unfavorable) included patients with at least one unfavorable feature at final pathology.

The primary objective of the study was to determine the correlation between clinical and biopsy determinants with high-risk characteristics at final pathology, thereby defining unfavorable low-risk PCa. Moreover, research aimed to establish the incidence of upgrading and upstaging, as well as adverse pathologic features on postsurgical specimens.

Statistical analysis

Continuous variables are presented as mean ± SD, and differences between groups were analyzed using the Mann–Whitney U test. Categorical variables are presented as counts and percentages. Non-parametrically distributed continuous variables are presented using the median, minimum, and maximum values. Finally, the relationship between biopsy determinants and GU/TU at final pathology was examined using multivariable logistic regression analysis. All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY, USA).

Ethics: All patients provided written consent prior to their enrollment in the study. The treatment protocol was approved by the Ethics Committee of the Clinical Centre of Montenegro (No. 03/01-9360/2). The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

RESULTS

Overall, 173 patients met the low-risk criteria defined by the study. The average patient age was 65.4 ± 6.1 years, and the median preoperative PSA was 6.7 ± 2.2 ng/ml. GU was detected in 104 (60.1%) patients: 86 (49.7%) to 3 + 4, nine (5.2%) to 4 + 3, three (1.7%) to 4 + 4, and five (2.8%) to 4 + 5 PCa. In RP specimens, 50 patients (28.9%) were staged as pT2b-c, 30 patients (17.3%) were staged as pT3a, and 14 patients (8.1%) were referred as T3b at final pathology (Table 1). No statistically significant differences were observed between the two groups regarding the number of patients ($p = 0.6$), mean patient age ($p = 0.4$), and apical involvement on surgical specimens ($p = 0.09$) between the two groups. In Group 2, preoperative PSA (0.04), PSA density ($p = 0.03$), clinical stage T2a ($p = 0.01$), PNI ($p < 0.01$), LVI ($p < 0.01$), TV ($p = 0.03$) and P+ ($p = 0.04$) were statistically higher than in Group 1. Furthermore, multifocal surgical margin positivity (19.1% *vs.* 9.5%, $p = 0.03$) and multifocal high-grade PIN (66.2% *vs.* 13%; $p = 0.01$) were found to be significantly higher in Group 2.

In total, 18 patients from Group 2 (20.2%) were upgraded to a GS ≥ 4 + 3, and in 94.4% of these cases, the biopsy report revealed both PNI and LVI. Moreover, TU was detected in 49.4% of patients from Group 2, with 33.7%, and 15.7% of patients exhibiting pT3a or pT3b, respectively. Biopsy reports were positive for both PNI and LVI in 60% of patients with pT3a upstaging and in 85.7% of patients with pT3b upstaging on final histology. Additionally, six out of seven patients (85.7%) with positive lymph nodes after surgery had both PNI and LVI on prostate needle biopsy pathology (Figure 1).

Table 2. Multivariable analysis of clinical/biopsy variables and high-risk (unfavorable) characteristics at final pathology

Biopsy and clinical variables	Multivariable	
	OR (95% CI)	p
Model 1 – upgrading on final histology (GS ≥ 4 + 3)		
Preoperative PSA	0.95 (0.88–2.11)	0.09
Clinical T-stage (1–2a)	1.69 (0.96–2.99)	0.1
Tumor volume	13.6 (4.5–31.2)	0.3
PNI	4.97 (2.16–9.67)	< 0.01
LVI	3.51 (1.13–8.71)	0.03
P+ (>50%)	1.13 (1.03–1.31)	0.04
PSA density	1.24 (0.99–1.55)	0.06
Multifocal high-grade PIN	*1.4 (1.25–1.58)*	*0.04*
Model 2 – upstaging on final histology (≥ pT3, N+)		
Preoperative PSA	1.00 (0.98–1.03)	0.7
Clinical T-stage (cT2a)	0.93 (0.67–1.31)	0.8
Tumor volume	0.76 (0.64–1.51)	0.3
PNI	3.35 (1.16–7.56)	< 0.01
LVI	5.34 (2.02–11.2)	< 0.01
P+ (>50%)	0.96 (0.94–1.02)	0.2
PSA density	1.47 (0.98–2.2)	0.07
Multifocal hg PIN	0.88 (0.11–2.31)	0.09

GS – Gleason score; PSA – prostate-specific antigen; PNI – perineural invasion; LVI – lymphovascular invasion; hg PIN – high-grade intraepithelial neoplasia

Multivariate logistic regression analysis revealed that PNI (OR = 4.97; 95% CI: 2.16–9.67; $p = 0.001$), LVI (OR = 3.51; 95% CI: 1.13–8.71; $p = 0.01$), percentage of P+ (OR = 41.5; 95% CI: 4.82–283.16; $p = 0.02$), and multifocal high-grade PIN (OR = 1.77; 95% CI: 0.87–2.56; $p = 0.031$) were independently associated with GU, while PNI (OR = 3.35; 95% CI: 1.16–7.56; $p < 0.001$) and LVI (OR = 5.34; 95% CI: 2.02–11.2; $p < 0.001$) were identified as independent predictors of TU. Although not statistically significant, the association of PSA density (OR = 1.24; 95% CI: 0.99–1.55; $p = 0.057$ and OR = 1.47; 95% CI: 0.98–2.2; $p = 0.07$) was notable (Table 2).

DISCUSSION

AS is a convenient therapeutic approach for PCa as it avoids overtreatment of patients with clinically inapparent disease while offering curative therapy to patients with progressive disease [16]. Nevertheless, during treatment of low-risk PCa, clinical predictors associated with GU or TU on surgical pathology should be strongly considered to identify subsets of patients who may have more aggressive disease and require more appropriate treatment [10]. Previous studies have documented that independent predictors of TU in low-risk PCa are associated with older age and higher PSA [14, 17], a higher proportion of P+ [10] and tumor involvement greater than 50% in each core [14]. Moreover, PNI appears to be a strong predictor of GU (over four-fold) in low-risk PCa [5, 6] with a previously

established correlation to biochemical failure [5, 11]. The present research indicated that a higher proportion of P+, multifocal high-grade PIN, and the presence of LVI and PNI were independent predictors of GU in the surgical specimen with the latter two showing a stronger association (3.51- and 4.97-fold) than the former (1.13- and 1.77-fold). In addition, LVI and PNI independently increased the risk of TU on final histology (3.35- and 5.34-fold), identifying them as the most reliable unfavorable predictors of both GU and TU. The risk of GU was even higher for patients with combined PNI and LVI in the same biopsy specimen, with 94.4% having pGS ≥ 4 + 3 and 85.7% having pT3b or pN1 disease, which are both considered very high-risk factors [18, 19]. Thus, many patients with PNI and LVI on biopsy specimens have occult high-risk disease that may go undetected prior to surgery. Therefore, additional evaluation is mandatory in these patients to improve risk classification. Zumsteg et al. [19] reached a similar conclusion for intermediate-risk PCa, where two or more unfavorable intermediate-risk factors on a biopsy specimen led to a 41% incidence of high-risk features on final pathology (Gleason pattern 5, pT3b-T4, pN1).

There is growing evidence demonstrating the importance of proper grading and staging of PCa on initial biopsy and prior to treatment decision. A large randomized study by Bill-Axelson et al. [20] reported seven men with initially low-risk disease who died from PCa after surgery. In six of these patients, tumors were upgraded to GS 7 or 8 at prostatectomy, leading to the conclusion that PCa-related death in men with low-risk disease often results from unrecognized high-grade disease [20, 21]. These findings suggest that high-grade disease on surveillance biopsies likely represents misclassification at diagnosis rather than true disease progression [20, 21, 22]. Therefore, developing a clinical predictive model to identify unfavorable biopsy features associated with advanced disease on RP is crucial.

Studies have emphasized the discordance between biopsy and RP specimens with a high incidence of tumor upgrading on final histology. Despite the adoption of second-opinion pathology reviews, the accuracy rate in evaluating RP specimens remains low [23, 24]. Our study corroborates these findings, with GU detected in 60.1% of final pathology specimens and the International Society of Urological Pathology grade 2 being the predominant one (49.7%).

Some authors suggested that pGS of at least 4 + 3 = 7, pT3b, and pN1 are the strongest predictors of long-term outcomes after surgery [14, 18, 19]. Therefore, we selected grade group 3 and pT3a as the pathologic threshold for defining high-risk characteristics at final pathology in order to identify unfavorable biopsy features. Although several biopsy and clinical variables were selected as predictors of tumor upgrading and upstaging, a clear definition of favorable and unfavorable predictive factors for low-risk PCa is still lacking, unlike the established definitions for intermediate-risk cancer [25]. Porcaro et al. [10] proposed a stratification system for low-risk PCa, based on PSA value and the proportion of P+ on prostate biopsy, but they did not include a biopsy report of PNI and LVI, which were significant predictors of advanced prognostic features in our study. Additionally, the "DETECTIVE" study [26] identified LVI and PNI in needle biopsy as exclusion criteria for AS, supporting our earlier finding that these variables likely represent significant baseline features associated with high-risk tumors on final pathology. Moreover, multiple studies have demonstrated a higher risk of biochemical recurrence (BCR) after RP, progression to metastatic disease, and cancer-specific mortality when PNI is seen in the biopsy tissue [27, 28]. Nevertheless, the clinical significance of PNI in low-risk PCa remains to be fully established.

PNI has been shown to be associated with an increased risk of both pathological [hazard ratio (HR) 2.21, 95% CI: 0.92–5.33, p = 0.076] and clinical progression (HR 2.39, 95% CI: 1.1–4.94, p = 0.019) among PCa patients on AS [13]. Furthermore, Cohn et al. [29] observed that PNI was associated with a higher rate of exclusion from AS due to biopsy-confirmed disease progression, aligning with the findings of the aforementioned "DETECTIVE" trial [26]. These conclusions corroborate the results from our study, where PNI was found to be the strongest predictor of tumor upgrading and the second most prominent predictor of disease upstaging on final histology. In contrast to the aforementioned studies, our research also identified LVI as an unfavorable biopsy prognostic factor for both GU and TU on final pathology. Considering these findings, we propose stratifying low-risk PCa into unfavorable (presence of PNI and LVI, with or without multifocal high-grade PIN and P+ on prostate biopsy) and favorable (absence of these variables) categories based on biopsy specimens.

On the other hand, it should be emphasized that only a few recent studies have investigated the potential significance of PNI or LVI in GU and TU in these patients. In one such recently published study, the authors used univariate Cox regression models and reported that lymphovascular or PNI correlated with a higher BCR rate [30]. However, after considering standard pathologic tumor features, lymphovascular or PNI were not statistically associated with a higher BCR as the Gleason grade group and pathologic tumor stage were strongly associated with PNI and LVI [30].

Although our study was not designed to focus on limitations, several should be acknowledged. Primarily, its retrospective nature and the small sample size are significant limitations. Furthermore, the absence of data from advanced imaging (such as multiparametric magnetic resonance imaging) or biomarkers (e.g., Genomic Prostate Score or Decipher) is a drawback. This study also did not address the outcomes of subsequent adjuvant or salvage treatment during follow-up, as it was outside the scope of our research. Finally, we did not estimate cancer-specific deaths or progression-free survival rates between the two groups, thus the definitive prognostic value of PNI, LVI, and P+ remains incomplete. Despite these limitations, our study provides significant findings that can assist physicians in making effective decisions regarding optimal patient treatment modalities.

CONCLUSIONS

Approximately one in three men with low-risk PCA on biopsy who undergo RP are found to have undesirable pathologic features. While stratifying low-risk patients into favorable and unfavorable categories is a positive step, traditional clinical and pathological criteria have not proven effective in identifying the unfavorable subset. Future large, prospective studies integrating clinical, pathological, and imaging modalities into a comprehensive prognostic model are needed to draw definitive conclusions. Meanwhile, the presence of both PNI and LVI in biopsy specimens may serve as a useful clinical predictor of TU or upgrading and an important tool in the treatment strategy for low-risk PCa patients. Furthermore, multifocal high-grade PIN or more than 50% P+ on biopsy may enhance this prognostic accuracy.

Conflict of interest: None declared.

REFERENCES

1. Karpinski MJ, Hüsing J, Claassen K, Möller L, Kajüter H, Oesterling F, et al. Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study. Lancet Oncol. 2024;25(9):1188–201. [DOI: 10.1016/S1470-2045(24)00326-7] Erratum in: Lancet Oncol. 2024;25(12):e626. [DOI: 10.1016/S1470-2045(24)00635-1] [PMID: 39089299]
2. Ploussard G, Fiard G, Barret E, Brureau L, Créhange G, Dariane C, et al. French AFU Cancer Committee Guidelines - Update 2022–2024: prostate cancer - Diagnosis and management of localised disease. Prog Urol. 2022;32(15):1275–372. [DOI: 10.1016/j.purol.2022.07.148] [PMID: 36400483]
3. Sequeira JP, Salta S, Freitas R, López-López R, Díaz-Lagares Á, Henrique R, et al. Biomarkers for Pre-Treatment Risk Stratification of Prostate Cancer Patients: A Systematic Review. Cancers (Basel). 2024;16(7):1363. [DOI: 10.3390/cancers16071363] [PMID: 38611041]
4. Krilaviciute A, Kaaks R, Seibold P, de Vrieze M, Lakes J, Radtke JP, et al. Risk-adjusted Screening for Prostate Cancer-Defining the Low-risk Group by Data from the PROBASE Trial. Eur Urol. 2024;86(6):493–500. [DOI: 10.1016/j.eururo.2024.04.030] [PMID: 38749854]
5. Ola IO, Talala K, Tammela T, Taari K, Murtola TJ, Kujala P, et al. Long-term Risk of Prostate Cancer Mortality Among Men with Baseline Prostate-specific Antigen Below 3 ng/ml: Evidence from the Finnish Randomized Study of Screening for Prostate Cancer. Eur Urol Oncol. 2024:S2588-9311(24)00272-4. [DOI: 10.1016/j.euo.2024.11.010] [PMID: 39643505]
6. Finati M, Davis M, Stephens A, Chiarelli G, Cirulli GO, Morrison C, et al. The Role of Baseline Prostate-specific Antigen Value Prior to Age 60 in Predicting Lethal Prostate Cancer: Analysis of a Contemporary North American Cohort. Eur Urol Oncol. 2024;7(6):1535–42. [DOI: 10.1016/j.euo.2024.06.014] [PMID: 38991891]
7. Schroeder DW, Foster BR, Young DJ, Coakley FV. Targeted biopsy of the prostate. Abdom Radiol (NY). 2025;50(1):261–71. [DOI: 10.1007/s00261-024-04452-z] [PMID: 38976055]
8. Lunenfeld B, Mskhalaya G, Zitzmann M, Corona G, Arver S, Kalinchenko S, et al. Recommendations on the diagnosis, treatment and monitoring of testosterone deficiency in men. Aging Male. 2021;24(1):119–38. [DOI: 10.1080/13685538.2021.1962840] [PMID: 34396893]
9. Lokeshwar SD, Nguyen J, Rahman SN, Khajir G, Ho R, Ghabili K, et al. Clinical utility of MR/ultrasound fusion-guided biopsy in patients with lower suspicion lesions on active surveillance for low-risk prostate cancer. Urol Oncol. 2022;40(9):407.e21-407.e27. [DOI: 10.1016/j.urolonc.2022.06.005] [PMID: 35811206]
10. Porcaro AB, Siracusano S, de Luyk N, Corsi P, Sebben M, Tafuri A, et al. Low-Risk Prostate Cancer and Tumor Upgrading in the Surgical Specimen: Analysis of Clinical Factors Predicting Tumor Upgrading in a Contemporary Series of Patients Who were Evaluated According to the Modified Gleason Score Grading System. Curr Urol. 2017;10(3):118–25. [DOI: 10.1159/000447164] [PMID: 28878593]
11. Vukovic M, Kavaric P, Magdelinic A, Nikomanis P, Tomovic S, Pelicic D. Perineural invasion on biopsy specimen as predictor of tumor progression in aging male treated with radical prostatectomy. Could we use it for pre-surgical screening? Aging Male. 2020;23(5):720–5. [DOI: 10.1080/13685538.2019.1581758] [PMID: 30843451]
12. Hekman L, Barrett A, Ross D, Palaganas E, Giridhar P, Elumalai T, et al. A Systematic Review of Clinical Trials Comparing Radiation Therapy Versus Radical Prostatectomy in Prostate Cancer. Clin Genitourin Cancer. 2024;22(5):102157. [DOI: 10.1016/j.clgc.2024.102157] [PMID: 39084158]
13. Moreira DM, Fleshner NE, Freedland SJ. Baseline Perineural Invasion is Associated with Shorter Time to Progression in Men with Prostate Cancer Undergoing Active Surveillance: Results from the REDEEM Study. J Urol. 2015;194(5):1258–63. [DOI: 10.1016/j.juro.2015.04.113] [PMID: 25988518]
14. Valdez-Vargas AD, Sánchez-López HM, Badillo-Santoyo MA, Maldonado-Valadez RE, Manzo-Pérez BO, Pérez-Abarca VM, et al. Recurrence rate of localized prostate cancer after radical prostatectomy according to D'amico risk classification in a tertiary referral hospital: association study. Cir Cir. 2021;89(4):520–7. [DOI: 10.24875/CIRU.200007601] [PMID: 34352860]
15. Hu X, Miao J, Huang J, Qian L, Zhang D, Wei H. Influence of Active Surveillance on Gleason Score Upgrade and Prognosis in Low- and Favorable Intermediate-Risk Prostate Cancer. Curr Oncol. 2022;29(10):7964–78. [DOI: 10.3390/curroncol29100630] [PMID: 36290907]
16. Ruane-McAteer E, Prue G. Psychological aspects of active surveillance. World J Urol. 2022;40(1):9–13. [DOI: 10.1007/s00345-020-03553-w] [PMID: 33388921]
17. Zhang H, Doucette C, Yang H, Bandyopadhyay S, Grossman CE, Messing EM, et al. Risk of adverse pathological features for intermediate risk prostate cancer: Clinical implications for definitive radiation therapy. PLoS One. 2021;16(7):e0253936. [DOI: 10.1371/journal.pone.0253936] [PMID: 34264975]
18. Kawamura N, Hayashi T, Nagahara A, Nakai Y, Nakayama M, Ikawa T, et al. Outcomes in patients with high- and very high-risk localized prostate cancer treated with definitive IMRT and long-term hormone therapy. Jpn J Clin Oncol. 2024;54(3):346–51. [DOI: 10.1093/jjco/hyad178] [PMID: 38146119]
19. Zumsteg ZS, Chen Z, Howard LE, Amling CL, Aronson WJ, Cooperberg MR, et al. Number of Unfavorable Intermediate-Risk Factors Predicts Pathologic Upstaging and Prostate Cancer-Specific Mortality Following Radical Prostatectomy: Results from the SEARCH Database. Prostate. 2017;77(2):154–63. [DOI: 10.1002/pros.23255] [PMID: 27683213]
20. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2011;364(18):1708–17. [DOI: 10.1056/NEJMoa1011967] [PMID: 21542742]
21. Berenguer CV, Pereira F, Câmara JS, Pereira JAM. Underlying Features of Prostate Cancer-Statistics, Risk Factors, and Emerging Methods for Its Diagnosis. Curr Oncol. 2023;30(2):2300–21. [DOI: 10.3390/curroncol30020178] [PMID: 36826139]
22. Sorce G, Flammia RS, Hoeh B, Chierigo F, Hohenhorst L, Panunzio A, et al. Grade and stage misclassification in intermediate unfavorable-risk prostate cancer radiotherapy candidates. Prostate. 2022;82(10):1040–50. [DOI: 10.1002/pros.24349] [PMID: 35365851]
23. Maehara T, Sadahira T, Maruyama Y, Wada K, Araki M, Watanabe M, et al. A second opinion pathology review improves the diagnostic concordance between prostate cancer biopsy and radical prostatectomy specimens. Urol Ann. 2021;13(2):119–24. [DOI: 10.4103/UA.UA_81_20] [PMID: 34194136]
24. Maruyama Y, Sadahira T, Araki M, Mitsui Y, Wada K, Rodrigo AGH, et al. Factors predicting pathological upgrading after prostatectomy in patients with Gleason grade group 1 prostate cancer based

on opinion-matched biopsy specimens. Mol Clin Oncol. 2020;12(4):384–9. [DOI: 10.3892/mco.2020.1996] [PMID: 32190323]
25. Preisser F, Cooperberg MR, Crook J, Feng F, Graefen M, Karakiewicz PI, et al. Intermediate-risk Prostate Cancer: Stratification and Management. Eur Urol Oncol. 2020;3(3):270–80. [DOI: 10.1016/j.euo.2020.03.002] [PMID: 32303478]
26. Lam TBL, MacLennan S, Willemse PM, Mason MD, Plass K, Shepherd R, et al. EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur Urol. 2019;76(6):790–813. [DOI: 10.1016/j.eururo.2019.09.020] [PMID: 31587989]
27. Teramoto Y, Numbere N, Wang Y, Miyamoto H. Clinical Significance of Perineural Invasion by Prostate Cancer Detected on Needle Core Biopsy. Am J Clin Pathol. 2023;159(2):116–9. [DOI: 10.1093/ajcp/aqac142] [PMID: 36494055]
28. Teramoto Y, Wang Y, Miyamoto H. Risk Stratification by Quantification of Perineural Cancer Invasion on Prostate Needle Core Biopsy: Should It Be Counted? J Urol. 2023;210(4):639–48. [DOI: 10.1097/JU.0000000000003618] [PMID: 37433144]
29. Cohn JA, Dangle PP, Wang CE, Brendler CB, Novakovic KR, McGuire MS, et al. The prognostic significance of perineural invasion and race in men considering active surveillance. BJU Int. 2014;114(1):75–80. [DOI: 10.1111/bju.12463] [PMID: 24106869]
30. Siech C, Wenzel M, Grosshans N, Cano Garcia C, Humke C, Koll FJ, et al. The Association Between Lymphovascular or Perineural Invasion in Radical Prostatectomy Specimen and Biochemical Recurrence. Cancers (Basel). 2024;16(21):3648. [DOI: 10.3390/cancers16213648] [PMID: 39518086]

Неповољни фактори код болесника са нискоризичним карциномом простате предвиђају патолошко погоршање и напредовање након радикалне простатектомије: докази за даљу подкласификацију?

Александар Магделинић[1], Александар Спасић[2], Марко Вуковић[1]

[1]Клинички центар Црне Горе, Клиника за урологију, Подгорица, Црна Гора;
[2]Војномедицинска академија, Клиника за урологију, Београд, Србија

САЖЕТАК

Увод/Циљ Циљ истраживања је био да се потврди стратификација нискоризичног карцинома простате (*PCa*) на „повољне“ и „неповољне“ подгрупе болесника који су подвргнути радикалној простатектомији, према корелацији различитих карактеристика биопсије са карактеристикама високог ризика на коначној патологији.

Методе У ову студију су укључена 173 болесника која су у време операције изабрана као кохорте са ниским ризиком од *PCa*. Планирана стратификација укључивала је повољан и неповољан *PCa* ниског ризика, у складу са повећањем Глисоновог степена и статусом повећања стадијума тумора код крајње патологије. Неповољан *PCa* ниског ризика дефинисан је као присуство резултата биопсије који корелирају са високоризичним карактеристикама у коначној патологији [патолошки Глисонов скор ≥ 4 + 3, или ≥ *pT3a*, или *pN1*)]. Болесници су подељени у складу са присуством високоризичних обележја у коначној патологији у Групу 1 ($n = 84$, повољно) и Групу 2 ($n = 89$, неповољно).

Резултати Осамнаест болесника из Групе 2 (20,2%) има Глисонов скор ≥ 4 + 3, а у 94,4% случајева њихови биопсијски извештаји су открили и перинеуралну инвазију (ПНИ) и лимфоваскуларну инвазију (ЛВИ). Штавише, болесници са напредовањем *pT3a* или *pT3b* показали су и ПНИ и ЛВИ у 60% и 85,7% случајева, респективно. Мултиваријантна анализа је показала да су ПНИ (*OR* = 3,35; 95% *CI*: 1,16–7,56; $p < 0,001$) и ЛВИ (*OR* = 5,34; 95% *CI*: 2,02–11,2; $p < 0,001$) независно повезани и са повећањем Глисоновог степена и са повећањем стадијума тумора.

Закључак Докази о ПНИ и ЛВИ у биопсији простате повезани су и са клинички значајним напредовањем и са преокретом после патолошког прегледа простате, што представља неповољне карактеристике биопсије.

Кључне речи: рак простате; низак ризик; неповољан низак ризик; Глисонов скор; раст тумора

DOI: https://doi.org/10.2298/SARH241121040G
UDC: 616.718.49-001.5-089

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Does closer placement of cerclage wire enhance functional outcomes in tension band wiring of patellar fractures?

Yaşar Samet Gökçeoğlu[1], Şahin Karalar[2], Metin Yaptı[1], Ali Levent[3]

[1]Sanliurfa Mehmet Akif İnan Training and Research Hospital, Department of Orthopedics and Traumatology, Sanliurfa, Turkey;
[2]İstanbul Medipol University, Faculty of Medicine, Department of Orthopaedics and Traumatology, İstanbul, Turkey;
[3]Private Metrolife Hospital, Department of Orthopedics and Traumatology, Sanliurfa, Turkey

SUMMARY

Introduction/Objective Patellar fractures are commonly treated with tension band wiring (TBW). The distance between the cerclage wire and the superior pole of the patella is crucial for surgical outcomes. This study evaluates the impact of this distance on clinical and functional results.

Methods A retrospective cohort study of 64 patients with transverse patellar fractures treated with TBW was conducted. Patients were categorized based on the distance of the cerclage wire from the bone: < 4 mm, 4–8.5 mm, and > 8.5 mm. Clinical outcomes included bone union, implant failure, and wound complications. Functional outcomes were assessed using range of motion (ROM) and modified Hospital for Special Surgery (HSS) knee score values.

Results Significant differences were observed in outcomes depending on wire placement. Patients with cerclage wires < 4 mm from the bone exhibited poorer functional results, with a mean modified HSS Knee Score of 70 ± 9.2 and an average ROM of 103.6 ± 42.4°. Patients with wires positioned 4–8.5 mm from the bone demonstrated better functional recovery, achieving higher knee scores and greater ROM. Statistical analysis confirmed that closer wire placement negatively affected clinical outcomes ($p < 0.05$).

Conclusion This study suggests that positioning cerclage wires too close to the bone (< 4 mm) may impair functional outcomes despite presumed mechanical stability. An optimal distance of 4–8.5 mm balances mechanical stability and soft tissue protection, offering improved clinical and functional results. These findings challenge conventional surgical approaches, emphasizing the importance of precise wire positioning in TBW procedures.

Keywords: patellar fractures; tension band wiring; cerclage wire; clinical outcomes; functional outcomes; surgical techniques

INTRODUCTION

Fractures of the patella pose a challenge to orthopedic trauma management because of the important role of the patella in the extensor mechanism of the knee. The treatment of patellar transverse fractures has traditionally been performed using tension band wiring (TBW) for restoration of the articular surface and early mobilization [1, 2]. However, it is also noted that there are methodologically more updated approaches and meta-analyses findings which should be incorporated to have a better perspective on TBW outcomes and biomechanics [3, 4]. The configuration of the cerclage wire in TBW, especially its distance from the bone, is important in determining the biomechanical stability of the fixation and therefore clinical results. Early mobilisation and good biomechanical fixation reduce pain and improve quality of life [5].

Among the biomechanical properties, stability provided by the cerclage wire is an important area of concern for TBW that can influence both bone-union rates and the incidence of post-operative complications [6, 7]. The proximity of the cerclage wire to the bone has specific implications for the biomechanics of the fixation [3]. For instance, Zhang et al. demonstrated that TBW with the cerclage wire positioned near the bone surface significantly reduces micromotion at the fracture site, facilitating bone healing [8, 9]. Conversely, an increased distance between the cerclage wire and the bone may lead to sub-optimal compression and stability, raising the risk of implant failure and delayed union [10]. This observation underscores the need for meticulous surgical practice and indicates that further, specific endeavours to clarify these effects are needed [3]. Further, poor positioning of the wire has been associated with increased post-operative complications, including migration of the wire and soft-tissue irritation [11]. Though these problems have been described in prior research, more elaborate investigation and comparison with existing literature would be helpful for a fuller understanding of optimal positioning and its effects [3]. There is a gap in the literature regarding the proximity of the cerclage wire to the bone, and the safe distance

Received • Примљено: November 21, 2024
Accepted • Прихваћено: May 27, 2025
Online first: May 28, 2025

Correspondence to:
Yaşar Samet GÖKÇEOĞLU
Sanliurfa Mehmet Akif Inan Training and Research Hospital
Ertugrul gazi mah. Haliliye/ Sanliurfa
Sanliurfa 63300, Turkey
sametgokceoglu@gmail.com

in patellar fractures treated with tension-band wiring remains under-explored. Therefore, the aim of our study was to calculate the effect of the distance of the cerclage wire to the bone on clinical and functional outcomes and to determine the safe distance in patients with transverse patellar fractures treated with TBW. This will reduce the margin of error in surgical technique and provide a touchstone for the clinician regarding the distance of the cerclage wire during surgery.

METHODS

Study design and population

This is a retrospective cohort study including a total of 108 patients aged 18–65 years with C1 and C2 transverse patellar fractures (AO classification) who had undergone TBW with two Kirschner wires. The patients were treated between January 2015 and December 2022 at a single tertiary-care centre. The exclusion criteria were multiple-trauma patients, multiple fractures of the same limb, systemic, metabolic and infectious diseases, application of cerclage to tension-band wiring, use of cannulated screws, and periprosthetic or pre-existing pathological conditions of the knee. Such criteria were aimed at providing homogeneous groups of patients, thus excluding factors that could influence results.

Surgical technique

All surgeries were performed under general anaesthesia. A standard midline knee incision with medial parapatellar arthrotomy was made to gain access to the fracture site. The skin incision was deepened, and the fractures were reduced using reduction clamps, with reduction confirmed under fluoroscopy. From the superior pole of the patella, two K-wires were introduced distally. The cerclage wire was passed around these K-wires and then tightened to compress the fracture fragments. The tips of the proximal end were cut, and the K-wires were then bent and fixed. The surgeon's experience and frequency of performing this technique were recorded to determine whether these factors influenced surgical outcomes. The knee was immobilised using an immobiliser for two weeks post-operatively to facilitate initial healing.

Post-operative care and follow-up

Patients began static isometric quadriceps-strengthening exercises on the first post-operative day. Two weeks later, range-of-motion (ROM) exercises were started under the supervision of a physiotherapist. The follow-up period included evaluations at one, three, six, 12 and 24 months post-operation. Clinical assessments included wound healing, pain level and functional recovery. Radiographic evaluations were performed at each visit to assess both fracture union and fixation integrity.

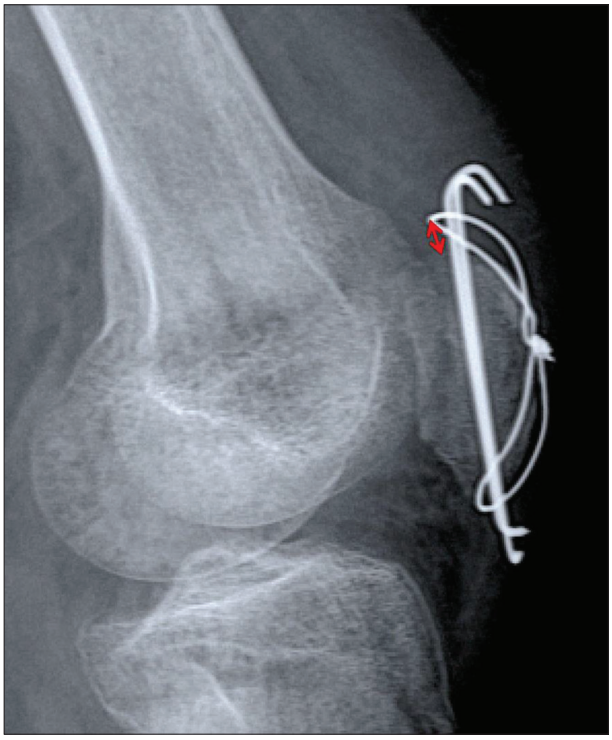


Figure 1. X-ray image of knee with cerclage wire and K-wire fixation

Data collection

The main outcome measurement was the distance of the wire from the bone, measured directly from the lateral postoperative radiograph (Figure 1). A consistent measurement protocol was used to ensure exact values. To ascertain measurement validity, inter-observer and intra-observer reliability tests were performed. The following outcomes were evaluated: clinical and functional outcomes, incidence of wound complications, union rates and overall clinical follow-up. The patients' medical records and radiographs were critically reviewed to support interpretation of the findings. In addition, ROM and functional outcomes were assessed at the last follow-up using the Modified Hospital for Special Surgery (HSS) Knee Scores [12]. The properties and application techniques of the cerclage wires were detailed, including material composition and tensioning method.

Statistical analysis

Data were analysed using IBM SPSS Statistics, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were summarised to provide participant demographics and clinical characteristics. Frequencies, means and standard deviations were calculated for age, distance between the cerclage wire and bone, knee ROM values and Modified HSS Knee Scores. Data were tested for normality using the Shapiro–Wilk test. For normally distributed data, Student's t-test was used, whereas Mann–Whitney U tests were applied to non-normally distributed data. Additionally, ROC-curve analysis determined the threshold value of the cerclage-wire distance that best predicted patients' outcomes. Identifying the point that maximises

the sensitivity and specificity of cerclage-wire distance for predicting clinical and functional outcomes is essential. χ^2 tests compared categorical data regarding the presence or absence of wound complications and implant failures, with statistical significance set at $p = 0.05$.

Ethics: All participants provided written informed consent prior to inclusion in the study. The study protocol was approved by the Institutional Ethics Committee of Harran University (Approval No: HRU-24/11/35) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical principles.

RESULTS

This study is a retrospective cohort of 64 patients who had undergone tension-band wiring for transverse fractures of the patella. The following means and ranges were derived from the demographic profile: mean age (years) = 44.8 ± 17.1 (18–65 years) and mean follow-up period = 15.2 ± 5.4 months (range = 9–24 months). The sex distribution comprised 35 male patients (54.7%) and 29 female patients (45.3%) (Table 1).

Table 1. Demographic data

Variable		Value
Age, years		44.8 ± 17.1 (18–65)
Sex	Men	35
	Women	29
Follow-up, months		15.2 ± 5.4 (9–24)
Cerclage wire – patella superior pole distance, mm		6.3 ± 4.03 (1–20.4)
İmplant failure		10
Cerclage wire breakage		2
Cerclage wire displaced over K-wire		7
K-wire migration		1
Nonunion		2
Wound complications		3

The mean distance between the cerclage wire and the superior pole of the patella was 6.3 ± 4.03 mm. The distance ranged 1–20.4 mm. Clinical outcomes showed non-union in two cases (3.1%), in which partial patellectomy was performed. Site complications occurred in three wound-site cases (4.7%), and implant failures were noted in 10 cases (15.6%) (Table 1).

We observed K-wire migration in one patient (1.6%). Displacement of the cerclage wire over the K-wire was observed in seven patients (10.9%). Wire breakage was also observed in two patients (3.1%).

To assess the predictive value of cerclage-wire distance for clinical and functional outcomes, ROC-curve analysis was employed. The area under the curve (AUC) of 0.91 indicates high prognostic accuracy. This study also showed that this distance has high sensitivity and specificity for predicting implant failure (Figure 2).

Mean Modified HSS Knee Scores for different cerclage-wire distance categories were plotted to visualize the effect

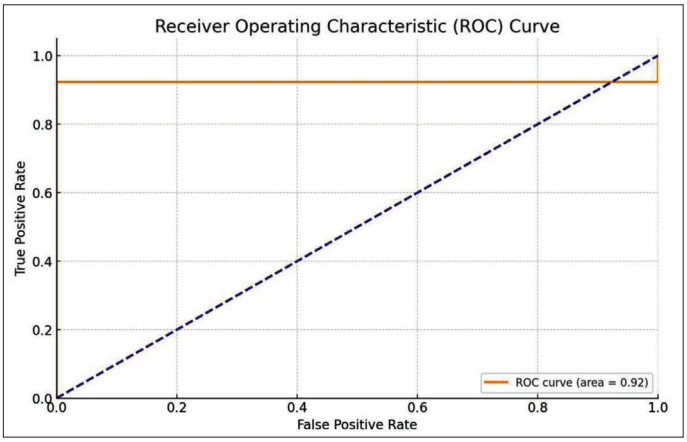


Figure 2. ROC curve predicting implant failure based on cerclage wire distance

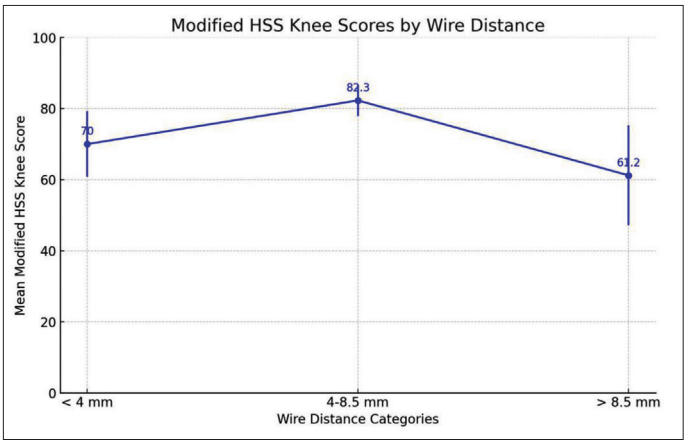


Figure 3. Modified Hospital for Special Surgery (HSS) Knee Scores by wire distance

of wire distance on functional outcomes (Figure 3). The highest mean score was observed in the 4–8.5 mm category, indicating better functional outcomes.

The effects of the distance between the bone and the cerclage wire on knee range of motion (ROM) were investigated. The knee ROM is illustrated in Figure 3 for different distances of the cerclage wire. The data show that there is a relationship between knee ROM and the distance from the cerclage wire to the bone. Patients with a distance < 4 mm had an average knee ROM of 108.6°. On average, patients with a 4–8.5 mm distance exhibited the highest knee ROM at 126.6°, whereas those with a distance > 8.5 mm reached only 80.6°. These results indicate that cerclage-wire distance significantly affects knee ROM. Placing the wire close to the bone (< 4 mm) or within the mid-range (4–8.5 mm) increases joint flexibility [11], whereas distances > 8.5 mm reduce motion. These findings are essential for defining an ideal cerclage-wire-to-bone gap. Patients with a distance between the cerclage and the superior pole of the patella < 8.5 mm were divided into two groups: group 1 and group 2. Age, union rates, implant failures and wound-site problems were analysed, showing no significant relationship with patient outcome. Among patients who did experience non-union, two of them (100% of non-union cases, 3.1% of all cases) also suffered implant failures. Of the three patients with wound complications, two (66.7%) also experienced implant failure (3.1% of cases) (Table 2).

Table 2. Parameter measurements

Variables	Group 1 (> 8.5 mm)	Group 2 (< 8.5 mm)	p
Knee ROM	126.6 ± 17.3°	80.6 ± 27.5°	> 0.001
Modified HSS Knee Score	82.3 ± 4.4	61.2 ± 14	> 0.001

ROM – range of motion; HSS – Hospital for Special Surgery

The mean arc of motion for the knees was 103.6 ± 22.4°, ranging from 60°–150°. The arc of motion differed significantly between the < 8.5 mm groups ($p = 0.001$) (Figure 3). The mean Modified HSS Knee Score was 71.7 ± 9.2, and individual scores ranged 45–100. The Modified HSS Knee Score was significantly reduced for cerclage-wire distances > 8.5 mm (p = 0.001) (Figure 2). Subgroup analysis, further within group 1, including patients whose cerclage-wire distances were > 4 mm and < 8.5 mm, showed that the former subgroup of patients had significantly lower clinical scores and ROM when compared to the latter subgroup at 4 mm and below (p = 0.03 and 0.04, respectively) (Table 3).

Table 3. Subgroup analysis

Variables	Group 1 (> 8.5 mm)		p
	> 4 mm	4–8.5 mm	
Knee ROM	120.4 ± 24.6°	132.9 ± 10.1°	0.04
Modified HSS Knee Score	74.2 ± 5.3	90.4 ± 3.5	0.03

ROM – range of motion; HSS – Hospital for Special Surgery

DISCUSSION

Our study aimed to evaluate how the distance that separates the cerclage wire from the bone affects clinical and functional outcomes in patients treated for patellar fractures using tension-band wiring (TBW). With wires in cerclage, we assumed that closer proximity would yield better function, reflecting the traditional surgical belief that greater mechanical stability leads to superior results.

In our results, the complications and clinical outcomes we observed with cerclage wires mirror similar studies in the literature. In the study conducted by Zhai et al. [13] it was reported that all patella fractures treated with percutaneous cerclage wire in geriatric patients healed and there were no serious complications such as infection or wire migration. In this study, one case of wire breakage was reported after six months. Yan et al. [14], in another study, treated combined patella fractures with a separate vertical-wire method supported by a cerclage wire. According to the study results, no complications such as loss of reduction, implant breakage, non-union or skin irritation were observed during an average follow-up period of 18.9 months. Li et al. [15] evaluated patellar fractures treated with modified cerclage wire in elderly patients. During a mean follow-up period of 22.2 months, fracture healing was achieved in all patients and no significant postoperative complications were reported [15]. Monaco et al. [16] compared patellar fractures treated using suture tape and metallic cerclage wire. The study reported no significant differences in re-operation rates, fracture-healing rates and functional outcomes between the two methods [16].

Our findings demonstrate that cerclage wire remains an efficacious technique in patellar-fracture management and, despite complications in some instances, generally produces good clinical results. Research studies reviewed here support the efficacy and safety of cerclage wire in treating patellar fractures.

Our findings reveal the influence of the distance between the cerclage wire and bone on knee ROM and functional outcomes. Modified HSS Knee Scores averaged across different distance categories showed that the 4–8.5 mm category achieved the highest scores. This is indicative of better functional outcomes. Therefore, we evaluated the effects of different cerclage-wire distances on knee ROM and their relationship. According to Yan et al. [14], using a separate vertical-wire method with a cerclage wire at an optimal distance yielded an average knee ROM of 131.3°. Kumar and Kumar found that anterior cerclage-wire insertion allowed knee flexion up to 125.4° [17]. Ninety-two percent of patients in a study by Kachare et al. [18] attained active flexion of 90° after one week following cerclage wiring with a figure-of-eight TBW technique. It clearly showed better functional results with correct placement of cerclage wires at an appropriate distance.

Our results confirm the effect of cerclage-wire distance on knee ROM and functional outcomes. Average Modified HSS Knee Scores again showed that the 4–8.5 mm group had the highest average score. It shows better functional results. Zhai et al. [13] reported effective treatment with percutaneous cerclage wire in elderly patients, with all fractures healing successfully. Mahajan et al. [19] indicated that stable fixation was achieved with low non-union rates when cerclage wire was used in combination. Meng et al. [20] found satisfactory clinical outcomes and low complication rates when using modified cerclage wire. A study by Raja et al. [21] demonstrated clinical improvement and reduced complications with cerclage-wire application. These findings suggest that correct use of cerclage wire improves knee ROM and functional outcomes.

The study found that clinical outcomes and knee ROM were better in patients with a cerclage-wire distance < 8.5 mm. Modified tension-band wire with cerclage was recorded to reduce postoperative complications by Yu et al. [22]. Harna et al. [23], in surgically managed non-union patellar fractures, demonstrated similar ROM. This is supported by a study by Kachare et al. [18], indicating low complication rates and rapid recovery with cerclage or figure-eight configurations. This therefore substantiates the claim that accurate cerclage-wire placement can improve clinical outcomes. Consequently, according to Xiang et al. [7], patients treated with absorbable cannulated screws and high-strength sutures experienced less displacement and improved clinical results. Such findings show that positioning is crucial for cerclage-wire distance in managing patellar fractures and, if done accurately, can improve overall treatment success.

The study, however, has some limitations: the wide age range (18–65 years) may introduce variability in bone quality and healing capacity that might influence outcomes independently of surgical technique. It is further beyond

our control that the study is retrospective, limiting adjustment for potential confounders.

Another limitation is that fractures were classified by AO type, which could bias results for more complex patterns [24]. Some patients had immobilisation for up to four weeks, especially those with implant failure. This could theoretically affect knee ROM and recovery, confounding the effects attributed to cerclage-wire distance.

To overcome these limits and better validate our results, future prospective studies with narrower age ranges and stronger design are required. Further histological analyses may unveil mechanisms underlying the biological impact of cerclage-wire proximity on surrounding soft tissues. In general, our study highlights an understudied aspect of patellar-fracture treatment. By addressing this gap, we add to refined knowledge of TBW techniques that should foster better surgical outcomes and more-precise treatment protocols.

CONCLUSION

This study assessed the effect of cerclage wire proximity to the bone in tension band wiring for patellar fractures. Contrary to common traditional belief, it was found that wires placed very close to the bone (4 mm and below) resulted in poorer outcomes. This has important implications for wire placement: Mechanical stability must be weighed against tissue integrity, specifically avoiding adverse effects on the quadriceps muscle. These findings challenge existing surgical dogma and suggest that further research is needed to refine surgical guidelines that balance both biomechanical and biological considerations for the ultimate benefit of patient outcomes.

Conflict of interest: None declared.

REFERENCES

1. Melvin JS, Mehta S. Patellar fractures in adults. J Am Acad Orthop Surg. 2011;19(4):198–207. [DOI: 10.5435/00124635-201104000-00004] [PMID: 21464213]
2. Chloros GD, Kotsarinis G, Christou CD, Giannoudis PV. What's new in the management of patella fractures? Injury. 2022;53(6):1730–6. [DOI: 10.1016/j.injury.2022.03.035] [PMID: 35643733]
3. Zderic I, Stoffel K, Sommer C, Höntzsch D, Gueorguiev B. Biomechanical evaluation of the tension-band wiring principle: a comparison between two different techniques for transverse patella fracture fixation. Injury. 2017;48(8):1749–57. [DOI: 10.1016/j.injury.2017.05.037] [PMID: 28622833]
4. Gao Y, Wu G, Zhu H, Bian K, Wu D, Wei H. Dual tension band technique for patellar fractures involving articular surface and inferior pole: a retrospective cohort study and finite element analysis. Front Bioeng Biotechnol. 2025;13:1530745. [DOI: 10.3389/fbioe.2025.1530745] [PMID: 40104771]
5. Jurišić-Škevin A, Grbović V, Stanković I, Radunović A, Nurković J, Milošević B, et al. The impact of pain on functionality and health-related quality of life in patients with knee osteoarthritis. Srp Arh Celok Lek. 2019;147(1–2):45–51. [DOI: 10.2298/SARH171020009J]
6. Ho TYG, Lee Syn Yuk M. Fixation of patella fracture with non-metallic implant. J Orthop Trauma Rehabil. 2023;31(1):104–10. [DOI: 10.1177/22104917231197234]
7. Xiang F, Xiao Y, Li D, Ma W, Chen Y, Yang Y. Tension band high-strength suture combined with absorbable cannulated screws for treating transverse patellar fractures: finite element analysis and clinical study. Front Bioeng Biotechnol. 2024;12:1340482. [DOI: 10.3389/fbioe.2024.1340482] [PMID: 38515618]
8. Zhang ZS, Li PF, Zhou F, Tian Y, Ji HQ, Guo Y, et al. Comparison of a novel tension band and patellotibial tubercle cerclage in the treatment of comminuted fractures of the inferior pole of the patella. Orthop Surg. 2020;12(1):224–32. [DOI: 10.1111/os.12616] [PMID: 31958886]
9. Chang SM, Ji XL. Open reduction and internal fixation of displaced patella inferior pole fractures with anterior tension band wiring through cannulated screws. J Orthop Trauma. 2011;25(6):366–70. [DOI: 10.1097/BOT.0b013e3181dd8f15] [PMID: 21577073]
10. Kakazu R, Archdeacon MT. Surgical management of patellar fractures. Orthop Clin North Am. 2016;47(1):77–83. [DOI: 10.1016/j.ocl.2015.08.010] [PMID: 26614923]
11. Oh HK, Choo SK, Kim JW, Lee M. Internal fixation of displaced inferior pole of the patella fractures using vertical wiring augmented with Krachow suturing. Injury. 2015;46(12):2512–15. [DOI: 10.1016/j.injury.2015.09.026] [PMID: 26482481]
12. Evanich CJ, Tkach TK, von Glinski S, Camargo MP, Hofmann AA. Six- to ten-year experience using countersunk metal-backed patellas. J Arthroplasty. 1997;12(2):149–54. [DOI: 10.1016/S0883-5403(97)90060-7] [PMID: 9139096]
13. Zhai Q, Yang J, Zhuang J, Gao R, Chen M. Percutaneous cerclage wiring for type 34-C patella fracture in geriatric patients. Injury. 2020;51(6):1436–42. [DOI: 10.1016/j.injury.2020.03.040] [PMID: 32291087]
14. Yan SG, Li D, Cui Y, Hua X, Hemmann P, Schmidutz F. Management of comminuted inferior patellar pole fractures with cerclage-wire-augmented separate vertical wiring: a retrospective clinical study. Arch Orthop Trauma Surg. 2023;143(1):247–54. [DOI: 10.1007/s00402-021-04034-4] [PMID: 34232348]
15. Li L, Zhang Q, Tao F, Wang D, Dong J, Zhou D, et al. Management and outcome of elderly patients with patellar fracture treated with novel modified cerclage wiring. Geriatr Orthop Surg Rehabil. 2023;14:21514593231177983. [DOI: 10.1177/21514593231177983] [PMID: 37250018]
16. Monaco E, Saithna A, Cardarelli S, Bruni G, Carrozzo A, Annibaldi A, et al. No difference in clinical and radiological outcomes following fixation of transverse patella fractures with either suture tape or metallic cerclage: a retrospective comparative study. Orthop Traumatol Surg Res. 2021;107(8):103053. [DOI: 10.1016/j.otsr.2021.103053] [PMID: 34530129]
17. Kumar P, Kumar M. Fracture patella: fixation with cancellous screws and anterior cerclage wiring. Int J Orthop Sci. 2021;7(1):618–22. [DOI: 10.22271/ORTHO.2021.V7.I1N.2586]
18. Kachare A, Jagiasi J, Jadhav P, Munde K. Achieving rapid healing and low complication rates in patellar fracture fixation: the benefits of cerclage and figure-of-eight configuration. Cureus. 2023;15(5):e39059. [DOI: 10.7759/cureus.39059] [PMID: 37323351]
19. Mahajan A, Rathi M, Mahajan R, Kumar A, Saini M. Management of non-union patella fractures with modified tension band wiring and supplementary cerclage: a case series. J Clin Orthop Trauma. 2021;17:50–6. [DOI: 10.1016/j.jcot.2021.06.004] [PMID: 37065521]
20. Meng D, Xu P, Shen D, Chen Y, Zhu C, Hou C, et al. A clinical comparison study of three different methods for treatment of transverse patellar fractures. J Orthop Sci. 2019;24(1):142–6. [DOI: 10.1016/j.jos.2018.08.026] [PMID: 30316657]
21. Raja BS, Jain A, Paul S, Choudhury AK, Kalia RB. Plate osteosynthesis in patellar fractures: a systematic review and meta-analysis. Eur J Orthop Surg Traumatol. 2022;32(8):1627–40. [DOI: 10.1007/s00590-021-03143-5] [PMID: 34664117]
22. Yu T, Wu Z, Mohamed SO, Ju W, Liu X, Qi B. Modified tension band wiring of patellar fracture as a technique to minimize postoperative complications. Medicine (Baltimore). 2020;99(12):e19576. [DOI: 10.1097/MD.0000000000019576] [PMID: 32195969]
23. Harna B, Gupta P, Singh J, Rousa S, Gupta A. Surgical management of non-union patella fracture: a case series and review of the literature. Arch Bone Jt Surg. 2020;8(4):455–62. [DOI: 10.22038/ABJS.2020.49755.2472] [PMID: 34692939]
24. Lenz JE, Schraag AD, Plank L, von Rüden C, Alt V, Weber J. Mapping of patellar fracture patterns: a multicenter study of 237 patients. J Clin Med. 2025;14(4):1335. [DOI: 10.3390/jcm14041335] [PMID: 40004864]

Да ли ближе постављање серклажне жице побољшава функционалне резултате фиксације прелома пателе тензионом жичаном траком?

Јашар Самет Гокчеоглу[1], Шахин Каралар[2], Метин Јапти[1], Али Левент[3]

[1]Наставно-истраживачка болница „Мехмет Акиф Инан", Одељење за ортопедију и трауматологију, Шанлиурфа, Турска;
[2]Универзитет „Медипол" у Истанбулу, Медицински факултет, Одељење за ортопедију и трауматологију, Истанбул, Турска;
[3]Приватна болница „Метролајф", Одељење за ортопедију и трауматологију, Шанлиурфа, Турска

САЖЕТАК

Увод/Циљ Преломи пателе најчешће се фиксирају техником тензионе жичане траке. Растојање између серклажне жице и горњег пола пателе сматра се пресудним за хируршки исход. Циљ студије био је да процени утицај овог растојања на клиничке и функционалне резултате.

Методе Спроведена је ретроспективна кохортна студија која је обухватила 64 болесника с попречним преломом пателе лечених техником тензионе жичане траке. Болесници су подељени у три групе на основу удаљености серклажне жице од кости: < 4 *mm*, 4–8,5 *mm* и > 8,5 *mm*. Клинички исходи обухватили су срастање кости, отказивање имплантата и компликације ране, док су функционални исходи оцењивани на основу опсега покрета и модификоване *HSS* (*Hospital for Special Surgery*) оцене за колено.

Резултати Исходи су значајно варирали у зависности од положаја жице. Болесници код којих је серклажна жица била постављена на мање од 4 *mm* од кости постигли су слабије функционалне резултате (средња модификована *HSS* оцена 70 ± 9,2; просечан опсег покрета 103,6 ± 42,4). Најбољи опоравак забележен је код болесника са жицом удаљеном 4–8,5 *mm*, који су остварили више оцене функције колена и већи опсег покрета. Статистичка анализа потврдила је да ближе постављање жице негативно утиче на клиничке исходе ($p < 0,05$).

Закључак Постављање серклажне жице сувише близу кости (< 4 *mm*) може да наруши функционалне резултате упркос очекиваној механичкој стабилности. Оптимално растојање од 4–8,5 *mm* обезбеђује бољу равнотежу између механичке стабилности и заштите меког ткива, што доводи до побољшаних клиничких и функционалних исхода. Ови налази доводе у питање конвенционалне хируршке приступе и наглашавају значај прецизног позиционирања жице у техници тензионе жичане траке.

Кључне речи: преломи пателе; тензиона жичана трака; серклажна жица; клинички исходи; функционални исходи; хируршке технике

DOI: https://doi.org/10.2298/SARH250428046Z
UDC: 616.833-073-053.32

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cranial ultrasound as a complementary method to the general movements assessment in preterm infants for predicting the neurological outcome – a single center experience

Dragan Zlatanović[1,2], Hristina Čolović[1,2], Vesna Živković[1,2], Anita Stanković[2], Milica Kostić[2], Vuk Pejčić[2], Vukota Radovanović[2]

[1]University of Niš, Faculty of Medicine, Department for Physical Medicine and Rehabilitation, Niš, Serbia; [2]Niš University Clinical Centre, Physical Medicine and Rehabilitation Clinic, Niš, Serbia

SUMMARY

Introduction/Objective Implementing cranial ultrasound (CUS) into daily clinical practice represents a major advance in the diagnosis and treatment of newborns. Preterm birth is considered a risk factor for abnormal neurological development. The study aimed to evaluate the significance of CUS in preterm infants as a complementary method to the General Movements Assessment for predicting neurological outcomes. The study focused on a cohort of infants without significant neonatal morbidity.

Methods The study included 160 preterm infants and was designed as a prospective clinical study. Statistical analysis included cranial ultrasound findings and the assessment of spontaneous motor activity in the first five days after birth ("Writhing" period), perinatal data, and pregnancy data.

Results There was a statistically significant association between abnormal CUS findings and cerebral palsy in the final neurological outcome ($p < 0.001$). Pathological CUS findings were significantly more frequent in preterm infants born before 30 weeks of gestation ($p < 0.001$), those delivered by cesarean section ($p < 0.001$), and infants with an Apgar score < 8 at one and five minutes ($p < 0.001$). The specificity of a normal CUS was 86% but increased to 100% when combined with a normal General Movements Assessment.

Conclusion This research confirms that CUS can be a valuable tool for predicting neurological outcomes in preterm infants. It can provide data that can guide the judicious use of different monitoring methods and rationalize their examinations.

Keywords: preterm infants; cranial ultrasound; General Movements; Prechtl's method; neurodevelopmental outcome

INTRODUCTION

Motor development in newborns, infants, and young children relies on the health of the central nervous system (CNS), and is influenced by genetic patterns and external stimuli. Mental and motor development are closely connected, with significant neurological changes occurring within the first days and months of life. To assess these changes accurately, repeated evaluations, or developmental monitoring, are essential, as a single assessment may not detect certain neurological issues due to the immature CNS's variable responses [1, 2, 3].

Special clinical attention is drawn to newborns who have some risk of developing disorders of the CNS. The most common perinatal factors are prematurity, low birth weight of the newborn, low Apgar score, multiple pregnancies, birth trauma, inadequate presentation of the fetus, and termination of delivery by cesarean section (C-section) [3–6]. Premature newborns (born before the gestational age of 37 weeks) have a higher risk of sudden death syndrome and complications in general, compared to full-term infants [7, 8, 9].

Apart from the neurological and neurokinesiological examination of newborns and infants, additional diagnostic methods used in clinical practice to detect neurological abnormalities are cranial ultrasound (CUS) examination and magnetic resonance imaging. Implementing CUS into daily clinical practice represents a major advance in the diagnosis and treatment of newborns [10–13].

The general motor assessment (GMA) in premature infants is defined as a high-certainty method for predicting neurological outcomes. Still, this type of examination should only be performed by a trained and certified physician, who is not available in every hospital [14, 15, 16]. For that reason, this study aimed to evaluate the significance of the initial CUS in preterm infants as a widely available, complementary method of examination to GMA for predicting neurological outcomes.

METHODS

This study was designed as a prospective clinical study and included preterm infants (gestational age ≤ 37 weeks), born in the Gynecology and Obstetrics Clinic of the University Clinical Center Niš between 2012 and 2014. During this study period, 7 142 children were born

Received • Примљено: April 28, 2025
Revised • Ревизија: June 5, 2025
Accepted • Прихваћено: June 6, 2025
Online first: June 9, 2025

Correspondence to:
Dragan ZLATANOVIĆ
Department of Physical Medicine and Rehabilitation
Faculty of Medicine
81 Dr Zoran Đinđić Blvd.
18000 Niš, Serbia
draganzlatanovic1@gmail.com

at the University Clinical Center Niš. Among them, 629 (8.8%) were born prematurely. All children who had any serious perinatal complications such as sepsis, necrotizing enterocolitis, and lung disease were excluded from the study. Additionally, some of the preterm infants were excluded from the study due to the presence of deformities or congenital anomalies, as well as genetic syndromes of a newborn, invalid video recordings of neonatal motions, parental refusal to participate in the study, or non-attendance in the follow-up in our institution. A two-year follow-up was completed for 160 preterm infants, and they were analyzed in this study.

For each infant included in the research, detailed perinatal data were taken: sex, gestational age / gestational weeks (GW) (< 30 weeks; 30–37 weeks), body weight at birth, body length at birth, head circumference, Apgar score value at the first and fifth minutes, data on method of delivery (C-section or not), data on multiple (twin) pregnancy and CUS findings.

GMA was carried out according to the basic principles of the Prechtl method within five days after the birth ("Writhing" period) and was based on video analysis and performed by a licensed person for GMA expertise [14, 15, 16]. To get good video recordings (lasting up to 25 minutes), the baby needed to be awake, calm, not crying, with open eyes, without irregular breathing, and moving ("State 4"). For premature babies younger than 36 GW, recordings were made when they started moving, even if they were asleep.

General movements (GMs) were classified into four types [14, 15, 16]:

1. Normal Writhing Movements (N): smooth, twisting movements with low to moderate strength and slow to moderate speed, oval or twisting in shape;
2. Poor Repertoire (PR): limited variety and less complex than normal (baby starts a movement but doesn't finish it, making the sequence look incomplete or broken);
3. Cramped Synchronized Movements (CS): abnormal movements where the muscles of the body and limbs tighten and relax at the same time; movements are stiff and lack the smooth flow of normal writhing movements;
4. Chaotic Movements (CH): sudden, jerky movements with very large and random motions of the arms and legs, uncoordinated with a lack of smoothness or pattern.

Definitive neurological outcome was assessed based on a detailed neurological examination at the age of 24 months (corrected calendar age). The examination was performed by a certified neurologist specializing in pediatric neurology. Neurological outcome was classified as normal findings (completely normal neurological findings); minimal neurological dysfunction (MND), according to Touwen Infant Neurological Examination criteria or non-specific signs without clear and definitive signs of cerebral palsy [17, 18]; cerebral palsy (CP) was classified according to Surveillance of Cerebral Palsy in Europe criteria [19].

CUS examination was performed with LOGIQ™ (GE Healthcare, Chicago, Il, USA) machine with a high-frequency linear probe (7–11 MHz) within five days after the birth. Repeat CUS examination was performed two weeks after the birth, but statistical analysis included only the findings of the first examination. All CUS examinations were performed by the same person and categorized into five groups of interest (according to the guidelines from the ELGAN study [13] and Prechtl's recommendations [14, 15, 16]):

- CUS 1 – normal finding;
- CUS 2 – hyperechogenicity of the brain parenchyma lasting up to 14 days;
- CUS 3 – hyperechogenicity of the brain parenchyma that lasts longer than 14 days;
- CUS 4 – intraventricular hemorrhage;
- CUS 5 – periventricular leukomalacia.

The medical doctor who analyzed spontaneous motor activity in newborns and the medical doctor who analyzed CUS findings did not have access to any results or data on the newborns.

Statistical analysis was conducted using IBM SPSS Statistics, Version 20.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables in defined groups was determined. Anthropometric mode values were presented as percentiles based on child growth standards. Continuous variable comparisons between groups utilized the Mann-Whitney test, while qualitative variables were analyzed with Pearson's χ^2 test. For category variables with samples fewer than 5, Pearson χ^2 or Fisher's exact tests were used. To evaluate the CUS method, sensitivity, specificity, positive predictive value (PPV), negative predictive value, and diagnostic odds ratio (DOR) were calculated based on normal CUS findings and final neurological outcomes. A two-tailed p-value of < 0.05 was considered statistically significant.

Ethics: The study was performed in line with the Declaration of Helsinki and approved by the Ethics Board of the University Clinical Center Niš (Decision No. 5718/1).

RESULTS

A statistically significant difference in neurological outcome after 24 months existed between infants born before and after 30 weeks ($p < 0.001$). Lower body weight of newborns ($p < 0.001$), body length ($p < 0.05$), and Apgar score at the first and fifth minutes ($p < 0.001$) were statistically significantly associated with a worse neurological outcome. The prevalence of different types of GMs in the observation period of up to five days differed statistically significantly between the different outcomes ($p < 0.001$). The outcome after a follow-up of 24 months was normal in 124, qualified as MND in 22, and diagnosed as CP in 14 preterm infants (Table 1).

Pathological CUS findings were statistically significantly more common in preterm infants born before 30 GW ($p < 0.001$), delivered via C-section ($p < 0.001$), and those with an Apgar score < 8 at both the first and fifth minutes after birth ($p < 0.001$) (Table 2).

Table 1. Clinical characteristics of subjects according to outcome after 24 months

Clinical characteristics		Outcome after 24 months			Summarized (n = 160)	p
		Normal (n = 124)	MND (n = 22)	CP (n = 14)		
[a,b]Gestational age mode (min–max)		35 (29–36) GW	35 (33–35) GW	29 (27–29) GW	35 (27–36) GW	0.014
≥ 30 weeks		122 (98.39%)	22 (100%)	0 (0%)	144 (90%)	< 0.001
< 30 weeks		2 (1.61%)	0 (0%)	14 (100%)	16 (10%)	
[a]Sex	Female	60 (48.39%)	10 (45.45%)	8 (57.14%)	78 (48.75%)	0.78
	Male	64 (51.61%)	12 (54.55%)	6 (42.86%)	82 (51.25%)	
[a]Twins	No	92 (74.19%)	18 (81.82%)	14 (100%)	124 (77.5%)	0.079
	Yes	32 (25.81%)	4 (18.18%)	0 (0%)	36 (22.5%)	
[a]Caesarean section	No	80 (64.52%)	12 (54.55%)	6 (42.86%)	98 (61.25%)	0.227
	Yes	44 (35.48%)	10 (45.45%)	8 (57.14%)	62 (38.75%)	
[b]Birth weight (g) mode (min–max) mode in percentiles		2150 (2000–2350) 18.9%	1750 (1350–2400) 3.4%	1320 (1250–1350) 57.1%	2125 (1250–2400) 18.9%	< 0.001
[b]Birth body length (cm) mode (min–max) mode in percentiles		45 (42–47) 24.5%	44 (43–45) 14.9%	39 (35–40) 55.2%	44 (42–47) 14.9%	0.021
[b]Head circumference (cm) mode (min–max) mode in percentiles		30 (29–32) 7.5%	30 (28–32) 7.5%	28 (26–29) 75.2%	30 (26–32) 7.5%	0.114
[b]Apgar score (1– minute) mode (min–max)		8 (8–9)	8 (8–8)	6 (1–7)	8 (1–9)	< 0.001
[b]Apgar score (5– minute) mode (min–max)		9 (8–9)	8 (8–8)	7 (5–8)	9 (5–9)	< 0.001
[a]GMs within 5 days						
N		94 (75.81%)	0 (0%)	0 (0%)	94 (58.75%)	< 0.001
PR		30 (24.19%)	22 (100%)	2 (14.29%)	54 (33.75%)	
CS		0 (0%)	0 (0%)	12 (85.71%)	12 (7.5%)	
CM		0 (0%)	0 (0%)	0 (0%)	0 (0%)	

MND – minimal neurological dysfunction; CP – cerebral palsy; GW – gestational weeks; min – minimum; max – maximum; GM – general movements; N – normal writhing movements; PR – poor repertoire; CS – cramped synchronized movements; CM – chaotic movements;
[a]Pearson's χ^2 test;
[b] Mann–Whitney test

Table 2. Distribution of normal and abnormal cranial ultrasound findings in relation to clinical characteristics of preterm newborns

Clinical characteristics		Cranial ultrasound finding		p
		Normal (n = 96)	Abnormal (n = 64)	
Sex	Female (n = 78)	52 (66.7%)	26 (33.3%)	0.108
	Male (n = 82)	44 (53.7%)	38 (46.3%)	
Gestational age	≥ 30 weeks (n = 144)	94 (65.3%)	50 (34.7%)	< 0.001
	< 30 weeks (n = 16)	2 (12.5%)	14 (87.5%)	
Twins	No (n = 124)	76 (61.3%)	48 (38.7%)	0.566
	Yes (n = 36)	20 (55.6%)	16 (44.4%)	
Cesarean section	No (n = 98)	70 (71.4%)	28 (28.6%)	< 0.001
	Yes (n = 62)	26 (41.9%)	36 (58.1%)	
Apgar score (1-minute)	9 (n = 52)	38 (73.1%)	14 (29.6%)	< 0.001
	8 (n = 82)	52 (63.4%)	30 (36.6%)	
	< 8 (n = 26)	6 (23.1%)	20 (76.9%)	
Apgar score (5-minute)	9 (n = 90)	64 (71.7%)	26 (28.9%)	< 0.001
	8 (n = 52)	30 (57.7%)	22 (42.3%)	
	< 8 (n = 18)	2 (11.1%)	16 (88.9%)	

Pearson's χ^2 test

Among six preterm infants with an Apgar score of 1 in the first minute, four scored 2 and two scored 5 in the fifth minute. Four developed CP, with two having scores of 1 and 2, and two with scores of 1 and 5. All CP cases showed hyperechogenicity of brain parenchyma detectable for up to 14 days. Additionally, two preterm infants diagnosed with MND had scores of 1 in the first minute and 2 in the fifth minute, with hyperechogenicity lasting longer than 14 days. Due to the small sample size, more research is necessary to draw definitive conclusions about this subgroup.

Previously determined statistically significant clinical characteristics of preterm infants for the final outcome also showed a statistically significant relation with CUS findings (Table 3).

Table 4 indicates that deviations from normal CUS findings are smallest in subjects with a normal final neurological outcome. A significant association was observed between CP in the final outcome and abnormal CUS findings ($p < 0.001$). Pathological CUS findings varied significantly among the groups based on final neurological outcomes (normal, MND, CP) ($p < 0.05$). Altered findings were most prevalent in subjects with CP and least frequent in those with a normal outcome.

Table 5 indicates that a normal CUS finding has a high specificity of 72.2% for a normal final neurological outcome, though its sensitivity is lower at 67.8%. The specificity of normal CUS findings improves when assessing

Table 3. Distribution of different cranial ultrasound findings in relation to previously significant clinical characteristics of preterm newborns

Clinical characteristics		Cranial ultrasound finding					p
		CUS 1 (n = 96)	CUS 2 (n = 36)	CUS 3 (n = 20)	CUS 4 (n = 6)	CUS 5 (n = 2)	
Gestational age	≥ 30 weeks (n = 144)	94 (65.3%)	30 (20.8%)	18 (12.5%)	2 (1.4%)	0 (0%)	< 0.001
	< 30 weeks (n = 16)	2 (12.5%)	6 (37.5%)	2 (12.5%)	4 (25%)	2 (12.5%)	
Cesarean section	No (n = 98)	70 (71.4%)	16 (16.3%)	8 (8.2%)	2 (2%)	2 (2%)	0.002
	Yes (n = 62)	26 (41.9%)	20 (32.3%)	12 (19.4%)	4 (6.5%)	0 (0%)	
Apgar score (1-minute)	9 (n = 52)	38 (73.1%)	12 (23.1%)	2 (3.8%)	0 (0%)	0 (0%)	< 0.001
	8 (n = 82)	52 (63.4%)	16 (19.5%)	12 (14.6%)	2 (2.4%)	0 (0%)	
	< 8 (n = 26)	6 (23.1%)	8 (30.8%)	6 (23.1%)	4 (15.4%)	2 (7.7%)	
Apgar score (5-minute)	9 (n = 90)	64 (71.1%)	18 (20%)	8 (8.9%)	0 (0%)	0 (0%)	< 0.001
	8 (n = 52)	30 (57.7%)	10 (19.2%)	8 (15.4%)	8 (8.9%)	2 (3.8%)	
	< 8 (n = 18)	2 (11.4%)	8 (44.4%)	4 (22.2%)	4 (22.2%)	0 (0%)	

CUS 1 – normal finding; CUS 2 – hyperechogenicity of the brain parenchyma lasting up to 14 days; CUS 3 – hyperechogenicity of the brain parenchyma that lasts longer than 14 days; CUS 4 – intraventricular hemorrhage; CUS 5 – periventricular leukomalacia; Pearson's χ^2 test

Table 4. Distribution of different cranial ultrasound findings in relation to different neurological outcomes

Neurological outcome	Cranial ultrasound finding					p
	Normal (n = 96)	Abnormal (n = 64)				
Normal (n = 124)	84 (67.74%)	40 (32.26%)				< 0.001
MND (n = 22)	10 (45.45%)	12 (54.55%)				
CP (n = 14)	2 (14.29%)	12 (85.71%)				
	CUS 1 (n = 96)	CUS 2 (n = 36)	CUS 3 (n = 20)	CUS 4 (n = 6)	CUS 5 (n = 2)	
Normal (n = 124)	84 (67.74%)	28 (22.58%)	12 (9.68%)	0 (0%)	0 (0%)	0.003
MND (n = 22)	10 (45.45%)	4 (18.18%)	6 (27.27%)	2 (9.09%)	0 (0%)	
CP (n = 14)	2 (14.29%)	4 (28.57%)	2 (14.29%)	4 (28.57%)	2 (14.29%)	

MND – minimal neurological dysfunction; CP – cerebral palsy; CUS 1 – normal finding; CUS 2 – hyperechogenicity of the brain parenchyma lasting up to 14 days; CUS 3 – hyperechogenicity of the brain parenchyma that lasts longer than 14 days; CUS 4 – intraventricular hemorrhage; CUS 5 – periventricular leukomalacia; Pearson's χ^2 test

outcomes without CP or with CP. Combining CUS and GMA achieved 100% specificity and PPV in ruling out deviations from normal neurological outcomes.

DISCUSSION

Periventricular subependymal hemorrhage and intraventricular hemorrhage are complications that usually occur in the first days after birth and are characteristics of premature babies. Frequency of these hemorrhages in newborns who weigh < 1500 g and are < 32 GW of age is up to 25%. In newborns who weigh < 1000 g, this frequency is up to 40%. Extremely low birth weight and extremely low gestational age represent a strong predisposition for long-term complications, including CP/MND [9, 20].

Prechtl found that increased brain tissue echodensity is temporary and has limited prognostic value when lasting less than two weeks [12]. Other studies recommend the first CUS on the third day after birth and a follow-up before the end of two weeks [21]. In our study, 96 subjects (60%) had normal CUS findings at the first examination. Among them, 10 had MND, and two were diagnosed with CP. Both infants were born before 30 GW, suggesting that their early preterm birth affected the maturation of their CNS.

Our study on CUS findings shows differences compared to existing literature, likely due to the smaller sample sizes often used in those studies [21]. For instance, a large study of premature infants born after 33 weeks of gestation noted pathological CUS findings in 13%. The authors highlighted that even slight differences in gestational age can affect CUS specificity, complication rates, and neurological outcomes [22]. While some studies report that C-section is not significantly linked to poor neurological outcomes, factors like Apgar scores and head circumference are associated with these outcomes [22, 23]. In contrast, our study found a significant association between C-section delivery and unfavorable neurological outcomes, likely influenced by the overlap of low Apgar scores and head circumferences in C-section cases.

The availability of CUS as a diagnostic method and its application in daily clinical practice represents a major diagnostic advance. In a recent study, normal CUS findings have a PPV for the final normal neurological outcome of 89.4%, and PPV increases to 97.9% for a final neurological outcome that excludes CP. These results indicate that the subjects with a normal finding on the CUS may have a pathological neurological outcome and it correlates with the already described studies. Recent research supports the fact that the pathological CUS finding has a predictive value for later neurological deviations. The sensitivity of these findings was not high, which indicates the need to follow up on the development of children who, in the first five days after birth, had abnormal findings, either during the examination by CUS or during the GMA. Pathological CUS findings are statistically significantly more frequent in subjects who had CP in the final outcome ($p < 0.05$).

The diagnostic odds ratio of CUS findings without pathology in all examined combinations is > 1, which implies the ability of the single method to determine the final outcome. DOR doubles in the case of determination of

Table 5. Distribution of different cranial ultrasound findings in relation to final neurological outcomes and evaluation of the method significance

		CUS finding		Sensitivity = 67.8%	
		Normal	Abnormal	Specificity = 72.2%	
Neurological outcome	Normal	84 (67.7%)	40 (32.3%)	PPV = 89.4%	p = 0.005
	Abnormal	10 (27.8%)	26 (72.2%)	NPV = 39.4%	
				DOR = 5.42	
		CUS finding		Sensitivity = 63%	
		Normal	Abnormal	Specificity = 85.7%	
Neurological outcome	Non-CP	92 (63%)	54 (37%)	PPV = 97.9%	p = 0.018
	CP	2 (14.3%)	12 (85.7%)	NPV = 18.2%	
				DOR = 10.26	
		CUS and GMA finding		Sensitivity = 51.6%	
		Normal	Abnormal	Specificity = 100%	
Neurological outcome	Normal	64 (48.4%)	60 (51.6%)	PPV = 100%	p < 0.001
	Abnormal	0 (0%)	36 (100%)	NPV = 37.5%	
				DOR = infinity	
		CUS and GMA finding		Sensitivity = 43.9%	
		Normal	Abnormal	Specificity = 100%	
Neurological outcome	Non CP	64 (43.8%)	82 (56.2%)	PPV = 100%	p = 0.038
	CP	0 (0%)	14 (100%)	NPV = 14.6%	
				DOR = infinity	

CUS – cranial ultrasound; CP – cerebral palsy; GMA – general movements assessment; PPV – positive predictive value; NPV – negative predictive value; DOR – diagnostic odds ratio; Pearson's χ^2 test and determination of the sensitivity, specificity, PPV, NPV, and DOR

non-CP/CP in the final outcome (DOR = 10.26) compared to normal/abnormal determination (DOR = 5.42). A DOR value > 10 indicates excellent diagnostic value. Results combining CUS and GMA are impressive. In the case of determining DOR about non-CP/CP in the final outcome as well as normal/abnormal final outcome, DOR tends to infinity because in no case of both normal CUS findings and normal GMA findings did MND or CP develop.

In this study, 100% of preterm infants with periventricular leukomalacia developed CP, which is in agreement with the research of other authors who indicate the high predictive value of this finding for the later development of CP [24]. All subjects with a finding of intraventricular hemorrhage had one of the pathological outcomes (MND/CP) in the final outcome. Periventricular echodensity in the frontal white matter, which disappeared for up to 14 days, did not affect spontaneous motor activity, but periventricular echodensity in the same zone lasting longer than 14 days was associated with abnormal development of spontaneous motor activity.

A recent study included a limited number of preterm infants due to various exclusion criteria, primarily focusing on those born at or above 30 GW, which comprised 90% of participants. Most infants were not delivered via C-section or from twin pregnancies. After a 24-month follow-up, most subjects showed normal neurological findings; however, the majority of those who developed CP were born before 30 GW (14 out of 16). This suggests that insufficient maturity of the CNS may be a contributing factor. Given that preterm infants with serious complications were excluded from this study, it should be emphasized that results show the prognostic values of CUS and GMA for relatively "low-risk" preterm infants. This fact represents a limiting factor for the generalizability of our results.

Future research should involve more infants (both "low-risk" and "high-risk"), especially those under 30 GW, and a more detailed categorization of CUS and neurological outcomes could enhance the findings' applicability. Studies indicate that preterm infants can show abnormal GM in the first week after birth, often due to factors like electrolyte imbalances or changes in cerebral blood flow, despite later having normal neurological outcomes. To prevent misleading results, it is recommended that the first GM evaluation be conducted after the first week [25]. In our study, we performed the first GMA earlier due to some newborns leaving the maternity ward before this period, following Prechtl's recommendations [14, 15] while excluding those with significant complications. All newborns with normal GM findings at the initial evaluation had a normal neurological outcome at 24 months.

GMA has better predictive value in later periods of development, with the best predictive value in the "fidgety" period (50–54 GW) [14, 15, 16]. Recognizing the importance of initial examinations and effectively incorporating them into practice is crucial for timely therapy application. This study suggests that developing a prognostic model for predicting neurological outcomes in a larger, multicentric study could be beneficial. This model should integrate GMA and CUS findings along with statistically significant perinatal clinical characteristics and pregnancy data from preterm cases.

CONCLUSION

This study highlights the strong link between clinical characteristics, CUS findings, and neurological outcomes in preterm infants. Pathological CUS findings were more prevalent in those born before 30 weeks of gestation, delivered by C-section, and with lower Apgar scores. Normal CUS results were highly specific for normal neurological outcomes, especially when combined with GMA. Prolonged hyperechogenicity and conditions like periventricular leukomalacia were significant predictors of CP. These findings underscore the importance of early multimodal diagnostics, particularly CUS and GMA, in predicting long-term neurological outcomes and guiding interventions.

ACKNOWLEDGMENTS

We would like to thank the parents of prematurely born children for their permission to present the results of the analyses of their loved ones.

Conflicts of interest: None declared.

REFERENCES

1. Colver A, Fairhurst C, Pharoah P. Cerebral palsy. Lancet. 2014;383(9924):1240–9. [DOI: 10.1016/S0140-6736(13)61835-8] [PMID: 24268104]
2. Fahey MC, MacLennan AH, Kretzschmar D, Gecz J, Kruer MC. The genetic basis of cerebral palsy. Dev Med Child Neurol. 2017;59(5):462–9. [DOI: 10.1111/dmcn.13363] [PMID: 28042670]
3. Sato J, Vandewouw MM, Bando N, Branson HM, O'Connor DL, Unger SL, et al. White matter alterations and cognitive outcomes in children born very low birth weight. Neuroimage Clin. 2021;32:102843. [DOI: 10.1016/j.nicl.2021.102843] [PMID: 34601309]
4. Kyono Y, Nishiyama M, Kawamura A, Oikawa S, Tokumoto S, Yamaguchi H, et al. Association of perinatal factors with neurodevelopmental referrals in a population-based cohort study in Japan. Sci Rep. 2024;14:3492. [DOI: 10.1038/s41598-024-54167-w] [PMID: 38347064]
5. Yoshida T, Matsumura K, Hatakeyama T, Inadera H; Japan Environment, Children's Study Group. Association between Cesarean section and neurodevelopmental disorders in a Japanese birth cohort. BMC Pediatr. 2023;23:306. [DOI: 10.1186/s12887-023-04128-5] [PMID: 37331958]
6. Haga M, Kanai M, Ishiguro A, Nishimura E, Minamitani Y, Iwatani A, et al. Changes in in-hospital survival and long-term neurodevelopmental outcomes of extremely preterm infants: a retrospective study of a Japanese tertiary center. J Pediatr. 2023;255:166–74.e4. [DOI: 10.1016/j.jpeds.2022.11.024] [PMID: 36462685]
7. Boileau P, Letouzey M, Morgan AS, Lorthe E, Kaminski M, Coquelin A, et al. Circumstances, causes and timing of death in extremely preterm infants admitted to NICU: The EPIPAGE-2 study. Acta Paediatr. 2023;112(10):2066–74. [DOI: 10.1111/apa.16894] [PMID: 37402152]
8. Horne RS, Harrewijn I, Hunt CE. Physiology during sleep in preterm infants: implications for increased risk for the sudden infant death syndrome. Sleep Med Rev. 2024;78:101990. [DOI: 10.1016/j.smrv.2024.101990] [PMID: 39116607]
9. Bourneuf AL, Pabic EL, de Visme S, Levieux K, Pladys P; OMIN study group. Risk factors for unexpected infant death among very premature infants in France. Arch Pediatr. 2024;31(3):195–201. [DOI: 10.1016/j.arcped.2023.12.003] [PMID: 38538469]
10. Richer EJ, Riedesel EL, Linam LE. Review of neonatal and infant cranial US. Radiographics. 2021;41(7):E206–7. [DOI: 10.1148/rg.2021210089] [PMID: 34723697]
11. Gumus M, Oommen KC, Squires JH. Contrast-enhanced ultrasound of the neonatal brain. Pediatr Radiol. 2022;52(4):837–46. [DOI: 10.1007/s00247-021-05157-x] [PMID: 34333692]
12. Plut D, Prutki M, Slak P. The use of contrast-enhanced ultrasound in the evaluation of the neonatal brain. Children (Basel). 2023;10(8):1303. [DOI: 10.3390/children10081303] [PMID: 37628302]
13. Kuban K, Adler I, Allred EN, Batton D, Bezinque S, Betz BW, et al. Observer variability assessing US scans of the preterm brain: the ELGAN study. Pediatr Radiol. 2007;37(12):1201–8. [DOI: 10.1007/s00247-007-0605-z] [PMID: 17901950]
14. Prechtl HF. The neurological examination of the full-term newborn infant. Cambridge (UK): Cambridge University Press; 1991.
15. Prechtl HF. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. Early Hum Dev. 1990;23(3):151–8. [DOI: 10.1016/0378-3782(90)90011-7] [PMID: 2253578]
16. Zlatanovic D, Čolović H, Živković V, Stanković A, Kostić M, Vučić J, et al. The importance of assessing general motor activity in premature infants for predicting neurological outcomes. Folia Neuropathol. 2022;60(4):427–35. [DOI: 10.5114/fn.2022.119593] [PMID: 36734385]
17. Hadders-Algra M, Heineman KR, Bos AF, Middelburg KJ. The assessment of minor neurological dysfunction in infancy using the Touwen Infant Neurological Examination. Dev Med Child Neurol. 2010;52(1):87–92. [DOI: 10.1111/j.1469-8749.2009.03305.x] [PMID: 19549207]
18. Straathof EJM, Hamer EG, Hensens KJ, La Bastide-van Gemert S, Heineman KR, et al. Development of muscle tone impairments in high-risk infants: associations with cerebral palsy and cystic periventricular leukomalacia. Eur J Paediatr Neurol. 2022;37:12–8. [DOI: 10.1016/j.ejpn.2021.12.015] [PMID: 35007848]
19. Surveillance of Cerebral Palsy in Europe (SCPE). Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2000;42(12):816–24. [DOI: 10.1017/S0012162200001511] [PMID: 11132255]
20. Cai Y, Li X, Zhao X, Song Y, Zhou W. Risk assessment and early prediction of intraventricular hemorrhage in extremely preterm infants. Sci Rep. 2025;15:17346. [DOI: 10.1038/s41598-025-02061-4] [PMID: 40389542]
21. Diwakar RK, Khurana O. Cranial sonography in preterm infants: short review of literature. J Pediatr Neurosci. 2018;13(2):141–9. [DOI: 10.4103/jpn.JPN_60_17] [PMID: 30090126]
22. Ballardini E, Tarocco A, Baldan A, Antoniazzi E, Garani G, Borgna-Pignatti C. Universal cranial ultrasound screening in preterm infants with gestational age 33–36 weeks. Pediatr Neurol. 2014;51(6):790–4. [DOI: 10.1016/j.pediatrneurol.2014.08.012] [PMID: 25456299]
23. Syböck K, Hartmann B, Kirchengast S. Maternal prepregnancy obesity affects foetal growth, birth outcome, mode of delivery, and miscarriage rate in Austrian women. Int J Environ Res Public Health. 2023;20(5):4139. [DOI: 10.3390/ijerph20054139] [PMID: 36901147]
24. Skovgaard AL, Zachariassen G. Cranial ultrasound findings in preterm infants predict the development of cerebral palsy. Dan Med J. 2017;64(2):A5330. [PMID: 28157062]
25. Ploegstra WM, Bos AF, de Vries NK. General movements in healthy full-term infants during the first week after birth. Early Hum Dev. 2014;90(1):55–60. [DOI: 10.1016/j.earlhumdev.2013.10.004] [PMID: 24231002]

Кранијални ултразвук као комплементарна метода процени општих покрета код превремено рођене деце за предвиђање коначног неуролошког исхода – искуство једног центра

Драган Златановић[1,2], Христина Чоловић[1,2], Весна Живковић[1,2], Анита Станковић[1,2], Милица Костић[2], Вук Пејчић[2], Вукота Радовановић[2]

[1]Универзитет у Нишу, Медицински факултет, Катедра за физикалну медицину и рехабилитацију, Ниш, Србија;
[2]Универзитетски клинички центар у Нишу, Клиника за физикалну медицину и рехабилитацију, Ниш, Србија

САЖЕТАК

Увод/Циљ Примена ендокранијалног ултразвука (ЕУЗ) у свакодневној клиничкој пракси представља велики напредак у дијагностици и лечењу новорођенчади. Превремени порођај сматра се фактором ризика за поремећај неуролошког развоја. Циљ студије био је да се процени значај ЕУЗ код превремено рођене деце као комплементарне методе процени општих покрета за предвиђање коначног неуролошког исхода. Студија је била фокусирана на кохорту новорођенчади без значајног неонаталног морбидитета.

Методе Студија је обухватила 160 превремено рођене деце и осмишљена је као проспективна клиничка студија. Статистичка анализа је обухватила налазе ЕУЗ и процену спонтане моторичке активности у првих пет дана након рођења (*writhing* период), перинаталне податке и податке о трудноћи.

Резултати Статистички значајна повезаност постојала је између групе деце код које је церебрална парализа забележена у коначном неуролошком исходу и абнормалних налаза ЕУЗ ($p < 0,001$). Статистички значајно чешћи патолошки ЕУЗ налаз пронађен је код превремено рођене деце пре 30. недеље гестације ($p < 0,001$), новорођенчади рођене царским резом ($p < 0,001$) и оних који су имали Апгар скор мањи од осам у првом и петом минуту након рођења ($p < 0,001$). Специфичност нормалног ЕУЗ је 86%, али се повећава на 100% када се комбинује са нормалним налазом опште моторичке активности код превремено рођене деце.

Закључак Ово истраживање потврђује да ЕУЗ може бити значајна метода за предвиђање неуролошких исхода, може пружити податке за критичку употребу различитих метода праћења превремено рођене деце и може рационализовати њихове прегледе.

Кључне речи: превремено рођена деца; ендокранијални ултразвук; општи покрети; Прехтлова метода; неуроразвојни исход

DOI: https://doi.org/10.2298/SARH240710042L
UDC: 616-001.16-085

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Care of a patient with heat stroke combined with multi-organ failure treated with extracorporeal membrane oxygenation combined with continuous renal replacement therapy

Haiying Li, Lu Yan, Fang Cheng, Jinting Lang, Ying Li
Department of Critical Care Medicine, Jin Cheng People's Hospital

SUMMARY
Introduction Heat stroke (HS) can cause many complications, including acute kidney injury and acute respiratory distress syndrome. To date, the use of extracorporeal membrane oxygenation (ECMO) combined with continuous renal replacement therapy (CRRT) in the treatment of patients with HS and multiple organ failure has not been studied. We describe a patient with HS who was treated for the first time with ECMO combined with CRRT. This case report aims to contribute insights into the clinical management of heat -related illness by disseminating information pertaining to the treatment processes.
Case outline A 34-year-old male patient with HS and multiple organ dysfunction was admitted to the intensive care unit (ICU) for emergency symptomatic treatment. The comprehensive diagnosis encompassed HS, multiple organ dysfunction syndrome, electrolyte imbalance and hypoalbuminemia. The patient's vital signs, including heart rate, blood pressure, respiratory rate and oxygen saturation, were monitored, and ECMO and CRRT life-support therapies were rapidly applied. The patient was successfully weaned off ECMO, CRRT, and mechanical ventilation, and showed stable vital signs; thereafter, he was transferred out of the ICU.
Conclusion This case demonstrates that prompt symptomatic treatment and early ECMO combined with CRRT can effectively treat patients with severe HS. Additionally, it is crucial for healthcare professionals to be vigilant in detecting changes in the patient's vital signs and to collaborate effectively in administering the necessary treatments.
Keywords: heat stroke; acute respiratory distress syndrome; extracorporeal membrane oxygenation; continuous renal replacement therapy; nursing care

INTRODUCTION

Heat stroke (HS) is a clinical syndrome caused by central thermoregulatory dysfunction, characterized by elevated core temperature (> 40°C) due to an imbalance between heat production and heat dissipation following exposure to a hot environment and/or strenuous exercise; the mortality rate is up to 60% in patients with severe HS [1]. Studies have shown that severe complications of HS include rhabdomyolysis, acute kidney injury, disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS) [1]; ARDS is a direct threat to the patient's life.

Patients managed with extracorporeal membrane oxygenation (ECMO) benefit from its ability to provide oxygenation and circulation independently of mechanical ventilation, supporting the patient's respiratory needs while allowing for better management of lung function. When conventional mechanical ventilation cannot meet the oxygenation needs of patients with ARDS, ECMO can be used to replace lung function, meet the body's oxygenation needs, maintain the stability of vital signs and gain time for other treatments [2]. Moreover, continuous renal replacement therapy (CRRT) can reduce the inflammatory response, remove excess fluid, clear toxic metabolites and correct electrolyte and acid–base imbalances, thereby maintaining homeostasis [3, 4]. Although CRRT has been extensively studied for its effectiveness in treating sepsis [5, 6], its potential benefits in HS therapy warrant further exploration.

This report describes the first instance in which ECMO combined with CRRT has been used to treat a patient with HS. Given the acute onset, rapid progression, complexity and difficulty of care associated with HS, ECMO support and CRRT were administered, totaling 161 hours from the second to the ninth day of admission. We present detailed information about the diagnostic and therapeutic processes for HS to provide a theoretical basis and reference for clinical nurses collaborating with physicians in the treatment and care of patients with HS.

CASE REPORT

Case information

On July 3, 2021, a patient with severe HS was admitted to the Department of Critical Care

Received • Примљено: July 10, 2024
Revised • Ревизија: May 22, 2025
Accepted • Прихваћено: May 30, 2025
Online first: June 2, 2025

Correspondence to:
Lu YAN
Department of Critical Care Medicine
Jin Cheng People's Hospital
No. 456 Wenchang East Street
Jincheng Urban District
Shanxi Province 048000
China
yanlu_ll@163.com

Medicine of our hospital with the primary complaint of 'fever and fatigue for two days and unconsciousness for two hours after working in high temperature.' The patient had a body temperature of 40°C with multiple organ dysfunction and was diagnosed with HS, multiple organ dysfunction syndrome, electrolyte disorder, and hypoproteinemia. The patient's respiratory rate was 18/minute, blood pressure was 77/39 mmHg, oxygen saturation (SpO_2) was 97%, and blood glucose was 1.2 mmol/L. On the day of admission, the patient's condition worsened further, with sudden loss of consciousness, generalized convulsions, airway spasms and continuous decrease in oxygen saturation. The patient's laboratory results showed a blood creatinine of 420.25 μmol/L, blood urea nitrogen of 29.63 mmol/L, alanine aminotransferase of 147.74 U/L, and total bilirubin of 82.47 μmol/L.

Therapeutic measure

Upon admission, emergency endotracheal intubation and mechanical ventilation were performed to assist with breathing and to ensure that the patient had an adequate oxygen supply (respiratory rate of 8–20 breaths/minute). Simultaneously, symptomatic treatments – such as organ-function protection, maintenance of internal-environment stability, early enteral nutrition using a short-peptide enteral-nutrition suspension via nasogastric tube at 50 mL/hour and parenteral nutrition including intravenous amino acids, multivitamins, and fat emulsions – were administered (enteral-nutrition-solution composition: 38 g of protein, 34 g of fat, 138 g of carbohydrates, 0.26 g of vitamins, and 4.24 g of trace elements per 1000 mL. Calorie density was 2.4 kcal/mL, 2000 mL required daily, total calories ≈ 4800 kcal. Daily amino-acid supplementation 3–5 g/kg, fat-emulsion supplementation 10–20%). Probiotics (*Bacillus subtilis*, 0.5 g TID) and itopride hydrochloride (50 mg TID) were administered to regulate intestinal flora [7]. Sedation was achieved with remifentanil 160 μg/hour and midazolam 5 mg/hour, with dosages adjusted as needed. Blood microbiological analyses were followed by anti-infective therapy including piperacillin–tazobactam (initially 3.75 g Q8h, then 4.5 g Q8h), cefoperazone–sulbactam 4.5 g Q8h, and minocycline 100 mg Q12h, guided by procalcitonin levels. Dopamine 1–5 μg/kg·min and norepinephrine 0.1–2 μg/kg·min were used as needed to stabilize hemodynamics. Measures such as a hypothermia-treatment device, warm-water bath (preventing hypothermia while managing the patient's elevated temperature) and ice-saline enema were employed to control body temperature.

Rapid cooling is a key factor in HS treatment. Upon admission, the patient's rectal temperature was 40.2°C. Immediately, an ice-blanket hypothermia-treatment device was used (water 4–10°C) while continuous surface-temperature monitoring was performed via thermocouple. Additionally, a 40% alcohol sponge bath was applied. However, after one hour, these cooling methods reduced the surface temperature only to 38.8°C, while rectal temperature remained at 40°C. Therefore, 4°C saline was infused for rehydration and 4°C enema fluid was used. One hour later, rectal temperature was 39.8°C, but cooling was still unsatisfactory. To achieve better core-temperature reduction, we initiated CRRT. After right femoral vein catheterization, continuous venovenous hemodialysis started. Replacement fluid (10°C) ran at 150 mL/hour blood-flow and 2000 mL/hour of replacement-fluid with zero fluid removal. After three hours, rectal temperature fell to 38.3°C and surface temperature to 37.5°C. To prevent excessive cooling and arrhythmias, replacement fluid at room temperature was then used.

Subsequently, the patient developed severe electrolyte imbalances (potassium 3.07 mmol/L, sodium 127.7 mmol/L, calcium 1.67 mmol/L). Continuous blood purification was therefore continued to reinforce temperature control and maintain internal environment stability. Routine monitoring (vital signs, respiratory function, hemodynamics, etc.) was maintained, and nurses observed cerebral oxygen supply. On the second day, the patient's condition deteriorated further: blood pressure remained unstable and cardiopulmonary function was severely impaired, causing hypoxemia. Therefore, ECMO was used to support heart and lung function via extracorporeal circulation, improving oxygenation and maintaining organ perfusion. A venovenous ECMO (VV ECMO) mode was selected, and intravenous heparin was continued for anticoagulation. To avoid local bleeding or hematoma from frequent puncture, an arterial catheter was placed in the right radial artery before systemic heparinization, providing real-time hemodynamic monitoring and easy blood sampling; a peripheral venous needle was left in the left upper limb for transfusion. During ECMO, D-dimer was checked every six hours; the results are shown in Figure 1.

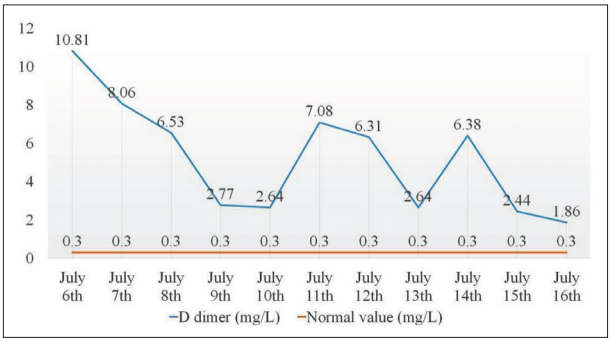


Figure 1. Changes of D dimer in the patient

Between day 2 and day 9, 161 hours of ECMO life support were performed, during which the ECMO flow rate was 3.4 L/min, and the centrifugal pump speed was 3500 rpm. Continuous renal replacement therapy was initiated using a high-flux filter to remove excess fluid, metabolic waste, toxins and inflammatory mediators, correct electrolyte imbalances and support renal recovery. The CRRT was performed continuously during the ECMO support using a Prismaflex system (Baxter International Inc., Deerfield, IL, USA) with an AN69ST filter. Anticoagulation was maintained with unfractionated heparin to ensure extracorporeal circuit patency. Specific CRRT parameters included a blood flow rate of 150–200 mL/min, dialysate flow of

Table 1. Changes in the patient's temperature and management measures

Time	4:20	7:00	11:00	15:00	19:00	23:00	3:00	7:00	11:00	19:00	19:00	23:00
Body surface temperature (°C)	40	38.8	37.4	37.5	37.2	36.3	37.5	35.9	35.2	35.5	36.2	36
Anal temperature (°C)	40.2	40	38.7	38.3	37.9	38.1	38	36.3	35.5	36.1	36.3	36.2
Cooling measures	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB	MHT-IB
	-	-	-	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT	CRRT
	WWSB	ASB	ASB	-	-	-	-	-	ECMO	ECMO	ECMO	ECMO

MHT-IB – use mild hypothermia therapeutic instrument (ice blanket); WWSB – warm-water sponge bath; ASB – alcohol sponge bath

Table 2. Changes of brain natriuretic peptide in the patient

Day	Brain natriuretic peptide (pg/ml)	D dimer (mg/L)	White blood cell ($\times 10^9$/L)	Myoglobin (μg/L)	Creatinine (mg/dL)	C-reactive protein (mg/L)
1	604	10.81	9.39	19.34	10.3	17.6
2	1075.9	8.06	-		-	-
3	498	6.53	-		-	-
4	352.4	2.77	8.61	8.46	8.7	15.3
5	232.2	2.64	-		-	-
6	293.1	7.08	-		-	-
7	246	6.31	7.45	5.07	6.4	12.6
8	193.4	2.64	-		-	-
9	160.6	6.38	-		-	-
10	170.1	2.44	-		-	-
11	112	1.86	7.13	3.9	5	8.7

1000 mL/hour and replacement fluid at 500 mL/hour. Coagulation profiles and electrolyte levels were closely monitored throughout the treatment period to optimize therapeutic efficacy and patient safety. After a series of treatments, when hemodynamic parameters demonstrated stability and there was effective oxygenation and efficient carbon dioxide removal, the ECMO and CRRT were successfully removed on day 9, and the patient was successfully transferred out of the intensive care unit (ICU) on day 15. The detailed laboratory parameters, metabolic indicators, inflammation markers, and myoglobin levels, along with their trends over time during the patient's treatment, are summarized and presented in Tables 1, 2, and 3.

Ethics: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

DISCUSSION

This report describes a case of severe HS treated in our ICU. Because conventional treatments, such as assisted ventilation, CRRT and hypothermia therapy, were unable to control the condition, the ECMO rescue plan was immediately initiated. Due to the patient's underlying conditions, which included hepatitis B and coagulopathy, the treatment and care of the patient posed significant challenges. Through meticulous treatment and nursing care, the patient's condition was successfully stabilized from a critical state. Rapid cooling and organ support have been effective strategies for treating HS, but mortality is high. In one study, the HS mortality within 28 days after a heat wave was as high as 58% [8]. Ni et al. [9] reviewed 138 HS patients admitted over the previous seven years who presented with systemic multiple-organ dysfunction. Significant improvement was seen with hyperbaric oxygen therapy, with mortality rates of 0% and 8.49% in the hyperbaric and control groups, respectively. Elbashir et al. [10] also found in the treatment of patients ranging from heat stroke to multi-organ failure that the patients were gradually stabilized through 18 days in the ICU. In this case, the patient's condition progressed rapidly, and ventilator-assisted breathing and high-dose vasoactive drugs could not maintain the stability of his vital signs. In this emergency, ECMO was used to rapidly capture key changes in the patient's vital signs at each stage of the condition's development; important condition information was fed back to the doctor to provide the basis for the next treatment [11]. Brain tissue hypoxia is one of the main characteristics of heat-related illness [12]. Therefore, based on routine monitoring (vital signs, respiratory function, hemodynamics, etc.), nurses monitored the cerebral oxygen supply at the same time, allowing them to apply the corresponding treatment. Moreover, in the context of

Table 3. The change of procalcitonin and the dosage of antibiotics in this patient

Day	1	2	3	4	5	6	7	8	9	10	11
Procalcitonin	21.59	16.51	19.92	19.99	15.6	12.3	7.68	5.04	4.87	3.32	2.02
Antibiotic	PST[1] 3.75 g Q8h	PST 3.75 g Q8h	PST 3.75 g Q8h	PST 3.75 g Q8h	PST 3.75 g Q8h	PST 3.75 g Q8h	-	-	-	-	-
	-	-	-	-	-	-	PST 4.5g Q8h	PST 4.5g Q8h	PST 4.5g Q8h	-	-
	-	-	-	-	-	-	-	-	-	CPSB 4.5g Q8h	CPSB 4.5g Q8h

PST – piperacillin sodium and tazobactam sodium; CPSB – cefoperazone and sulbactam

CRRT, precise ultrafiltration proves beneficial in mitigating organ oedema and alleviating cardiac overload. A study treating 16 patients with HS reported improved hemodynamics, reduced serum-enzyme concentrations and zero mortality [13]. The study by Ni et al. [9] demonstrated that HS-related parameters exhibited a significant reduction in the CRRT group compared with the control group. These findings suggest that CRRT effectively eliminates serum enzymes and metabolic by-products, interrupts the cascade of inflammatory mediators and mitigates metabolite-induced damage to renal tubules. Importantly, there was a significantly lower mortality rate in the CRRT group than in the control group. Consequently, early initiation of CRRT therapy should be considered for patients with HS, particularly as HS carries a high mortality risk in its advanced stages, especially when associated with DIC. In conclusion, reviewing the whole rescue process, rapid hypothermia, strict condition observation, timely initiation of ECMO life support, appropriate anticoagulation strategy, refined volume management and strict infection prevention and control ensured the smooth progress of all treatments and brought the patient to safety. This patient presented with a sudden onset, rapid progression and complex condition, making the nursing care extremely challenging. Nurses played a crucial role in the implementation of cooling measures, close monitoring of vital signs, ECMO management and CRRT administration, all of which were key aspects of the life-saving treatment.

Conflict of interest: None declared.

REFERENCES

1. Zhang Z, Wu X, Zou Z, Shen M, Liu Q, Zhangsun Z, et al. Heat stroke: pathogenesis, diagnosis, and current treatment. Ageing Res Rev. 2024;100:102409. Epub ahead of print. [DOI: 10.1016/j.arr.2024.102409] [PMID: 38986844]
2. Levin NM, Ciullo AL, Overton S, Mitchell N, Skidmore CR, Tonna JE. Characteristics of patients managed without positive-pressure ventilation while on extracorporeal membrane oxygenation for acute respiratory distress syndrome. J Clin Med. 2021;10(2):251. [DOI: 10.3390/jcm10020251] [PMID: 33445504]
3. Miller MK, Spiller RE, Mount CA, Colombo C, Khayat MI. Novel use of Seraph-100™ blood purification therapy in heat stroke. Mil Med. 2023;188(1–2):407–9. [DOI: 10.1093/milmed/usac124] [PMID: 35569924]
4. Ronco C, Reis T. Continuous renal replacement therapy and extended indications. Semin Dial. 2021;34(6):550–60. [DOI: 10.1111/sdi.12963] [PMID: 33711166]
5. Kühn D, Metz C, Seiler F, Wehrfritz H, Roth S, Alqudrah M, et al. Antibiotic therapeutic drug monitoring in intensive-care patients treated with different modalities of extracorporeal membrane oxygenation and renal replacement therapy: a prospective observational single-center study. Crit Care. 2020;24(1):664. [DOI: 10.1186/s13054-020-03397-1] [PMID: 33239110]
6. Zhu CY, Pan AJ, Mei Q, Chen T. Successful cure of a patient with urosepsis using a combination of extracorporeal membrane oxygenation and continuous renal replacement therapy: case report and literature review. Chin J Traumatol. 2020;23(6):372–5. [DOI: 10.1016/j.cjtee.2020.09.006] [PMID: 33039249]
7. Yang W, Qin K, Zheng X. Pharmacological supervision of nutritional support therapy. Beijing: People's Health Publishing House; 2022. p. 345.
8. Wang L, Jiang D, Zhang Y, Shen J, Chen Z, Jia H, et al. The diagnostic significance of combined detection of serum indicators for severe heatstroke: analysis of clinical data of 70 patients. Occup Health Emerg Rescue. 2022;40(2):180–6. [DOI: 10.16369/j.oher.issn.1007-1326.22.02.011]
9. Ni XX, He NB, Guo YQ, Dou YX, Xie XJ, Liu ZF. Effect of hyperbaric oxygen treatment on patients with heatstroke complicated by multiple organ dysfunction: a retrospective study. Heliyon. 2024;10(6):e28139. [DOI: 10.1016/j.heliyon.2024.e28139] [PMID: 38545173]
10. Elbashir H, Saeed L, Sabir D, Morgom M, Abuazab Y, Madebo T, et al. From heat stroke to multi-organ failure: a survivor's case report. Cureus. 2023;15(11):e48984. [DOI: 10.7759/cureus.48984] [PMID: 38111401]
11. Hayes K, Hodgson CL, Webb MJ, Romero L, Holland AE. Rehabilitation of adult patients on extracorporeal membrane oxygenation: a scoping review. Aust Crit Care. 2022;35(5):575–82. [DOI: 10.1016/j.aucc.2021.08.009] [PMID: 34711492]
12. Wang Z, Zhu J, Zhang D, Lv J, Wu L, Liu Z. The significant mechanism and treatments of cell death in heatstroke. Apoptosis. 2024;29(7–8):967–80. [DOI: 10.1007/s10495-024-01979-w] [PMID: 38886312]
13. Huang Y, Long L, Huang Q, Wang Q, Jin K, Ju T, et al. Observation on the efficacy of continuous veno-venous hemodiafiltration combined with hemoperfusion HA380 in the treatment of heat stroke with multiple organ dysfunction syndrome. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2024;36(5):532–7. [DOI: 10.3760/cma.j.cn121430-20230728-00561] [PMID: 38845502]

Нега болесника са топлотним ударом удруженим са мултиорганском инсуфицијенцијом леченим екстракорпоралном мембранском оксигенацијом уз континуирану реналну заменску терапију

Хајинг Ли, Лу Јан, Фанг Ченг, Ђинтинг Ланг, Јинг Ли

Народна болница у Ђинченгу, Одељење за интензивну медицину, Ђинченг, Шанси, Кина

САЖЕТАК

Увод Топлотни удар (ТУ) може изазвати бројне компликације, укључујући акутно оштећење бубрега и синдром акутног респираторног дистреса. До сада није проучавана примена екстракорпоралне мембранске оксигенације (ЕКМО) у комбинацији са континуираном реналном заменском терапијом (*CRRT*) у лечењу болесника са ТУ и вишеструком дисфункцијом органа. У овом раду је описан први случај болесника са ТУ који је лечен применом ЕКМО удруженог са *CRRT*-ом, са циљем да се пружи увид у клиничко збрињавање топлотних обољења путем детаљног приказа терапијских поступака.

Приказ болесника Мушкарац стар 34 године, са ТУ и мултиорганском дисфункцијом, примљен је на одељење интензивне неге ради симптоматске реанимације. Дијагноза је обухватила ТУ, синдром мултиорганске дисфункције, дисбаланс електролита и хипоалбуминемију. Пажљиво су праћене виталне функције болесника – срчана фреквенција, крвни притисак, респираторна фреквенција и засићење крви кисеоником, а животно потпорне терапије ЕКМО и *CRRT* примењене су без одлагања. Болесник је успешно одвојен од ЕКМО, *CRRT*-а и механичке вентилације, уз стабилне виталне знакове, а потом пребачен из Јединице интензивне неге.

Закључак Овај случај показује да правовремена симптоматска терапија и рано увођење ЕКМО у комбинацији са *CRRT*-ом могу ефикасно да лече тешке форме ТУ. Такође је од кључне важности да здравствени радници будно прате промене виталних параметара болесника и сарађују у спровођењу неопходних терапијских мера.

Кључне речи: топлотни удар; синдром акутног респираторног дистреса; екстракорпорална мембранска оксигенација; континуирана ренална заменска терапија; нега болесника

DOI: https://doi.org/10.2298/SARH240822036S
UDC: 616.24-002-02

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Cryptogenic organizing pneumonia – wrongfully neglected disease

Ivana Sekulović Radovanović[1], Filip Marković[1], Mihailo Stjepanović[1,2], Nikola Čolić[2,3], Dragana Marić[1,2,]

[1]University Clinical Center of Serbia, Clinic for Pulmonology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Center for Radiology and Magnetic Resonance Imaging, Belgrade, Serbia

SUMMARY
Introduction Cryptogenic organizing pneumonia (COP) is a type of organizing pneumonia with an unknown primary etiology. Diagnosis of COP requires exclusion of any other possible cause. The disease manifests with nonspecific symptoms and clinical findings resembling respiratory infection. Diagnosis of COP should be considered after the radiographic signs of pneumonia persist despite applied therapy, or show a migratory pattern. Due to a diverse differential diagnostic palette, establishing the correct diagnosis is often delayed, resulting in delayed administration of adequate therapy.
Outlines of cases In this paper, we present three female patients diagnosed with COP in our clinic. We outline all challenges in the diagnostic pathways, from managing initial symptoms, through all necessary laboratory tests and diagnostic procedures, to establishing the diagnosis and starting treatment. After presenting radiological findings before and after starting corticosteroid treatment, we also reevaluated the clinical response to the administered treatment initially and during the subsequent follow-up period.
Conclusion To diagnose COP, we must first remind ourselves to consider it when treating patients with recurrent pneumonia. When COP is finally diagnosed, the quality of life of these patients improves, as this avoids excessive antimicrobial therapy and repeated hospitalizations. A multidisciplinary approach is needed, both in diagnosing and treating patients, owing to comorbidities and the need to exclude any other potential cause of organizing pneumonia. Corticosteroid treatment provides rapid resolution of symptoms followed by long remission periods.
Keywords: cryptogenic organizing pneumonia; diagnosis; differential diagnosis

INTRODUCTION

Cryptogenic organizing pneumonia (COP) is an idiopathic form of organizing pneumonia, formerly called bronchiolitis obliterans organizing pneumonia. It is a type of diffuse interstitial lung disease that affects distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar walls without disrupting lung architecture. Apart from the cryptogenic form, secondary organizing pneumonia is an organizing pneumonia with known triggering factors and is mainly caused by connective-tissue diseases, autoimmune diseases, infections, malignancies, and drug exposure, with an increasing prevalence related to new biological therapies, interferons, and monoclonal antibodies [1, 2, 3]. To diagnose COP, clinicians must first identify organizing pneumonia and then exclude every possible cause [1].

COP commonly presents with a relatively short duration (up to two months) of pseudo-flu-like symptoms, persistent non-productive cough, dyspnea, fever, malaise, weight loss, and chest pain [1, 2, 4]. Physical examination can show normal pulmonary findings in one-quarter of patients [5]. Chest radiograph and computed-tomography manifestations of COP commonly appear as peripheral bilateral consolidations or ground-glass opacities, with a tendency to recur and to migrate [6]. There are no laboratory tests specific for COP, but results may show leukocytosis and elevated levels of C-reactive protein (CRP) and erythrocyte-sedimentation rate [2, 7]. Treatment for COP requires prolonged administration of corticosteroids. The initial dose depends on the disease severity, clinical symptoms, potential progression, and radiological findings [2, 4]. When treated with corticosteroids, recovery with complete clinical and physiologic improvement and normalization of chest radiographs is found in two-thirds of patients [1].

We present three cases of COP diagnosed and treated at the Clinic for Pulmonology, University Clinical Center of Serbia, in the previous three years.

REPORTS OF CASES

Case No. 1

A female patient, 52 years old, was repeatedly hospitalized in a regional secondary medical center over five months under the diagnosis of pneumonia, presenting with high fever, fatigue, chest pain, and generalized myalgia. She was a former smoker with known chronic illnesses and therapy for diabetes mellitus and

Received • Примљено: August 22, 2024
Revised • Ревизија: May 11, 2025
Accepted • Прихваћено: May 13, 2025
Online first: May 14, 2025

Correspondence to:
Ivana SEKULOVIĆ RADOVANOVIĆ
Clinic for Pulmonology
University Clinical Center of Serbia
Koste Todorovića 26
11000 Belgrade, Serbia
ivanasekulovic@yahoo.com

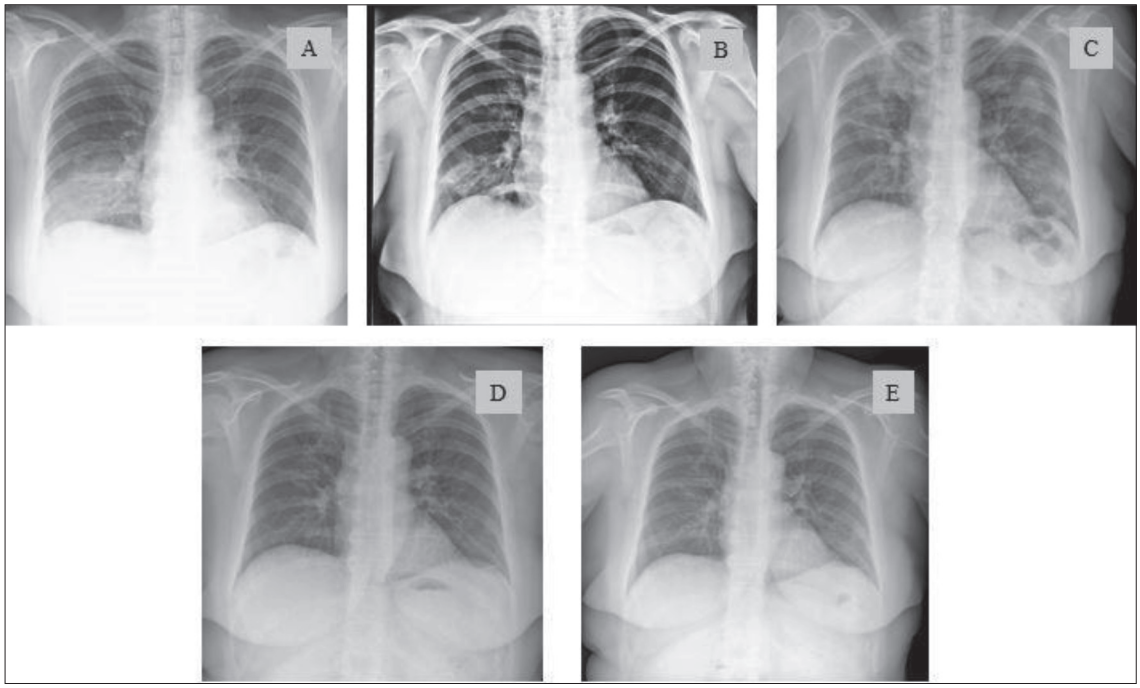


Figure 1. Chest radiographs from Case No. 1 patient chronologically, from the first manifestation of the disease during the first hospitalization at the regional medical center (RMC) (A), after initial empiric antibiotics treatment at RMC (B), when admitted to our clinic due to developing deterioration of the general condition (C), 10 days after initial corticosteroid treatment (D), and on the second follow-up after hospital discharge (E)

arterial hypertension. Her symptoms were accompanied by CRP levels up to 220 mg/L and chest-radiograph findings of lung-parenchyma consolidations at different sites. Each time she was treated with empiric parenteral antibiotics and corticosteroids, resulting in almost complete radiographic regression and lowered CRP levels. No infectious agents were detected in serum or sputum. After each discharge, she gradually redeveloped the symptoms, with escalating myalgia and fatigue. During a prehospital ambulatory episode, a chest CT showed a 70 × 60 mm irregular consolidation of the right upper lobe with a negative bronchus sign and several smaller consolidations of the left lower lobe. After significant clinical deterioration of general condition followed by dyspnea and fever of 38.3°C, she was referred to our institution. Laboratory findings at the beginning of hospitalization showed elevated level of CRP (107 mg/L) and leukocytes (12.2×10^9/L), with slight predominance of neutrophils in the leukocytic formula (7.7×10^9/L) and normal levels of eosinophils. Physical examination showed normal pulmonary findings.

During hospitalization at our clinic various diagnostic procedures and tests were performed. Immunology testing excluded autoimmune diseases, including myositis, systemic connective-tissue disease, and vasculitis (negative ANA-Hep-2, ANCA, normal creatine kinase). Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL) showed normal endoscopic findings. Tuberculosis was excluded by negative microscopy and Löwenstein cultures of sputum and fiber-aspirate (FA). Additional tests of blood, FA, and sputum excluded fungal, bacterial, and viral infective agents.

By analyzing cytology of BAL, the pathologist concluded that, with elevated percentage presentation of macrophages (half of them were foamy macrophages), lymphocytosis 30% with CD4/CD8 lymphocytes ratio of 0.3, and 10% of neutrophils, findings support the diagnosis of COP. Pathohistology of transbronchial biopsy was inconclusive for interpretation due to the small tissue sample.

A radiologist performed additional interpretation of chest CT scan and concluded that consolidations by appearance and distribution, considering the migratory effect, are suggestive of COP.

During the hospitalization at our clinic, the patient was treated initially with empiric parenteral antibiotics in accordance with the established guidelines for community-acquired pneumonia (CAP), taking into consideration the patient's clinical status, risk factors, and local epidemiology. Control laboratory tests showed lower CRP but control chest radiograph showed progression in the size of lung consolidation and developing new lesions. The administration of antibiotics was discontinued, and after excluding all potential causes of bilateral progressive consolidations of the lung, continuous corticosteroid therapy was initiated on June 7, 2024. Firstly, parenteral administration of methylprednisolone at a dose of 60 mg/day was performed. The patient showed significant improvement in general condition, followed by absence of high body temperature and dyspnoea. Control chest radiograph showed almost complete regression of previously visualized lesions (Figure 1). With control laboratory tests showing a CRP level of 14.5 mg/L, the patient was discharged from clinic and continued corticosteroid therapy in tablet form (60 mg/day of prednisone).

At the first follow-up visit two weeks after discharge from our hospital, with control chest radiograph showing complete regression, the dose of prednisone was lowered

to 40 mg/day, and, due to the previously known condition of diabetes mellitus as a comorbidity, the patient was referred to an endocrinologist in case of need for correction of doses of metformin, due to known effects of corticosteroids on serum glucose levels. In the next follow-up control six weeks after the first one, another de-escalation of the dose of prednisone was done, lowered to 30 mg/day. The patient was under regular follow-ups by a pulmonologist at intervals of 6–8 weeks. Follow-up chest radiographs were performed, and corticosteroid therapy was gradually tapered. On February 19, 2025, based on comprehensive clinical assessment, corticosteroids were discontinued, and a subsequent follow-up was scheduled in six months.

Case No. 2

Female patient, 63 years old, was in the period of eight months several times hospitalized in a regionally affiliated secondary medical center due to high fever, elevated CRP levels, and chest radiographic signs of repeated bilateral pneumonia. With no other comorbidities than periodical episodes of vertigo, each time she was treated with empiric antibiotic therapy in accordance with the established guidelines for CAP, resulting only in lowering the levels of CRP and body temperature, without complete radiographic regression. Three CT chest scans were performed during that period, showing only consolidations with ground-glass opacifications. She was admitted to our clinic with high fever and bilateral lung consolidations (described this time in the left lobe and right lower lobe) verified by the latest CT chest scan. CRP level was 44.2 mg/L, immunology tests were all negative. Bronchoscopy was performed, finding only endoscopic signs of inflammation (hyperemic mucosa of the tracheo-bronchial tree with pus, dominantly in the left lower lobe). Results of cytological and microbe analysis of the FA of bronchi were nonspecific (classic BAL was not performed). Radiologist performed additional interpretation of all three CT scans. Because of the nature of described irregular, organizing consolidations with dominantly migrating effect, refractory to any other applied treatment, we suspected the presence of COP. After the numerous laboratory and invasive diagnostics were performed, excluding any autoimmune or systemic and soft-tissue disease, malignant or infectious etiology of described consolidations, we started treatment with oral corticosteroids. Continuous parenteral corticosteroid therapy was initiated on 22 October 2022, starting with a 40 mg dose of methylprednisolone. The first follow-up was two weeks after hospital discharge, when the first de-escalation of dose of corticosteroids was done (from 40 mg to 30 mg of prednisone). At the time of first control after the discharge from our clinic, control chest radiograph showed complete regression of previously registered consolidations, followed by normal levels of CRP (Figure 2). She was treated with oral corticosteroids in de-escalating doses for seven months, without signs of relapse of the disease. After the corticosteroid treatment was stopped in May 2023, the patient still showed no signs of disease relapse in the total period of two years; she is regularly scheduled for annual check-ups.

Case No. 3

Female patient, 74 years old, with symptoms of prolonged pain in body joints and high body temperature up to 38.3°C, high level of CRP (175 mg/L) and radiographic signs of bilateral pneumonia, started oral antibiotics treatment (cefixime, levofloxacin) suggested by her physician. After developing shortness of breath and extreme fatigue, elevation of CRP level to 257 mg/L, registered low blood-oxygen level and progression of radiological findings, she was admitted to our clinic, where she was treated with parenteral antibiotics (meropenem, levofloxacin). The patient showed clinical improvement after the treatment. CT chest scan after finished antibiotics treatment showed presence of bilateral consolidation of lung in lower lobes and upper right lobe with lesions of interstitium of the lung. She was discharged, and scheduled for pulmonologist control in two months with control chest CT scan. Bronchoscopy was advised, but was never conducted as the patient refused the proposed diagnostic procedure.

In the following period, due to repeated joint pains, followed by high fever of up to 40°C, and again elevated CRP level to 170 mg/L, the patient was admitted to the Institute for Rheumatology, where she was treated with parenteral empiric antibiotic therapy in accordance with

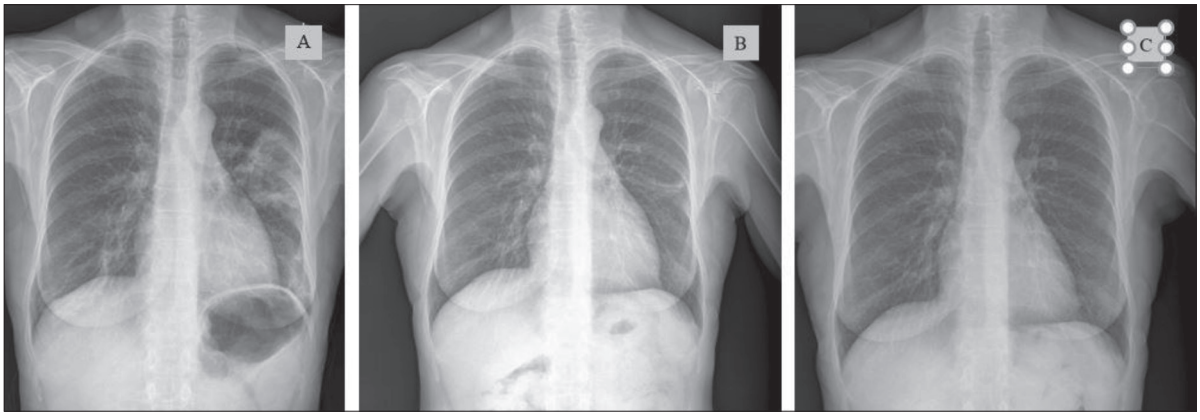


Figure 2. Chest radiographs from patient Case No. 2, before administering corticosteroid therapy (A), one month after corticosteroid treatment started (B), and one year after starting treatment of COP (C)

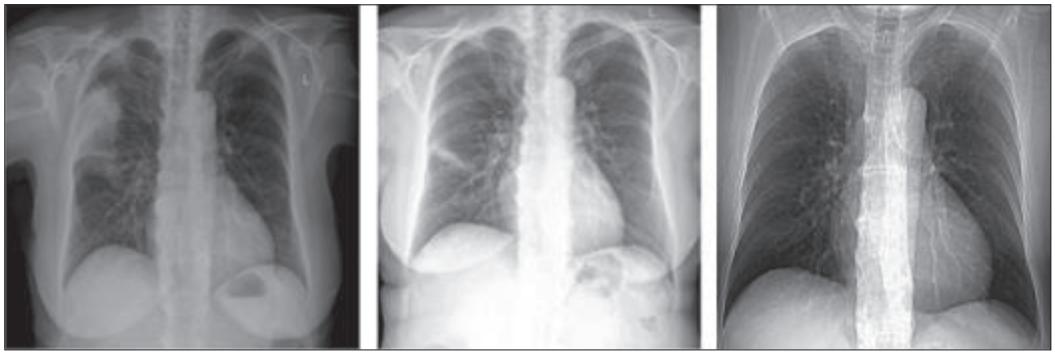


Figure 3. Chest radiographs of Case No. 3 patient, before (on the left), one month after starting corticosteroid therapy (in the middle), and on the annual follow up control (on the right)

the established guidelines for CAP. After numerous laboratory tests, arthritis and other soft-tissue diseases were excluded. During the beginning of that hospitalization, control chest CT scan was performed, describing previously detected lung lesions/consolidations still present. After several days of hospitalization, treatment with corticosteroid therapy was introduced in February 2022 (deflazacort, 30 mg/day), and with clinical improvement she was discharged from the Clinic with gradually de-escalating oral doses of corticosteroids (deflazacort).

Considering the persistency of CT findings, during the next follow-up control by her pulmonologist, a radiologist was consulted and both previously performed CT scans were compared. The radiologist concluded that CT findings were highly suggestive of COP.

After considering all clinical manifestations and improvements, both clinical and in general condition, developed after the initiation of corticosteroids into treatment, she was diagnosed with COP (Figure 3). She continued oral corticosteroid therapy as previously advised. During the next follow-up period she had one relapse of the disease two months after the diagnosis of COP was made, which was regulated in short-term elevation of corticosteroid dose (the dose of deflazacort was increased to 45 mg in total duration of eight weeks). After remission, the dose of deflazacort was gradually tapered to the maintenance dose of 7.5 mg per day, and in the following year when she attended regularly follow-up appointments with the pulmonologist, she experienced no relapses of the disease.

Ethics: The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved. Written consent to publish all shown material was obtained from the patients.

DISCUSSION

Regarding all presented cases, all cases showed a significant time delay in making the right diagnosis. With a clinical presentation of infective disease, minimal respiratory symptoms but alarming radiological signs, it can be easily misleading to suspect yet another common case or pneumonia caused by infective agents. In our experience, patients underwent, on average, three hospitalizations until making the right diagnosis, not including the time between hospitalizations when they were treated as ambulatory patients with antibiotics. Repeated hospitalizations with intensive medication treatment resulting in a lack of expected response can harm patients' quality of life in many ways.

Not suspecting COP in patients with progressive migratory lung lesions followed by deterioration of general condition can result in the rapid administration of broad-spectrum antibiotics (including reserve antibiotics) or antifungal medications. Uncritical widespread use of antibiotics can cause antimicrobial resistance, especially by using reserve antibiotics [8]. Prolonged antibiotic exposure is also a major risk factor for *Clostridioides difficile* infection, as it reduces the population of non-pathogenic anaerobes that normally inhabit the gut, thereby allowing *C. difficile* to proliferate [9]. A patient with COP and a potential *C. difficile* infection who is scheduled to begin corticosteroid therapy, which suppresses the general immune response, is at increased risk of developing severe gastrointestinal complications, as immunosuppression may exacerbate the course of the infection.

It is crucial to emphasize the importance of a clinical and systematic approach to the problem, with a well-organized algorithm in the process of excluding differential diagnoses. This is often impracticable in many hospitals and healthcare centers due to insufficient availability of invasive diagnostics and laboratory and immunology tests.

The current diagnostic algorithm for COP includes histopathological confirmation of the disease. Although opinions vary, invasive diagnostic procedures are generally recommended in cases of unclear clinical or radiological presentation, or when there is an inadequate response to initial therapy. Surgical lung biopsy is necessary to establish a diagnosis when vasculitides are part of the differential diagnosis. However, histopathological confirmation of organizing pneumonia alone should not be considered a sufficient criterion for diagnosis [10, 11].

In our cases, two of the three patients had bronchoscopy, but only one showed confirmation of the disease by analyzing the BAL. Analyzing the FA of the bronchi to exclude infectious disease is also very important. When resources are scarce, it is not always necessary to conduct

invasive diagnostics, but it is preferable, considering the wide differential-diagnosis palette.

Clinical improvement is typically observed within 24–72 hours after the initiation of corticosteroid therapy in responsive patients, often manifesting as reduced symptoms and improved overall condition. Complete remission is generally confirmed after approximately three months [4].

When initiating corticosteroid therapy, consider possible risks of cumulative steroid dosage and side effects of prolonged therapy and refer patients to other subspecialties. At the beginning of treatment, patients need frequent follow-up controls, due to possible side effects of the therapy and the disease's potential for relapses, which would require correction of medication doses. Routine follow-up with chest radiographs and pulmonary function tests every two–three months is recommended during corticosteroid treatment [12].

Most relapses occur within the first year of treatment, often upon tapering or discontinuation of corticosteroids. Relapses typically respond well to corticosteroids. In the management of disease relapse, one study showed no difference in clinical outcomes between increasing prednisone to 20 mg/day versus higher doses, while higher doses were associated with more side effects. Reinitiating treatment at 20 mg/day with gradual tapering is suggested to be the most adequate approach [4, 13].

A recent retrospective observational study on clinical outcomes in COP patients aimed to identify predictors of relapse by comparing those who showed clinical improvement with those who did not. Elevated serum Krebs-von-den-Lungen-6 levels and chest CT findings indicative of pulmonary fibrosis were associated with poor clinical response. In contrast, markers of systemic inflammation, such as elevated CRP, increased neutrophil percentage, and decreased lymphocyte percentage, were linked to a shorter time to the first relapse among patients who initially responded to treatment [14].

The presence of nonspecific symptoms and radiologic features that mimic other pulmonary diseases complicates the diagnostic process so a multidisciplinary approach (considering radiologists, immunologists, allergologists) is necessary to exclude any known factors that can cause organizing pneumonia [15]. A multidisciplinary approach is also needed in managing potential negative effects of prolonged corticosteroid therapy in patients with comorbidities like diabetes mellitus, osteoporosis, arterial hypertension.

Our cases are examples that COP is often a wrongfully neglected disease, insufficiently considered as a possible diagnosis. Suspecting the presence of COP is the first step in the diagnostic process. With the right diagnostic algorithm that excludes any other cause and at the same time exhibits a characteristic CT pattern, once diagnosed, it is easily treated, resulting in complete regression and long remissions. Hence, it is important to always consider COP when treating a patient with migratory lung lesions, clinically resembling bacterial pneumonia.

Conflict of interest: None declared.

REFERENCES

1. Cordier JF. Cryptogenic organising pneumonia. Eur Respir J. 2006;28(2):422–46. [DOI: 10.1183/09031936.06.00013505] [PMID: 16880372]
2. King TE Jr, Lee JS. Cryptogenic Organizing Pneumonia. N Engl J Med. 2022;386(11):1058–69. [DOI: 10.1056/NEJMra2116777] [PMID: 35294814]
3. Radzikowska E, Fijolek J. Update on cryptogenic organizing pneumonia. Front Med (Lausanne). 2023;10:1146782. [DOI: 10.3389/fmed.2023.1146782] [PMID: 37153105]
4. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia: characteristics of relapses in a series of 48 patients. Am J Respir Crit Care Med. 2000;162(2 Pt 1):571–7. [DOI: 10.1164/ajrccm.162.2.9909015] [PMID: 10934089]
5. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med. 1985;312(3):152–8. [DOI: 10.1056/NEJM198501173120304] [PMID: 3965933]
6. Tiralongo F, Palermo M, Distefano G, Vancheri A, Sambataro G, Torrisi SE, et al. Cryptogenic organizing pneumonia: evolution of morphological patterns assessed by HRCT. Diagnostics (Basel). 2020;10(5):262. [DOI: 10.3390/diagnostics10050262] [PMID: 32365469]
7. Marwah V, Peter DK, Sharma N, Bhattacharjee S, Hegde A, Shelly D, et al. Clinico-etiological characteristics of organizing pneumonia: a retrospective study. Lung India. 2021;38(2):144–8. [DOI: 10.4103/lungindia.lungindia_105_20] [PMID: 33687008]
8. Maki G, Zervos M. Health care-acquired infections in low- and middle-income countries and the role of infection prevention and control. Infect Dis Clin North Am. 2021;35(3):827–39. [DOI: 10.1016/j.idc.2021.04.014] [PMID: 34362546]
9. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. Nat Rev Dis Primers. 2016;2:16020. [DOI: 10.1038/nrdp.2016.20] [PMID: 27158839]
10. Raghu G, Meyer KC. Cryptogenic organising pneumonia: current understanding of an enigmatic lung disease. Eur Respir Rev. 2021;30(161):210094. [DOI: 10.1183/16000617.0094-2021] [PMID: 34407978]
11. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63(Suppl 5):v1–58. [DOI: 10.1136/thx.2008.101691] [PMID: 18757459]
12. Saito Z, Kaneko Y, Hasegawa T, Yoshida M, Odashima K, Horikiri T, et al. Predictive factors for relapse of cryptogenic organizing pneumonia. BMC Pulm Med. 2019;19(1):10. [DOI: 10.1186/s12890-018-0764-8] [PMID: 30626371]
13. Jo YS, Park JS, Park SH, Joh JS, Jang HJ, Lee HK; Korean Interstitial Lung Disease Study Group. Korean guidelines for diagnosis and management of interstitial lung disease: cryptogenic organizing pneumonia. Tuberc Respir Dis (Seoul). 2025. Epub ahead of print. [DOI: 10.4046/trd.2024.0167] [PMID: 40078018]
14. Taniguchi Y, Arai T, Tsuji T, Sugimoto C, Tachibana K, Akira M, et al. Cryptogenic organizing pneumonia: clinical outcomes of 60 consecutive cases. J Thorac Dis. 2024;16(5):3129–41. [DOI: 10.21037/jtd-24-225] [PMID: 38883617]
15. Arı M. Current approaches in the diagnosis and treatment of organizing pneumonia. Anatolian Curr Med J. 2025;7(1):89–93. [DOI: 10.38053/acmj.1599119]

Криптогена организујућа пнеумонија – неправедно занемарена болест

Ивана Секуловић Радовановић[1], Филип Марковић[1], Михаило Стјепановић[1,2], Никола Чолић[2,3], Драгана Марић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за пулмологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Центар за радиологију и магнетну резонанцу, Београд, Србија

САЖЕТАК

Увод Криптогена организујућа пнеумонија (КОП) је тип организујуће пнеумоније непознатог примарног узрочника. Дијагноза КОП се поставља када се искључе сви други могући узрочници. Манифестује се неспецифичним тегобама и клиничким симптомима који иду у прилог респираторној инфекцији, а сумња на КОП се јавља када упркос примењеној терапији радиографски налази пнеумоније перзистирају, или добијају миграторни ефекат. С обзиром на широку диференцијалну дијагностичку палету, постављање дијагнозе је пролонгирано, па је самим тим и примена одговарајуће терапије одложена.

Приказ болесникâ У раду су приказане три болеснице којима је у нашој установи постављена дијагноза криптогене организујуће пнеумоније. Представљени су сви изазови и путеви сваке болеснице од почетка развоја симптома до постављања дијагнозе. Обрађене су све учињене лабораторијске анализе и дијагностичке процедуре на основу којих је закључено постојање ове болести. Уз илустрацију приказа радиолошких налаза пре и након започињања кортикостероидне терапије, обрађен је и клинички одговор на примењену терапију и начин на који су болеснице амбулантно праћене.

Закључак Да би се поставила дијагноза КОП, прво на њу треба посумњати. Уз правовремено постављање дијагнозе могуће је побољшати квалитет живота болесника, избегавањем екцесивне употребе антимикробне терапије и честих хоспитализација. Постављање дијагнозе али и само лечење често захтева мултидисциплинарни приступ, како због пратећих коморбидитета тако и због потребе елиминисања других могућих узрочника организујуће пнеумоније. Примена кортикостероидне терапије доводи до брзог изостанка тегоба праћеног дугим периодима ремисије.

Кључне речи: криптогена организујућа пнеумонија; дијагноза; диференцијална дијагноза

DOI: https://doi.org/10.2298/SARH241210033D
UDC: 616.36-001-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Blunt liver trauma with concomitant injuries to the abdominal viscus – a dilemma for trauma surgeons

Yi Dong, Yuyang Guo, Yuxing Jiang, Wenfei Liu, Yong Fang
The People's Liberation Army No. 305 Hospital, Department of General Surgery, Beijing, China

SUMMARY
Introduction Blunt liver trauma is predominantly managed non-surgically, yet the optimal treatment and timing for addressing its late complications remain uncertain. This study aims to evaluate treatment approaches and outcomes for blunt liver trauma with concomitant abdominal visceral injuries.
Case Outline We present two cases of adult males who sustained severe liver and other organ injuries due to road traffic accidents. Both patients underwent comprehensive treatment, including urgent laparotomy. The first case resulted in severe complications and eventual mortality, while the second case had a favorable outcome with conservative management of the liver hematoma.
Conclusion Retaining blood clots around the liver wound during surgical intervention may enhance hemostasis and reduce infection risks. Further controlled studies with larger samples are necessary to validate these findings.
Keywords: blunt liver trauma; concomitant injury; operative intervention; non-operative management; urgent laparotomy

INTRODUCTION

Blunt liver trauma is primarily caused by shear stress resulting from rapid deceleration, commonly seen in road traffic accidents and falls. Liver rupture accounts for 15–20% of all abdominal injuries, with right liver rupture being more prevalent than the left [1]. A study involving 3196 patients with liver trauma identified higher mortality risks in individuals over 64 years, pedestrians involved in motor vehicle accidents, and those with renal failure, liver cirrhosis, or concurrent head, chest, or other abdominal injuries [2]. Although non-surgical management is increasingly adopted, the optimal intraoperative strategy for patients requiring laparotomy, particularly those with concomitant abdominal visceral injuries, remains controversial. A critical debate centers on whether to retain or remove blood clots surrounding liver wounds during surgery. This study specifically examines the hypothesis that preserving perilesional blood clots in blunt liver trauma with concurrent visceral injuries may enhance hemostasis and reduce postoperative infectious risks, thereby aligning with damage control principles.

To contextualize this hypothesis, a retrospective analysis of 450 patients with liver trauma revealed that 72% with closed liver injuries received non-surgical treatment [3]. However, surgical interventions remain indispensable for hemodynamically unstable cases or those with concomitant injuries [4]. The existing literature lacks a consensus on clot retention as a deliberate hemostatic measure during laparotomy, particularly in complex trauma scenarios. Herein, we present two contrasting cases of blunt liver trauma with abdominal visceral injuries, focusing on the role of intraoperative clot management in outcomes.

CASE REPORTS

Case 1

A 43-year-old man was injured in a road traffic accident on August 12, 2018, and was admitted to a local hospital's Emergency Department due to severe abdominal pain and fractures of the right ribs. He underwent urgent laparotomy four hours post-accident for diffuse peritonitis. Intraoperatively, a 5 × 3 cm laceration in the small intestine mesentery with venous bleeding and a ruptured sub-capsular liver hematoma with multiple parenchymal disruptions (largest approximately 5 cm) in the right lobe were identified. Massive intra-peritoneal hemorrhage (approximately 1800 mL) was evacuated. After repairing the mesenteric laceration, capillary bleeding persisted at the liver wound despite packing, necessitating hepatorrhaphy. The surgery lasted five hours, with blood loss exceeding 2150 mL, which was managed with six units of erythrocyte suspension and 400 mL of plasma.

Postoperatively, the patient remained unconscious and was intubated due to dyspnea. Two days later, urine output decreased to 200 mL/day, with elevated creatinine and transaminase levels. Seven days post-surgery, he developed hyperpyrexia despite continuous renal replacement therapy and meropenem prophylaxis, leading to his transfer to our institute on August 22, 2018. Upon admission,

Received • Примљено: December 10, 2024
Revised • Ревизија: April 7, 2025
Accepted • Прихваћено: April 19, 2025
Online first: April 29, 2025

Correspondence to:
Yong FANG
The People's Liberation Army No. 305 Hospital
Department of General Surgery
Wenjin Street 13
Xicheng District
100017 Beijing
China
yongfang288@163.com

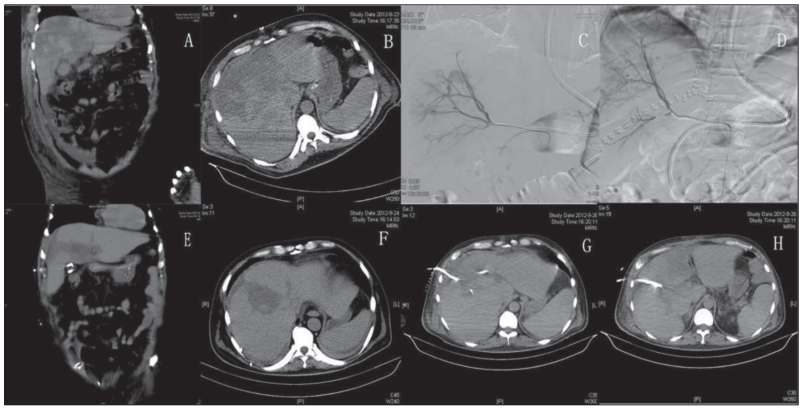


Figure 1. Case 1. A, B – a computed tomography (CT) scan of the abdomen taken 10 days after hepatorrhaphy; C, D – a hepatic arteriography showing active bleeding from the hepatic artery; the angioembolisation contributed to a lack of contrast extravasation from the artery; E, F – a CT scan of the abdomen taken 43 days after hepatorrhaphy, demonstrating that several abscess cavities and necrosis areas had formed in the liver; G, H – the abscess cavities were managed by percutaneous catheter drainage

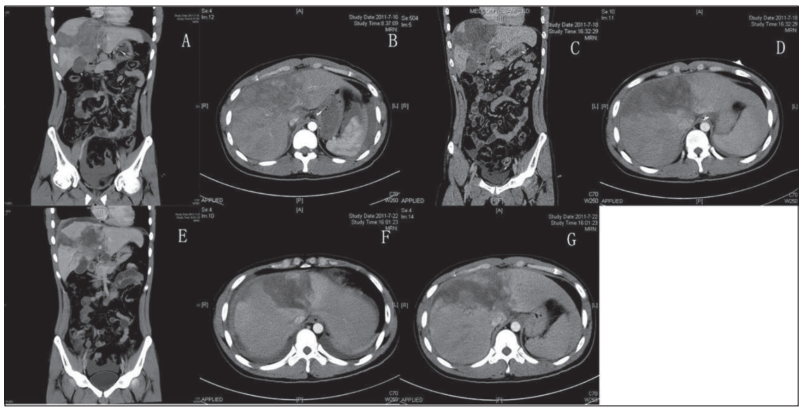


Figure 2. Case 2. A, B – a computed tomography (CT) scan of the abdomen taken four hours after injury demonstrated liver rupture and pulmonary contusions; C, D – a repeat CT scan of the abdomen taken two days after injury; E, F, G – a repeat CT scan of the abdomen taken six days after injury demonstrated that the hematoma in the liver had been gradually reabsorbed with no progression of the lesion

abdominal computed tomography (CT) scans (Figure 1A and 1B) indicated severe sepsis (white blood count: 37.8 × 10^9/L; procalcitonin: 78.83 ng/mL; creatinine: 712 μmol/L; urea nitrogen: 58.4 mmol/L; total bilirubin: 174.7 μmol/L).

Hepatic arteriography on the sixth day post-admission revealed active hepatic artery bleeding, which was embolized using a spring coil (5 mm × 5 cm), effectively stopping contrast extravasation (Figure 1C and 1D). Subsequently, the patient experienced upper gastrointestinal bleeding, evidenced by 700 mL of tarry stool and 300 mL of dark red liquid via a nasogastric tube. Urgent arteriography identified bleeding from a right gastric artery branch, but embolization was unfeasible. Gastroscopy confirmed an actively bleeding duodenal ulcer, which was managed endoscopically.

The patient's recovery was marred by relapse, gastrointestinal bleeding, and severe sepsis. Despite no active bleeding on angiography, daily blood product transfusions were required. A repeat CT 43 days post-hepatorrhaphy showed multiple liver abscesses and necrotic areas (Figure 1E and 1F), which were managed by percutaneous catheter drainage (Figure 1G and 1H). On September 29, 2018, the patient developed a 40°C fever, excreted 3000 mL of dark, bloody stool and experienced a sharp blood pressure drop, leading to ventricular flutter and subsequent death despite resuscitation efforts.

Case 2

A 42-year-old man was involved in an automobile crash on July 16, 2020, and was admitted to our Emergency Department four hours later with multiple abdominal and waist injuries. He presented with abdominal pain, lower limb weakness, retrograde amnesia and diffuse peritonitis. Abdominal CT scans revealed liver rupture, pulmonary contusions and a transverse lumbar vertebra fracture (Figure 2A and 2B). Despite decompression and an enema, the pain persisted. Peritoneal aspiration retrieved over 10 mL of gross blood, prompting exploratory laparotomy.

Intraoperatively, there was a massive intraperitoneal hemorrhage (> 1600 mL), a 7 cm parenchymal disruption on the liver's lower edge and a 2 × 2 cm liver capsule laceration. Erythema and blood clots surrounded the liver wounds without pulsatile bleeding. Additionally, a 1 cm duodenal laceration with intestinal content leakage and a 3 × 4 cm ileocecal mesentery laceration with venous bleeding were identified. After evacuating the hemorrhage, the duodenal and mesenteric lacerations were repaired. Blood clots around the liver wounds were retained to control bleeding. The surgery lasted two hours, with a blood loss of 2150 mL.

Postoperatively, the patient received microbial prophylaxis and hemostasis treatment. Repeat CT scans on July 18 and July 22, 2020, showed gradual absorption of the liver hematoma without lesion progression (Figure 2C–G). The patient recovered well (red blood count: 3.73 × 10^{12}/L; hemoglobin: 113 g/L) and was discharged on July 22, 2020. Follow-up via telephone indicated normal liver function without fever or jaundice. A recommended repeat abdominal CT was declined due to economic reasons.

Ethics: This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethics Committee of The People's Liberation Army No. 305 Hospital (ethical approval number: KYLL-SPJ-2024-04). Written informed consent was obtained from all participants.

DISCUSSION

This study presents two cases of severe blunt liver injury with concomitant abdominal visceral injuries resulting from road traffic accidents, both accompanied by diffuse peritonitis. Both patients underwent exploratory

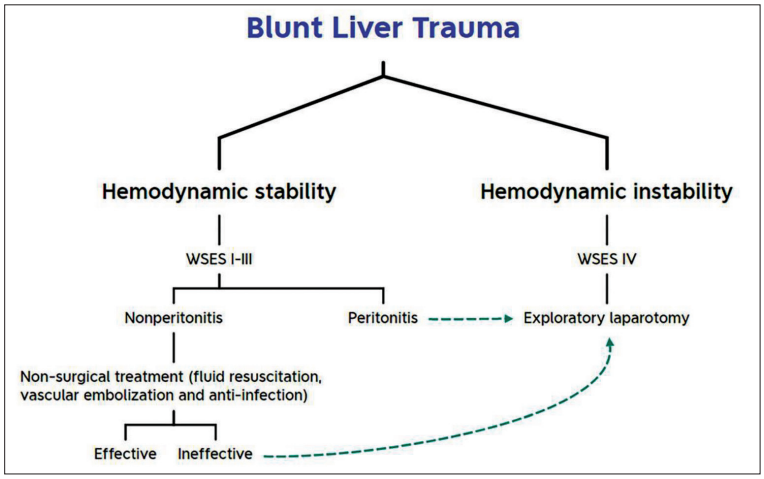


Figure 3. The clinical practice chart of blunt liver trauma; WSES – the 2020 World Society of Emergency Surgery guidelines

laparotomy, revealing mesenteric lacerations. In the first case, the removal of blood clots around the liver led to persistent bleeding, severe sepsis, gastrointestinal hemorrhage, and eventual death. In contrast, in the second case, blood clots around the liver were retained, resulting in hematoma absorption, and patient recovery. This suggests that preserving blood clots around liver wounds may enhance hemostasis and reduce infection risks.

The liver's rich blood supply and complex structure make it susceptible to severe injuries, often leading to hemorrhagic shock and biliary peritonitis with high mortality and complication rates. Cavernous hemangioma is the most common benign hepatic tumor, and trauma can trigger bleeding from these lesions [5]. Patients with trauma and massive bleeding are at risk of metabolic acidosis, hypothermia, and coagulopathy, necessitating fluid resuscitation, blood transfusion, and correction of coagulopathies [6]. Damage control surgery involving sutures and tamponades, along with resuscitation, improves survival rates despite the high mortality [7].

Retained perilesional blood clots in blunt liver trauma may confer protection through four mechanisms:

1) Hemostatic scaffolding: clots provide a scaffold for platelet aggregation and fibrin deposition, enhancing mechanical compression;

2) Mechanical barrier: clots prevent bacterial translocation from the gut;

3) Inflammatory modulation: clots sequester pro-inflammatory cytokines (IL-6/TNF-α) and release anti-inflammatory mediators (TGF-β);

4) Tissue repair: fibrin matrices store growth factors (VEGF/PDGF), promoting angiogenesis [8, 9].

These mechanisms align with the 2020 World Society of Emergency Surgery (WSES) guidelines, supporting clot retention as a damage control strategy [10].

Most liver injuries from motor vehicle accidents can be managed non-surgically, with early vascular embolization being crucial in selected cases [11]. However, blunt liver trauma with additional abdominal visceral injuries requires careful consideration. According to the 2018 American Association for the Surgery of Trauma liver injury scale, emergency laparotomy is indicated for similar intraperitoneal hemorrhages and liver injury classifications (grade IV) [12]. Patients with hemodynamically stable blunt hepatic trauma without other surgical indications may initially receive non-surgical treatment, reserving exploratory laparotomy for those with hemodynamic instability, peritonitis or failure of conservative management [13] (Figure 3).

Surgical techniques for liver trauma include perihepatic packing, liver repair, hepatectomy, and selective hepatic artery ligation [14]. However, these interventions can increase complication rates, such as surgical urinary wounds, respiratory tract sepsis, and intra-abdominal abscesses [15]. Selective non-surgical strategies and endovascular interventions are becoming more prevalent, with non-surgical treatments showing lower or comparable complication rates [16]. Nonetheless, surgical interventions remain necessary for controlling major bleeding sites. The 2020 WSES guidelines explicitly recommend clot retention as part of damage control surgery (Grade 1B), emphasizing its role in hemostasis and infection prevention [10].

Non-surgical treatment complications include persistent bleeding, biliary hemorrhage, bile leakage, and severe sepsis [17]. Successful non-surgical management has an 85–99% success rate, with hepatic convergence and bile leakage being the most common complications [18]. Biliary leakage is a significant cause of sepsis in patients with blunt liver injury and can be managed with closed suction tubes, percutaneous drainage, cholangiography, or endoscopic stenting [19]. Major liver injuries and progressive coagulopathy are frequent indications for damage control surgery, necessitating precise surgical judgment and meticulous open abdomen management to limit morbidity [20].

In this case series, we observed that retaining blood clots around liver wounds during surgical intervention in two hemodynamically distinct scenarios appeared to enhance hemostasis and reduce infection risks. The contrasting outcomes between Case 1 (clot removal) and Case 2 (clot retention) suggest a potential biological rationale for clot preservation, particularly in damage control surgery for complex trauma. However, this hypothesis requires validation through prospective multi-center studies with standardized protocols and larger cohorts. Until such evidence emerges, trauma surgeons should weigh clot retention strategies against individual patient risks, guided by real-time hemodynamic status and institutional expertise.

ACKNOWLEDGMENT

Funding: This research received funding from the Independent Research Fund of The People's Liberation Army No. 305 Hospital (NO. 24ZZJJLW-006).

Conflict of Interest: None declared.

REFERENCES

1. Le ACM, Bohlin T, Grønvold L, Rognerud ØH, Jørgensen JJ, Landquist M. Sprukket lever [Ruptured liver]. Tidsskr Nor Laegeforen. 2023;143(8). Norwegian. [DOI: 10.4045/tidsskr.22.0805] [PMID: 37254990]
2. Chien LC, Lo SS, Yeh SY. Incidence of liver trauma and relative risk factors for mortality: a population-based study. J Chin Med Assoc. 2013;76(10):576–82. [DOI: 10.1016/j.jcma.2013.06.004] [PMID: 23890836]
3. Fischer NJ. Mortality following severe liver trauma is declining at Auckland City Hospital: a 14-year experience, 2006–2020. N Z Med J. 2021;134(1540):16–24. [PMID: 34482385]
4. Thomas MN, Whaba R, Datta RR, Bunck AC, Stippel DL, Bruns CJ. Management und Versorgung von Leberverletzungen nach stumpfem Bauchtrauma [Management and treatment of liver injuries after blunt abdominal trauma]. Chirurgie (Heidelb). 2023;94(8):669–74. German. [DOI: 10.1007/s00104-023-01858-1] [PMID: 37142798]
5. Bioulac-Sage P, Laumonier H, Laurent C, Blanc JF, Balabaud C. Benign and malignant vascular tumors of the liver in adults. Semin Liver Dis. 2008;28(3):302–14. [DOI: 10.1055/s-0028-1085098] [PMID: 18814083]
6. Cirocchi R, Montedori A, Farinella E, Bonacini I, Tagliabue L, Abraha I. Damage control surgery for abdominal trauma. Cochrane Database Syst Rev. 2013;2013(3):CD007438. [DOI: 10.1002/14651858.CD007438.pub3] [PMID: 23543551]
7. Iaselli F, Mazzei MA, Firetto C, D'Elia D, Squitieri NC, Biondetti PR, et al. Bowel and mesenteric injuries from blunt abdominal trauma: a review. Radiol Med. 2015;120(1):21–32. [DOI: 10.1007/s11547-014-0487-8] [PMID: 25572542]
8. El-Menyar A, Mekkodathil A, Al-Ansari A, Asim M, Elmenyar E, Rizoli S, et al. Platelet-Lymphocyte and Neutrophil-Lymphocyte Ratio for Prediction of Hospital Outcomes in Patients with Abdominal Trauma. Biomed Res Int. 2022;2022:5374419. [DOI: 10.1155/2022/5374419] [PMID: 35178450]
9. Doudakmanis C, Bouliaris K, Kolla C, Efthimiou M, Koukoulis GD. Bacterial translocation in patients undergoing major gastrointestinal surgery and its role in postoperative sepsis. World J Gastrointest Pathophysiol. 2021;12(6):106–14. [DOI: 10.4291/wjgp.v12.i6.106] [PMID: 34877025]
10. Coccolini F, Coimbra R, Ordonez C, Kluger Y, Vega F, Moore EE, et al. Liver trauma: WSES 2020 guidelines. World J Emerg Surg. 2020;15(1):24. [DOI: 10.1186/s13017-020-00302-7] [PMID: 32228707]
11. Wongweerakit O, Akaraborworn O, Sangthong B, Thongkhao K. Acute portal vein thrombosis in an isolated, blunt, minor liver injury near the porta hepatis. Chin J Traumatol. 2025;28(1):76–8. [DOI: 10.1016/j.cjtee.2023.09.003] [PMID: 37838579]
12. Vyčítal O, Horský O, Rosendorf J, Liška V, Skalický T, Třeška V. Treatment of liver injuries at the Trauma Centre of the University Hospital in Pilsen. Rozhl Chir. 2019 Winter;98(12):488–91. English. [DOI: 10.33699/PIS.2019.98.12.488-491] [PMID: 31958962]
13. Martellotto S, Melot C, Raux M, Chereau N, Menegaux F. Depacked patients who underwent a shortened perihepatic packing for severe blunt liver trauma have a high survival rate: 20 years of experience in a level I trauma center. Surgeon. 2022;20(3):e20–e25. [DOI: 10.1016/j.surge.2021.04.012] [PMID: 34154925]
14. Leenellett E, Rieves A. Occult Abdominal Trauma. Emerg Med Clin North Am. 2021;39(4):795–806. [DOI: 10.1016/j.emc.2021.07.009] [PMID: 34600638]
15. Cartu D, Margaritescu D, Sandulescu S, Bratiloveanu T, Ramboiu S, Bica M, et al. Nonoperative Treatment of Abdominal Trauma Involving Liver and Spleen. Chirurgia (Bucur). 2021;116(6):689–99. [DOI: 10.21614/chirurgia.116.6.689] [PMID: 34967714]
16. Schembari E, Sofia M, Latteri S, Pesce A, Palumbo V, Mannino M, et al. Blunt liver trauma: effectiveness and evolution of non-operative management (NOM) in 145 consecutive cases. Updates Surg. 2020;72(4):1065–71. [DOI: 10.1007/s13304-020-00861-z] [PMID: 32851597]
17. Nguyen PD, Nahmias J, Aryan N, Samuels JM, Cripps M, Carmichael H, et al. Observation-first versus angioembolization-first approach in stable patients with blunt liver trauma: A WTA multicenter study. J Trauma Acute Care Surg. 2024;97(5):764–9. [DOI: 10.1097/TA.0000000000004372] [PMID: 39443838]
18. Virdis F, Podda M, Di Saverio S, Kumar J, Bini R, Pilasi C, et al. Clinical outcomes of non-operative management and clinical observation in non-angioembolised hepatic trauma: A systematic review of the literature. Chin J Traumatol. 2022;25(5):257–63. [DOI: 10.1016/j.cjtee.2022.04.004] [PMID: 35487854]
19. Mehta N, Babu S, Venugopal K. An experience with blunt abdominal trauma: evaluation, management and outcome. Clin Pract. 2014;4(2):599. [DOI: 10.4081/cp.2014.599] [PMID: 25332759]
20. Stracieri LD, Scarpelini S. Hepatic injury. Acta Cir Bras. 2006;21 Suppl 1:85–8. [DOI: 10.1590/s0102-86502006000700019] [PMID: 17013521]

Тупа повреда јетре са пратећим повредама абдоминалних органа – дилема за трауматолошке хирурге

Ји Донг, Јујанг Гуо, Јусјинг Ђанг, Венфеј Лју, Јонг Фанг

305. болница Народноослободилачке армије, Одељење за општу хирургију, Пекинг, Кина

САЖЕТАК

Увод Тупа повреда јетре претежно се лечи нехируршки, али оптималан приступ лечењу и време решавања њених касних компликација нису јасно дефинисани. Циљ ове студије је да процени приступе лечењу и исходе тупе повреде јетре код болесника са истовременим повредама других абдоминалних органа.

Прикази болесника Приказујемо два случаја одраслих мушкараца који су у саобраћајним незгодама задобили тешке повреде јетре и других органа. Оба пацијента су подвргнута опсежном лечењу, укључујући хитну лапаротомију. Први болесник је преминуо услед тешких компликација, док је код другог конзервативно лечење хематома јетре довело до повољног исхода.

Закључак Остављање крвних угрушака око ране на јетри током хируршке интервенције може побољшати хомеостазу и смањити ризик од инфекције. Потребна су даља истраживања са већим узорцима за потврду ових налаза.

Кључне речи: тупа повреда јетре; пратеће повреде; оперативно лечење; неоперативно лечење; хитна лапаротомија

DOI: https://doi.org/10.2298/SARH241116038M
UDC: 616.717.5/.6-001.5-089

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Monteggia fracture associated with olecranon fracture-dislocation Mayo IIIB

Filip Maljković[1], Aleksandar Stanojković[1], Boris Zekić[1], Filip Milanović[2], Branislav Krivokapić[1,3]

[1]Banjica Institute for Orthopedics, Belgrade, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]University of Belgrade, Medical Faculty, Belgrade, Serbia

SUMMARY

Introduction Monteggia fractures involving olecranon fractures and dislocations present complex challenges due to the need for simultaneous stabilization of multiple joint components. These injuries require precise surgical planning and execution to restore elbow function and minimize complications such as joint instability, nonunion, and reduced mobility. Modern surgical techniques, including the use of locking plates and careful anatomical reduction, have shown to significantly improve long-term outcomes.

Case outline This case report discusses the management of a 30-year-old female patient with a Monteggia fracture and olecranon fracture-dislocation following a cycling accident. The patient underwent delayed surgery due to severe soft tissue injuries. The procedure involved ulna fixation with an olecranon plate and radial head stabilization using a FiberTape® system (Arthrex, Naples, FL, USA). Despite incomplete rehabilitation, the patient showed satisfactory recovery with only minor limitations in elbow movement. This case emphasizes the importance of early intervention, precise reduction, and the use of modern fixation techniques in optimizing recovery for complex elbow injuries.

Conclusions Effective treatment of Monteggia fractures associated with olecranon dislocation requires early intervention, precise anatomical reduction, and the use of modern fixation techniques to ensure optimal functional outcomes and minimize long-term complications.

Keywords: Monteggia fracture; olecranon fracture-dislocation; locking plates

INTRODUCTION

Monteggia fractures, first described in 1814, involve the dislocation of the radial head with an ulna fracture. Although rare, these injuries require careful surgical planning due to the risk of complications like nonunion or limited elbow motion. Monteggia fractures account for only 1–5% of fractures in the elbow region. Today, the term "Monteggia" or "Monteggia-like" injury includes a wide range of different fracture patterns of the proximal ulna and radial head. The treatment of these injuries in modern traumatology remains a subject of debate regarding different treatment strategies [1, 2]. When combined with an olecranon fracture-dislocation, treatment becomes even more complex, as both joint parts must be stabilized to achieve the best functional outcome [2]. Various surgical techniques have been described to manage this type of injury. Locking compression plates are used for ulna fixation, helping to reduce the risk of nonunion and the need for revision surgery [1]. Proper anatomical alignment is also crucial for restoring elbow movement [2]. Monteggia fractures combined with olecranon dislocation are among the most challenging elbow injuries, requiring precise diagnosis and surgery to ensure stable fixation and maintain joint function. Studies show that treating such complex fractures often requires a combination of different surgical approaches, including lateral and posterior techniques, to access the elbow joint fully [1]. The best surgical approach for this type of injury is the posterior approach due to the subcutaneous location of the ulna. Additionally, the posterior approach allows for extension because it provides access to the elbow joint from both the medial and lateral aspects. Successful outcomes depend heavily on accurate anatomical reduction, and incorrect implant placement can cause complications like joint instability and reduced movement [2, 3]. Despite improvements in surgical methods, long-term risks such as osteoarthritis and limited elbow mobility remain. This highlights the importance of using precise techniques during surgery [3].

The aim of this paper is to present a rare case of a Monteggia fracture combined with an olecranon fracture-dislocation and to analyze the surgical approach and postoperative outcome based on current studies.

CASE REPORT

A 30-year-old woman, injured in a cycling accident, was examined at the Banjica Institute of Orthopedics, on June 5, 2024. She had over 20 lacerations, likely from glass. X-rays and computed tomography scans confirmed a Monteggia-type fracture with an olecranon fracture-dislocation (Figure 1). Due to swelling

Received • Примљено: November 16, 2024
Revised • Ревизија: March 6, 2025
Accepted • Прихваћено: May 13, 2025
Online first: May 15, 2025

Correspondence to:
Branislav KRIVOKAPIĆ
Mihaila Avramovića 28
11000 Belgrade
Serbia
banedoctor1984@gmail.com

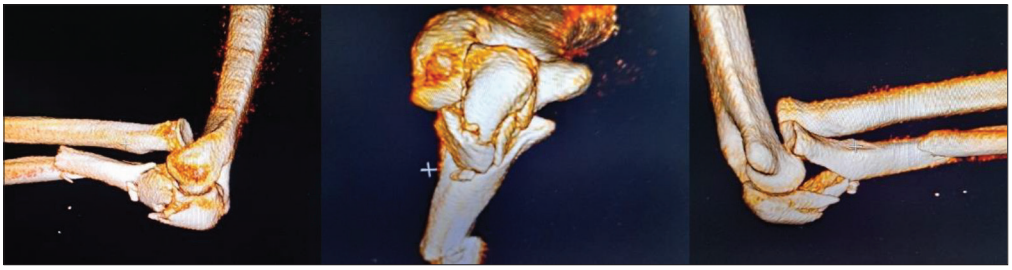


Figure 1. Preoperative computed tomography imaging revealed a Monteggia fracture associated with a comminuted fracture-dislocation of the olecranon

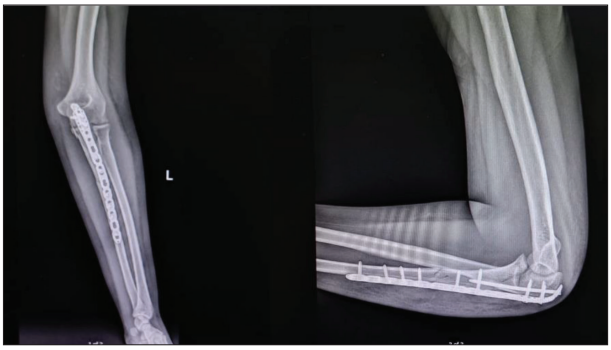


Figure 2. Postoperative radiological images demonstrate satisfactory fragment repositioning and preserved joint congruence

and the location of the wounds, we delayed the surgery for two weeks. The operation was done under nerve block anesthesia, with the arm positioned by the patient's side. A direct approach was made to the ulna, and after visualizing and mobilizing the fragments, proper alignment of the elbow was achieved. A long olecranon plate was used for fixation, aiming to restore the joint's anatomy. The radial head was repositioned through the Kocher approach, and the annular ligament was reconstructed using a FiberTape® system (Arthrex, Naples, FL, USA). For additional stability, the radial head was temporarily fixed with a K-wire, which was removed after two weeks (Figure 2). At the one-month follow-up, the patient reported feeling well, though there was a 20° loss of elbow extension, 10° loss of flexion, full supination, and about 25° reduced pronation, as well as the presence of radiographic signs of fracture consolidation.

Ethics: The authors affirm that the article adheres to the ethical guidelines established by the Serbian Archives of Medicine, as well as the ethical standards set by each author's respective institution. Written informed consent was secured from the patient participating in the study.

DISCUSSION

Monteggia fractures combined with olecranon fracture and dislocation require a well-thought-out surgical strategy. Ensuring elbow stability and proper anatomical reduction of the ulna, olecranon, and radial head are critical for functional recovery. Studies show that locking plates improve stability and reduce nonunion compared to older methods [1]. These types of injuries are complicated by the presence of fractures and dislocations within the elbow, making surgery more challenging. If stable fixation is not achieved, long-term complications like chronic instability, pain, and limited movement can occur [1, 2]. Outcomes are influenced by the type of fracture and the timing of surgery. Early surgery generally leads to better results, while delayed intervention increases the risk of complications like arthrofibrosis and limited movement [2]. Surgical treatment of these complex fractures remains challenging due to the anatomical and functional importance of the elbow. Key elements of successful treatment include stable fixation of the ulna and olecranon, which in turn stabilizes the radial head and restores normal elbow function [1, 3]. Wong et al. [3] stress that anatomical reduction and mechanical stability are vital for long-term recovery. Failure to achieve these can result in chronic instability, pain, and reduced mobility. They also highlight that proper reduction of the ulna and olecranon helps stabilize the radial head, reducing the risk of postoperative instability and pain [3]. Long-term outcomes depend on quick diagnosis and efficient rehabilitation. Good results can be achieved if complete reduction and stable fixation of all elbow components are obtained, particularly if the contours and dimensions of the trochlear notch are restored. Post-traumatic arthritis and limited joint function remain potential risks [4–9]. Zeiders and Patel [10] emphasize the need for individualized surgical approaches, particularly for injuries involving the radial head and olecranon, which often require a combination of lateral and posterior techniques. In our case, early surgery was not possible due to significant swelling and wounds. We followed the principles of stabilizing the elbow, anatomical reduction, and using locking plates. However, the patient did not fully comply with early rehabilitation, affecting the final outcome. Despite this, our results were satisfactory. Lubberts et al. [11] stress the importance of analyzing fracture lines before surgery. This allows for the best choice of technique and implant, improving functional outcomes and reducing complications [11]. Das et al. [12] point out that choosing the right fixation technique is critical, especially when dealing with radial head dislocations. They suggest that combining posterior and lateral approaches provides better visibility and allows for more secure fixation [12]. Additionally, soft tissue and ligament damage often accompany these injuries, making surgery more difficult. Proper reconstruction of the ligamentous structures is essential to ensure long-term joint stability and prevent instability after surgery. The surgical treatment of Monteggia fractures with associated olecranon fracture-dislocation is highly challenging, but

modern techniques, including the use of locking plates and carefully planned procedures, significantly improve long-term outcomes for patients [1, 2, 13–17]. The complexity of treating Monteggia fractures associated with olecranon dislocation demands an individualized approach and careful planning. Locking plates, accurate anatomical reduction, and timely intervention are key factors in achieving the best functional outcomes.

Conflict of interest: None declared.

REFERENCES

1. Weber MM, Rosteius T, Schildhauer TA, Königshausen M, Rausch V. Monteggia fractures and Monteggia-like-lesions: a systematic review. Arch Orthop Trauma Surg. 2023;143(7):4085–93. [DOI: 10.1007/s00402-022-04576-1] [PMID: 36056930]
2. Öztürkmen Y, Şükür E, Akman YE, Şenel A, Gürpınar T. Clinical and radiological evaluation of surgical management in olecranon fracture–dislocations. Musculoskelet Surg. 2020;104(3):321–8. [DOI: 10.1007/s12306-019-00623-0] [PMID: 31583519]
3. Wong JC, Getz CL, Abboud JA. Adult Monteggia and Olecranon Fracture Dislocations of the Elbow. Hand Clin. 2015;31(4):565–80. [DOI: 10.1016/j.hcl.2015.06.006] [PMID: 26498546]
4. Ring DM, Jupiter JB, Simpson NS. Monteggia fractures in adults. J Bone Joint Surg Am. 1998;80(12):1733–44. [DOI: 10.2106/00004623-199812000-00003] [PMID: 9875931]
5. Konrad GG, Kundel K, Kreuz PC, Oberst M, Südkamp NP. Monteggia fractures in adults: long-term results and prognostic factors. J Bone Joint Surg Br. 2007;89(3):354–60. [DOI: 10.1302/0301-620X.89B3.18199] [PMID: 17356149]
6. Shashank S, Shetty SK, Ks D. Neglected Monteggia fracture-dislocation in a child: A case report. Int J Orthop Sci. 2024;10(3):1–6. [DOI: 10.22271/ortho.2024.v10.i3a.3569]
7. Veillette CJH, Steinmann SP. Olecranon fractures. Orthop Clin North Am. 2008;39(2):229–36. [DOI: 10.1016/j.ocl.2008.01.002] [PMID: 18374813]
8. Bae DS, Waters PM. Surgical treatment of acute and chronic Monteggia fracture-dislocations. Oper Tech Orthop. 2005;15(4):308–14. [DOI: 10.1053/j.oto.2005.08.001]
9. Siebenlist S, Buchholz A, Braun KF. Fractures of the proximal ulna: current concepts in surgical management. EFORT Open Rev. 2019;4(1):1–9. [DOI: 10.1302/2058-5241.4.180022] [PMID: 30800474]
10. Zeiders GJ, Patel MK. Management of unstable elbows following complex fracture-dislocations: the "terrible triad" injury. J Bone Joint Surg Am. 2008;90(1):75–84. [DOI: 10.2106/JBJS.H.00893] [PMID: 18984720]
11. Lubberts B, Mellema JJ, Janssen SJ, Ring D. Fracture line distribution of olecranon fractures. Arch Orthop Trauma Surg. 2017;137(1):37–42. [DOI: 10.1007/s00402-016-2593-7] [PMID: 27832347]
12. Das SP, Vj G, R P, Sondur S, Naik A, Gulia A, et al. Outcomes of the Posterior Approach for the Treatment of Radial Head Fractures and Associated Elbow Injuries: A Retrospective Observational Study. Cureus. 2023;15(1):e34041. [DOI: 10.7759/cureus.34041] [PMID: 36824544]
13. Tille E, Seidel L, Schlüßler A, Beyer F, Kasten P, Bota O, et al. Monteggia fractures: analysis of patient-reported outcome measurements in correlation with ulnar fracture localization. J Orthop Surg Res. 2022;17(1):303. [DOI: 10.1186/s13018-022-03195-1] [PMID: 35672754]
14. Wang W, Xiong Z, Huang D, Li Y, Huang Y, Guo Y, et al. Risk factors for unsuccessful reduction of chronic Monteggia fractures in children treated surgically: a review of 209 cases. Bone Jt Open. 2024;5(7):581–91. [DOI: 10.1302/2633-1462.57.BJO-2024-0004.R2] [PMID: 38991554]
15. De Maio F, Gorgolini G, Caterini A, Luciano C, Covino D, Farsetti P. Treatment of olecranon fractures in childhood: A systematic review. Front Pediatr. 2022;10:1046243. [DOI: 10.3389/fped.2022.1046243] [PMID: 36467486]
16. Zhang R, Wang X, Xu J, Kang Q, Hamdy RC. Neglected Monteggia fracture: a review. EFORT Open Rev. 2022;7(4):287–94. [DOI: 10.1530/EOR-21-0087] [PMID: 35446261]
17. Xiao RC, Chan JJ, Cirino CM, Kim JM. Surgical management of complex adult Monteggia fractures. J Hand Surg Am. 2021;46(11):1006–15. [DOI: 10.1016/j.jhsa.2021.07.023]

Монтеђијев прелом удружен са преломом и дислокацијом олекранона, тип Мајо III*B*

Филип Маљковић[1], Александар Станојковић[1], Борис Зекић[1], Филип Миланović[2], Бранислав Кривокапић[1,3]

[1]Институт за ортопедију „Бањица", Београд, Србија;
[2]Универзитетска дечја клиника Тиршова, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Увод Монтеђијеви преломи удружени са преломом и дислокацијом олекранона представљају сложене изазове због потребе за истовременом стабилизацијом више компоненти зглоба. Ове повреде захтевају прецизно планирање и извођење хируршке интервенције како би се повратила функција лакта и минимизовале компликације као што су нестабилност зглоба, несрастање и смањен опсег покрета. Савремене хируршке технике, укључујући употребу закључавајућих плоча и пажљиве анатомске репозиције, показале су значајна побољшања дугорочних резултата.

Приказ болесника Овај рад разматра третман повреде код 30-годишње пацијенткиње са Монтеђијевим преломом удруженим са преломом и дислокацијом олекранона након бициклистичке несреће. Пацијенткиња је подвргнута одложеној операцији због озбиљних повреда меких ткива. Процедура је обухватила фиксацију улне са дугачком плочом за олекранон и стабилизацију радијалне главе помоћу система *FiberTape*® (*Arthrex*, Напуљ, ФЛ, САД). Упркос непотпуној рехабилитацији, пацијенткиња је показала задовољавајући опоравак са само мањим ограничењима у покретима лакта. Овај случај наглашава важност раног захвата, прецизне редукције и употребе модерних техника фиксације у оптимизацији опоравка код сложених повреда лакта.

Закључак Ефективно лечење Монтеђијевог прелома повезаног са дислокацијом олекранона захтева рану интервенцију, прецизну анатомску редукцију и употребу савремених техника фиксације како би се обезбедили оптимални функционални резултати и минимизовале дугорочне компликације.

Кључне речи: Монтеђијев прелом; прелом и дислокација олекранона; закључавајућа плоча

DOI: https://doi.org/10.2298/SARH241108044S
UDC: 616.61-006.03

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Wunderlich syndrome, inside out – a case report and brief literature review

Mirjana Stojanović, Perica Adnađević, Tijana Kosanović, Lejla Hajdarpašić, Marjana Đorđević
Dr Dragiša Mišović – Dedinje University Hospital Center, Department of Radiology, Belgrade, Serbia

SUMMARY
Introduction Renal angiomyolipomas (AMLs) are neoplasms that can rarely rupture, causing hemorrhagic shock as the most serious complication. This pathological condition, (referring to AML) is classified as a benign tumor arising from the proliferation of epithelioid cells, consisting of fat tissue, blood vessels, and smooth muscle. Wunderlich syndrome describes a spontaneous, non-traumatic bleeding into the subcapsular or perirenal space. Most individuals with renal AML exhibit no symptoms and are often diagnosed incidentally; however, some may experience life-threatening complications such as rupture, hemorrhage, and circumstantial hypovolemic shock.
Case outline We describe a clinical presentation of AML with rupture in a female patient with a brief overview of other cases of AML in the literature.
Female patient, 68 years old, admitted for examination due to sudden severe pain in the abdomen with propagation to the right lumbar region accompanied by nausea and fatigue. After a complete physical examination, an abdominal ultrasound, and a computed tomography scan, surgery was performed during which the right kidney was removed alongside the hematoma and the kidney envelopes, which were sent for histopathological analysis. The result of the histopathological analysis confirmed that it was AML.
Conclusion AMLs are benign neoplasms with potentially serious complications. The most serious complication of AML is rupture, leading to retroperitoneal hemorrhage, with tumor size being a significant risk factor. Considering the clinical importance of this potential complication, it is important to establish a swift and accurate radiological diagnosis, with the aim of timely therapeutic intervention and reduction of potential additional complications.
Keywords: renal angiomyolipoma; radiological diagnosis; rupture; management

INTRODUCTION

Renal angiomyolipomas (AMLs) are neoplasms that can rarely rupture, causing hemorrhagic shock as the most serious complication. This pathological condition, (referring to AML) is classified as a benign tumor arising from the proliferation of epithelioid cells, consisting of fat tissue, blood vessels, and smooth muscle. AMLs larger than 4 cm carry a notably increased risk of rupture; however, rupture can also occur in smaller tumors, while larger AMLs may remain stable. The median age for rupture of solitary renal AMLs is around 50 years. The overall incidence is approximately 0.13%, with a higher prevalence in females, which is thought to be related to hormonal influences. About 80% of renal AMLs occur sporadically, whereas the remaining cases are linked to tuberous sclerosis (TS) [1]. Wunderlich syndrome describes spontaneous, non-traumatic bleeding into the subcapsular or perirenal space. The appropriate management of this syndrome depends on confirming the diagnosis of perinephric hemorrhage and identifying its underlying cause [2]. Most individuals with renal AML exhibit no symptoms and are often diagnosed incidentally, however, some may experience life-threatening complications such as rupture, hemorrhage, or hypovolemic shock. Traditionally, a tumor size of 4 cm has been used as a threshold, initially proposed in 1986, to differentiate between patients suitable for watchful waiting and those needing intervention. Nevertheless, this criterion is now subject to debate, with recent research suggesting that relying solely on size could result in unnecessary treatment in certain cases [3, 4].

This case report describes a female patient who experienced spontaneous perinephric bleeding due to a ruptured renal AML, alongside a short review of this syndrome.

CASE REPORT

A female patient, aged 68, was admitted to the emergency care unit of Dr Dragiša Mišović – Dedinje University Hospital Center, Belgrade, in October, 2023, due to severe, sudden pain in the right lumbar region. The pain started three days before the clinical exam with localization in the left lower back. She was initially examined by a physiatrist, who determined that the pain was of spinal origin and prescribed dexamethasone. Although she felt better for a short time, on the day of the examination, the pain reappeared, with propagation to the right, accompanied by vomiting and weakness. The following medical tests were performed:

General exam: blood pressure 115/70 mmHg, pulse 64 bpm. Soft abdomen, painfully sensitive to deep palpation on the right.

Received • Примљено: November 8, 2024
Revised • Ревизија: May 21, 2025
Accepted • Прихваћено: May 31, 2025
Online first: June 4, 2025

Correspondence to:
Mirjana STOJANOVIĆ
Beranska 34
11000 Belgrade
Serbia
mirjana.stojanovic@dragisamisovic.bg.ac.rs

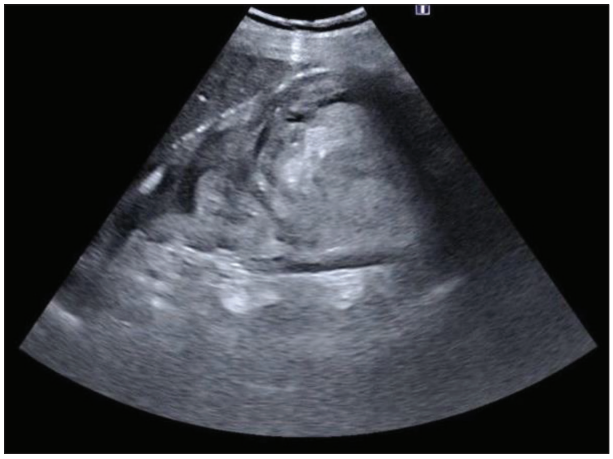


Figure 1. Abdominal ultrasound: the right kidney is enlarged, with a hyperechoic mass encompassing the interpolar region and the upper pole of the kidney, extending into the renal sinus; within the mass there are irregular anechoic fields; along the lateral contour of the kidney, there is an anechoic, dense, fluid collection with hyperechoic streaks, and inflamed perirenal fatty tissue, suggestive of a hematoma originating from a bleeding angiomyolipoma

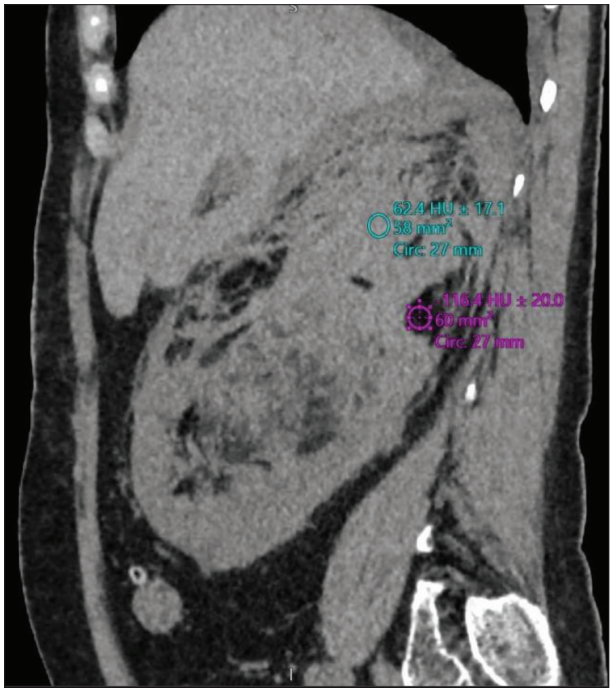


Figure 2. Sagittal unenhanced computed tomography imaging of the abdomen and pelvis showing altered right kidney with a mass situated within the interpolar region and at the upper pole of the kidney, measuring 175 × 110 × 65 mm, with central fat density, alongside perirenal fluid with density measuring 50–60 Hounsfield unit (density of fresh blood), 50 mm in diameter

Laboratory analyses: leukocytes 20.4 × 10^9/L, hemoglobin 128 g/L, erythrocytes 4.28 × 10^{12}/L.

Abdominal ultrasound: The right kidney was enlarged, with a hyperechoic mass encompassing the interpolar region and the upper pole of the kidney, extending into the renal sinus. Within the mass there were irregular anechoic fields, with a total diameter of approximately 90 × 60 mm. Along the lateral contour of the kidney, there was an anechoic, dense, fluid collection with hyperechoic streaks, and inflamed perirenal fatty tissue, suggestive of a hematoma originating from a bleeding AML (Figure 1).

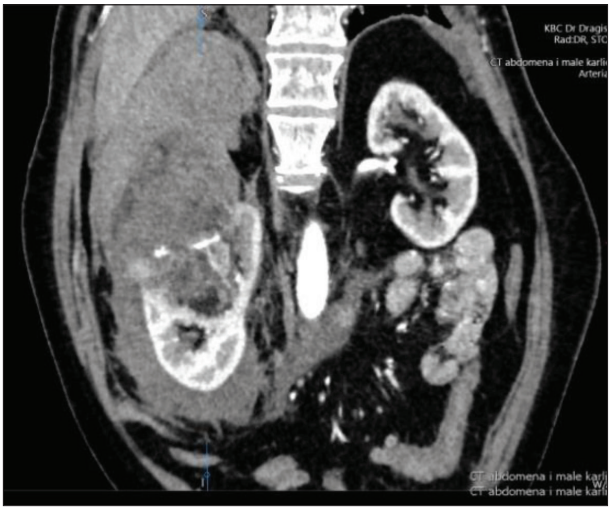


Figure 3. An intravenous-contrast-enhanced coronal computed tomography image shows perirenal hematoma of the right kidney and free fluid

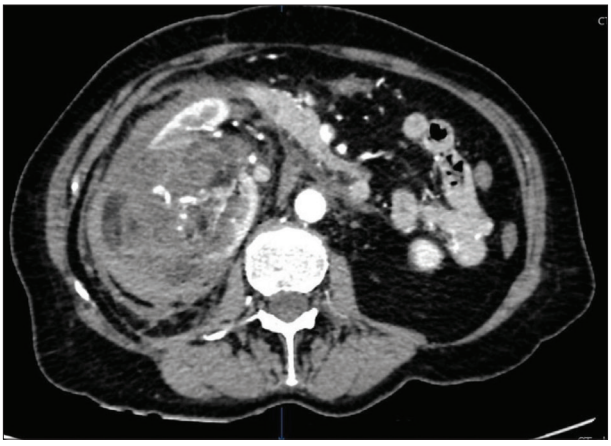


Figure 4. An intravenous-contrast-enhanced coronal computed tomography image revealed retroperitoneal hematoma, from the level of L2 vertebra

Computed tomography (CT): Non-contrast and contrast-enhanced CT scans of the abdomen and pelvis revealed significant changes in the right kidney. A heterodense formation, measuring about 85 × 60 mm with hypodense zones (of negative density – fat) was observed, likely corresponding to the previously described AML. Perirenal fluid was observed with density measuring 50–60 Hounsfield units (density of fresh blood), 50 mm in diameter. Additionally, perirenal adipose tissue appeared inflamed, permeated with hyperechoic streaks. The fluid collection propagated medially into the para-aortic space in the upper retroperitoneum. Subhepatic free fluid with a layer thickness of approximately 12 mm was present. The right adrenal gland was not visualized, in addition to the described fluid collection. The left kidney had a CC diameter of 92 mm, with several focal changes of fat density in the parenchyma, reaching a diameter of up to 8 mm, characteristic of AML.

In conclusion, these findings support acute bleeding into the right perirenal space, most likely originating from a large AML situated in the superior portion of the right kidney (Figures 2, 3, and 4).

After the completion of the diagnostic procedures, a surgery was performed in which the right kidney was removed alongside the hematoma and the kidney envelopes, which were then sent for histopathological analysis. On the cross-section of the kidney, a tumorous change was observed in the upper half of the kidney parenchyma, spreading to the fatty tissue of the hilum, of a soft consistency and with areas of hemorrhage, with an approximate size of 96 × 80 mm. Histopathological analysis revealed that it was an AML.

Ethics: Patient consent was obtained in writing, and the case report adheres to ethical protocols in accordance with institutional guidelines and applicable regulations.

DISCUSSION

AMLs are uncommon neoplasms first characterized by Morgan, Straumfjord, and Hall in 1951. Although the majority of these tumors are found within the kidneys, they can also occur in other anatomical sites such as the liver, spleen, uterus, and fallopian tubes. Renal AML represents a benign neoplasm that presents sporadically and in association with genetic syndromes like TS and lymphangioleiomyomatosis. Renal AMLs consist of mesenchymal elements of the kidney and are composed of varying amounts of mature adipose tissue, smooth muscle, and vessels with excessively thickened walls, which is why they are referred to as renal hamartomas [5, 6]. AMLs are categorized into three main types: classic AML, fat-deficient AML, and epithelioid AML [7]. The most significant risk linked to AML is bleeding into the retroperitoneal space, which occurs when the tumor ruptures. Conventionally, the evaluation of risk has been primarily based on tumor dimensions, with tumors exceeding 4 cm regarded as having a greater propensity for aneurysm formation and rupture. However, recent insights suggest that additional factors such as aneurysm presence, pregnancy, trauma, coagulopathies, hormonal fluctuations, and comorbidities like TS and lymphangioleiomyomatosis, also play significant roles in influencing rupture risk. There is evidence suggesting that genetic irregularities may serve as an early contributing factor in the intricate interplay of various risk elements associated with tumor rupture [8]. The development of aneurysms may play a significant role in the risk of tumor rupture, with the contribution largely dependent on the presence and size of these vascular dilations. Aneurysms are classified into two main categories based on their pathology: true aneurysms and pseudoaneurysms. True aneurysms, also known as primary aneurysms, involve all three layers of the arterial wall. In contrast, pseudoaneurysms, sometimes referred to as false aneurysms, are hematomas restricted by surrounding tissues. These often result from traumatic injuries or other breaches in the vessel wall [9, 10]. Pregnancy is also a significant factor influencing both the progression and the potential rupture of these tumors. The hormonal and hemodynamic changes that occur during gestation can accelerate tumor growth and increase the likelihood of complications such as rupture [11]. CT remains the most frequently employed imaging technique for the diagnosis of AML. The classic form of AML typically manifests as a lesion with predominant fatty attenuation, easily identifiable by its characteristic low-density appearance. In contrast, fat-poor AMLs tend to exhibit attenuation levels that are similar to or higher than surrounding tissues, often showing uniform enhancement after contrast administration. However, epithelioid AMLs generally appear as hyperattenuating masses with a heterogeneous enhancement pattern, sometimes resembling multilocular cystic structures. This variability in imaging features reflects the diverse pathological compositions of these tumor subtypes [12]. Management of all AMLs must be based on a clear diagnosis combined with a thorough evaluation of the potential for tumor rupture. Reasons to initiate treatment encompass concerns of cancerous transformation as well as episodes of spontaneous bleeding, risk of rupture, and risk for other complications. Treatment options range from drug therapy to embolization to surgical extirpation and depend on each individual case [8].

Recent studies published in leading urology and radiology journals have highlighted significant progress in understanding Wunderlich syndrome. Advances in imaging technologies, particularly contrast-enhanced CT, have greatly enhanced the ability to diagnose spontaneous renal hemorrhages efficiently, often before hemodynamic instability occurs [8]. Additionally, the latest research focuses on minimally invasive interventions, such as superselective embolization, which effectively control bleeding while preserving renal function and minimizing recovery times [13]. Furthermore, recent reviews emphasize the importance of early detection of underlying vascular anomalies, like aneurysms or malformations, which are critical for preventing recurrence and planning targeted therapy [14]. The evolving understanding of AML has contributed to increased awareness and underscored the importance of developing personalized, minimally invasive treatment approaches aimed at enhancing patient outcomes, including prognosis and quality of life for those affected by Wunderlich syndrome.

Although they are non-cancerous lesions of the renal tissue, AMLs can, in rare cases, rupture and trigger hemorrhagic shock due to sudden bleeding. Described as a non-malignant growth, this lesion arises from the unchecked multiplication of epithelioid cells and is composed of a mixture of fat tissue, vascular structures, and smooth muscle fibers. Retroperitoneal hemorrhage, stemming from the rupture of the tumor, stands out as the primary complication linked to AML. The probability of this complication increases with larger tumor dimensions, making size a key predisposing factor. Taking into account the clinical importance and seriousness of this potential complication, it is important to establish an accurate radiological diagnosis in a timely manner with the aim of timely therapeutic intervention and reducing the risk of potential additional complications.

Conflict of interest: None declared.

REFERENCES

1. Young J, Kalczynski J, Emerling A, Bianchi W. Renal angiomyolipoma rupture in a young female with COVID-19. Am J Emerg Med. 2021;47:316.e1–316.e3. [DOI: 10.1016/j.ajem.2021.02.012] [PMID: 33741199]
2. Gaffoor N, Mysorekar VV, Gunadal S, Divyashree BN, Sandeepa S, Murali N. Wun-derlich syndrome: a rare case associated with bleeding renal angiomyolipoma. Indian J Nephrol. 2024;34(3):271–3. [DOI: 10.4103/ijn.ijn_397_23] [PMID: 39114393]
3. Restrepo JCÁ, Millan DAC, Sabogal CAR, Bernal AFP, Donoso WD. New trends and evidence for the management of renal angiomyolipoma: a comprehensive narrative review of the literature. J Kidney Cancer VHL. 2022;9(1):33–41. [DOI: 10.15586/jkcvhl.v9i1.177] [PMID: 35096516]
4. Liu Z, Zou Y, Lv T, Guan H, Fan Z. Spontaneous rupture of enormous renal angiomyolipoma in a pregnant tuberous sclerosis patient: a rare case. BMC Nephrol. 2020;21(1):455. [DOI: 10.1186/s12882-020-02124-w] [PMID: 33129297]
5. Thapa N, Maharjan S, Hona A, Pandey J, Karki S. Spontaneous rupture of renal angiomyolipoma and its management: a case report. Ann Med Surg (Lond). 2022;79:104037. [DOI: 10.1016/j.amsu.2022.104037] [PMID: 35860139]
6. Anwaier A, Xu WH, Tian X, Ding T, Su JQ, Wang Y, et al. Evaluation of clinicopathological profiles and development of a risk model in renal epithelioid angiomyolipoma patients: a large-scale retrospective cohort study. BMC Urol. 2022;22(1):148. [DOI: 10.1186/s12894-022-01101-9] [PMID: 36096809]
7. Hatano T, Egawa S. Renal angiomyolipoma with tuberous sclerosis complex: how it differs from sporadic angiomyolipoma in both management and care. Asian J Surg. 2020;43(10):967–72. [DOI: 10.1016/j.asjsur.2019.12.008] [PMID: 31959574]
8. Shah J, Gandhi D, Prasad SR, Sandhu PK, Banker H, Molina R, et al. Wunderlich syndrome: comprehensive review of diagnosis and management. Radiographics. 2023;43(6):e220172. [DOI: 10.1148/rg.220172] [PMID: 37227946]
9. Courtney M, Mulholland D, O'Neill D, Redmond C, Ryan J, Geoghegan T, et al. Natural growth pattern of sporadic renal angiomyolipoma. Acta Radiol. 2020;62(2):276–80. [DOI: 10.1177/0284185120918372] [PMID: 32321277]
10. Abouelkheir RT, El-Ksas M, SA Fattah, Tamer T, El-Diasty T. Efficacy and safety of selective renal arterial embolization in renal angiomyolipoma: a prospective single-center study. Egyptian J Radiol Nucl Med. 2022;53(1):6–10. [DOI: 10.1186/s43055-022-00848-3]
11. Khor V, Mohd Naim MY, Fahmy O, Lee CKS, Azli S, Rahim EA, et al. Wunderlich syndrome in pregnancy: life-threatening bleeding renal angiomyolipoma in first and third trimesters—two case reports and literature review. Afr J Urol. 2024;30(1):2–4. [DOI: 10.1186/s12301-024-00457-8]
12. Fejes Z, Sánta F, Jenei A, Király I, Varga L, Kuthi L. Angiomyolipoma of the kidney—clinicopathological analysis of 52 cases. Pathol Oncol Res. 2023;28:2–10. [DOI: 10.3389/pore.2022.1610831] [PMID: 36699622]
13. Priyadarshee P, Baskar G, Murugan G, Indiran V, Ashwinkumar A. Wunderlich syndrome – minimally invasive treatment. J Neonatal Surg. 2025;14(19S):417–20. [DOI: 10.63682/jns.v14i19S.4784]
14. Albornoz MA, Branca L, Samoyedny A. Acute retroperitoneal hemorrhage due to multi-vessel aneurysmal bleeding as the initial manifestation of polyarteritis nodosa in a previously healthy female. Cureus. 2023;15(9):e45718. [DOI: 10.7759/cureus.45718] [PMID: 37868509]

Вундерлихов синдром – приказ болесника и кратак преглед литературе

Мирјана Стојановић, Перица Аднађевић, Тијана Косановић, Лејла Хајдарпашић, Марјана Ђорђевић

Клиничко-болнички центар „Др Драгиша Мишовић – Дедиње", Одељење радиологије, Београд, Србија

САЖЕТАК

Увод Ренални ангиомиолипоми (АМЛ) су бенигне неоплазме са ниским ризиком од спонтане руптуре, које могу узроковати хеморагијски шок као најтежу компликацију. АМЛ се састоје од масног ткива, крвних судова и глатких мишића. Вундерлихов синдром се односи на спонтано, нетрауматско крварење из бубрега у субкапсуларни и/или перирenални простор. Већина пацијената са реналним АМЛ-ом је асимптоматска и дијагноза се поставља приликом рутинских прегледа, док неки могу доживети озбиљне компликације попут руптуре, крварења или хиповолемичног шока.

Приказ болесника У раду се описује клиничка презентација АМЛ-а са руптуром код пацијенткиње, уз кратак преглед других случајева АМЛ-а у литератури.

Пацијенткиња, старости 68 година, примљена је у хитну службу због изненадних, јаких болова у стомаку који су се ширили у десни лумбални регион и били праћени мучнином и слабошћу. Након клиничког прегледа, ултразвука абдомена и компјутеризоване томографије абдомена и карлице, урађена је операција током које су десни бубрег и хематом одстрањени и послати на патохистолошку анализу. Резултат патохистолошке анализе потврдио је да се ради о АМЛ-у.

Закључак АМЛ су бенигне неоплазме са могућим озбиљним компликацијама. Најтежа компликација је руптура, која доводи до ретроперитонеалног крварења, при чему је величина тумора значајан фактор ризика. С обзиром на клиничку важност ове могуће компликације, битно је успоставити брзу и тачну радиолошку дијагнозу, са циљем правовремене терапијске интервенције и смањења могућих додатних компликација.

Кључне речи: ренални ангиомиолипом; радиолошка дијагноза; руптура; лечење

DOI: https://doi.org/10.2298/SARH240302047N
UDC: 616.711-002.9

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Hydatid cyst of the thoracic spine – where can we make a mistake?

Uroš Novaković[1,2], Milan Savić[2,3], Miloš Vasić[1], Valerija Teodosić[1,2], Slaviša Zagorac[1,2]

[1]University Clinical Center of Serbia, Clinic for Orthopedic Surgery and Traumatology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Clinic of Thoracic surgery, Belgrade, Serbia

SUMMARY

Introduction Spinal hydatid cyst disease, caused by *Echinococcus granulosus*, is a rare yet challenging condition often overlooked in differential diagnoses.

Case outline We present the case of a 41-year-old woman with a spinal hydatid cyst initially misdiagnosed despite persistent thoracic spine pain, night fevers, and a history of chiropractic and physical therapy treatments. Diagnostic confusion persisted despite various examinations, including X-rays, computed tomography scans, and magnetic resonance imaging, with radiological findings initially suggestive of osteomyelitis or neoplastic changes. Ultimately, surgical intervention revealed a hydatid cyst, emphasizing the diagnostic challenges posed by its nonspecific radiographic features. Treatment involved a corpectomy with spinal stabilization and postoperative albendazole therapy. Regular radiographic monitoring showed no recurrence or dissemination of the cyst.

Conclusion Despite the rarity of spinal hydatid cysts, they should be considered in cases of cystic lesions causing spinal compression. Surgery remains the cornerstone of treatment, often combined with long-term chemotherapy. This case underscores the importance of considering uncommon diagnoses in persistent spinal pathology and highlights the complexities of diagnosing and managing spinal hydatid cyst disease.

Keywords: spinal hydatid cyst; *Echinococcus granulosus*; misdiagnosis; surgical treatment; chemotherapy

INTRODUCTION

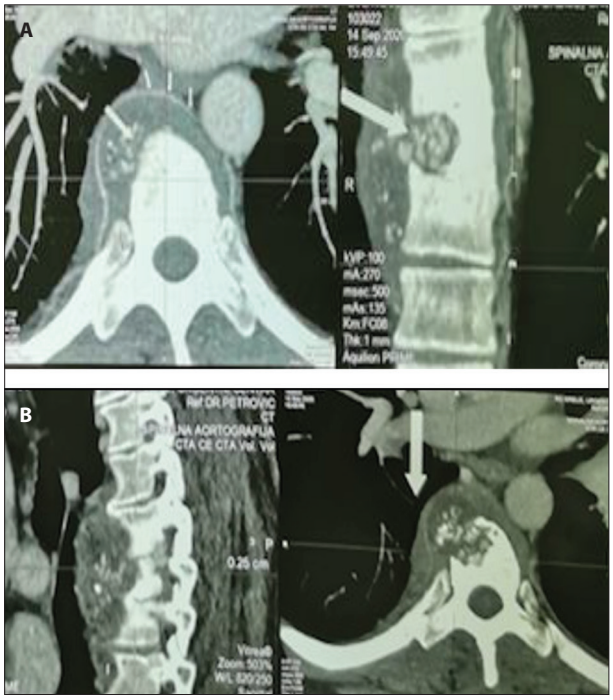
Infection of the spinal column are still one of the leading problems in diagnosis and treatment around the world. Most common is vertebral osteomyelitis and ranges from 2% to 16.7% of all cases. With an incidence peak from younger od 20 years of age and above 50 years of age and a predominance for male patients (male to female ratio 2:1 and 5:1 respectively). Mortality ranges from 2–4% and the dominant cause is monomicrobial bacterial infections (30–80%), but either a combination of bacterial agents or other microorganism can be the cause of rare spinal infections [1]. Among them, parasite *Echinococcus granulosus* is the cause of the hydatid cyst disease [2]. Humans can contract it as an intermediate host in the hydatid disease biological cycle. They become infected either directly from a dog bite or indirectly via consuming water or food that has been tainted with parasite eggs [3]. Cysts are typically seen in parenchymal organs, like the brain, liver, and lung, but it can be present in every part of the body, from the head to the toe, although the bone involvement is quite uncommon [4]. The incidence of osseous echinococcosis is low (approximately 0.5–4%). In osseous echinococcosis, spinal involvement is the most common form, though rare overall approximately 0.2–1% [5]. The most common spinal location is the thoracic spine (approximately 50%), followed by the lumbosacral region (approximately 29%) and the lumbar spine (approximately 21%) [6]. Spinal hydatid cysts have become a raising problem in recent years. Although vast array of laboratory tests and radiological diagnostic tools are available the spinal hydatid disease are generally overlooked in differential diagnosis possibly due to the rate of occurrence and to medical community lack of awareness [7]. In this case, we present a female patient with spinal hydatid cyst, which has been misdiagnosed.

CASE REPORT

A 41-year-old female presented with a several-month history of pain in her thoracic spine, accompanied by night pain and fever with no neurological impairment. She was physically very active and had no underlying comorbidities. She refused to undergo examination, and went to a chiropractor treatment who performed periarticular infiltrations, but there was no improvement. Subsequently, she initiated private physical therapy independently, without prior medical advice or referral. Despite long-term physical and drug therapy, the pain was still present, she underwent X-ray examination, which were with no pathological finding. Laboratory results revealed a slight elevation in the erythrocyte sedimentation rate. She also underwent psychiatric examination; a

Received • Примљено: March 2, 2024
Revised • Ревизија: June 4, 2025
Accepted • Прихваћено: June 5, 2025
Online first: June 6, 2025

Correspondence to:
Valerija TEODOSIĆ
University Clinical Center of Serbia
Clinic for Orthopedic Surgery and Traumatology
Pasterova 2
11000 Belgrade
Serbia
valerija.teodosic996@gmail.com



Figures 1A and 1B. Preoperative computed tomography scan of thoracic spine: axial and sagittal section of multiple levels of thoracic spine which showed paravertebral and prevertebral change from Th5–Th9 with infiltration and osteolysis of vertebral bodies, disc space and spinal canal, with connection to S6 lung segment

diagnosis of anxiety had been established. Despite drugs and physical therapy, the pain was worsening. Finally, three months after the initial onset of symptoms, the patient underwent a computed tomography (CT) scan, which showed paravertebral and prevertebral change from Th5–Th9 with infiltration and osteolysis of vertebral bodies, disc space and spinal canal, with connection to S6 lung segment. Radiological conclusion was osteomyelitis or lung tumor with lymphadenopathy (T3N1M1a) (Figures 1A and 1B). A nuclear magnetic resonance imaging (MRI) of the thoracic spine was conducted which revealed changes from Th5 to Th8, posterior ribs VI and VII, prevertebral and paravertebral, and in the lung, spread epidural with foramina infiltration and compression on roots Th6 and Th7. The radiological conclusion: tuberculous (TBC) spondylitis or neoplastic change (Figure

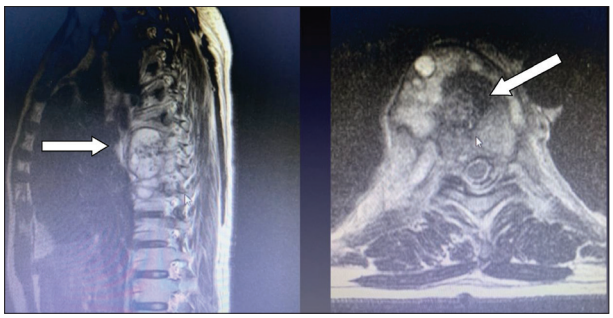


Figure 2. Preoperative nuclear magnetic resonance of thoracic spine: axial and sagittal section of multiple levels of thoracic spine which showed a visible cyst that invades most of several vertebral bodies and the spinal canal, also S6 lung segment

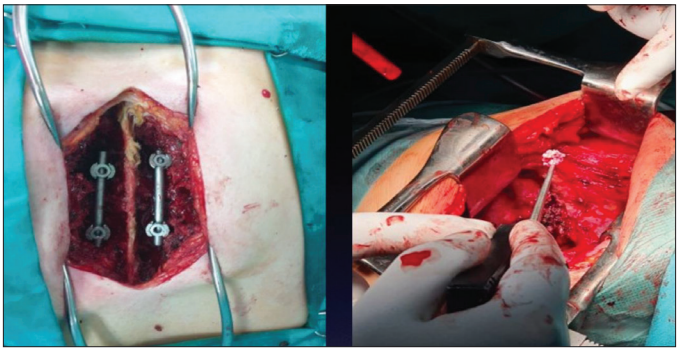


Figure 3. Intraoperative findings: transpedicular stabilization with screws

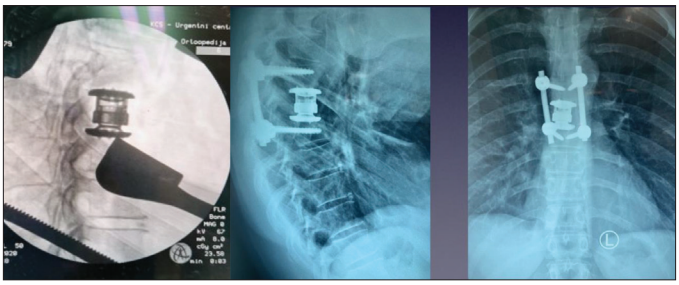


Figure 4. Postoperative findings: X-ray – anteroposterior and lateral view: properly positioned osteosynthesis material

2). She underwent bronchoscopy (with normal findings), QuantiFERON-TB test (the findings were negative) and a Tru-cut biopsy of the lungs which have shown monocyte/histocyte proliferation, possible inflammatory myofibroblastic tumor or pneumonitis. The patient was referred to an oncologist who indicated radiotherapy of the infiltrated segment. However, the patient declined this modality of treatment, and was referred to a spinal surgeon. After a clinical examination and a thorough reviewing existent medical documentation and available radiographic sources, we suggested surgical treatment, open transthoracic approach with a biopsy of the affected region and a corpectomy with an implantation of an expandable cage and subsequently a posterior transpedicular stabilization (Figures 3 and 4). Postoperatively there was no neurological impairment. Biopsy of the lesion has shown a hydatid cyst caused by *Echinococcus granulosus*. Postoperatively, the patient was treated with albendazole for six months and routinely monitored by both a spinal surgeon and an infectious diseases specialist. Follow-up imaging was performed at three, six, 12, and 24 months, with no evidence of cyst recurrence or dissemination.

Ethics: The study was approved by the Ethics Committee of the University of Belgrade Faculty of Medicine (Decision number 1051/3), and carried out in accordance with the Helsinki Declaration and its amendments. This case report analyzes data collected in the period preceding the writing of this article, in accordance with the provisions of the Law on the Protection of Personal Data of the Republic of Serbia. Insight into the patient records in this case report was obtained in accordance with Article 3 of the above-mentioned Law, which necessitates a precise definition of how this data may be used. Informed consent was obtained

from the patient. In keeping with the University Clinical Center of Serbia regulations, the patient consented to participate in any retrospective studies by signing her consent to hospitalization and treatment, as well as to the use of her medical data in this case report.

DISCUSSION

Spinal hydatid cyst illness is a rare and challenging condition to manage. An endemic condition, spinal hydatid cyst disease is typically observed in nations along the Mediterranean and in the Middle East [8]. The most common spinal location is the thoracic spine (approximately 50%) and most patients with thoracic spine echinococcosis had a history of extraspinal cystic echinococcosis, most commonly of the lungs, liver, kidneys, and soft tissues [9]. Our patient had no comorbidities. Hydatid cysts typically extend beyond the vertebral bodies, frequently affecting the intervertebral discs, spinal cord, and posterior elements, with potential growth into the spinal canal [10]. Radiographic diagnosis is challenging because there are no specific findings consistent with spinal echinococcosis; misdiagnosis is common with radiographs only and the lesions can be confused with tumors such as metastases and chondroblastoma, or other infections such as tuberculosis, spinal or paraspinal abscess [11]. In our case, the X-ray were without any radiological features which are pathognomonic for hydatid cyst (zones of multilocular osteolysis) [12]. Typical CT finding is multilocal, round cyst, with erosion of vertebral body and posterior elements. Further, the cyst density can be measured in order to confirm diagnosis, which was not done in our case. MRI is more sensitive than CT and revealed multiple cystic, fluid-filled lesions with internal septations, forming a "bunch of grapes" appearance at multiple spinal levels [13]. Regarding laboratory findings, polymerase chain reactions, Western blots, indirect hemagglutination tests, and serological enzyme-linked immunosorbent assays are utilized for diagnosis [14]. In our case, CT and MRI scans revealed changes in anterior parts of vertebral body, including disc space. Our case was challenging regarding proper diagnosis and surgical approach. Our patient had a paravertebral and prevertebral change from Th5–Th9 with infiltration and osteolysis of vertebral bodies, disc space, and spinal canal, with connection to S6 lung segment. What was confusing for radiologist is involvement of disc space, which is not characteristic for hydatid cyst [15].

The diagnostic procedures that were conducted were bioscopy, QuantiFERON-TB test, and a Tru-cut biopsy of the lungs, as well as a CT scan and a nuclear MRI scan. Biopsy is indicated when other radiological findings are not clear [16]. However, in hydatid cyst, biopsy can lead to the rupture and systematic reaction, hence biopsy should be avoided. After Tru-cut biopsy in our case, the diagnosis of inflammatory pseudo tumor has been established. We had no experience with this kind of tumor and in the literature, we found many names related to this lesion like fibrous xanthoma, plasma cell granuloma, pseudosarcoma, lymphoid hamartoma, myxoid hamartoma, inflammatory myofibrohistiocytic proliferation, benign myofibroblastoma, and most recently, inflammatory myofibroblastic tumor [17]. The treatment is based on two pillars: chemotherapy and surgical treatment. Surgical treatment is the treatment of choice. Among diverse surgical approaches and techniques, posterior laminectomy and fusion is the treatment of choice. However, it can be combined with thoracotomy [18]. According to literature, the main drawbacks regarding the surgical treatment are: systematic allergic reaction, recurrence, and general contraindications [19]. Pharmacologic treatment consists of administration of anti-parasitic drugs such as benzimidazoles (albendazole and mebendazole) [20]. According to the Turgut [21], patients that have a low rate of recurrence are those with combined pharmacological therapy (5% in patients treated with combined modalities, and 32% in those patients who only underwent surgery). We were against radiation therapy and chemotherapy, which was suggested by radiologist and we offered surgical treatment in order to confirm diagnosis, to make complete resection of the lesion and to stabilize the spinal column, which was expected after complete removal of the cyst. The aim of spinal surgery, depending on where the condition is located, is to decompress the spinal cord and, if necessary, to stabilize the spinal column to make up for the stability that was lost during cyst excision. This postulate is related to all spinal pathologies. We performed corpectomy with an implantation of an expandable cage, and a posterior transpedicular stabilization and cyst removal, as we could not perform anterior fixation due to lack of availability of implants. Albendazole can be helpful in preventing or delaying recurrence as well as preventing intraoperative dissemination of the cyst, even though it is well known that it cannot guarantee recovery or prevent recurrence when used alone [3]. This is especially true when used as an auxiliary application in patients who are ineligible for surgery or in conjunction with surgical treatment. Our patient was treated with albendazole (intravenously administered) for six months after the initial surgery. A cysticidal substance (hypertonic 30% saline, cetrimide, or 70–95% ethanol) can be used. During the procedure our patient underwent, we did not use any type of cysticidal substance, only hypertonic saline solution was used as an irrigation method as well as an iodine solution [22]. The risk of recurrence has varied between 30% and 100% [23, 24]. Our patient underwent regular radiological follow-up at three, six, 12, and 24 months post-surgery, with no evidence of cyst recurrence or dissemination. The limitation was that the patient was lost to follow up after two years of initial operation. We are aware that spinal hydatid cyst has been already described in literature and the diagnosis and treatment options are well known and evidence-based. However, our opinion was that this case is interesting due to several peculiarities: wrong patient behavior, wrong working diagnosis, histopathological finding of the biopsy, as well as the type of surgical treatment.

Our case showed that hydatid cyst is still a challenging medical issue, despite available diagnostic tools, due to the various and unspecific clinical and radiological features.

The clinical course leading to diagnosis can be long and difficult. The spinal hydatid cyst should be considered in the differential diagnosis when there are cystic lesions that cause osteolysis and spinal compression. The therapy of choice should always be surgery and long-term chemotherapy.

Conflict of interest: None declared.

REFERENCES

1. Tsantes AG, Papadopoulos DV, Vrioni G, Sioutis S, Sapkas G, Benzakour A, et al. Spinal Infections: An Update. Microorganisms. 2020;8(4):476. [DOI: 10.3390/microorganisms8040476] [PMID: 32230730]
2. McManus DP, Zhang W, Li J, Bartley PB. Echinococcosis. Lancet. 2003;362(9392):1295–304. [DOI: 10.1016/S0140-6736(03)14573-4] [PMID: 14575976]
3. Neumayr A, Tamarozzi F, Goblirsch S, Blum J, Brunetti E. Spinal cystic echinococcosis--a systematic analysis and review of the literature: part 1. Epidemiology and anatomy. PLoS Negl Trop Dis. 2013;7(9):e2450. [DOI: 10.1371/journal.pntd.0002450] [PMID: 24086783]
4. Meng Y, Ren Q, Xiao J, Sun H, Huang Y, Liu Y, et al. Progress of research on the diagnosis and treatment of bone cystic echinococcosis. Front Microbiol. 2023;14:1273870. [DOI: 10.3389/fmicb.2023.1273870] [PMID: 37920269]
5. Ammar A, Riahi H, Chaabouni M, Venturelli N, Renault V, Dray B, et al. The multifaceted musculoskeletal hydatid disease. Skeletal Radiol. 2024;53(10):2181–94. [DOI: 10.1007/s00256-024-04644-0] [PMID: 38483570]
6. Sioutis S, Reppas L, Bekos A, Soulioti E, Saranteas T, Koulalis D, et al. Echinococcosis of the spine. EFORT Open Rev. 2021;6(4):288–96. [DOI: 10.1302/2058-5241.6.200130] [PMID: 34040806]
7. Bhake A, Agrawal A. Hydatid disease of the spine. J Neurosci Rural Pract. 2010;1(2):61–2. [DOI: 10.4103/0976-3147.71715] [PMID: 21808504]
8. Padayachy LC, Ozek MM. Hydatid disease of the brain and spine. Childs Nerv Syst. 2023;39(3):751–8. [DOI: 10.1007/s00381-022-05770-7] [PMID: 36443475]
9. Monge-Maillo B, Olmedo Samperio M, Pérez-Molina JA, Norman F, Mejía CR, Tojeiro SC, et al. Osseous cystic echinococcosis: A case series study at a referral unit in Spain. PLoS Negl Trop Dis. 2019;13(2):e0007006. [DOI: 10.1371/journal.pntd.0007006] [PMID: 30779741]
10. Gao S, Fulati M, Sheng W. Extensive hydatid cysts involving the lumbosacral vertebrae and pelvis. IDCases. 2023;31:e01677. [DOI: 10.1016/j.idcr.2023.e01677] [PMID: 36654737]
11. Lao X, Hu D, Ji L, Zhan T, Li T, Luo S, et al. Magnetic resonance imaging and next-generation sequencing for the diagnosis of cystic echinococcosis in the intradural spine: a case report. J Med Case Rep. 2023;17(1):466. [DOI: 10.1186/s13256-023-04197-1] [PMID: 37946273]
12. Baykan AH, Aydin E, Koc M, Sahin H, Karul A, Baykan ME, et al. Hydatid disease: imaging, treatment, and beyond. Clin Radiol. 2025;80:106748. [DOI: 10.1016/j.crad.2024.106748] [PMID: 39631363]
13. Singh N, Anand T, Singh DK. Imaging diagnosis and management of primary spinal hydatid disease: a case series. Egypt J Radiol Nucl Med. 2022;53:106. [DOI: /10.1186/s43055-022-00785-1]
14. AlRashed FM, AlShahrani DA. Infected pulmonary hydatid cyst: A challenging diagnosis. Saudi Med J. 2024;45(4):433–6. [DOI: 10.15537/smj.2024.45.4.20230078] [PMID: 38657978]
15. Song X, Liu D, Wen H. Diagnostic pitfalls of spinal echinococcosis. J Spinal Disord Tech. 2007;20(2):180–5. [DOI: 10.1097/01.bsd.0000211288.37013.42] [PMID: 17414991]
16. Ozdemir O, Calisaneller T, Yildirim E, Altinors N. Percutaneous CT-guided treatment of recurrent spinal cyst hydatid. Turk Neurosurg. 2011;21(4):685–7. [PMID: 22194140]
17. Siemion K, Reszec-Gielazyn J, Kisluk J, Roszkowiak L, Zak J, Korzynska A. What do we know about inflammatory myofibroblastic tumors? A systematic review. Adv Med Sci. 2022;67(1):129–38. [DOI: 10.1016/j.advms.2022.02.002] [PMID: 35219201]
18. Saul D, Seitz MT, Weiser L, Oberthür S, Roch J, Bremmer F, et al. Of Cestodes and Men: Surgical Treatment of a Spinal Hydatid Cyst. J Neurol Surg A Cent Eur Neurosurg. 2020;81(1):86–90. [DOI: 10.1055/s-0039-1693707] [PMID: 31486051]
19. Herrera A, Martínez AA, Rodríguez J. Spinal hydatidosis. Spine (Phila Pa 1976). 2005;30(21):2439–44. [DOI: 10.1097/01.brs.0000184688.68552.90] [PMID: 16261123]
20. Ganji A, Jalali-Mashayekhi F, Hajihossein R, Eslamirad Z, Bayat PD, Sakhaie M. Anti-parasitic effects of resveratrol on protoscolices and hydatid cyst layers. Exp Parasitol. 2022;241:108360. [DOI: 10.1016/j.exppara.2022.108360] [PMID: 35995249]
21. Turgut M. Hydatid disease of the spine: a survey study from Turkey. Infection. 1997;25(4):221–6. [DOI: 10.1007/BF01713148] [PMID: 9266261]
22. Chaouch MA, Ben Jabra S, Sayadi M, Toumi O, Noomen F. Severe Hypernatremia During Hydatid Cyst Surgery: An Anusual Cause Of Acute Abdomen. Ann Parasitol. 2023;69(3–4):115–8. [DOI: 10.17420/ap6903/4.515] [PMID: 38423520]
23. Obame FLO, Dokponou YCH, Mohcine S, Elmi SM, Imbunhe N, El Kacemi I, et al. Surgical outcome and prognostic factors for 39 recurrent spinal hydatid cysts. Surg Neurol Int. 2023;14:347. [DOI: 10.25259/SNI_667_2023] [PMID: 37810304]
24. Trifa A, Maamri K. Aggressive behavior and recurrent spinal hydatid cyst. Pan Afr Med J. 2021;40:202. [DOI: 10.11604/pamj.2021.40.202.32389] [PMID: 35136465]

Хидатидна циста торакалне кичме – где можемо погрешити?

Урош Новаковић[1,2], Милан Савић[2,3], Милош Васић[1], Валерија Теодосић[1,2], Славиша Загорац[1,2]

[1]Универзитетски клинички центар Србије, Клиника за ортопедску хирургију и трауматологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за торакалну хирургију, Београд, Србија

САЖЕТАК

Увод Цистична ехинококоза (или хидатидна циста) локализована на кичменом стубу, узрокована цестодом *Echinococcus granulosus*, представља ретко али изазовно стање, које се често занемарује у диференцијалној дијагностици.

Приказ случаја Представљамо случај 41-годишње жене са цистичном ехинококозом на кичменом стубу, која је првобитно погрешно дијагностикована упркос упорним боловима у торакалној кичми, ноћној грозници и историји киропрактичне и физикалне терапије. Неизвесност у дијагностиковању болести трајала је упркос разним прегледима, укључујући рендгенске снимке, скенере и магнетну резонанцу, са радиолошким налазима који су првобитно указивали на остеомијелитис или неопластичне промене. На крају, хируршка интервенција је открила хидатидну цисту, наглашавајући дијагностичке изазове које представљају њене неспецифичне радиографске карактеристике. Лечење је било оперативно, урађена је корпектомија са стабилизацијом кичме, а укључивало је и постоперативну терапију албендазолом. Редовно радиографско праћење није показало рецидив или дисеминацију цисте.

Закључак Иако су хидатидне цисте на кичменом стубу ретке, треба их узети у обзир у случајевима цистичних лезија које изазивају компресију кичмене мождине. Хирургија остаје основни начин лечења, често у комбинацији са дуготрајном хемиотерапијом. Овај случај наглашава важност разматрања неуобичајених дијагноза у трајној патологији кичменог стуба, као и сложеност дијагностиковања и лечења болести хидатидне цисте локализоване на кичменом стубу.

Кључне речи: хидатидна циста; кичмени стуб; *Echinococcus granulosus*; погрешна дијагноза; хируршко лечење; хемиотерапија

DOI: https://doi.org/10.2298/SARH240109039V
UDC: 616.853; 617.751

REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Visual functioning and cerebral visual impairment in children with infantile spasms – West syndrome

Vesna Vučinić[1], Valentina Martać[1], Nataša Cerovac[2,3], Miroslav Stamenković[1,4]

[1]University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University Clinical Center of Serbia, Clinic for Neurology and Psychiatry for Children and Youth, Belgrade, Serbia;
[4]Zvezdara Clinical Centre, Belgrade, Serbia

SUMMARY
Cerebral visual impairment (CVI) is the most common cause of visual impairment in children in both developed and developing countries, making it a relevant research topic on the functional status of neuro-risk children in recent decades. The multifactorial nature of West syndrome (WS) and the variability in visual functions and functioning hinder the timely diagnosis of this type of visual impairment. The atypical ways of following stimuli, establishing and maintaining visual contact, and sustaining visual attention are the first indicators of deviations in visual behavior that may suggest neuro-risk. Changes in visual behavior may manifest as alterations in the quality or absence of visual responsiveness, deficits in various visual functions and oculomotor skills, often associated with atypical findings in visual evoked potentials. Cortically mediated visual functions, such as visual acuity, visual field, contrast sensitivity, and oculomotor skills, are also at risk in children with infantile spasms and WS. In addition to basic visual functions, visuo-perceptual and visuo-motor skills are significantly affected, which is manifested in everyday behavior and motivation to observe. The degree and manifestations of CVI in children with infantile spasms depend on numerous factors. Multidisciplinary diagnostic procedures that determine whether cerebral visual impairment results from genetic factors, WS, or other neurological conditions are crucial for creating treatment plans and predicting outcomes.
Keywords: visual impairment; epilepsy; functional vision

INTRODUCTION

West syndrome (WS) is a severe form of childhood epilepsy characterized by a specific type of seizure (infantile spasms), an electroencephalogram finding showing hypsarrhythmia, and, depending on the age, developmental regression or delay [1–5]. Infantile spasms occur at an early age, between four and seven months. They are most often the result of hypoxic-ischemic encephalopathy, cortical dysplasia, or genetic anomalies [6]. The onset of this type of seizure can be very subtle, making it difficult to recognize milder forms when the first symptoms appear [7]. These seizures are most commonly manifested as flexions and extensions of individual muscle groups, usually after waking up or before sleep. Myoclonus can last from 5–30 minutes and consist of 5–100 spasms [8]. If medication therapy is ineffective, the seizures negatively affect the condition of the immature brain, leading to delays or regression in the child's development [9, 10].

WS is a cause of generalized epilepsy. However, it can be associated with localized cerebral damage, primarily in the temporal–occipital regions. Infantile spasms can pathologically affect the optic radiation and/or visual cortical areas, leading to cerebral visual impairment (CVI). Timely recognition of this association is a significant challenge for pediatric ophthalmologists and neuro-ophthalmologists [11, 12]. The multifactorial nature of WS and the variability in visual functions and visual functioning hinder timely diagnosis. Some studies have confirmed that visual functioning deteriorates with the onset of the first spasms caused by WS, leading to impairments in visual functions controlled by the cerebral cortex, such as visual acuity, visual field, and visual attention [13]. Deficits in visual functioning, primarily related to damage to the visual pathways after the chiasm and cerebral structures, are commonly referred to as cerebral visual impairment [11, 14]. Cerebral visual impairment is the most common cause of pediatric visual impairment [15], i.e., disturbances in visual functioning and visual perception in children in both developed and developing countries [15, 16, 17]. In recent decades, cerebral visual impairment has been a highly relevant research topic on the functional status of neuro-risk children [18, 19].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF CVI

The extensive literature on this impairment uses three terms: cortical visual impairment,

Received • Примљено: January 9, 2025
Revised • Ревизија: May 9, 2025
Accepted • Прихваћено: May 17, 2025
Online first: May 20, 2025

Correspondence to:
Valentina MARTAĆ
University of Belgrade
Faculty of Special Education and Rehabilitation
Visokog Stevana 2
11000 Belgrade, Serbia
valentinamartac@fasper.bg.ac.rs

cerebral visual impairment, and cognitive visual impairment, all abbreviated as CVI [20]. The need to determine the appropriate term arises from the fact that limitations in visual functioning cannot be attributed to ocular damage. The term "cortical" explains bilateral vision loss due to damage to the visual areas of the cerebral cortex [21], with normal pupil response and clinical examination [18]. The term "cerebral" encompasses a broader range of lesions within the central nervous system, with visual impairments not only related to the cortex but also to subcortical structures [22]. One of the recent papers by Costa [20] emphasizes the importance of terminological alignment. This author believes that terminology should serve to integrate anatomical and physiological characteristics and that central visual impairment (CVI) should be the umbrella term encompassing both cortical visual impairment (CoVI) and cerebral visual impairment (CeVI).

Cerebral visual impairment is associated with various neurological conditions, such as hypoxic-ischemic encephalopathy, periventricular leukomalacia, intraventricular hemorrhages, syndromes, etc. [15]. These conditions often cause co-occurring disorders and impairments, such as cerebral palsy, hemiparesis, microcephaly, hydrocephalus, epilepsy, hearing problems, developmental delays, etc. Therefore, differential diagnosis is essential for treatment purposes [12, 23, 24]. Researchers state that it is challenging to isolate cases in which CVI is genetically determined or congenital from those resulting from WS or other neurological conditions. Lack of interest in the environment, which is typical of autism or intellectual disability, inability to perform saccades (rapid eye movements) in a child with motor apraxia, or delays in visual maturation can mimic CVI. In these cases, the diagnosis may be rushed, incorrect, and not reflect the child's actual condition [11]. Symptoms of cerebral visual impairment include the absence of social communication and smooth eye movements, difficulties in fixation, visual scanning, and searching the materials and the environment, as well as the presence of nystagmus [12]. However, without a detailed analysis of all parameters and transdisciplinary collaboration, a diagnosis cannot be made, and treatment cannot be proposed [14].

CVI – SPECIFIC FEATURES IN WEST SYNDROME

The relation between infantile spasms / WS and cerebral visual impairment derives from the fact that they have the same causes [25]. Infantile spasms coincide with the most intensive visual development, which explains the difficulties in visual functioning [5]. These difficulties may be a signal for detecting neurological changes, particularly when the seizures are subtle and cannot be timely identified by parents or professionals [1, 7].

CVI is a complex condition, most commonly caused by damage to cerebral structures and/or visual pathways. Authors increasingly report that ocular problems, such as anomalies of the fundus or optic papilla and damage to other structures of the peripheral visual system, are also observed alongside cerebral structural damage [26]. Conditions such as strabismus, refractive errors, nystagmus, etc. frequently co-occur with CVI, negatively impacting visual functioning [27]. In acquired CVI, the most common ocular changes include strabismus, visual field deficits or alterations, and a pale optic papilla [14]. The range of these changes indicates that difficulties in visual functioning can vary from delayed to complete absence of visual responsiveness [14, 28]. These changes may manifest as alterations in the quality or absence of visual responsiveness, deficits in various visual functions, and oculomotor skills [13], often associated with altered findings in visual evoked potentials. The first deviations in visual behavior observed by parents involve the way a child tracks stimuli, maintains visual attention, and establishes and sustains eye contact [29]. Loss of social contact and visuo-social responsiveness may signal the presence of WS [4]. Furthermore, studies have shown that the loss of visual responsiveness coincides with the onset of seizures [30]. Numerous researchers identify unstable visual attention and fixation disorders as primary symptoms of cerebral visual impairment [31]. Cortically mediated visual functions – visual acuity, visual field, contrast sensitivity, and oculomotor skills – are at risk in children with infantile spasms and WS [5, 32]. Oculomotor disturbances are common, with upward gaze deviation and nystagmus being the most frequently observed [13, 30]. According to some authors, these disturbances result from pathological changes in brain activity [33]. Delayed fixation shifts and brief visual attention are already noticeable at the age of three months and may be associated with sleep difficulties and damage to ascending tracts [13, 30]. In WS, the visual tracking skill is often absent or inconsistent and fragmented [33]. Visual behavior in children with CVI and WS is characterized by frequent blinking, eye squinting, and latency in detecting stimuli during visual scanning [14, 30, 32]. In addition to basic visual functions, visuo-perceptual and visuo-motor abilities, particularly hand–eye coordination, are significantly impaired in children with CVI and WS [13]. Difficulties in visuospatial abilities, caused by reduced blood flow in the parieto-occipital region, are manifested during orientation and mobility, as well as while determining spatial relations [34]. Regression in cognitive functioning affects the motivation for observing and maintaining visual attention, making visual scanning and searching the materials and the environment challenging for these children [30, 35].

INFANTILE SPASMS – WEST SYNDROME THERAPY AND VISUAL FUNCTIONING

Determining therapy with favorable long-term effects is closely related to the timing of seizure detection and identifying the cause, i.e., the etiology of infantile spasms (IS), which often requires genetic testing [6]. In 70% of cases, typically in symptomatic IS, the etiology of seizures can be identified, while the remaining cases are of unknown origin [6]. Changes in visual functioning, as well as other developmental domains, are closely related to seizure

control and the use of medication therapy. If the therapy does not have the expected effect, it is necessary to make adjustments, monitor the child's development, and conduct assessments every six months [2]. In children with infantile spasms leading to cerebral visual impairment, the results are noticeable after a few months of therapy unless severe visual system damage previously occurred [11, 31].

The negative impact of infantile spasms on all domains of development and functioning, along with pronounced resistance to numerous antiepileptics, sometimes requires the implementation of more aggressive therapy. Therapy for infantile spasms is based on the use of valproate (valproic acid) or adrenocorticotropic hormone (ACTH) [2, 8]. Medications used in treating infantile spasms, such as vigabatrin or corticosteroids, often have sedative effects and can influence visual attention and visual functioning, manifested through prolonged visual latency. However, it is sometimes difficult to determine whether this behavior is a result of the medication or the persistence of seizures [1, 30].

Vigabatrin is the medication of choice for treating infantile spasms. However, its toxic effects on the retina are often emphasized, as evidenced by findings obtained through electroretinography and optical coherence tomography [10]. Long-term vigabatrin therapy can lead to permanent concentric narrowing of the visual field. On the other hand, exposure to this medication for less than nine months is not a significant risk factor for visual impairment, especially in children who started therapy after their first year of life [36, 37]. In some children, difficulties in visual functioning are not related to the use of vigabatrin, as they were present before the medication was administered [10]. Most researchers agree that the results depend on the medication dosage, the therapy duration, and the presence of additional ophthalmological conditions [36, 37]. Unlike valproate, adrenocorticotropic hormone and prednisone do not have a negative impact on visual functions [2]. Alternative forms of therapy include medications such as topiramate, zonisamide, and clonazepam, as well as the implementation of a ketogenic diet under strict professional supervision. Studies have shown that these medications successfully control seizures in individual cases. However, there is no evidence that they are more effective than primary therapy, making them only a potential supplementary option [2].

IMPLICATIONS FOR EARLY INTERVENTION

When considering the role of vision in brain development, particularly the importance of early visual experience, the right of children with WS to be included in early intervention programs focused on vision and visual functioning is indisputable. In children with infantile spasms, assessing visual functioning alongside an ophthalmological examination is essential to form a comprehensive visual profile and select a treatment to improve functional vision [18]. Direct functioning assessment in children with CVI and multiple disabilities is very challenging since there is often no appropriate way for the examiner to cooperate with them. Therefore, researchers worldwide have developed various assessment methods, including both quantitative and qualitative measures [38]. The principle that various child characteristics require multiple methods, i.e., thorough assessment, plays a key role in the comprehensive diagnosis and selection of rehabilitation programs for children with CVI [39]. We can gain insight into the child's functional vision and visual functioning by observing the child in various situations, collecting data from family members about the specifics of visual behavior, and directly assessing visual abilities [11]. This is particularly significant at an early age, especially in the presence of risk factors that may lead to difficulties in visual attention, processing, and understanding what is observed. The assessment of unique behavioral characteristics in children with CVI, timely inclusion in vision (re)habilitation, and monitoring the impact of epilepsy and medication therapy on visual functioning, using different protocols, allows for the observation of the child's progress over time [40]. According to data from 2020, 1.4 million people in Serbia had some form of visual impairment, of which 116,000 face serious consequences in visual functioning [41]. Given that there is no official registry for CVI and that priority in treatment is given to the primary condition, it can be assumed that the number of people who need support in the area of visual functioning is significantly higher. Although consensus on terminology, diagnostic methods, monitoring, and rehabilitation has not yet been reached, when CVI is confirmed through multiple assessment methods, various types of adaptations in everyday conditions and visual training can improve the child's visual functioning [38]. The relation between visual functioning and cognitive abilities strongly indicates the importance of vision rehabilitation [13], and the unique characteristics allow for creating individualized intervention guidelines, which include environment modifications and counseling for parents. Along with vision rehabilitation based on the assessment of vision and visual functioning, an individualized approach can contribute to creating conditions for achieving optimal development levels in children with WS [4]. Considering that there is often a white-matter reduction in these children, the consequences on cognitive functioning can be diametrically different [6, 9], leading to a significant number of uncertainties related to the planning, course, and outcomes of treatment.

CONCLUSION

The diversity of factors that influence the functioning characteristics of individuals with WS (epidemiology, location of damage, frequency of infantile spasms, age of onset, etc.) makes this population highly heterogeneous, presenting specialists with complex tasks related to the assessment of functioning, treatment planning, and predicting treatment outcomes. The pathological impact of this type of epilepsy on the optic radiation and/or visual cortex areas, visual functions, and visual functioning clearly emphasizes the importance of controlling the spasms. Timely detection of

sometimes subtle behavioral changes in a child and inclusion in diagnostic procedures to detect central nervous system damage, specifically WS, can mitigate its impact on visual functions and visual functioning. If CVI is identified in children with WS, environmental adaptation should be implemented in accordance with the degree of visual difficulties. The results of intervention-oriented transdisciplinary assessment form the basis for creating a treatment plan. Future research should aim to develop standardized assessment protocols for CVI specifically adapted to the needs of children with infantile spasms.

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

ACKNOWLEDGEMENT

This paper was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (contract number 451-03-137/2025-03/200096).

Conflicts of interest: None declared.

REFERENCES

1. Janicot R, Shao LR, Stafstrom CE. Infantile spasms: an update on pre-clinical models and EEG mechanisms. Children. 2020;7(1):5. [DOI: 10.3390/children7010005] [PMID: 31935804]
2. Messer R, Knupp KG. Infantile spasms: opportunities to improve care. Semin Neurol. 2020;40(2):236–45. [DOI: 10.1055/s-0040-1705121] [PMID: 32143232]
3. Minić S, Trpinac D, Novaković I, Cerovac N, Dobrosavljević Vukojević D, Rosain J. Challenges in rare-disease diagnostics: incontinentia pigmenti with heterozygous GBA mutation. Diagnostics. 2022;12(7):1711. [DOI: 10.3390/diagnostics12071711] [PMID: 35885615]
4. Prygunova TM. [West syndrome: long-term outcomes depending on etiology and treatment]. Russ Zh Detsk Nevrol (Russian). 2018;13(4):53–63. [DOI: 10.17650/2073-8803-2018-13-4-53-63]
5. Fortini S, Valenzuela GR, Fasulo L, Caraballo R. West syndrome: a study of 26 patients receiving short-term therapy. Epilepsy Behav. 2021;114(Pt A):107235. [DOI: 10.1016/j.yebeh.2020.107235] [PMID: 32694038]
6. Riikonen R. Infantile spasms: outcome in clinical studies. Pediatr Neurol. 2020;108:54–64. [DOI: 10.1016/j.pediatrneurol.2020.01.015] [PMID: 32305143]
7. Pavone P, Polizzi A, Marino SD, Corsello G, Falsaperla R, Marino S, et al. West syndrome: a comprehensive review. Neurol Sci. 2020;41(12):3547–62. [DOI: 10.1007/s10072-020-04600-5] [PMID: 32827285]
8. Sharma S, Kaushik JS, Srivastava K, Goswami JN, Sahu JK, Vinayan KP, et al. AOCN–Indian Epilepsy Society consensus guidelines for West syndrome. Indian Pediatr. 2021;58(1):54–66. [DOI: 10.1007/s13312-021-2097-6] [PMID: 33452776]
9. Bhanudeep S, Madaan P, Sankhyan N, Saini L, Malhi P, Suthar R, et al. Long-term outcomes in children with West syndrome. Epilepsy Res. 2021;173:106629. [DOI: 10.1016/j.eplepsyres.2021.106629] [PMID: 33862315]
10. McFarlane MT, Wright T, McCoy B, Snead OC III, Westall CA. Retinal defects in children with infantile spasms. Neurology. 2020;94(6):e575–82. [DOI: 10.1212/WNL.0000000000008686] [PMID: 31792095]
11. Vučinić V, Stanimirov K, Alimović S, Anđelković M. [Cerebral visual impairment – diagnostic criteria and treatment]. Specijalna edukacija i rehabilitacija (Serbian). 2019;18(3):353–81. [DOI: 10.5937/specedreh18-23964]
12. Jimenez-Gomez A, Fisher KS, Zhang KX, Liu C, Sun Q, Shah VS. Longitudinal analysis of pediatric cerebral visual impairment. Front Hum Neurosci. 2022;16:772353. [DOI: 10.3389/fnhum.2022.772353] [PMID: 36051970]
13. Rando T, Bancale A, Baranello G, Bini M, De Belvis AG, Epifanio R, et al. Visual function in infants with West syndrome. Epilepsia. 2004;45(7):781–6. [DOI: 10.1111/j.0013-9580.2004.41403.x] [PMID: 15230702]
14. Vučinić V, Anđelković M, Jablan B, Žigić V. [Cortical visual impairment: characteristics and treatment]. Specijalna edukacija i rehabilitacija (Serbian). 2014;13(3):313–31. [DOI: 10.5937/specedreh13-6827]
15. Chang MY, Borchert MS. Advances in evaluation and management of cortical visual impairment. Surv Ophthalmol. 2020;65(6):708–24. [DOI: 10.1016/j.survophthal.2020.03.001] [PMID: 32199940]
16. Chang MY, Borchert MS. CVI classification using eye-tracking oculomotor measures. Ophthalmology Sci. 2025;3:100728. [DOI: 10.1016/j.xops.2025.100728]
17. Williams C, Pease A, Goodenough T, Breheny K, Gaunt D, Sinai P, et al. Improving outcomes for primary-school children at risk of CVI. BMJ Open. 2021;11(5):e044830. [DOI: 10.1136/bmjopen-2020-044830] [PMID: 33952548]
18. Morelli F, Aprile G, Martolini C, Ballante E, Olivier L, Ercolino E, et al. Visual function and neuropsychological profile in CVI. Children. 2022;9(6):921. [DOI: 10.3390/children9060921] [PMID: 35740858]
19. Bennett CR, Bauer CM, Bailin ES, Merabet LB. Neuroplasticity in cerebral visual impairment. Neurosci Biobehav Rev. 2020;108:171–81. [DOI: 10.1016/j.neubiorev.2019.10.011] [PMID: 31655075]
20. Costa MF. Cerebral versus cortical visual impairment: renewing terminology. BMC Ophthalmol. 2024;24(1):213. [DOI: 10.1186/s12886-024-03469-8] [PMID: 38755573]
21. Chang MY, Merabet LB, Borchert M, Chandna A, Heidary G, Kran B, et al. NIH CVI workshop definition. Ophthalmology. 2024;131(12):1359–65. [DOI: 10.1016/j.ophtha.2024.09.017] [PMID: 39572128]
22. Pamir Z, Bauer CM, Bailin ES, Bex PJ, Somers DC, Merabet LB. Impaired global-motion perception in CVI. Neuroimage Clin. 2021;32:102821. [DOI: 10.1016/j.nicl.2021.102821] [PMID: 34628303]
23. Vučinić V, Anđelković M. Rana intervencija za decu sa oštećenjem vida. Belgrade: Faculty for Special Education and Rehabilitation; 2021. Serbian.
24. Martać V, Vučinić V, Anđelković M. Plan development for improving visual functioning in CVI and multiple disabilities: case study. In: Creating Early Childhood Intervention Together; 2023 May 15–16; Prague. Společnost pro ranou péči; 2023. Available from: https://www.researchgate.net/publication/390271955
25. Baranello G, Randò T, Bancale A, D'Acunto MG, Epifanio R, Frisone MF, et al. Auditory attention at onset of West syndrome. Brain Dev. 2006;28(5):293–9. [DOI: 10.1016/j.braindev.2005.10.004] [PMID: 16481138]
26. Ben Itzhak N, Vancleef K, Franki I, Laenen A, Wagemans J, Ortibus E. Visuoperceptual profiles in CVI. Dev Med Child Neurol. 2020;62(8):969–76. [DOI: 10.1111/dmcn.14448] [PMID: 31889310]
27. West MR, Borchert MS, Chang MY. CVI and cerebral palsy: ophthalmologic outcomes. J AAPOS. 2021;25(4):223.e1–e6. [DOI: 10.1016/j.jaapos.2021.03.011] [PMID: 34271208]
28. Goodenough T, Pease A, Williams C. Parent and child perspectives of CVI. Front Hum Neurosci. 2021;15:689683. [DOI: 10.3389/fnhum.2021.689683] [PMID: 34305554]
29. Domańska M, Zawadzka M, Konieczna S, Mazurkiewicz-Bełdzińska M. Cognitive impairment in focal epilepsy. Heliyon. 2023;9(6):e17210. [DOI: 10.1016/j.heliyon.2023.e17210]
30. Guzzetta F, Frisone MF, Ricci D, Randò T, Guzzetta A. Development of visual attention in West syndrome. Epilepsia. 2002;43(7):757–63. [DOI: 10.1046/j.1528-1157.2002.34601.x] [PMID: 12102680]
31. Choi SA, Kim YO. West syndrome with hyperkinesia and CVI: GRIN1 encephalopathy. J Genet Med. 2021;18(1):55–9. [DOI: 10.5734/JGM.2021.18.1.55]
32. Vancleef K, Janssens E, Petré Y, Wagemans J, Ortibus E. Tool for visual-perception deficits in CVI. Dev Med Child Neurol. 2020;62(1):111–7. [DOI: 10.1111/dmcn.14303] [PMID: 31267521]

33. Iinuma K, Haginoya K, Nagai M, Kon K, Yagi T, Saito T. Visual abnormalities and occipital EEG discharges in West syndrome. Epilepsia. 1994;35(4):806–9. [DOI: 10.1111/j.1528-1157.1994.tb02515.x] [PMID: 8082626]
34. Chokron S, Dutton GN. Impact of CVI on motor skills. Front Psychol. 2016;7:1471. [DOI: 10.3389/fpsyg.2016.01471] [PMID: 27757087]
35. Martać V, Anđelković M, Vučinić V. [Functional-vision assessment in children with multiple disabilities]. In: Nikolić M, Vantić-Tanjić M, editors. XIII International Scientific Conference "Improving the Quality of Life of Children and Youth"; 2022 Jun 24–26; Aranđelovac. Tuzla: Faculty for Special Education and Rehabilitation; 2022. p. 557–65. Serbian.
36. Schwarz MD, Li M, Tsao J, Zhou R, Wu YW, Sankar R, et al. Vision loss in vigabatrin-treated infantile spasms: UCLA experience. Epilepsy Behav. 2016;57(Pt A):29–33. [DOI: 10.1016/j.yebeh.2016.01.012] [PMID: 26921595]
37. Clayton LM, Dévilé M, Punte T, Kallis C, de Haan GJ, Sander JW, et al. Retinal nerve-fiber layer in vigabatrin-exposed patients. Ann Neurol. 2011;69(5):845–54. [DOI: 10.1002/ana.22266] [PMID: 21246602]
38. McConnell EL, Saunders KJ, Little JA. Assessments for diagnosing CVI in children: systematic review. Ophthalmic Physiol Opt. 2021;41(2):224–44. [DOI: 10.1111/opo.12776] [PMID: 33368471]
39. Lueck AH, Chokron S, Dutton GN. Commentary: profiling children with CVI. Semin Pediatr Neurol. 2023;47:101070. [DOI: 10.1016/j.spen.2023.101070]
40. Roman-Lantzy C. Cortical Visual Impairment: An Approach to Assessment and Intervention. 2nd ed. New York: American Foundation for the Blind; 2018.
41. Risimic D, Babović S, Cekić S, Ćuk J, Davidović S, Hadži-Manić A, et al. Prevention and Treatment of Retinal Diseases in Serbia 2024: Policy Report. SSRN; 2024. [DOI: 10.2139/ssrn.5077884]

Визуелно функционисање и церебрално оштећење вида код деце са инфантилним спазмима – Вестовим синдромом

Весна Вучинић[1], Валентина Мартаћ[1], Наташа Церовац[2,3], Мирослав Стаменковић[1,4]

[1]Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитетски клинички центар Србије, Клиника за неурологију и психијатрију за децу и омладину, Београд, Србија;
[4]Клиничко-болнички центар „Звездара", Београд, Србија

САЖЕТАК

Церебрално оштећење вида најчешћи је узрок оштећења вида код деце у развијеним и земљама у развоју, што га последњих неколико деценија чини актуелном истраживачком темом у оквиру дисциплина које се баве функционалним статусом неуроризичне деце. Мултифакторска условљеност Вестовог синдрома и варијабилност стања визуелних функција и визуелног функционисања отежавају благовремену дијагностику ове врсте оштећења вида. Атипичан начин праћења стимулуса, успостављања и одржавања визуелног контакта, као и задржавање визуелне пажње, први су показатељи одступања у домену визуелног понашања, који могу да укажу на постојање неуроризика. Промене у визуелном понашању могу да се манифестују кроз промену квалитета или изостанак визуелне респонзивности, дефиците у различитим видним функцијама и окуломоторици, што се повезује са измењеним налазом визуелних евоцираних потенцијала. Кортикално посредоване видне функције – оштрина вида, видно поље, осетљивост на контраст и окуломоторика код деце са инфантилним спазмима и Вестовим синдромом такође су у ризику. Осим базичних видних функција, значајно су угрожене визуоперцептивне и визуомоторичке способности, што се манифестује у свакодневном понашању и утиче на мотивацију за гледање. Степен и манифестације церебралног оштећења вида код деце са инфантилним спазмима зависе од бројних фактора. Мултидисциплинарни дијагностички поступци којима се може установити да ли је церебрално оштећење вида последица генетских фактора, Вестовог синдрома или других неуролошких стања, од великог су значаја за креирање плана и предвиђање исхода третмана.

Кључне речи: оштећење вида; епилепсија; функционални вид

DOI: https://doi.org/10.2298/SARH250117035J
UDC: 613.880.4-056.36

REVIEW ARTICLE / ПРЕГЛЕДНИ РАД

Risky sexual behavior of people with developmental disabilities and prevention

Branka Jablan, Vesna Vučinić, Dunja Stekić Đinđić
University of Belgrade, Faculty of Special Education and Rehabilitation, Belgrade, Serbia

SUMMARY
The paper analyzes the results of studies that have explored the causes and prevention of risky sexual behavior in individuals with developmental disabilities.
The importance of the chosen topic lies in the fact that sexuality is one of the fundamental dimensions of human existence, which is influenced by biological, psychological, socio-economic, cultural, ethical, religious, and other factors.
Recent studies suggest that risky sexual behavior, including unprotected and unsafe sexual relationships, result from a lack of appropriate prevention and education programs, limited access to healthcare information, misunderstanding of instructions and safety warnings, difficulty communicating with healthcare professionals, inadequate societal care, and a lack of self-esteem.
The authors of the studies analyzed recommend that the content of preventive programs be adapted to individuals with developmental disabilities, in order to develop appropriate attitudes toward sexuality and a sense of responsibility for one's own health and the health of a partner. Providing informational brochures and guidelines on sexual health and the consequences of risky sexual behavior tailored to the reading abilities of people with developmental disabilities would improve accessibility and increase the quality of healthcare services.
Involving parents in empowerment programs and providing timely information about their children's sexuality and sexual health, as well as encouraging children with developmental disabilities to participate in conversations with parents about these sensitive topics, can have a positive impact on preventing risky forms of sexual behavior.
Keywords: developmental difficulties and disorders; sexuality and risks; information about sexuality

INTRODUCTION

As a topic significant for their overall functioning, the sexual life of people with developmental disabilities has been at the margins of researchers' interest [1, 2, 3]. The sensitive nature of this topic and methodological barriers have also contributed to neglecting this research field. A significant number of studies focus on appropriate sexual behavior, with special emphasis on children with autism spectrum disorder and intellectual disability [4]. Risky sexual behavior is considered a significant factor affecting reproductive and overall health in young people. It is the cause of teenage pregnancies, sexually transmitted infections, sexual victimization, and other adverse health effects [5, 6].

Various factors can influence the occurrence of risky sexual behavior. They can be divided into environmental and personal factors, but are always interrelated. The most important environmental factors include, but are not limited to, the availability of psychoactive substances, poor financial situation, unemployment, inadequate connection with the community, a family history of problematic behaviors (e.g., alcohol and substance abuse, domestic violence and abuse), problematic behavior of peers the person interacts with, social isolation, and school failure [6, 7]. Personality traits are closely related to substance abuse and, thus, low self-esteem, emotional problems, and developmental disabilities belong to the group of factors associated with engaging in risky sexual relations. The likelihood of risky sexual behavior is much greater when multiple risk factors are present simultaneously, such as low self-esteem, developmental disability, associating with peers who exhibit problematic behaviors, substance abuse, etc. [7].

Young people with developmental disabilities are characterized by significant variability, and regardless of this, they are at greater risk of engaging in behaviors that may further endanger their health [8]. Social psychological factors, namely identity, affect and coping style, are inextricably entwined with sexual behavior and, thus, sexual health outcomes [9]. When they begin exploring their sexuality, people with developmental disabilities face numerous challenges in accessing information and support. Usually, what is "accessible" to them is a set of "rules" that emphasize gender norms, focus on heterosexuality, and convey the message that sex and sexual relations are something to be afraid of [10].

The paper analyzes the results of studies that have investigated risky sexual behavior and the prevention of risky sexual behavior in individuals with developmental disabilities. The Consortium of Serbian Libraries for

Received • Примљено: January 8, 2025
Revised • Ревизија: April 25, 2025
Accepted • Прихваћено: April 30, 2025
Online first: April 30, 2025

Correspondence to:
Branka JABLAN
University of Belgrade
Faculty of Special Education and Rehabilitation
Visokog Stevana 2
11000 Belgrade, Serbia
brankajablan@fasper.bg.ac.rs

Coordinated Acquisition (KoBSON) and Google Scholar's Advanced Search tool were used to search and review the research. The search was conducted using the following terms in Serbian and English: sexual behavior, risky sexual behavior, prevention of risky sexual behavior, and individuals with developmental disabilities.

Considering the heterogeneity of the population with developmental disabilities, 30 papers published in the last five years and available in full text were selected and analyzed. In order to gain a more comprehensive understanding of the selected topic, the results of studies published before 2020 were also included in the analysis.

RISKY SEXUAL BEHAVIOR OF PEOPLE WITH DEVELOPMENTAL DISABILITIES

The lack or inaccessibility of information about sexuality, difficulties in accessing reproductive and sexual health institutions, as well as myths and prejudices, significantly influence the formation of beliefs that developmental disabilities negatively affect the sexual and reproductive lives of people with these disabilities [11, 12]. A significant number of individuals with developmental disabilities are sexually active [13, 14]. At the same time, a large percentage of these individuals are exposed to various risks, such as sexually transmitted diseases, unintended pregnancies, sexual violence, etc. [12, 15]. In addition to the lack of knowledge, information, and healthcare support, risky sexual behavior of people with developmental disabilities is predominantly determined by their psychosocial characteristics, lack of self-esteem, and low levels of social skills [16].

The study conducted by Touko et al. [15] states that people with developmental disabilities more often engage in unprotected and unsafe sexual relationships than typically developing participants, and are more exposed to sexually transmitted diseases. The research focused on premature sexual activity, awareness of protective measures, knowledge of sexually transmitted diseases, and human immunodeficiency virus (HIV). By comparing the sexual behavior of individuals with motor disabilities and typically developing young individuals 15–16 years of age, Maart and Jelsma [17] found no significant difference in the prevalence of various forms of risky behavior between these two groups. The sample of participants with motor disabilities included 91 students, a quarter of whom were sexually active. Some had engaged in sexual activities at a younger age, had multiple partners, and did not use protection. In addition, many believed that there was no risk of getting HIV through sexual activity and, thus, felt no need to protect themselves or others, which indicates that, considering their overall health and level of independence, they are often at greater risk of contracting sexually transmitted infections.

The incidence of different types of risky sexual behavior and involvement in the system of services provided by centers dealing with the consequences of HIV were examined in a sample of young individuals with visual impairment, hearing impairment, and motor disabilities [18]. The results show that almost half of the participants were sexually active, that they rarely used protection against unintended pregnancy and sexually transmitted diseases, that one-third of the participants had sexual relations with multiple partners at a younger age, and that the participants with hearing impairment used the services of HIV centers more often.

Risky sexual behavior of young people with visual impairment is associated with the lack of appropriate preventive and educational programs, as well as the inaccessibility or unavailability of healthcare institutions and services [19]. People with visual impairment report difficulties in accessing information and disparities in access to health screenings, but they believe that healthcare institutions do not play a primary role in providing information on these topics [20, 21, 22], which is consistent with the results of studies that have examined this topic in samples of young people without visual impairment [23, 24, 25]. The sexual experiences of young blind people and young people without visual impairment are similar; however, the fact that blind people have limited access to health information indicates that there is a need to provide them with information brochures and guidance on sexual health and behavior in a reading medium appropriate to their needs [26]. A Brazilian study that aimed to examine how blind individuals contact rehabilitation professionals, as well as their level of awareness and knowledge about sexuality, reproductive and sexual health, and HIV and AIDS, determined that they lack knowledge about the transmission and prevention of sexually transmitted diseases, which is directly related to their limited education access [27]. This limitation may be associated with the professionals' unpreparedness to confidentially and effectively address the needs of individuals with visual impairment and communication barriers. Neglecting the rights of women with visual impairment regarding their sexual and reproductive healthcare is a significant finding of some studies, indicating that these women often do not know where to obtain information on sexuality-related topics [28]. Research on a sample of blind adults showed that physical attraction and the material status of partners played a secondary role for them during adolescence. Emotional maturity and qualities that are "not visible to the eye" but are crucial in life were the most significant [29].

Alongside risky sexual behavior, we can also discuss certain aspects of sexual abuse experienced by children and young people with visual impairment. Kvam [30] compared the frequency of reporting sexual abuse between individuals with visual impairment 18–65 years of age who lost their vision before the age of 18, and a group without visual impairment. The results showed that the participants with visual impairment reported sexual abuse more frequently and that the consequences of the abuse were serious.

The position of individuals with visual impairment can often lead to prolonged suffering, failing to report sexual abuse, and engaging in risky behaviors. Their dependence on caregivers helps the perpetrator, who is often a close person, to have control over the victim. People with visual

impairment may internalize negative societal attitudes, such as discrimination and stigmatization, leading them to lose self-esteem and blame themselves, which, together with the fear of abandonment (losing a "caregiver"), keeps them in abusive relationships [31].

For many years, the sexuality of people with intellectual disability was viewed as a societal issue, and eugenic goals focused on the need to protect society from their supposed deviance and promiscuity [32]. The studies on the sexual lives of individuals with intellectual disability are highly varied and include the following findings: that they are sexually active; that most, especially women, lack sexual activity; they generally lack knowledge about the use and effects of contraceptives; that they are victims of sexual harassment more often than their peers without intellectual disability; that they have a higher prevalence of unintended pregnancies, sexual abuse, and exploitation [33–36]. Interestingly, studies that found them to be sexually active also emphasized that emotional closeness with another person is of primary importance to them [36]. People with mental health problems are also a risk group, since they do not practice safe sex due to their limited knowledge about the use of contraceptives and financial difficulties [37].

PREVENTION OF RISKY SEXUAL BEHAVIOR

Protecting the reproductive and sexual health of young people with developmental disabilities involves developing awareness of the potential consequences of risky behaviors. The content structure of prevention programs should aim to impact knowledge acquisition, healthy attitudes toward sexuality, and a sense of responsibility for their own health and the health of their partners [38]. Knowledge about the potential consequences of irresponsible behavior, unintended pregnancies, and sexually transmitted infections is a prerequisite for taking responsibility and making the right decisions about engaging in sexual activities [39].

Relying on superficial information from peers or the media and not knowing the consequences of risky sexual behavior can cause serious problems for young people with developmental disabilities [40]. Although parents of children with developmental disabilities state that they lack information about sexual and reproductive health and do not know where to seek necessary guidance [14], it is essential to emphasize their important role in educating their children about sexuality and all its domains from the earliest age. Sexual and reproductive health education is considered a priority for young people with disabilities, as they still receive little or no formal sexual health education [19, 39]. The joint responsibility of families and schools is to provide support in growing up, recognizing human values, and enabling children and young people to develop their potential to face various challenges, which can often lead to multiple adverse consequences. For example, it has been found that blind adolescents consider informational and emotional support from the education system extremely important and that they expect teachers to provide them with future-oriented information. In addition, special support is expected to be provided to both students and parents [41]. However, the sexual health of young people with disabilities remains a "blind spot" in health promotion. This claim is supported by the fact that research on this topic often focuses on priority interventions, which should be based on needs, specifically, the need for sexual health education. The role of special educators is often not recognized. However, they can be key partners, as they understand disability and possess specific skills that make them suitable to be involved in the various stages of intervention [42]. Conversations about the consequences of risky sexual behavior conducted by well-informed parents have a positive influence and reduce the percentage of young people who enter risky situations [43]. Parental support and interest in all aspects of their child's development positively affect the timing of first sexual relationships and avoiding risky sexual behaviors. When parents avoid this topic, adolescents seek information from unreliable sources or follow advice from peers, which sometimes, though unintentionally, encourages risky sexual behavior [5, 43].

Nowadays, social media provides easy access to information on various topics. However, after the family, school is the most important factor in acquiring knowledge and developing attitudes about sexuality and safe sexual behavior [40, 43]. Through different programs, the education system should warn young people about the consequences of engaging in risky sexual relations at an early age [44]. In collaboration with other professionals, teachers should create reliable and structured training programs on sexual and reproductive health, and implement them through panels, seminars, and workshops for children of different ages [25]. For example, Glumbić [45] recommends that sex education programs be highly individualized – that is, adapted to the specific needs of an individual with autism and their family; to respond appropriately, we must understand the function of a particular behavior; any activity we undertake should be consistent with the legal and customary norms and cultural characteristics of a given community; additionally, any sex education program should be implemented within the broader context of learning social skills and socially acceptable behaviors. In contrast, the findings of Wazakili et al. [16] show that topics such as infidelity, promiscuity, alcohol use, sexual abuse, and risky sexual behavior are not discussed within the family environments of persons with physical disabilities 15–24 years of age. The participants stated that most of them had participated in rehabilitation that focused on their physical disability, while the issues of sexuality and prevention measures against HIV were not addressed. The authors believe that rehabilitation professionals should make an effort to include sexual and reproductive health issues as part of their work with young people with disabilities [16]. The healthcare system should provide individuals with developmental disabilities with programs or forms of support on sexuality and the consequences of risky sexual behavior [14]. Stekić [46] determined that people with visual impairment 20–40 years of age have insufficient knowledge about sexually transmitted diseases, which raises a relevant

question about how they can protect themselves and recognize disease symptoms. Whether sex education is necessary for young people with developmental disabilities is no longer in question. The professionals are increasingly considering the education methods and contents to equip these young people with essential communication and decision-making skills, as well as help them become assertive and learn to say "no" when needed [45, 47]. Neglecting the need for sex education and the lack of appropriate healthcare access can result from stigma regarding the characteristics of sexuality (asexuality, hypersexuality) of young people with disabilities and not recognizing their needs, which violates their fundamental rights [45].

The National Program for the Preservation and Improvement of Sexual and Reproductive Health of Citizens of the Republic of Serbia ensures that sexual and reproductive healthcare is accessible to everyone, without distinction, and that their sexual and reproductive rights are respected. The same regulation emphasizes the significance of programs aimed at enhancing the sexual and reproductive health of marginalized and socially deprived groups, both locally and nationally, highlighting collaboration among healthcare institutions, local self-government units, and associations, along with including their representatives [48]. Networking community resources and sharing information in the process of creating educational programs and providing support are crucial for people with developmental disabilities in fostering a responsible attitude toward themselves and others [49]. Community resource lists should be made available to people with developmental disabilities, their parents, caregivers, and teachers as they represent important factors in achieving their well-being [50].

CONCLUSION

Sexuality as an indispensable part of human identity has long been neglected when it comes to people with developmental disabilities. This was mainly due to numerous stereotypes and prejudices, such as that these people are not interested in romantic or love relationships, that they have no sexual urges, or that their sexual needs are deviant. Numerous factors that affect sexuality and risky behaviors in the typical population (biological, psychological, socioeconomic, cultural, ethical and religious) intertwine much more complexly in people with developmental disabilities. A considerable number of these individuals are still denied their rights to sexuality and to sexual, intimate and partner relationships in various cultural environments. Based on studies conducted in countries that differ in cultural, ethical and religious influences on young people, it is hard to conclude their overall contribution to forming attitudes toward sexuality and finding strategies to meet their sexual needs without becoming victims of risky sexual behavior that could adversely affect their health and social acceptance. Studies comparing the sexual behavior of individuals with various developmental disabilities with that of adolescents with typical development showed different results with regard to different types of risk behavior. Developing awareness of the potential consequences of risky sexual behavior and implementing measures to protect the sexual and reproductive health of people with developmental disabilities is one of the most significant challenges of modern society. The implementation of such a serious task requires a general strategic framework and accompanying secondary legislation that sets the structural and functional standards for the education of all persons involved in the issue of sexual health of people with developmental disabilities. It is imperative to familiarize people with developmental disabilities with the consequences of early sexual intercourse, the risks of unplanned pregnancy and the consequences of sexually transmitted diseases, as well as protection against abuse of the position of dependence on the help of others, usually close people. Sexual education and harmonization of educational approaches for individuals with various developmental disabilities, continuous work with parents and access and availability of information are key factors in the prevention of risky sexual behavior of individuals with developmental disabilities

A comprehensive analysis of research focused on patterns of risky sexual behavior among different categories of individuals with developmental disabilities, with respect for regional and cultural specificities and a comparative evaluation of preventive measures applied at national levels, could significantly contribute to a deeper understanding of this complex issue.

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

ACKNOWLEDGEMENT

This paper was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (contract number 451-03-137/2025-03/200096).

Conflicts of interest: None declared.

REFERENCES

1. Aslan E, Acar Z, Yılmaz B. Reproductive and sexual health in males with physical, hearing, and vision disabilities. Int J Sex Health. 2021;33(2):210–21. [DOI: 10.1080/19317611.2021.1884164] [PMID: 38596751]
2. Crehan ET, Rocha J, Sclar J, Ward O, Donaghue A. Topics and timing of sexuality and relationship education for autistic and non-autistic adults in the United States. Disabil Health J. 2023;16(3):101466. [DOI: 10.1016/j.dhjo.2023.101466] [PMID: 37062650]
3. Michielsen K, Brockschmidt L. Barriers to sexuality education for children and young people with disabilities in the WHO European region: a scoping review. Sex Educ. 2021;21(6):674–92. [DOI: 10.1080/14681811.2020.1851181]
4. Sullivan A, Caterino LC. Addressing the sexuality and sex education of individuals with autism spectrum disorder. Educ Treat Child. 2008;31(3):381–94. [DOI: 10.1353/etc.0.0001]
5. Desrosiers A, Betancourt T, Kergoat Y, Servilli C, Say L, Kobeissi L. A systematic review of sexual and reproductive health interventions for young people in humanitarian and lower- and middle-income country settings. BMC Public Health. 2020;20(1):666. [DOI: 10.1186/s12889-020-08818-y] [PMID: 32398129]
6. Chakole S, Akre S, Sharma K, Wasnik P, Wanjari MB. Unwanted teenage pregnancy and its complications: a narrative review. Cureus. 2022;14(12):e32662. [DOI: 10.7759/cureus.32662] [PMID: 36686124]
7. Reis LF, Surkan PJ, Atkins K, Garcia-Cerde R, Sanchez ZM. Risk factors for early sexual intercourse in adolescence: a systematic review of cohort studies. Child Psychiatry Hum Dev. 2024;55(6):1677–90. [DOI: 10.1007/s10578-023-01519-8] [PMID: 36966237]
8. Argenyi MS, James TG. Sexual risk behavior and sexually transmitted infections among college students with disabilities. Sex Transm Dis. 2021;48(11):851–4. [DOI: 10.1097/OLQ.0000000000001443] [PMID: 33872223]
9. Jaspal R, Lopes B, Wignall L, Bloxsom C. Predicting sexual risk behavior in British and European Union university students in the United Kingdom. Am J Sex Educ. 2021;16(1):140–59. [DOI: 10.1080/15546128.2020.1869129]
10. Goulden A. 'A lot of social workers don't seem to understand or realize the harm that they cause': Disabled young people's experiences with sexual well-being in social work practice. Br J Soc Work. 2025;55(2):644–62. [DOI: 10.1093/bjsw/bcae171]
11. Fletcher J, Yee H, Ong B, Roden RC. Centering disability visibility in reproductive health care: dismantling barriers to achieve reproductive equity. Womens Health (Lond). 2023;19:17455057231197166. [DOI: 10.1177/17455057231197166] [PMID: 37675891]
12. França ISX, Coura AS, Sousa FS, Aragão JDS, Silva AFR, Santos SRD. Acquiring of knowledge about sexual health by blind people: an action research. Rev Lat Am Enfermagem. 2019;27:e3163. [DOI: 10.1590/1518-8345.3006.3163] [PMID: 31340347]
13. Horner-Johnson W, Senders A, Higgin Tejera C, McGee MG. Sexual health experiences among high school students with disabilities. J Adolesc Health. 2021;69(2):255–62. [DOI: 10.1016/j.jadohealth.2021.03.001] [PMID: 33902994]
14. Porat O, Heruti R, Navon-Porat H, Hardoff D. Counseling young people with physical disabilities regarding relationships and sexuality issues: utilization of a novel service. Sex Disabil. 2012;30(3):311–7. [DOI: 10.1007/s11195-011-9241-5]
15. Touko A, Mboua CP, Tohmuntain PM, Perrot AB. Sexual vulnerability and HIV seroprevalence among the deaf and hearing impaired in Cameroon. J Int AIDS Soc. 2010;13:5. [DOI: 10.1186/1758-2652-13-5] [PMID: 20181091]
16. Wazakili M, Mpofu R, Devlieger P. Should issues of sexuality and HIV and AIDS be a rehabilitation concern? The voices of young South Africans with physical disabilities. Disabil Rehabil. 2009;31(1):32–41. [DOI: 10.1080/09638280802280619] [PMID: 19194808]
17. Maart S, Jelsma J. The sexual behaviour of physically disabled adolescents. Disabil Rehabil. 2010;32(6):438–43. [DOI: 10.3109/09638280902846368] [PMID: 20113191]
18. Kumssa H. Risky sexual practice, accessibility and utilization of HIV service among people with disabilities in Addis Ababa [dissertation]. Addis Ababa: Addis Ababa University; 2011. Available from: https://etd.aau.edu.et/items/9f6d4dbe-49c3-4b66-9a07-e70bd7ebd96e
19. Jablan B, Sjeničić M. Reproductive health of visually impaired women. Teme. 2021;45(1):265–79. [DOI: 10.22190/TEME200407014J]
20. Besoain-Saldaña A, Bustamante-Bravo J, Rebolledo Sanhueza J, Montt-Maray E. Experiences, barriers, and facilitators to sexual and reproductive health care access of people with sensory impairments: a scoping review. Sex Disabil. 2023;41(2):411–49. [DOI: 10.1007/s11195-023-09778-y]
21. Qi W, Li H, Lian Q, Zuo X, Yu C, Lou C, et al. Knowledge level and access barriers related to sexual and reproductive health information among youth with disabilities in China: a cross-sectional study. Reprod Health. 2023;20(1):84. [DOI: 10.1186/s12978-023-01625-9] [PMID: 37280677]
22. Long-Bellil L. Disability inclusion in sexual and reproductive health in the United States. Oxf Res Encycl Glob Public Health. 2022. [DOI: 10.1093/acrefore/9780190632366.013.286]
23. Stekić D, Jablan B, Stanimirov K, Stojković I. Sources of information on reproductive health of people with visual impairment and people without visual impairment. In: Anđelković M, Sretenović I, editors. Evaluacija efekata inkluzivnog obrazovanja u Republici Srbiji. Zbornik radova nacionalnog naučnog skupa; 2020 Dec 21; Belgrade, Serbia. Belgrade: Faculty of Special Education and Rehabilitation, University of Belgrade; 2020. p. 159–68.
24. Corley AG, Sprockett A, Montagu D, Chakraborty NM. Exploring and monitoring privacy, confidentiality, and provider bias in sexual and reproductive health service provision to young people: a narrative review. Int J Environ Res Public Health. 2022;19(11):6576. [DOI: 10.3390/ijerph19116576] [PMID: 35682160]
25. Decker MJ, Dandekar S, Gutmann-Gonzalez A, Brindis CD. Bridging the gap between sexual health education and clinical services: adolescent perspectives and recommendations. J Sch Health. 2021;91(11):928–35. [DOI: 10.1111/josh.13084] [PMID: 34523133]
26. Kelly SM, Kapperman G. Sexual activity of young adults who are visually impaired and the need for effective sex education. J Vis Impair Blind. 2012;106(9):519–26. [DOI: 10.1177/0145482X1210600903]
27. Araújo AKF, França ISX, Coura AS, Santos SR, Ramos APA, Pagliuca LMF. Sociodemographic profile of blind people: associations with knowledge, attitude and practice about sexually transmitted infections. Rev Rene. 2015;16(5):738–45. [DOI: 10.15253/2175-6783.2015000500016]
28. Oliveira MG, Áfio ACE, Almeida PC, Machado MMT, Lindsay AC, Pagliuca LMF. Teaching blind women about the anatomy and physiology of the female reproductive system through educational manual. Rev Bras Saúde Matern Infant. 2018;18(4):755–61. [DOI: 10.1590/1806-93042018000400005]
29. Pinquart M, Pfeiffer JP. What is essential is invisible to the eye: intimate relationships of adolescents with visual impairment. Sex Disabil. 2012;30(2):139–47. [DOI: 10.1007/s11195-011-9248-y]
30. Kvam MH. Experiences of childhood sexual abuse among visually impaired adults in Norway: prevalence and characteristics. J Vis Impair Blind. 2005;99(1):5–14. [DOI: 10.1177/0145482X0509900102]
31. Plummer SB, Findley PA. Women with disabilities' experience with physical and sexual abuse: review of the literature and implications for the field. Trauma Violence Abuse. 2011;13(1):15–29. [DOI: 10.1177/1524838011426014] [PMID: 22070987]
32. Ilyes E. Psychology's eugenic history and the invention of intellectual disability. Soc Personal Psychol Compass. 2020;14(7):e12537. [DOI: 10.1111/spc3.12537]
33. Bernert J, Ogletree R. Women with intellectual disabilities talk about their perceptions of sex. J Intellect Disabil Res. 2013;57(3):240–9. [DOI: 10.1111/j.1365-2788.2011.01529.x] [PMID: 23379861]
34. Beltran-Arreche M, Fullana Noell J, Pallisera Díaz M. Perspectives of women with intellectual disabilities regarding affective sexual relationships: a systematic literature review. Sex Res Soc Policy. 2024;21(1):263–78. [DOI: 10.1007/s13178-023-00911-2]
35. Roden RC, Schmidt EK, Holland-Hall C. Sexual health education for adolescents and young adults with intellectual and developmental disabilities: recommendations for accessible sexual and reproductive health information. Lancet Child Adolesc Health. 2020;4(9):699–708. [DOI: 10.1016/S2352-4642(20)30098-5] [PMID: 32827491]

36. Matin BK, Ballan M, Darabi F, Karyani AK, Soofi M, Soltani S. Sexual health concerns in women with intellectual disabilities: a systematic review of qualitative studies. BMC Public Health. 2021;21(1):1965. [DOI: 10.1186/s12889-021-12027-6] [PMID: 34717594]
37. Berlan ED, Nikahd M, Kerlek AJ, Hyde J, Manos BE, Underwood AL, et al. Interest in contraceptive information and initiation among adolescents hospitalized with psychiatric disorders. J Adolesc Health. 2025;76(4):657–64. [DOI: 10.1016/j.jadohealth.2024.12.005] [PMID: 39918512]
38. Zsakai A, Ratz-Sulyok FZ, Koronczai B, Varro P, Toth E, Szarvas S, et al. Risk and protective factors for health behaviour in adolescence in Europe. Sci Rep. 2023;13(1):18638. [DOI: 10.1038/s41598-023-45800-1] [PMID: 37903868]
39. Jablan B, Sjeničić M. Sexuality and sexual health of the population with disabilities – with special reference to the population with visual impairment. Stanovništvo. 2021;59(2):65–82. [DOI: 10.2298/STNV200819001J]
40. Petani R, Vulin A. Sexual behavior of adolescents, their awareness, and opinions on sexuality. Acta Iadertina. 2018;15(1):35–58. [DOI: 10.15291/ai.1510]
41. Stanimirović D, Mijatović L, Jablan B. Društvena podrška obrazovnih ustanova učenicima sa oštećenjem vida i njihovim porodicama. Spec Eduk Rehabil. 2012;11(2):231–46. [DOI: 10.5937/specedreh1202231S]
42. Vivet N, de La Rochebrochard E, Martin P. Young people with disabilities and their sexual health: a descriptive review of needs, recommendations and interventions. BMC Public Health. 2025;25(1):930. [DOI: 10.1186/s12889-025-21927-w] [PMID: 40057702]
43. Whitaker DJ, Miller KS. Parent-adolescent discussions about sex and condoms: impact on peer influences of sexual risk behavior. J Adolesc Res. 2000;15(2):251–73. [DOI: 10.1177/0743558400152004]
44. Güdül Öz H, Yangın H, Akpınar A. Knowledge levels regarding sexually transmitted diseases among individuals with visual impairment: a cross-sectional study. Vulnerable Child Youth Stud. 2023;18(3):382–92. [DOI: 10.1080/17450128.2022.2038400]
45. Glumbić N. Sexuality of individuals with autism. In: Pucarević B, editor. Podrška porodicama dece sa teškoćama u razvoju i/ili invaliditetom. Niš: Udruženje građana „Nauči me"; 2023. p. 5–25.
46. Stekić D. Knowledge of persons with visual impairment and typically developing persons about sexually transmitted diseases. Spec Eduk Rehabil. 2022;21(3):195–209. [DOI: 10.5937/specedreh21-36240]
47. Ogur C, Olcay S, Baloglu M. An international study: teachers' opinions about individuals with developmental disabilities regarding sexuality education. Sex Disabil. 2023;41(4):739–56. [DOI: 10.1007/s11195-023-09810-1]
48. Republic of Serbia. Uredba o nacionalnom programu očuvanja i unapređenja seksualnog i reproduktivnog zdravlja građana Republike Srbije. Službeni glasnik RS. 2017;(120). Available from: http://demo.paragraf.rs/demo/combined/Old/t/t2018_01/t01_0025.htm
49. Vučinić VJ, Gligorović MG, Anđelković MM. Social skills in adults with visual impairment. Sociol Pregl. 2020;54(2):195–215. [DOI: 10.5937/socpreg54-22944]
50. Jablan B, Vučinić V, Jovanić N. Self-assessment social support and life satisfaction in visually impaired adults. In: Eminović F, Maksić J, editors. Edukativna i rehabilitaciona podrška detetu, porodici i instituciji. Zbornik radova sa nacionalnog naučnog skupa; 2019 Dec 23; Belgrade, Serbia. Belgrade: Faculty of Special Education and Rehabilitation, University of Belgrade; 2019. p. 85–90.

Ризично сексуално понашање особа са сметњама у развоју и превенција

Бранка Јаблан, Весна Вучинић, Дуња Стекић Ђинђић

Универзитет у Београду, Факултет за специјалну едукацију и рехабилитацију, Београд, Србија

САЖЕТАК

У раду су анализирани резултати студија које су се бавиле узроцима и превенцијом ризичног сексуалног понашања особа са сметњама у развоју. Значај изабране теме огледа се у чињеници да је сексуалност једна од темељних димензија људског постојања, на коју утичу биолошки, психолошки, социоекономски, културолошки, етички, религијски и други фактори.

Резултати новијих студија указују на то да је улазак у сферу ризичног сексуалног понашања, односно у незаштићене и небезбедне сексуалне односе, последица недостатка одговарајућих превентивних и едукативних програма, ограниченог приступа информацијама о заштити здравља, неразумевања инструкција и безбедносних обавештења, отежане комуникације са запосленим особама у здравственим установама, недовољне бриге друштва и недостатка самопоштовања.

Препоруке аутора анализираних студија су да садржај превентивних програма буде прилагођен особама са сметњама у развоју, да омогући формирање правилних ставова према сексуалности и осећаја одговорности за сопствено здравље и здравље партнера. Обезбеђивање информативних брошура и упутстава о сексуалном здрављу и последицама ризичног сексуалног понашања, који могу да задовоље читалачке могућности особа са сметњама у развоју, олакшало би доступност и подигло квалитет здравствене заштите. Укључивање родитеља у програме оснаживања и правовремено информисање о сексуалности и сексуалном здрављу њихове деце, као и охрабривање деце са сметњама у развоју да учествују у разговорима са родитељима о овим осетљивим темама, могу позитивно утицати на смањење ризичних облика сексуалног понашања.

Кључне речи: сметње и поремећаји у развоју; сексуалност и ризици; информисаност о сексуалности

DOI: https://doi.org/10.2298/SARH240927037S
UDC: 616.11-002

CURRENT TOPIC / АКТУЕЛНА ТЕМА

Acute pericarditis and cardiac tamponade – bridging the gap between diagnosis and management

Dejan Simeunović[1,2], Stefan Juričić[1], Nina Gatarić[1], Marko Ristić[1], Filip Simeunović[2], Ivan Milinković[1,2], Valerija Perić[1], Ratko Lasica[1,2], Arsen Ristić[1,2]

[1]University Clinical Center of Serbia, Clinic for Cardiology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY
Acute pericarditis arises from an inflammatory process affecting the pericardial tissue, leading to the subsequent formation of pericardial effusion as part of the body's inflammatory response. Cardiac tamponade occurs when a significant volume of fluid accumulates within the pericardial cavity, resulting in increased intrapericardial pressure and impaired diastolic filling, ultimately obstructing blood flow into the heart. Notably, even a relatively small pericardial effusion can precipitate tamponade, depending on the rate of fluid accumulation and the compliance of the pericardium. Pericardiocentesis remains the preferred intervention for the emergent management of patients presenting with cardiac tamponade. This procedure is typically performed via a subxiphoid or apical approach, with the selection of the access site guided by the distribution of the effusion as visualized on imaging. The timely execution of pericardiocentesis during the acute phase of tamponade is of paramount importance; failure to perform the procedure promptly may result in cardiovascular collapse, cardiac arrest, and ultimately, a potentially fatal outcome.
Keywords: acute pericarditis; pericarial effusion; cardiac tamponade; pericardiocentesis

INTRODUCTION

Pericardial diseases are most often categorized based on their duration and clinical course into three main types: acute (lasting less than six weeks), subacute, and chronic (lasting more than six months). These conditions are further classified into distinct syndromes according to their clinical presentation, which includes acute pericarditis, pericardial effusion, cardiac tamponade, recurrent pericarditis, and constrictive pericarditis – either transient or chronic in nature [1]. In routine clinical practice, patients diagnosed with acute pericarditis, provided the condition does not progress to pericardial effusion, generally exhibit a favourable prognosis. However, even a minimal accumulation of fluid within the pericardial space has the potential to induce cardiac tamponade, with clinical manifestations often occurring within hours of fluid build-up. These patients frequently present with symptoms and signs such as dyspnea, hypotension, tachycardia, jugular venous distention, diminished heart sounds, and paradoxical pulse. Cardiac tamponade is regarded as a medical emergency that calls for immediate intervention, typically in the form of pericardiocentesis. Failure to address this condition promptly can result in severe complications, including cardiac arrest and, ultimately, a fatal outcome if left untreated [2].

ACUTE PERICARDITIS

The pericardium, often referred to as the heart sac, consists of two primary layers: the visceral pericardium, a serous membrane that is separated by a small amount of fluid (ranging from 15–50 mL) from the fibrous parietal pericardium. In healthy individuals, the pericardium serves several critical functions, including the prevention of sudden and excessive expansion of the heart chambers during physical exertion or states of hypervolemia, which can impose a significant hemodynamic load on the heart due to the increased circulating blood volume. Under normal physiological conditions, the pressure within the pericardial space remains negative, which facilitates the smooth filling of the atria during systole. Moreover, the pericardium plays a vital role in maintaining the heart's anatomical position within the chest cavity, reducing friction between the heart and adjacent mediastinal structures, preventing the kinking or distortion of large blood vessels, and acting as a barrier to prevent the spread of inflammatory processes from the lungs or pleural space to the heart [1, 2].

Acute pericarditis represents the most prevalent pathological condition involving the pericardium, with its occurrence in the general population estimated to range from 0.2% to 0.5%. Autopsies reveal its incidental presence in up to 1% of cases. The etiology of acute pericarditis is multifactorial, with the most common cause being viral infections, especially those

Received • Примљено: September 27, 2024
Accepted • Прихваћено: May 13, 2025
Online first: May 14, 2025

Correspondence to:
Nina GATARIĆ
University Clinical Center of Serbia
Clinic for Cardiology,
Pasterova 2
11000 Belgrade
Serbia
gataricnina@gmail.com

caused by cardiotropic viruses such as Coxsackie, adenoviruses, and echoviruses. Additionally, the condition may arise from local or systemic autoimmune disorders, various metabolic disturbances, or, in more severe instances, from the infiltration of malignant cells into the pericardium [3, 4]. Acute pericarditis can also occur less frequently following chest radiotherapy, or as a result of fungal or parasitic infections, further emphasizing the broad spectrum of underlying causes for this condition [5–8].

The inflammatory process affecting the pericardial tissue induces severe pain due to the dense network of nerve endings derived from the phrenic nerve. This neural involvement also explains the characteristic radiation of pain to the trapezius muscle. Furthermore, any electrocardiographic changes, as well as potential rhythm disturbances and conduction abnormalities observed in acute pericarditis, stem from the inflammatory response in the myocardium, given that the pericardium itself is electrically neutral [9, 10]. The inflammatory involvement of the myocardium may further contribute to transient arrhythmias or alterations in cardiac conduction, necessitating close monitoring in affected patients.

Under normal physiological conditions, the pericardium exhibits selective permeability to water and electrolytes, which are integral components of pericardial fluid. This fluid remains in a state of dynamic equilibrium with the circulating blood. However, inflammation disrupts this delicate balance, leading to the localized release of pro-inflammatory mediators that stimulate excessive fluid secretion from the visceral pericardium. Additionally, the inflammatory response results in the accumulation of large molecular substances that further draw fluid into the pericardial space while simultaneously impairing its reabsorption, ultimately leading to the development of pericardial effusion [11, 12, 13]. The progressive accumulation of fluid may exert pressure on the heart chambers, potentially compromising hemodynamic stability.

The diagnosis of acute pericarditis necessitates the presence of at least two of the following clinical criteria: chest pain that worsens with deep inspiration, changes with body movement, and radiates to the trapezius muscle; auscultation of a pericardial friction rub; characteristic electrocardiographic changes, such as diffuse concave ST-segment elevation and PR-segment depression; low voltage in standard electrocardiogram leads (Figure 1); radiographic and echocardiographic evidence of pericardial effusion (Figure 2); and elevated inflammatory markers, particularly C-reactive protein [14, 15]. Early recognition and diagnosis are essential for timely intervention, to prevent potential complications associated with pericardial inflammation.

Accurate detection of clinical symptoms and signs that manifest during pericardial effusion or cardiac tamponade can often provide crucial diagnostic insights into the underlying etiology. The presence of cardiac tamponade without a concomitant elevation in inflammatory markers is associated with up to a threefold higher probability of a malignant origin. Additionally, patients with recurrent pericarditis who experience acute episodes that do not respond to nonsteroidal anti-inflammatory drugs (NSAIDs)

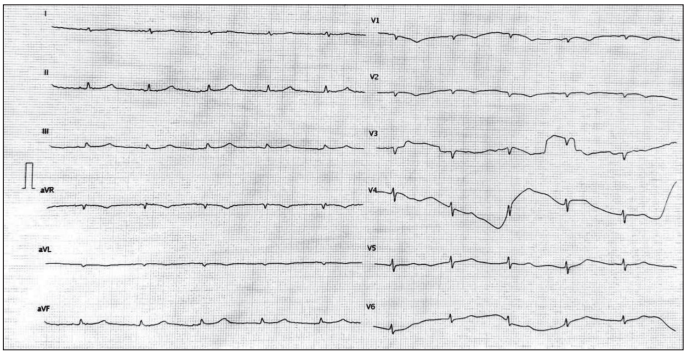


Figure 1. Typical electrocardiographic findings in cardiac tamponade (low voltage in standard leads)

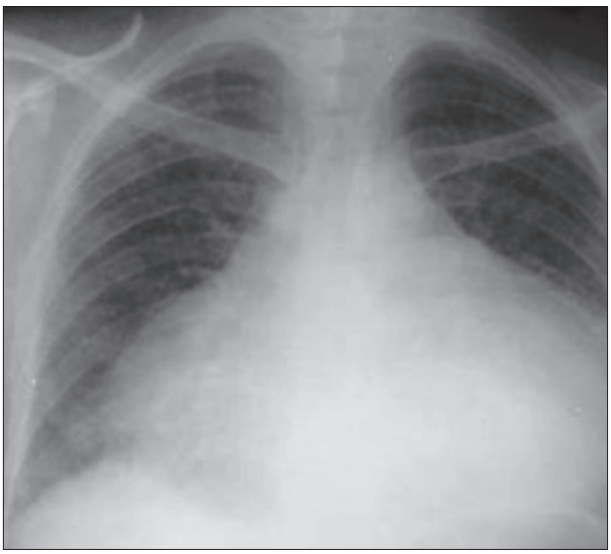


Figure 2. Radiography finding in pericardial effusion

exhibit a tenfold increased likelihood of pericardial effusion of malignant etiology. Furthermore, in oncological patients, the etiology of pericardial effusion is up to 20 times more likely to be malignant compared to individuals without a known malignancy, underscoring the need for thorough evaluation and appropriate management [16, 17].

The treatment of acute pericarditis of viral origin primarily focuses on symptom relief, the prevention of complications, and the management of the underlying cause. The initial approach includes the administration of analgesics and anti-inflammatory medications, which are gradually tapered as clinical symptoms improve. High-dose NSAIDs remain the cornerstone of acute pericarditis therapy, with commonly prescribed regimens including ibuprofen (600–800 mg, three times daily), indomethacin (25–50 mg, three times daily), or aspirin (750–1000 mg, three times daily). Adequate hydration and gastroprotective agents, such as proton pump inhibitors, are often recommended alongside NSAID therapy to mitigate gastrointestinal side effects [18, 19].

In addition to NSAIDs, colchicine is administered for a minimum duration of three months at a dose of 0.5 mg twice daily, or a reduced dose of 0.25 mg twice daily for patients weighing less than 70 kg. In recurrent pericarditis, Colchicine therapy may be extended to six months or

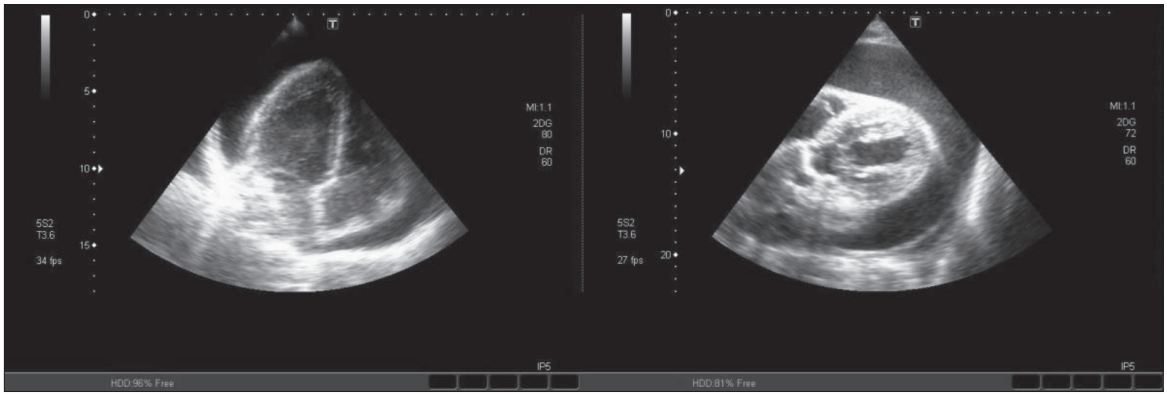


Figure 3. Echocardiographic findings in threatening cardiac tamponade; "Swinging heart" sign, where the heart moves like a pendulum within a massive pericardial effusion

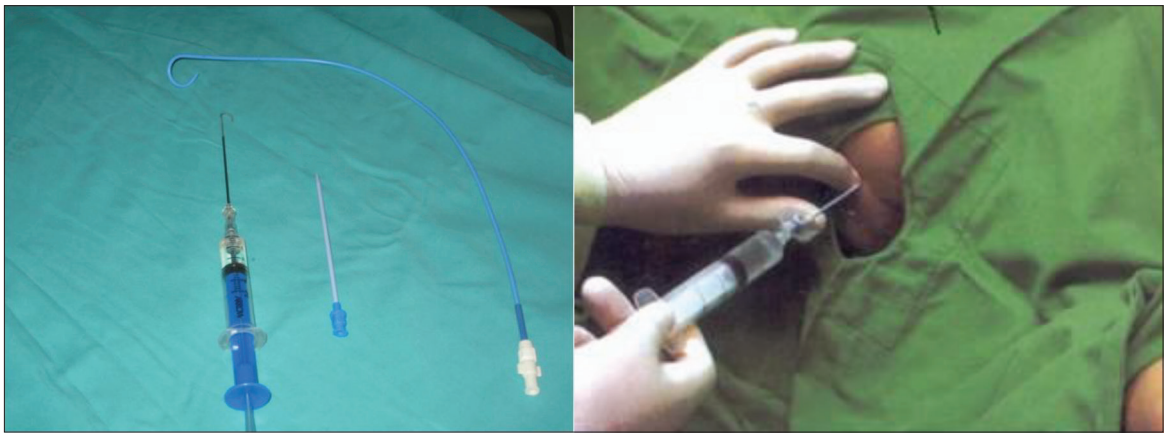


Figure 4. Pericardiocentesis set (left figure); intercostal punction is performed along the upper edge of the lower rib not to harm the intercostal arteries (right figure)

longer to reduce the risk of relapse. The use of corticosteroids is generally discouraged during the acute phase due to their potential to increase the risk of recurrence. However, in cases where patients fail to respond to NSAIDs and colchicine, corticosteroids (0.2–0.5 mg / kg / day of methylprednisolone) may be introduced with caution, with careful monitoring for potential complications such as opportunistic infections [20, 21].

Biologic therapy, particularly the interleukin-1 receptor antagonist anakinra (2 mg / kg / day up to 100 mg/day), is an emerging treatment option that has demonstrated efficacy in refractory or recurrent pericarditis. Ongoing clinical studies continue to evaluate its long-term benefits and safety profile. In patients with frequent and disabling relapses persisting for more than two years despite optimal medical therapy, surgical intervention in the form of pericardiectomy is often considered as a definitive treatment to prevent further episodes [22–25].

CARDIAC TAMPONADE

Cardiac tamponade refers to the accumulation of a significant volume of fluid within the pericardial cavity, resulting in hemodynamic compromise due to the obstruction of venous return and subsequent impairment of cardiac filling. This leads to reduced cardiac output and, if left untreated, can progress to cardiovascular collapse. The most common etiologies of cardiac tamponade include neoplastic and viral pericarditis, although it can also arise from intrapericardial hemorrhage due to trauma, malignancy, aortic dissection, post-myocardial infarction free wall rupture, or iatrogenic cardiac perforation during interventional procedures such as catheter-based interventions or pacemaker lead placement [26].

In some cases, even a relatively small volume of pericardial fluid (approximately 200 mL) can precipitate tamponade if it accumulates acutely, as the pericardium has limited time to adapt to the increased intrapericardial pressure. In contrast, chronic fluid accumulation over an extended period may allow the pericardium to stretch and accommodate volumes of up to 2000 mL, depending on factors such as myocardial compliance, pericardial elasticity, and intracardiac pressures. The classic "Beck's triad" of hypotension, elevated jugular venous pressure, and muffled heart sounds is typically observed only in cases of severe, rapidly developing cardiac tamponade. When tamponade develops more gradually, the clinical presentation often mimics that of congestive heart failure, manifesting as dyspnea, orthopnea, hepatomegaly, and jugular venous distension. Notably, pulmonary auscultation in these patients typically reveals no evidence of congestion, distinguishing tamponade from primary pulmonary causes of heart failure [27].

The earliest echocardiographic indication of evolving cardiac tamponade is right atrial collapse, followed

by right ventricular diastolic collapse, and in more severe cases, compression of the left atrium or left ventricle. In large pericardial effusions, the heart may appear to "swing" within the pericardial sac, a phenomenon referred to as the "swinging heart" or "floating heart" sign [14] (Figure 3). Given its life-threatening nature, cardiac tamponade constitutes an absolute indication for emergent pericardial drainage, which can be performed via pericardiocentesis (Figure 4) or, in select cases, surgical pericardial window creation (pericardotomy). Pharmacological interventions are considered adjunctive and should not delay definitive drainage of the effusion. Patients with hypovolemia should receive continuous intravenous fluid resuscitation to maintain preload, while those with hypoxia or impending respiratory failure should be promptly intubated and mechanically ventilated in preparation for pericardiocentesis [28].

Following pericardiocentesis, it is imperative to conduct a comprehensive biochemical, bacteriological, and cytological analysis of the evacuated pericardial fluid in all patients presenting with pericardial effusion. This step is critical for identifying the underlying etiology and guiding further therapeutic management. In cases where malignancy is suspected, additional diagnostic measures such as pericardial biopsy or advanced molecular testing may be warranted to confirm the diagnosis and tailor treatment strategies [26, 27, 28].

CONCLUSION

The overall prognosis for patients with acute pericarditis is generally favorable, particularly when the condition is promptly diagnosed and appropriately managed. Although acute pericarditis can occur at any age, it is more commonly observed in younger individuals and males. The clinical presentation varies, with most patients experiencing mild to moderate symptoms. However, in some cases, the initial symptoms can be severe, and a characteristic pericardial friction rub is frequently detected upon auscultation. The duration of the illness typically ranges from a few days to four weeks, but approximately 25% of patients may experience one or more recurrences. While some individuals may develop significant pericardial effusion, progression to cardiac tamponade remains uncommon.

Constrictive pericarditis, though rare, is a potential long-term complication often associated with recurrent episodes of the disease. This condition is characterized by pericardial thickening and fibrosis, leading to impaired diastolic filling of the heart. Given the severity of this complication, urgent clinical evaluation by an experienced invasive cardiologist is essential for optimal management. Echocardiography remains the gold standard for the rapid identification of acute cardiac tamponade, complemented by clinical assessment, electrocardiographic findings, and radiographic imaging. In cases of hemodynamically significant tamponade, immediate pericardial drainage is required. Pericardiocentesis, typically performed via a subxiphoid or apical approach under echocardiographic or fluoroscopic guidance, is the preferred intervention for emergent relief of pericardial pressure. Delayed intervention during the acute phase of cardiac tamponade may result in cardiovascular collapse, cardiac arrest, and potentially a fatal outcome. Therefore, prompt recognition and timely management are critical in reducing morbidity and mortality associated with this life-threatening condition.

Ethics: The authors hereby declare that this article was prepared in full compliance with the ethical standards set forth by the journal Serbian Archives of Medicine, as well as the ethical guidelines and institutional policies adhered to by each author involved in the research and writing process.

Conflict of interest: None declared.

REFERENCES

1. Sathirareuangchai S, Armstrong S. The pathology of pericarditis. Diagn Histopathol. 2022;28(4):191–8. [DOI: 10.1016/j.mpdhp.2022.01.002]
2. Ismail TF. Acute pericarditis: Update on diagnosis and management. Clin Med (Lond). 2020;20(1):48–51. [DOI: 10.7861/clinmed.cme.20.1.4] [PMID: 31941732]
3. Nassar AH, Abou Alaiwi S, El Zarif T, Denu R, Macaron W, Abdel-Wahab N, et al. Safety and efficacy of immune checkpoint therapy for the treatment of patients with cardiac metastasis: a multicenter international retrospective study. J Immunother Cancer. 2025;13(3):e009364. [DOI: 10.1136/jitc-2024-009364] [PMID: 40032601]
4. Michaels KC, Dougherty SC, Kurpiel BR, Douvas MG. Primary Mediastinal Synovial Sarcoma with Pericardial Involvement: A Case Report. Case Rep Oncol. 2024;18(1):76–84. [DOI: 10.1159/000542680] [PMID: 39980501]
5. Prakash A, Rawat SS, Russal Starlet A, Kumar A. Pericardial thymoma presenting as cardiac tamponade in an adult. BMJ Case Rep. 2025;18(1):e262379. [DOI: 10.1136/bcr-2024-262379] [PMID: 39890412]
6. Zamora KDV, Vera-Chávez JS, Aranda-Fraustro A, Duarte-Gutiérrez MA, Vargas-Guerrero A, Altamirano-Solorzano GA, et al. Recurrent Cardiac Tamponade by Pulmonary Artery Intimal Sarcoma. Echocardiography. 2025;42(1):e70068. [DOI: 10.1111/echo.70068] [PMID: 39737669]
7. Nakajima T, Mukawa K, Kouzu H, Kamada A, Kawaharada N. Prevention of cardiac tamponade by left intercostal Pericardiotomy for massive recurrent pericardial effusion: a case report. Oxf Med Case Reports. 2024;2024(11):omae139. [DOI: 10.1093/omcr/omae139] [PMID: 39588504]
8. Andreis A, Dossi FC, De Ferrari GM, Alunni G, Imazio M. Anakinra-Dependent Recurrent Pericarditis: The Role of the R202Q Variant of the MEFV Gene. J Clin Med. 2024;13(20):6051. [DOI: 10.3390/jcm13206051] [PMID: 39458001]
9. Klein AL, Wang TKM, Cremer PC, Abbate A, Adler Y, Asher C, et al. Pericardial Diseases: International Position Statement on New Concepts and Advances in Multimodality Cardiac Imaging. JACC Cardiovasc Imaging. 2024;17(8):937–88. [DOI: 10.1016/j.jcmg.2024.04.010] [PMID: 39111992]
10. Cremer PC, Klein AL, Imazio M. Diagnosis, Risk Stratification, and Treatment of Pericarditis: A Review. JAMA. 2024;332(13):1090–100. [DOI: 10.1001/jama.2024.12935] [PMID: 39235771]
11. Kivity S, Baran TZ, Reuveni MM, Irony A, Adler L, Alder Y, et al. The Longitudinal Incidence of Pericarditis in 1.6 Million Patients: A 20-Year Study. Am J Cardiol. 2024;223:70–2. [DOI: 10.1016/j.amjcard.2024.05.012] [PMID: 38777208]

12. Wan Muhamad Hatta SS, Mirza AR, Sunni N, Bashir A. Heart-breaking tumours: a case series of malignant pericardial effusion. Eur Heart J Case Rep. 2025;9(3):ytaf009. [DOI: 10.1093/ehjcr/ytaf009] [PMID: 40046975]
13. Buckley LF, Libby P. Colchicine's Role in Cardiovascular Disease Management. Arterioscler Thromb Vasc Biol. 2024;44(5):1031–41. [DOI: 10.1161/ATVBAHA.124.319851] [PMID: 38511324]
14. Collini V, Andreis A, De Biasio M, De Martino M, Isola M, Croatto N, et al. Efficacy of colchicine in addition to anakinra in patients with recurrent pericarditis. Open Heart. 2024;11(1):e002599. [DOI: 10.1136/openhrt-2023-002599] [PMID: 38490715]
15. Toker Dincer Z, Karup S, Yilmaz E, Corbali O, Azman FN, Melikoglu M, et al. Anakinra in idiopathic recurrent pericarditis: a comprehensive case series and literature review. Z Rheumatol. 2024;83(7):587–96. [DOI: 10.1007/s00393-023-01471-x] [PMID: 38277021]
16. Yesilyaprak A, Kumar AK, Agrawal A, Furqan MM, Verma BR, Syed AB, et al. Predicting Long-Term Clinical Outcomes of Patients With Recurrent Pericarditis. J Am Coll Cardiol. 2024;84(13):1193–204. [DOI: 10.1016/j.jacc.2024.05.072] [PMID: 39217549]
17. Adler Y, Ristić AD, Imazio M, Brucato A, Pankuweit S, Burazor I, et al. Cardiac tamponade. Nat Rev Dis Primers. 2023;9(1):36. [DOI: 10.1038/s41572-023-00446-1] [PMID: 37474539]
18. Imazio M, Andreis A, Lubian M, Lazaros G, Lazarou E, Brucato A, et al. The Torino Pericarditis Score: a new-risk stratification tool to predict complicated pericarditis. Intern Emerg Med. 2021;16(7):1921–6. [DOI: 10.1007/s11739-021-02803-y] [PMID: 34275095]
19. Lazaros G, Oikonomou V, Oikonomou E, Aznaouridis K, Vlachopoulos C, Vogiatzi G, et al. Recurrence of Pericardial Effusion After Pericardiocentesis: Does Catheter-Induced Acute Pericardial Inflammation Play a Role? Am J Med Sci. 2021;361(5):676–8. [DOI: 10.1016/j.amjms.2020.10.012] [PMID: 33243434]
20. Othon-Martinez D, Lopez OJ, Daza J, Malaga-Espinoza BX, Ganiyu S, Tijani A. Unlocking the Mystery: Resident-Led POCUS Intervention in Community Hospital Revealing Pericardial Tamponade in a Complex Case. J Investig Med High Impact Case Rep. 2025;13:23247096241298172. [DOI: 10.1177/23247096241298172] [PMID: 40019160]
21. Ebrahimi P, Taheri H, Bahiraie P, Rader F, Siegel RJ, Mandegar MH, et al. Incidence of secondary pericardial effusions associated with different etiologies: a comprehensive review of literature. J Cardiothorac Surg. 2025;20(1):141. [DOI: 10.1186/s13019-025-03370-5] [PMID: 39987086]
22. Mandyam S, Onteddu J, Ray R, Basso R, Bader F, Onteddu NK. Multicentric Reticulohistiocytosis Presenting As Acute Pericarditis With Moderate-Sized Pericardial Effusion: A Case Report and Review of Multicentric Reticulohistiocytosis Treatment. Cureus. 2023;15(6):e39953. [DOI: 10.7759/cureus.39953] [PMID: 37416020]
23. Simeunović DS, Milinković I, Polovina M, Trifunović Zamaklar D, Veljić I, Zaharijev S, et al. Safety and Efficacy of Echo- vs. Fluoroscopy-Guided Pericardiocentesis in Cardiac Tamponade. Medicina. 2025;61(2):265. [DOI: 10.3390/medicina61020265] [PMID: 40005382]
24. Lasica R, Asanin M, Vukmirovic J, Maslac L, Savic L, Zdravkovic M, et al. What Do We Know about Peripartum Cardiomyopathy? Yesterday, Today, Tomorrow. Int J Mol Sci. 2024;25(19):10559. [DOI: 10.3390/ijms251910559] [PMID: 39408885]
25. Lasica R, Djukanovic L, Mrdovic I, Savic L, Ristic A, Zdravkovic M, et al. Acute Coronary Syndrome in the COVID-19 Era-Differences and Dilemmas Compared to the Pre-COVID-19 Era. J Clin Med. 2022;11(11):3024. [DOI: 10.3390/jcm11113024] [PMID: 35683411]
26. Milinkovic I, Ašanin M, Simeunovic DS, Seferović PM. In the search for an ideal registry: Does the cloud have a silver lining? Eur J Prev Cardiol. 2018;25(9):956–9. [DOI: 10.1177/2047487318774420] [PMID: 29719967]
27. Milinković I, Polovina M, Simeunović DS, Ašanin M, Seferović PM. Oxidative stress and inflammation in heart failure: The best is yet to come. Eur J Prev Cardiol. 2020;27(5):490–3. [DOI: 10.1177/2047487319900294] [PMID: 32013599]
28. Shawamri S, Šačić D, Ristić M, Milivojević I. Concurrent Acute Myocardial Infarction and Stroke: Challenges in Diagnosis and Treatment. Int Heart J. 2024;65(5):956–9. [DOI: 10.1536/ihj.24-204] [PMID: 39343598]

Акутни перикардитис и тампонада срца – премошћавање јаза између дијагностике и лечења

Дејан Симеуновић[1,2], Стефан Јуричић[1], Нина Гатарић[1], Марко Ристић[1], Филип Симеуновић[2], Иван Милинковић[1,2], Валерија Перић[1], Ратко Ласица[1,2], Арсен Ристић[1,2]

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

САЖЕТАК

Акутни перикардитис настаје као последица запаљенског процеса у перикардном ткиву, а као одговор на инфламацију долази до развоја перикардног излива. Срчана тампонада представља накупљање значајне количине течности у перикардном простору, што онемогућава адекватан прилив крви у срце. Акутно накупљање чак и мање количине течности у перикардном простору може довести до срчане тампонаде. Перикардиоцентеза представља најчешће коришћени поступак за ургентно збрињавање болесника са срчаном тампонадом и обично се изводи субксифоидним или апикалним приступом, у зависности од дистрибуције излива. Правовремено извођење овог захвата током акутне фазе болести је од суштинског значаја, јер у супротном срчана тампонада може довести до срчаног застоја и тиме, потенцијално, до фаталног исхода.

Кључне речи: акутни перикардитис; перикардни излив; срчана тампонада; перикардиоцентеза

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови**,** наручени коментари, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу

оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant* – Cross Check (iThenticate). Радови код којих се докаже плагијаризам/аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (https://www.nlm.nih.gov/mesh/meshhome.html)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°*C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публи-

кације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примере навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *https://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs/en/submission-letter/SubmissionLetterForm2023.pdf*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био разматран за објављивање у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 9. Статута Друштва) и измирити накнаду за обраду чланака (*Article Processing Charge*) у износу од 3000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*Article Processing Charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и број телефона.

АДРЕСА:
Српско лекарско друштво
Уредништво часописа „Српски архив за целокупно лекарство“
Ул. краљице Наталије 1
11000 Београд
Србија

Телефони: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Интернет адреса: *http://www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

Before submitting their paper to the Editorial Office of the Serbian Archives of Medicine, authors should read the Instructions for Authors, where they will find all the necessary information on writing their manuscript in accordance with the journal's standards. It is essential that authors prepare their manuscript according to established specifications, as failure to do so will result in paper being delayed or rejected. Serbian Archives of Medicine provides no fee for published articles. By submitting a paper for publishing consideration, authors of a paper accepted for publication in the Serbian Archives of Medicine grant and assign all copyrights to the publisher – the Serbian Medical Society.

GENERAL INSTRUCTIONS. *Serbian Archives of Medicine* publishes papers that have not been, either in their entirety or partially, previously published, and that have not been accepted for publication elsewhere. *Serbian Archives of Medicine* publishes papers in English and Serbian. For better availability and citation, authors are encouraged to submit articles of all types in English. The journal publishes the following article types: editorials, original papers, preliminary and short communications, case reports, video-articles, images in clinical medicine, review articles, current topics, articles for practitioners, history of medicine articles, language of medicine articles, medical ethics (clinical ethics, publication ethics) and regulatory standards in medicine, congress and scientific meeting reports, personal view articles, invited commentaries, letters to the editor, book reviews, professional news, In memoriam and other articles. Original papers, case reports, preliminary and short communications, review articles, current topics, video-articles and images in clinical medicine are published in English only, while other article types may be published in Serbian if the Editorial Office reaches such decision.

The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., 99Tc, IL-6, O2, B12, CD8). If something is commonly written in italics, such as genes (e.g. BRCA1), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors (contained within the Submission Letter) declaring any potential interest or stating that the authors have no conflict of interest. For additional information on different types of conflict of interest, please see World Association of Medical Editors (WAME, *www.wame.org*) policy statement on conflict of interest.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism

control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*https://www.nlm.nih.gov/mesh/meshhome.html*) are to be used for selection of the keywords.

TRANSLATION INTO SERBIAN. The third page of the manuscript should include: title of the paper in the Serbian language; each author's full name and family name (no titles), indexed by numbers; official name, place and country of the institution in which authors work. On the fourth page of the manuscript the summary (100–250 words) and keywords (3–6) should be typed, but this refers only to papers in which a summary and keywords are compulsory. The terms taken from foreign literature should be translated into comprehensible Serbian. All foreign words or syntagms that have a corresponding term in Serbian should be replaced by that term.

If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine," etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

STRUCTURE OF THE MANUSCRIPT. All section headings should be in capital letters using boldface. Original articles and preliminary and short communications should have the following section headings: Introduction (objective is to be stated in the final paragraph of the Introduction), Methods, Results, Discussion, Conclusion, References. A review article and current topic include: Introduction, corresponding section headings, Conclusion, References. The firstly named author of a review article should cite at least five auto-citations (as the author or co-author of the paper) of papers published in peer-reviewed journals. Co-authors, if any, should cite at least one auto-citation of papers also published in peer-reviewed journals. A case report should consist of: Introduction (objective is to be stated in the final paragraph of the Introduction), Case Report, Discussion, References. No names of patients, initials or numbers of medical records, particularly in illustrations, should be mentioned. Case reports cannot have more than five authors. Letters to the editor need to refer to papers published in the *Serbian Archives of Medicine* within previous six months; their form is to be comment, critique, or stating own experiences. Publication of articles unrelated to previously published papers will be permitted only when the journal's Editorial Office finds it beneficial.

All enclosures (tables, graphs, photographs, etc.) should be placed at the end of the manuscript, while in the body of the text a particular enclosure should only be mentioned and its preferred place indicated. The final arrangement (position) of the enclosures will depend on page layout.

ABBREVIATIONS. To be used only if appropriate, for very long names of chemical compounds, or as well-known abbreviations (standard abbreviations such as DNA, AIDS, HIV, ATP, etc.). Full meaning of each abbreviation should be indicated when it is first mentioned in the text unless it is a standard unit of measure. No abbreviations are allowed in the title. Abbreviations in the summary should be avoided, but if they have to be used, each of them should be explained when first mentioned in the text of the paper.

DECIMAL NUMBERS. In papers written in English, including text of the manuscript and all enclosures, a decimal point should be used in decimal numbers (e.g. 12.5 ± 3.8), while in Serbian papers a decimal comma should be used (e.g. 12,5 ± 3,8). Wherever applicable, a number should be rounded up to one decimal place.

UNITS OF MEASURE. Length, height, weight and volume should be expressed in metric units (meter – m, kilogram – kg, gram – g, liter – l) or subunits. Temperature should be in Celsius degrees (°C), quantity of substance in moles (mol), and blood pressure in millimeters of mercury column (mm Hg). All results of hematological, clinical and biochemical measurements should be expressed in the metric system according to the International System of Units (SI units).

LENGTH OF PAPER. The entire text of the manuscript – title page, summary, the whole text, list of references, all enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian – must not exceed 5,000 words for original

articles, review articles and articles on history of medicine, and 3,000 words for case reports, preliminary and short communications, current topics, articles for practitioners, educational articles and articles for "Language of medicine", congress and scientific meeting reports; for any other section maximum is 1,500 words.

Video-articles are to last 5–7 minutes and need to be submitted in the flv video format. The first shot of the video must contain the following: title of the journal in the heading (*Serbian Archives of Medicine*), title of the work, last names and initials of first and middle names of the paper's authors (not those of the creators of the video), year of creation. The second shot must show summary of the paper, up to 350 words long. The final shot of the video may list technical staff (director, cameraman, lighting, sound, photography, etc.). Video-articles need to be submitted along with a separate summary (up to 350 words), a single still/photograph as an illustration of the video, and a statement signed by the technical staff renouncing copyrights in favor of the paper's authors. To check the required number of words in the manuscript, please use the menu *Tools-Word Count*, or *File-Properties-Statistics*.

ARTICLE ENCLOSURES are tables, figures (photographs, schemes, sketches, graphs) and video-enclosures.

TABLES. Each table, with its legend, should be self-explanatory. The title should be typed above the table and any explanatory information under the table. Tables should be numbered in Arabic numerals in order of citation in the text. Use *MS Word*, the menu *Table-Insert-Table*, inserting the adequate number of rows and columns. By the right click of the mouse, use the options *Merge Cells* and *Split Cells*. Use *Times New Roman*, font size 12 pt, with single line spacing and no indent to draw tables. Abbreviations used in tables should be explained in the legend below each respective table.

If the manuscript is entirely in the Serbian language, tables and corresponding legend should be both in Serbian and English. Also, the table cells should contain text in both languages (do not create two separate tables with a single language!).

FIGURES. Figures are all types of visual enclosures, and photographs, schemes, sketches and graphs are published as 'figures' in the *Serbian Archives of Medicine.* Figures should be numbered in Arabic numerals in order of citation in the text. Only original digital photographs (black-and-white or color), of minimum 300 dpi, and *jpg* or *tiff* format, are acceptable (small, blurry and photographs of poor quality will not be accepted for publishing!). If authors do not possess or are not able to provide digital photographs, then the original photos should be scanned in 300 dpi, and saved in original size. If a paper needs to be illustrated with a considerable number of figures, several figures will be published within the paper, and the rest will be available in the electronic version of the paper as a PowerPoint presentation (every figure needs to be numbered and be accompanied by legend). Video-enclosures (illustrations of a paper) can last 1–3 minutes and are submitted in the *flv* format. Along with the video, a still/photograph representative of the video is also needed, as it will be used as a placeholder in the electronic version of the paper, and as an illustration in the printed version.

If the manuscript is entirely in the Serbian language, photographs and corresponding legend should be both in Serbian and English.

Photographs may be printed and published in color, but possible additional expenses are to be covered by the authors.

GRAPHS. Graphs should be plotted in *Excel* in order to see the respective values distributed in the cells. The same graphs should be copied and pasted to the *Word* document, numbered in Arabic numerals by order of citation in the text. The text in the graphs should be typed in *Times New Roman*. Abbreviations used in graphs should be explained in the legend below the respective graph. In the printed versions of papers, graphs are generally published in black-and-white; therefore, it is suggested to avoid the use of colors in graphs, or to utilize colors of significant difference in brightness.

If the manuscript is entirely in the Serbian language, graphs and corresponding legend should be both in Serbian and English.

SCHEMES (SKETCHES). Schemes and sketches are to be submitted in *jpg* or *tiff* format. Schemes should be drawn in *CorelDraw* or *Adobe Illustrator* (programs for drawing vectors, curves, etc.). The text in the schemes should be typed in *Times New Roman*, font size 10 pt. Abbreviations used in schemes should be explained in the legend below the respective scheme. If the manuscript is entirely in the Serbian language, schemes and corresponding legend should be both in Serbian and English.

ACKNOWLEDGMENT. List all those individuals having contributed to preparation of the article but having not met the criteria of authorship, such as individuals providing technical assistance, assistance in writing the paper or running the department securing general support. Financial aid and all other support in the form of sponsorship, grants, donations of equipment and medications, etc., should be mentioned too.

REFERENCES. The reference list is the responsibility of the authors. Cited articles should be readily accessible to the journals readership. Therefore, following each reference, its DOI number and PMID number (if the article is indexed for MEDLINE/PubMed) should be typed. References should be numbered in Arabic numerals in order of citation in the text. The overall number of references should not exceed 30, except in review articles, where maximum of 50 is acceptable, and in meta-analysis, where

up to 100 references are allowed. The number of citations of original articles must be at least 80% of the total number of references, and the number of citations of books, chapters and literature reviews less than 20%. If monographs and articles written by Serbian authors could be included in the reference list, the authors are obliged to cite them. The majority of the cited articles should not be older than five years. Use of abstracts as references is not allowed. If it is important to comment on results published solely in the form of an abstract, it is necessary to do so within the text of the article. The references of articles accepted for publication should be designated as *in press* with the enclosed proof of approval for publication.

The references are cited according to the Vancouver style (*Uniformed Requirements for Manuscripts Submitted to Biomedical Journals*), rules and formats established by the International Committee of Medical Journal Editors (*http://www.icmje.org*), used by *the U.S. National Library of Medicine* and scientific publications databases. Examples of citing publications (journal articles, books and other monographs, electronic, unpublished and other published material) can be found on the web site *https://www.nlm.nih.gov/bsd/uniform_requirements.html*. In citation of references, the defined standards should be strictly followed, because it is one of the essential factors of indexing for classification of scientific journals.

SUBMISSION LETTER. The manuscript must be accompanied by the Submission Letter, which is signed by all authors and includes the following: 1) statement that the paper has never been published and concurrently submitted for publication to any other journal; 2) statement that the manuscript has been read and approved by all authors who have met the criteria of authorship; and 3) contact information of all authors of the article (address, email, telephone number, etc.). Blank Submission Letter form can be downloaded from the journal's web site (*http://www.srpskiarhiv.rs/en/submission-letter/SubmissionLetterForm2023.pdf*).

Additionally, the authors should submit the following copies of all permits for: reproduction of formerly published material, use of illustrations and publication of information on known people or disclosure of the names of people having contributed to the work.

MEMBERSHIP FEE AND SUBSCRIPTION RATES. For an article to be considered for publishing in the *Serbian Archives of Medicine*, all its authors and co-authors residing in Serbia (if they are medical doctors or doctors of dental medicine) must be members of the Serbian Medical Society (in accordance with Article 9 of the Society's Bylaw) for the year in which the paper is being submitted, and all authors and co-authors are obliged to pay an article processing charge for the evaluation of the paper for publication. Domestic authors pay 3000 RSD, while international authors pay €35 (4200 RSD if paid from within Serbia). An author who had already paid the fee can have more articles submitted for publishing consideration in the year the fee was paid. All domestic authors who pay this fee may, if they desire so, receive the printed version of the journal in the year when the fee is paid. Please note that the payment of this charge does not guarantee acceptance of the manuscript for publication and does not influence the outcome of the review procedure, in accordance with the Good Publication Practice. The journal accepts donations from sponsors to create a sum for payment reductions or waivers for authors unable to cover the article processing charge (a justification of the inability to pay should be provided in such cases). The requirement for paying the article processing charge does not apply to students or to journal subscribers. Institutions (legal entities) cannot by their subscription cover this condition on behalf of the authors (natural persons). Copies of deposit slips for membership and Article Processing Charge should be enclosed with the manuscript. Foreign authors are under no obligation to be members of the Serbian Medical Society. All the relevant information can be obtained via email address of the Editorial Office (*office@srpskiarhiv.rs*) and on the journal's web site (*http://srpskiarhiv.rs/en/subscription/*).

SUBMISSION. Our online submission system will guide you through the process of entering your article details and uploading your files. All correspondence, including notification of Editorial Office, requests for revision and Editor's decision will be sent by e-mail.

Please submit your manuscript and all enclosures via: ***http://www.srpskiarhiv.rs***.

NOTE. The papers not complying with these instructions will not be reviewed and will be returned to the authors for revision. Observing the instructions for preparation of papers for the *Serbian Archives of Medicine* will shorten the time of the entire process of publication and will have a positive effect on the quality and timely release of the journal's issues.

For further information, please contact us via the following address:

ADDRESS:
Serbian Archives of Medicine
Editorial Office
Kraljice Natalije 1
11000 Belgrade
Serbia
Phones: (+381 11) 409-2776, 409-4479
E-mail: *office@srpskiarhiv.rs*
Website: *www.srpskiarhiv.rs*

ISSN 0370-8179
ISSN Online 2406-0895
OPEN ACCESS

CIP – Каталогизација у публикацији
Народна библиотека Србије, Београд

61(497.11)

СРПСКИ архив за целокупно лекарство : званичан часопис Српског лекарског друштва = Serbian Archives of Medicine : official journal of the Serbian Medical Society / главни и одговорни уредник Гордана Теофиловски-Парапид. - Књ. 1 (1874)-књ. 2 (1875) ; књ. 3 (1879)- књ. 8 (1881) ; књ. 9 (1887)-књ. 10 (1888) ; књ. 11 (1894)-књ. 12 (1895) ; год. 1, бр. 1/2 (1895)- . - Београд : Српско лекарско друштво, 1874-1875; 1879-1881; 1887-1888; 1894-1895; 1895-(Београд : Службени гласник). - 29 cm

Двомесечно. - Текст на енгл. језику. - Има суплемент или прилог: Српски архив за целокупно лекарство. Суплемент = ISSN 0354-2793. - Друго издање на другом медијуму: Српски архив за целокупно лекарство (Online) = ISSN 2406-0895
ISSN 0370-8179 = Српски архив за целокупно лекарство
COBISS.SR-ID 3378434

Nimulid®

nimesulid

Amicus
a Swixx BioPharma company

PM-RS-2023-5-2231, maj 2023

The Journal Serbian Archives of Medicine is indexed in: Science Citation Index Expanded, Journal Reports/Science Edition, Web of Science, Scopus, EBSCO, Directory of Open Access Journal, DOI Serbia

CONTENTS